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The role of sex in cardiac arrhythmias and sudden cardiac death

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The role of sex in cardiac arrhythmias and sudden cardiac death

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Editorial: The role of sex in cardiac arrhythmias and sudden cardiac death

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Editorial on the Research Topic
The role of sex in cardiac arrhythmias and sudden cardiac death

Introduction

Sudden cardiac death (SCD) when it occurs in the public eye to professional athletes or celebrities, garners media attention and public health interest to improve understanding of its causes and prevention in other athletes. The aftermath is then to stratify the survivor's risk return to play. Sudden cardiac death, just like other cardiac arrhythmias, has been recognized that its epidemiology, and response to treatment differ significantly between men and women. There are known sex differences in cardiac electrophysiology and clinical outcomes. Women have higher resting heart rates and longer baseline electrocardiographic QT intervals which affect arrhythmic risk. Yet, despite all this understanding there is a lack of guideline directed screening or risk assessment for men and women in competitive sports.

Review of sudden cardiac death

Sudden cardiac death (SCD) in the United States remains a major driver of mortality. Estimates of prevalence site as many as 325,000 deaths annually and as many as 1,000 deaths per day (1). SCD accounts for as many as 50% of all cardiovascular deaths, with as many as half of those deaths marking the sentinel event in manifestation of CVD (2). Most causes of SCD are driven by ischemic heart disease, however, recently the incidence of ischemic driven SCD is decreasing, whereas the role of cardiomyopathies tightly linked to fibrosis and left ventricular hypertrophy are increasing (3). In addition, Haukilahti et al. (3) showed that although the annual rate of SCD in women is about half of that in men, the rate of SCD in men has been declining more rapidly than in women. Interestingly, during subgroup analysis, these investigators found primary myocardial fibrosis to have a higher prevalence of causing non-ischemic SCD among women as compared to men. However, there continues to be an under recognition of this increased risk for women as compared to men in much of the scientific literature.

Screening for arrhythmias

Athletes present a special population in SCD from arrhythmias due to the physical and emotional stress that they place on their cardiovascular support system. In their study of National Basketball Association (NBA) athletes, Waase et al. (4) discuss the accuracy of existing athlete-specific electrocardiographic (ECG) criteria used as part of the NBA's required yearly health screening. After analyzing ECG data, the authors concluded that abnormal classification rates were higher among NBA athletes than other athletic sports. Even after analyzing the data through three different classification systems. T-wave inversions were the most common ECG abnormality.

On January 2nd, 2023, professional football player Damar Hamlin suffered a direct blow to his chest from the head of an opposing player, causing a sudden collapse view by television viewers nationwide. He suffered SCD and required advanced cardiac resuscitation on the field while encircled by teammates—an event that shocked the sporting world and general media. Thankfully, after appropriate and swift therapy he is recovering well. It is thought that the event leading to his SCD was commotio cordis, ventricular fibrillation (VF) triggered by a non-penetrating blow to the chest which triggered a ventricular extra stimulus during the ventricular repolarization period, a "R on t" phenomenon inciting ventricular fibrillation. Although the exact incidence of commotio cordis is unknown, it is one of the most frequent causes of SCD in young athletes. In their 2010 review, Maron and Estes (5) found the most common sports where commotio cordis occurred were baseball and softball, followed by hockey and then football. Data on commotio cordis are limited, but insight regarding the intricacies and complications of commotio cordis may be gleaned from case reports such as that by Westreich et al. (6). They discuss the case of 35-year-old soccer player who had a blow to the chest, and was subsequently found to have sustained ventricular tachycardia (VT) during electrophysiology study after having an episode of regular wide complex tachycardia on the field 9 months after his initial commotio cordis event. Out of all the variables that must align to cause these rare events, the authors discuss that only blows occurring during the 20–40 ms window as the T wave is trending upwards can cause VF. The authors explain that adenosine triphosphate–sensitive potassium channels are activated by force to the chest causing problems with repolarization, ultimately leading to arrhythmia. Although the event is uncommon, it is often deadly.

How can we prevent these events in athletes? One aspect of prevention is related to screening, while the other may be related to increased protection. There is currently no international recommendation from professional societies regarding ubiquitous cardiac screening, specifically screening with electrocardiogram (ECG) or transthoracic echocardiography (TTE), and/or magnetic resonance imaging for athletes. Corrado et al. demonstrated that after following over 30,000 Italian athletes for 25 years, they were able to successfully identify athletes with hypertrophic cardiomyopathy in a manner that was adequately sensitive and cost-effective (7). They compared their rate of detection to prevalence in other countries and found the rates to be comparable given the populations (0.07% in Italy vs. 0.1% in the US by TTE). It is difficult to extrapolate cost and feasibility from studies done nearly 20 years ago, but screening with 12-lead ECG may still be the best way to identify those who may be predisposed to SCD due to structural heart disease, channelopathies or abnormalities in cardiac conduction. Commotio cordis may just be the event that exposed an underlying structural cardiac problem. With more widespread screening programs, athletes with these underlying anomalies would be evaluated and treated accordingly. However, Bickel et al. review some of the limitations of widespread screening, including a high number needed to screen (2,000), lack of cost-effectiveness from adding EKG to the history, and need to focus on secondary prevention instead of screening (8). The authors discuss the need to ensure AEDs are readily available at all major sporting events, as neurologically intact survival rates were found to be 3.9-fold higher in patients where an AED was onsite. Lastly, they discuss the differences between the European and American guidelines, the later deferring the use of 12-lead ECG screening given the lack of robust data and financial infeasibility. More debate is yet to come.

But even after surviving SCD, what are the requirements for return to play? A court ruling in the case of SCD in a collegiate basketball player, *Knapp* v. *Northwestern University*, Maron et al. (9) the legal decision of the United States Seventh District Court upheld the decision of team physicians at Northwestern University to prohibit an athlete from participating in competitive sports given his history of VF, a high risk medical conditions. The ruling cites that both the power and the responsibility fall with physicians to ensure that young athletes are safe to partake in competitive sports. The courts' arguments for allowing the university to prohibit the student from playing relied on three key factors, namely the decision of the team's physician, opinions from appropriate specialists, and consensus guidelines, such as those established at several Bethesda Conferences. Society, law, and medicine have all changed drastically since 1996 when this precedent was made and they are, by nature, ever evolving disciplines. The need for ongoing revision and evaluation of current guidelines based upon the evolution of scientific advancement if highlighted by Maron et al. (10) in their statement on eligibility for competitive athletes with cardiovascular anomalies. These consensus guidelines create a medical framework for how risk assess young athletes for safe and healthy participation in competitive sports. Some of the topics put forward by these statements include criteria on eligibility and disqualification from organized competitive sports. Of course, every athlete must be individually risk assessed, but having overarching goals helps to guide the individual provider. These statements remain the hallmark of medical decision making, and as mentioned above, will be forever changing.

One way to prevent commotio cordis would be to protect the chest from high-speed blunt trauma. Although football players currently wear cushioned plastic shoulder pads, a chest plate to disperse a physical impact on the heart may reduce the incidence of commotio cordis. Even more importantly, how can we prevent athletes from being struck by blunt objects in sports that don't even have baseline protection, such as softball and baseball? Although

Abbreviations: SCD, sudden cardiac death; CVD, cardiovascular disease; SCA, sudden cardiac arrest; VF, ventricular fibrillation; VT, ventricular tachycardia; NICM, non-ischemic cardiomyopathy; ECG, electrocardiogram; TTE, transthoracic echocardiography.

only evaluated in animal models, Kumar et al. (11) identified three chest plates that significantly lowered the risk of VF comparted to blunt trauma without a chest protector. We cannot directly link the results of animal studies to human subjects; however, it would be more pragmatic to accept the data as true and potentially modify uniforms to accommodate chest protection. Further investigation would be required to establish definite answers and guidelines, but it seems reasonable that athletes participating in sporting activities where blunt trauma to the chest may benefit from use of basic chest protection. A chest plate to lighten the blow of a high velocity blunt object should not interfere with performance. Baseball and softball players wear helmets for this very reason, why shouldn't their hearts deserve the same protection? However, the best medication is the one patient will take. Young athletes tend to skip out on equipment that they deem unnecessary. Implementation of protective equipment into sports that have not traditionally required such as chest protection will require some buy-in from athletes everywhere, and most importantly, at every level. The case of Damar Hamlin offers an opportunity to increase public awareness of SCD. Professional athletes are positioned to lead this charge. Now may be the best time to team with professional organizations to increase awareness of screening to assess risk for SCD, advocate having defibrillators at the ready at all sports events, and ensure availability of team members trained in advanced cardiac life support to keep sports safe for all who participate.

The media has recently brought to light the severity of commotio cordis in men, but there needs to be a conscious effort to emphasize that women are at risk too. There has been a growth of professional women's sports teams, and women are not just at risk, but likely at increased risk. Guidelines, risk assessment and stratification should also take into account sex differences between men and women. If chest protection for athletes are adopted, there should be various options which specifically accommodate the anatomical differences between men and women. In attempt to reduce bias when developing or suggesting new protective equipment for athletes, we must consider the individual physiology and anatomy of participants.

The role of arrhythmias and SCD in women

Historically, the role of SCD in women has been underrecognized. Tompkins et al. analyzed data from the MADIT trials to examine sex differences in mortality and device efficacy in patients that received implantable cardiac defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) implantation (1). Overall, the investigators found that death from an arrhythmogenic cause was similar between men and women following ICD or CRT-D implantation and not the main driver of mortality. Interestingly, they found that CRT-D decreases both all cause and cardiac mortality more in women than men. The findings highlight the important fact that women were found to have a higher all-cause mortality as compared to when in those with non-ischemic cardiomyopathy (NICM).

The role of arrhythmias and cardiac mortality in women both needs to be (1) better studied and (2) better publicized among health care providers. To equally serve female patients, we need to fully understand the underlying cause of the substrate that appears as differences in mortality in patients with NICM. For practitioners, there needs to be an emphasis on adjusting the pre-test probability of underlying differences when thinking about arrhythmogenic SCD in women.

Future directions

Knowing this information, the future should be to (1) ensure there is more public health information on SCD, implementation of risk assessment and risk stratification of SCD by health care providers that considers biological differences between men and women (2) implementation of new technology to ensure the rates of SCD in athletes for screening and prevention. The use of technology and how to better incorporate devices, techniques, systems, in sports requires interdisciplinary discussion amongst specialists in sports medicine, cardiology and public health. One thought is to leverage machine learning algorithms to develop better screening systems for athletes. Students entering middle school and high school sports events can receive yearly EKGs to help screen for underlying cardiac disease. Wearable devices that are appealing to a young audience, can be used to obtain reliable ECG data for screening, risk stratification and possibly diagnosis. If not now, then when?

Recent events on the football field cause shock and awe that recovery can be swift with timely defibrillation and resuscitation, but it is also a wakeup call that more still needs to be done. What can we do to further minimize the risk of SCD of male and female athletes in sports around the world. It is the responsibility of health care providers to speak up about the importance of keeping the hearts of athletes healthy and well.

Author contributions

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Conflict of interest

EW has been a consultant for Boston Scientific, Medtronic, Sanofi, Cardiologs, and Zoll.

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ORIGINAL RESEARCH
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Sex-Related Differences in Patients With Unexplained Syncope and Bundle Branch Block: Lower Risk of AV Block and Lesser Need for Cardiac Pacing in Women

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Objective: To analyze if there are sex-related differences in patients with unexplained syncope and bundle branch block (BBB).

Background: Despite increasing awareness that sex is a major determinant of the incidence, etiology, and the outcomes of different arrhythmias, no studies have examined differences in presentation and outcomes between men and women with syncope and BBB.

Methods: Cohort study of consecutive patients with unexplained syncope and BBB was included from January 2010 to January 2021 with a median follow-up time of 3.4 years [interquartile range (IQR) 1.7–6.0 years]. They were evaluated by a stepwise workup protocol based on electrophysiological study (EPS) and long-term follow-up with an implantable cardiac monitor (ICM).

Results: Of the 443 patients included in the study, 165 (37.2%) were women. Compared with men, women had less diabetes (25.5 vs. 39.9%, $p = 0.002$) and less history of ischemic heart disease (IHD; 13.3 vs. 25.9%, $p = 0.002$). Left bundle branch block (LBBB) was more frequent in women (55.2 vs. 27.7%, $p < 0.001$) while right bundle branch block (RBBB) was more frequent in men (41.5 vs. 67.7%, $p < 0.001$). His to ventricle (HV) interval in the EPS was shorter in women (58 ms [IQR 52–71] vs. 60 ms [IQR 52–73], $p = 0.035$) and less women had an HV interval longer than 70 ms (28.5 vs. 38.1%, $p = 0.039$), however, EPS and ICM offered a similar diagnostic yield in both sexes (40.6 vs. 48.9% and 48.4% vs. 51.1%, respectively). Women had a lower risk of developing atrioventricular block (AVB) (adjusted odds ratio [OR] 0.44–95% CI 0.26–0.74,

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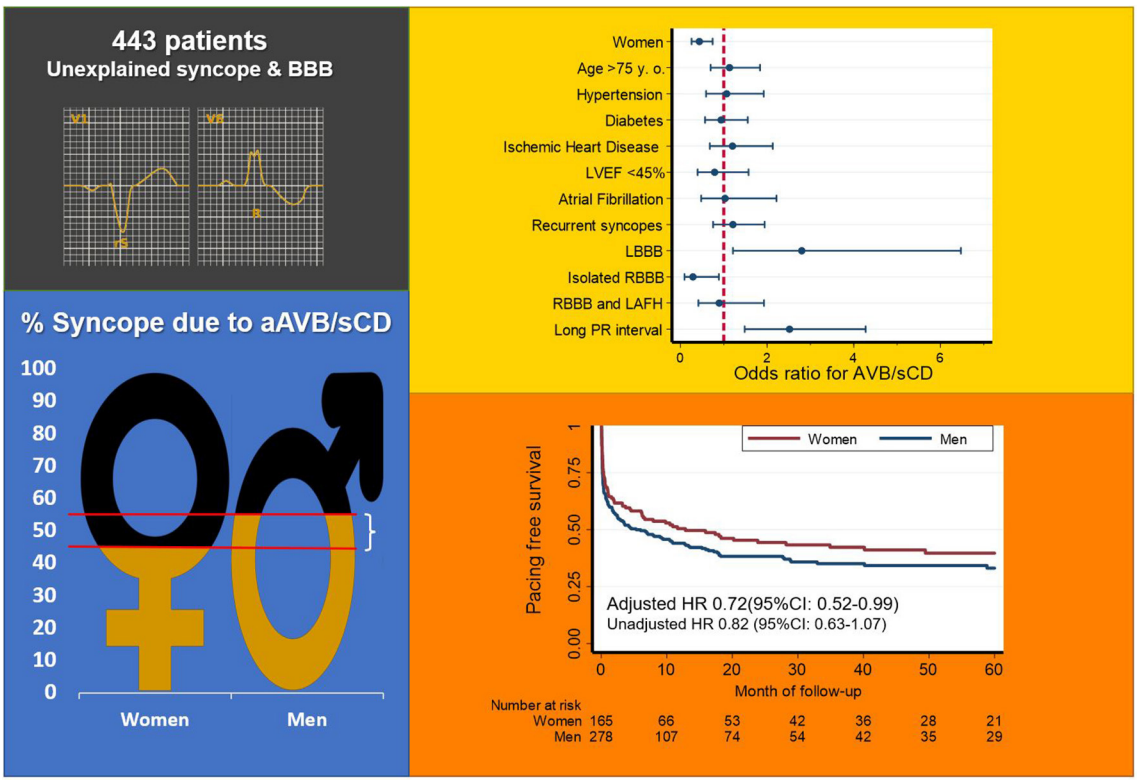
$p = 0.002$) and of requiring permanent pacemaker implantation (adjusted hazard ratio [HR] 0.72–95% CI: 0.52–0.99, $p = 0.046$). The mortality rate was lower in women (4.5 per 100 person-years [95% CI 3.1–6.4 per 100 person-years] vs. 7.3 per 100 person-years [95% CI 5.9–9.1 per 100 person-years]).

Conclusions: Compared to men, women with unexplained syncope and BBB have a lower risk of AVB and of requiring cardiac pacing. A stepwise diagnostic approach has a similar diagnostic yield in both sexes, and it seems appropriate to guide the treatment and avoid unnecessary pacemaker implantation, especially in women.

Keywords: syncope, pacemaker, electrophysiological study, loop recorder, cardiac monitor, gender differences, sex-related differences



GRAPHICAL ABSTRACT | Risk of AVB and need for cardiac pacing. Left: Percentage of patients diagnosed with aAVB/sCD in both sexes. Right-top: Multivariate logistic regression analyses for risk of aAVB/sCD. Odds ratio and 95% CI are plotted. Right-bottom: Kaplan-Meier pacemaker-free survival estimates curves in both sexes. aAVB/sCD, advanced atrio-ventricular block or severe conduction disturbances; HR, hazard ratio; CI, confidence interval; y.o, years old; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; BBB, bundle branch block; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block.

INTRODUCTION

Although syncope in patients with bundle branch block (BBB) is often due to paroxysmal advanced atrioventricular block (aAVB), other mechanisms may also be involved (1–4). A systematic diagnostic approach based on clinical evaluation, electrophysiological study (EPS), and the Implantable cardiac monitor (ICM) has shown to be safe and provide a high rate of etiological diagnosis (3, 5–7). However, due to the low predictive value of EPS, some investigators suggest that a pacemaker should be implanted on an empirical basis (2, 8), therefore, the best way to manage these patients remains controversial. Increasing knowledge of the disease characteristics can help clinicians to improve their management in specific subgroups of patients. Despite substantial efforts in recent years

Abbreviations: aAVB, Advanced atrioventricular block; sCD, Severe conduction disturbances; BBB, Bundle branch block; EPS, electrophysiological study; ICM, Implantable cardiac monitor; SND, Sinus node dysfunction.

to improve the understanding of the sex-related differences in cardiovascular disease, there is still insufficient knowledge of physiology, epidemiology, and outcomes in women, leading to a lack of sex-specific recommendations. In this regard, there is an increasing awareness that sex is a major determinant of the incidence, etiology, and clinical presentation of arrhythmias (9, 10). It is known that women have a major susceptibility to reflex syncope (11–14) and probably to sinus node dysfunction (SND) (9, 10, 15). However, no studies have examined differences between men and women in the presentation and outcomes of unexplained syncope and BBB.

Given the susceptibility of women to syncope due to other mechanisms and the different comorbidities of the female sex, we hypothesize that women with unexplained syncope and BBB would have a different risk of aAVB or severe conduction disturbances (sCDs) and a different risk of needing cardiac pacing compared to men. The aim of this study was to analyze the sex-related differences in patients with syncope and BBB concerning the prevalence of aAVB/sCD, the diagnostic yield of tests, and clinical outcomes.

METHODS

Study Population

We performed a prospective observational study on a consecutive patient cohort at a tertiary university hospital that is a reference center for cardiology and arrhythmias [Hospital Universitari Vall d'Hebron, Barcelona (Spain)]. From January 2010 to January 2021, we included those patients admitted for syncope with BBB, in whom no certain diagnosis was reached for the syncope in the initial assessment at the emergency department. We excluded patients under the age of 18 years, those with pacemakers or implantable cardiac defibrillators (ICD) *in situ*, patients with left ventricular ejection fraction (LVEF) <35% or with another ICD direct indication, and those who could not keep to the study's diagnostic protocol due to comorbidities or their own preference. In June 2021, we collected the final follow-up data of the patients. The patient's clinical details, syncope characteristics, therapeutic management, and follow-up were recorded at the time of hospital admission.

The study complies with the Helsinki declaration and was approved by the local ethics committee.

Study Protocol

Patients were systematically assessed and managed according to the local clinical protocol which is based on recommendations from the European Society of Cardiology (ESC) syncope guidelines (1).

In summary, the diagnostic protocol for syncope in this population was based on 3 phases or steps. Step 1, prior to the patients' inclusion in the study, consisted of the initial assessment in the emergency department. In a systematic manner, clinical history and physical examination were performed, such as testing for orthostatic hypotension and carotid sinus massage (if not contraindicated), general bloodwork, chest x-ray, 12-lead ECG, 12–24-h telemetry monitoring and a transthoracic echocardiogram (in cases where no prior echocardiogram from the last 6 months is available). Those cases with no certain or highly probable diagnosis were then considered unexplained syncope, and these patients were admitted to the hospital with continuous ECG monitoring. Other complementary diagnostic tests, such as exercise stress test, myocardial perfusion gamma scan, or MRI, were carried out at the treating clinician's discretion in line with the suspected diagnosis and applicable recommendations. Step 2 involved the hospital admission with continuous ECG monitoring and an invasive electrophysiology study. Step 3 involved implanting an ICM with subsequent clinical monitoring (**Figure 1**).

Electrophysiology Study

Two femoral venous accesses were gained and two tetrapolar catheters (Supreme, Abbott, St. Jude Medical, St. Paul, MN, USA) were used for basic measurements, atrial stimulation, and ventricular stimulation. Sinus node recovery time was obtained after 30 s of atrial pacing at 600 and 500 ms, and the highest value was corrected by basal heart rate. Programmed ventricular stimulation protocol utilized up to three extra stimuli delivered after eight paced ventricular cycle lengths at 600, 500, and 400 ms from de right ventricular apex and outflow tract in case no sustained ventricular tachycardia (VT) was induced before.

In cases with basal conduction disturbances where the His to ventricle (HV) interval was <70 ms, a class I drug (procainamide 10 mg/kg or flecainide 2 mg/kg intravenously) was administered. Continuous monitoring of the HV interval and atrial pacing was performed during the class I drug infusion and for 10 min after the infusion.

Electrophysiological study was considered positive according to current ESC guidelines (1) in the following cases: (1) baseline HV interval ≥70 ms or ≥100 ms after class I drug administration. (2) Second- or third-degree infra- or intra-Hisian block (with pacing cycle length above 400 ms) before or during incremental atrial pacing or after class I drug administration. (3) Induction of sustained VT.

Monitoring With Implantable Cardiac Monitor

In Step 3, a Reveal XT^{TM} (in patients included before 2014) or Linq^{TM} (Medtronic, Inc. Minneapolis, MN, USA) device was implanted. The implantation was performed under local anesthetic at the primary site recommended by the manufacturer (fourth left intercostal space). The patients were instructed on how to use it and were provided with a device for remote monitoring (Medtronic Carelink^{TM}). The ICM was programmed with the settings for syncope.

Implantable cardiac monitor was considered diagnostic in the event of being able to correlate recurrence of syncope or presyncope with the ICM's electrocardiographic trace, or when the following rhythm disorders were documented in an asymptomatic patient: complete or advanced AV block, asystole lasting >3 s while awake, or the presence of sustained VT.

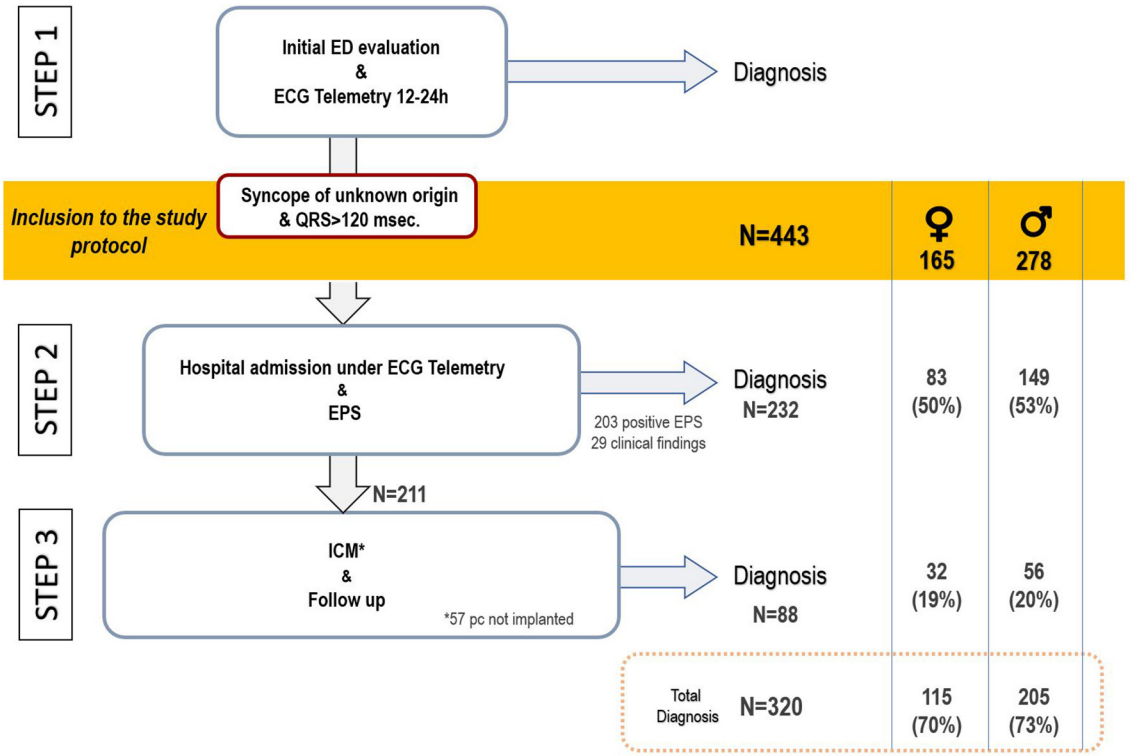


FIGURE 1 | Diagnostic protocol schema and flow chart of patient inclusion in the study. ED, emergency department; EPS, electrophysiological study; ICM, implantable cardiac monitor; pc, patients.

Treatment and Clinical Follow-Up

The syncope was treated appropriately following the clinical practice guidelines according to its etiology. In those patients with syncope secondary to a conduction disorder, the implantation of a cardiac stimulation device was indicated. In patients with syncope secondary to ventricular tachycardia, defibrillator implantation was indicated. The device type (pacemaker, defibrillator, or resynchronizer) and treatments, such as ablation, antiarrhythmic drugs, or angioplasty, were eventually discussed within the "heart team" and individualized according to the patient's functional status, the prior degree of heart failure, and patient preferences. In addition, all patients were educated on syncope and lifestyle changes to prevent and treat reflex syncope.

After hospital discharge, patients were followed up in the outpatient cardiology clinic, and those who had received a cardiac device were also followed up with the corresponding remote function.

Definitions and Endpoints

The main etiological mechanism of the syncope was established as certain or highly probable according to the definitions in the ESC guidelines on syncope (1) (**Supplementary Table S1**). aAVB/sCD was defined as the documentation of type II second degree, third degree, or high-grade AVB or the following diagnostic findings in the EPS: HV interval $\geq$ 70 ms or $\geq$100 ms after class I drug challenge, intra-Hisian, or infra-Hisian block (1, 16). The patient details were analyzed by two cardiologists specialized in syncope to establish the definitive diagnosis according to the definitions. The etiology of syncopal recurrences was defined in the same manner.

Sudden death was defined as death occurring instantaneously or within 1 h of the onset of symptoms, non-sudden cardiac death was defined as a cardiac death occurring 1 h after the onset of symptoms, and non-cardiac death as deaths not directly related to a cardiac or sudden condition.

The primary endpoint of the study was a diagnosis of the main syncope mechanism. The secondary endpoints were test diagnostic yields, need for cardiac pacing related to syncope, syncope recurrences, and mortality.

Statistical Analysis

The categorical variables are presented as absolute number (N) and percentages. The continuous quantitative variables are presented as the median and interquartile range (IQR). The comparison of numerical variables was performed using Student's *t*-test or Wilcoxon's rank-sum test, depending on the distribution of the variables. The Chi-squared test or Fisher's exact test was used to compare qualitative variables as

TABLE 1 | Baseline characteristics of patients included in the study.

Variable	Total (n = 443)	Men (n = 278)	Women (n = 165)	P
Age (years)[+]	77.9 [70.5–82.1]	77.0 [70.3–82.20]	78.7 [71.2–84.6]	0.122
Age >75 y.o, *n* (%)	273 (61.6)	167 (60.1)	106 (64.2)	0.383
Hypertension, *n* (%)	348 (78.6)	223 (80.2)	125 (75.8)	0.269
Diabetes, *n* (%)	153 (34.5)	111 (39.9)	42 (25.5)	0.002
Dyslipidemia, *n* (%)	266 (60.1)	168 (60.4)	98 (59.4)	0.829
No SHD, *n* (%)	346 (78.1)	212 (76.3)	134 (81.2)	0.223
Ischemic heart disease, *n* (%)	94 (21.2)	72 (25.9)	11 (13.3)	0.002
Old ST elevation infarction, *n* (%)	25 (5.6)	20 (7.2)	5 (3.0)	0.066
Non-ischemic dilated cardiomyopathy, *n* (%)	16 (3.6)	9 (3.2)	7 (4.2)	0.584
History of atrial fibrillation, *n* (%)	90 (20.3)	62 (22.3)	28 (17.0)	0.177
Previous syncope, *n* (%)	235 (53.1)	154 (55.4)	81 (49.1)	0.199
Use of negative chronotropic drugs, *n* (%)	149 (34.8)	95 (35.3)	54 (34.0)	0.776
Characteristics of the syncope				
Prodrome, *n* (%)	134 (30.5)	84 (30.3)	50 (30.8)	0.776
Severe trauma, *n* (%)	185 (42.1)	121 (43.6)	64 (39.5)	0.393
Echocardiogram				
EDD (mm)	47 [43–52]	48 [43–53]	46 [42–50]	<0.001
ESD (mm)	31 [26–35]	32 [27–36]	30 [26–34]	0.016
Interventricular septum (mm)	13 [11–14]	13 [12–14]	12 [10–15]	0.021
LVEF (%)	58 [51–62]	57 [50–62]	58 [52–62]	0.746
LVEF <45%, *n* (%)	61 (14.7)	38 (14.8)	23 (14.7)	0.970
ECG on admission				
Heart rate (bpm)	70 [62–80]	70 [60–80]	70 [63–80]	0.996
Atrial fibrillation, *n* (%)	78 (17.8)	49 (17.9)	29 (17.6)	0.935
Long PR, *n* (%)	152 (40.2)	104 (43.7)	48 (34.3)	0.720
QRS duration (msec)	140 [130–153]	140 [130–153]	140 [130–152]	0.891
LBBB morphology, *n* (%)	167 (37.9)	77 (27.7)	90 (55.2)	<0.001
Long PR and LBBB, *n* (%)	47 (10.6)	24 (8.6)	23 (13.9)	0.080
RBBB morphology, *n* (%)	259 (58.6)	191 (67.7)	68 (41.5)	<0.001
Isolated RBBB	50 (11.7)	34 (12.6)	16 (10.2)	0.449
RBBB and LAFB	159 (35.9)	116 (41.7)	43 (26.1)	0.001
Long PR and RBBB	96 (21.7)	75 (27.)	21 12.7)	<0.001
Long PR, RBBB and LAFB	71 (16.0)	52 (18.7)	19 (11.5)	0.046

[+]*The quantitative variables are expressed as medians [interquartile range].*

y.o, years old; mm, millimeters; bpm, beats per minute; msec, milliseconds; SHD, structural heart disease; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block. ESD, end-systolic diameter; EDD, end-diastolic diameter; LVEF, left ventricular ejection fraction.

appropriate. Wald's method was used to calculate the CI for the population rates and proportions. The survival functions were estimated using the Kaplan-Meier method and their comparison was performed by the log-rank test. A multivariable logistic regression model was used to assess the association between sex and aAVB/sCD and to adjust for possible confounder variables. Moreover, a Cox proportional hazards multivariate model was created to determine whether the sex was associated with pacemaker implantation adjusted by possible confounding variables. When we estimated both the Cox proportional hazards model and the logistic regression model, we checked the different possible interactions between pairs of explanatory variables and found no statistically significant results. A saturated model, such as all clinically relevant covariates (1, 4, 5, 7, 17–22), was estimated, and simplified models were evaluated. A relevant confounding effect was judged when the hazard ratios (HRs) or odds ratios (ORs) with and without the adjustment for the potential confounder differed more than 10%. The most precise model with all relevant clinical covariates was finally selected. A $p < 0.05$ was considered statistically significant for all tests. All of the statistical analyses were performed using Stata, version 15.1.0 (StataCorp LLC College Station, TX, USA).

RESULTS

Baseline Characteristics

A total of 443 patients were included in the study, of whom 165 (37.2%) were women. The patients' baseline characteristics

and the comparisons between men and women are shown in **Table 1**. The median age was 77.9 years [IQR 70.5–82.1] and 21.2% had ischemic heart disease (IHD). The median LVEF was 58% [IQR 51–62%] and 14.7% of the patients had a depressed LVEF (<45%). The median QRS duration was 140 ms [IQR 130–153 ms]. In the ECG on admission, 37.9% of patients had typical left bundle branch block (LBBB) morphology and 58.6% right bundle branch block (RBBB) morphology.

Compared with men, women had less diabetes (25.5 vs. 39.9%, $p = 0.002$) and less history of IHD (13.3 vs. 25.9%, $p = 0.002$). However, there were no differences regarding atrial fibrillation history and other comorbidities. The rate of conduction disturbances in the ECG on admission differed between both sexes: LBBB was more frequent in women (55.2 vs. 27.7%, $p < 0.001$) while RBBB was more frequent in men (41.5 vs. 67.7%, $p < 0.001$).

Etiology of the Syncope and Risk of aAVB/sCD

A certain or highly probable diagnosis of the main cause of syncope was reached in 320 patients (72.2%). In 232 (52.4%) patients, the diagnosis of syncope was reached in Step 2 (in 203 patients after a positive EPS and in another 29 due to presenting symptoms with diagnostic criteria during hospital stay). In Step 3, a definitive diagnosis was reached in an additional 88 (19.9%) patients (77 due to the ICM findings and 11 due to clinical criteria; **Figure 1**).

Table 2 summarizes the etiologies of syncope and the diagnoses reached in each step. Compared to men, women had less frequent aAVB/sCD (44.9 vs. 55.0%, $p = 0.038$), which represents a risk ratio (RR) of 0.81 (95% CI 0.67–0.99). Furthermore, in multivariate analyses, after adjusting for possible confounding variables (such as the type of BBB), women had a lower risk of developing aAVB/sCD than men [OR 0.44 (95% CI 0.26–0.74, $p = 0.002$); **Graphical Abstract** and **Supplementary Table S2**].

EPS and Implantable Cardiac Monitor

Overall, EPS was positive in 203 (45.8%) patients, and it was due to aAVB/sCD in 193 (43.6%). Details of the EPS results are listed in **Table 3**. Baseline HV interval was shorter in women (58 ms [IQR 52–71] vs. 60 ms [IQR 52–73], $p = 0.035$) than in men. Furthermore, fewer women had a baseline HV interval longer than 70 ms (28.5% vs. 38.1%, $p = 0.039$).

Among those patients with negative EPS at baseline [241 patients (55.1%)], class I drug challenge was positive in 25 (10.3%). No significant differences between men and women were found in the increase of HV interval (Delta HV) or in the positivity of the test (**Figure 2**).

Electrophysiological study had a similar diagnostic yield between women and men (40.6 vs. 48.9%, $p = 0.089$). In addition, EPS negative predictive value (NPV) was similar between both sexes (76.6% [95% CI 67.1–84.0%] vs. 76.6 % [95% CI 69.0–82.8%]).

Among 154 patients who received an ICM, in 77 patients (50% of the implanted patients) a diagnosis was reached, with a similar

TABLE 2 | Etiological diagnosis.

Diagnostic	Total				Step 2				Step 3			
	All patients (n = 443)	Men (n = 278)	Women (n = 165)	P	All patients (n = 443)	Men (n = 278)	Women (n = 165)	P	All patients (n = 211)	Men (n = 129)	Women (n = 82)	P
Unknown, *n* %	123 (27.8)	73 (26.3)	50 (30.3)	0.358	211 (47.6)	129 (46.4)	82 (49.7)	0.502	123 (58.3)	73 (56.6)	50 (61.0)	0.529
aAVB/sCD, *n* %	227 (51.2)	153(55.0)	74 (44.9)	0.038	194 (43.8)	120(46.8)	64 (38.8)	0.045	33 (15.6)	23 (17.8)	10 (12.2)	0.272
Orthostatic, *n* %	31 (7.0)	21 (7.6)	10 (6.1)	0.551	10 (2.3)	5 (1.8)	5 (3.3)	0.337	21 (10.0)	16 (12.4)	5 (6.1)	0.136
SND, *n* %	22 (5.0)	11 (4.0)	11 (6.7)	0.204	3 (0.7)	2 (0.7)	1 (0.6)	>0.999	19 (9.0)	9(7.0)	10 (12.2)	0.197
Reflex, *n* %	15 (3.4)	8 (2.9)	7 (4.2)	0.443	8 (1.8)	5 (1.8)	3 (1.8)	>0.999	7 (3.3)	3 (2.3)	4 (4.9)	0.435
Low cardiac output, *n* %	5 (1.1)	1 (0.4)	4(2.4)		5 (1.4)	1 (0.4)	4 (2.4)		0 (0)	0 (0)	0 (0)	
VT, *n* %	6 (1.4)	2 (0.4)	4 (1.2)		5 (1.1)	2 (0.7)	3 (1.8)		1 (0.5)	0 (0)	1 (1.2)	
Fast SVT/AF, *n* %	3 (0.7)	1 (0.4)	2 (1.2)		1 (0.2)	0 (0)	1 (0.6)		2 (1.0)	1 (0.8)	1 (1.2)	
CSH, *n* %	3 (0.7)	3 (1.1)	0 (0)		3 (0.7)	2 (0.7)	1 (0.6)		0 (0)	0 (0)	0 (0)	
Other, *n* %	8 (1.8)	5 (1.8)	3 (1.8)		3 (0.7)	1 (0.4)	2 (1.2)		5 (2.4)	4 (3.1)	1 (1.2)	

aAVB/sCD, advanced atrio-ventricular block or severe conduction disturbances; VT, ventricular tachycardia; SND, sinus node dysfunction; SVT, supraventricular tachycardia; AF, atrial tachycardia; CSH, carotid sinushypersensitivity.

TABLE 3 | Electrophysiological study and implantable cardiac monitor.

Variable	Total ($n = 443$)	Men ($n = 278$)	Women ($n = 165$)	P
Electrophysiological study				
Baseline HV interval (msec)	59 [52–73]	60 [52–73]	58 [52–71]	0.035
HV≥70, *n* (%)	153 (34.5)	106 (38.1)	47 (28.5)	0.039
Intra or infra-Hisian AV block, *n* (%)	30 (6.9)	14 (5.1)	16 (9.9)	0.06
Basal EPS positive for aAVB/sCD, *n* (%)	168 (37.9)	112 (40.3)	56 (33.9)	0.183
Class I drug challenge, *n* %	241 (55.1)	146 (53.1)	95 (58.6)	0.349
Procainamide, *n* %	93 (21.3)	59 (21.2)	34 (21.0)	
Flecainide, *n* %	147 (33.6)	87 (31.6)	60 (37.0)	
HV interval after class I challenge (msec)	69 [61-78]	69 [61-78]	71 [61-78]	0.689
Delta HV interval (msec)	15 [10–22]	15 [10–22]	15 [11–21]	0.77
HV≥100 after class I challenge, *n* (%)	14 (3.2)	11 (3.4)	3 (1.8)	0.27
Intra or infra-Hisian AV block after IC challenge, *n* (%)	15 (6.0)	10 (6.4)	5 (5.4)	0.749
Positive class I challenge, *n* (%)	25 (10.3)	17 (11.6)	8(8.4)	0.433
cSNRT (msec)	210 [153–280]	206 [150–278]	220 [160–294]	0.492
VT induction, *n* (%)	6 (3.6)	2 (1.9)	4 (6.1)	0.211
EPS positive for aAVB/sCD, *n* (%)	193 (43.6)	129 (46.4)	64 (37.8)	0.118
EPS positive for all diagnoses, *n* (%)	203 (45.8)	136 (48.9)	67 (40.6)	0.089
Implantable cardiac monitor				
Patients implanted	***n* = 154**	***n* = 92**	***n* = 62**	
ICM diagnostic, *n* (%)	77 (50)	47 (51.1)	30 (48.4)	0.742
Asymptomatic finding, *n* (%)*	23 (29.9)	14 (29.8)	9 (30.0)	0.984
Symptomatic finding, *n* (%)*	54 (70.1)	33 (70.2)	21 (70.0)	

** % refers to the total of patients diagnosed by ICM.*

HV, His to ventricle; aAVB/sCD, advanced atrio-ventricular block or severe conduction disturbances; VT, ventricular tachycardia; EPS, electrophysiological study; ICM, implantable cardiac monitor; cSNRT, corrected sinus node recovery time; msec, milliseconds.

diagnostic yield between both sexes (48.4% in women and 51.1% in men, $p = 0.742$; **Table 3** and **Figure 2**).

Pacemaker Implantation, Clinical Follow-Up, and Prognosis

Patients were followed for a median of 3.4 years [IQR 1.7–6.0 years]. A total of 252 (58.2%) patients required pacing due to bradycardia related to the syncope at the end of follow-up (**Table 4**; **Supplementary Table S3** shows the type of device implanted). Additionally, 2 ICD and 2 CRT-D were implanted due to ventricular tachycardia, 3 pacemakers due to post-surgical AV block, and 3 additional pacemakers because of chronotropic insufficiency. Two patients with VT were treated with antiarrhythmic drugs only due to their comorbidities. In a Cox multivariate analysis, after adjusting for possible confounding variables, women had a lower risk of needing permanent pacemaker implantation compared to men [adjusted HR 0.72 (95% CI: 0.52–0.99, $p = 0.046$); **Table 5** and **Figure 3**].

After the etiological diagnosis and appropriate treatment, 30 patients (8.9%) experienced a syncopal recurrence (**Table 4**), most of them due to a vagal or orthostatic mechanism (**Supplementary Table S4**).

A total of 111 (25.1%) patients died during the follow-up, 73% of them due to non-cardiovascular causes. Only 2 patients experienced sudden death, one 80 years old female with syncope of unknown origin and one 79 years old male with a pacemaker implanted due to AVB 4 years before. The mortality rate in women was 4.5 per 100 person-years (95% CI 3.1–6.4 per 100 person-years) and 7.3 per 100 person-years (95% CI 5.9–9.1 per 100 person-years) in men.

DISCUSSION

As far as we know, this is the first cohort study to specifically evaluate sex-related differences in patients with unexplained syncope and BBB. In addition, it is one of the largest patient cohorts published evaluating the etiology of syncope and outcomes in this population. The main findings of this study are that women with syncope of unknown origin and BBB are at lower risk of having aAVB/sCD and of requiring pacemaker implantation than men.

In the general population, syncope seems to be more frequent in women (1, 2, 14, 21, 23). In a recent national population-based cohort study that included more than 2.5 million participants, Fedorowsky et al. (21) found that 62% of the patients with syncope were women. However, this proportion is reversed when a cohort of patients with structural heart disease (6, 24, 25) or abnormal ECG (3, 5, 7, 26) is selected, probably because men have a higher prevalence of cardiovascular risk factors and other comorbidities. In our study, which included consecutive patients, 63% were men. Male patients had more diabetes and IHD. Moreover, RBBB was more frequent in men while

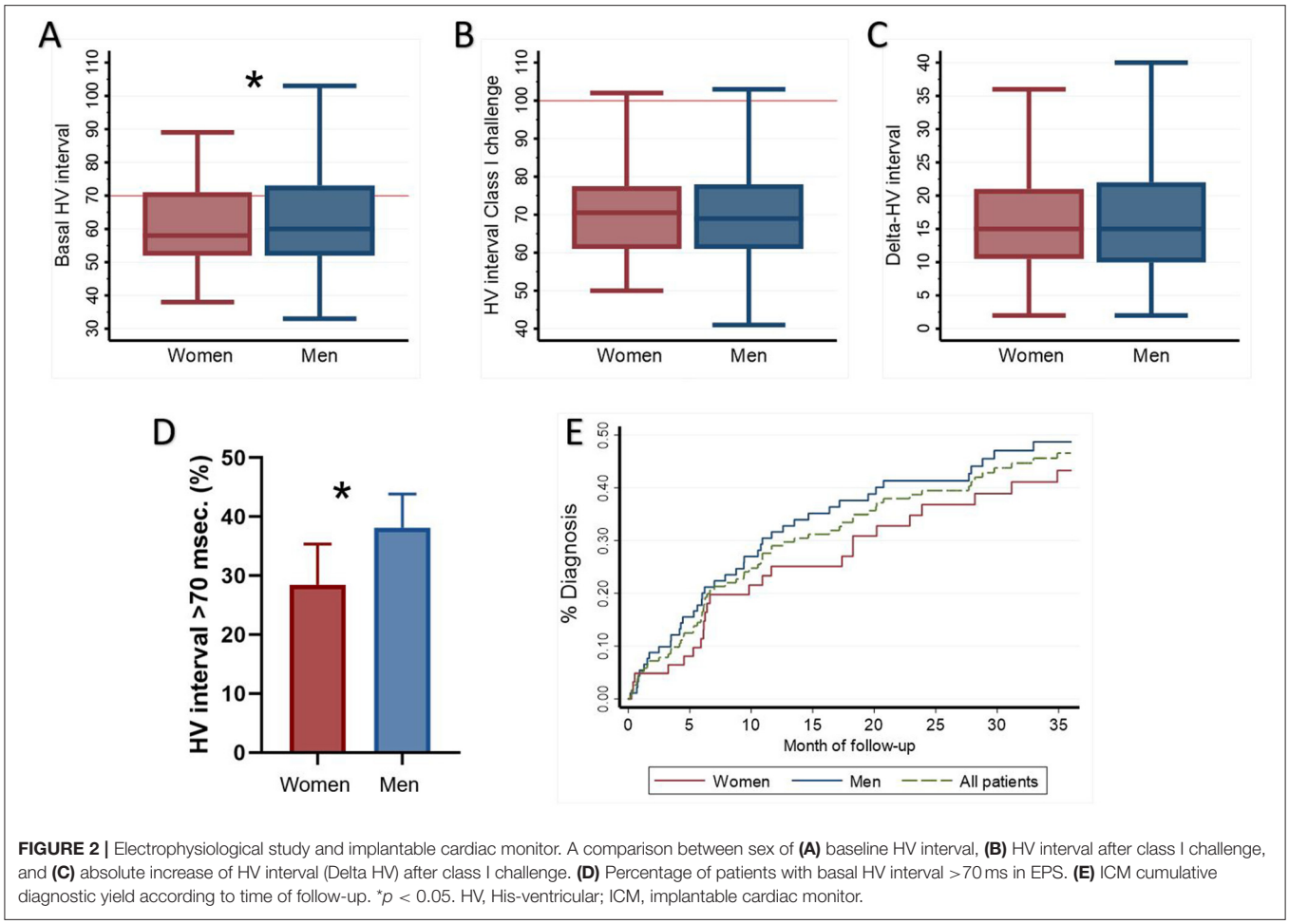


FIGURE 2 | Electrophysiological study and implantable cardiac monitor. A comparison between sex of **(A)** baseline HV interval, **(B)** HV interval after class I challenge, and **(C)** absolute increase of HV interval (Delta HV) after class I challenge. **(D)** Percentage of patients with basal HV interval >70 ms in EPS. **(E)** ICM cumulative diagnostic yield according to time of follow-up. *$p < 0.05$. HV, His-ventricular; ICM, implantable cardiac monitor.

LBBB morphology was more frequent in women. These findings in baseline characteristics are consistent with data previously published (3, 5, 7, 26–28), which suggests that patients included in the present study are likely representative of the population with syncope and BBB.

Paroxysmal aAVB is the most likely etiology of syncope in patients with BBB, but other causes also exist. In agreement with previous studies, we found that AVB is the mechanism of syncope in half of these patients, although significant differences were found between the sexes. Women less frequently had aAVB/sCD. In only 44.9% of women, compared to 55.0% of men, aAVB/sCD was found to be the cause of syncope, which represents a risk ratio of 0.81. In other words, women have a 19% lower risk of having aAVB/sCD. Even though there are some differences in patients' baseline characteristics, in multivariate analyses after adjusting for possible confounding variables, female sex was independently associated with a lower risk of advanced AVB (OR 0.44; 95% CI 0.26–0.74). Previous studies had shown that the risk of aAVB in the general population is higher in men (22, 29). For example, in a recent population-based cohort study, Kerola et al. (22) reported that male sex was an independent risk factor for the development of aAVB [adjusted HR 2.04 (95% CI 1.19–3.45)]. Thus, the present study reveals that these findings are also observed in patients with syncope and BBB and it is not explained by differences in the comorbidities alone.

It is well-known that women have a major susceptibility to reflex syncope (11–14). Moreover, previous studies have suggested that SND is also more prevalent in women (9, 10, 15). The higher prevalence of these etiologies in women observed in the general population is also applicable to patients with BBB and it may partially explain the relative lower rate of aAVB in these patients. In our study we only found small and not statistically significant differences in the incidence of these mechanisms between groups, probably because the study is underpowered. Moreover, it should be noted that some of these etiologies were usually diagnosed in Step 1 of the protocol that is not included in the analysis.

Interestingly, we found that the HV interval in the EPS was significantly longer in men. In particular, more men had an HV longer than 70 ms, suggesting that men have a more severe conduction disease. Despite these differences, EPS in women still offers a considerable diagnostic yield as has been previously reported (3, 8, 17), and even more importantly, NPV is similar between both sexes. In patients who were not diagnosed in Step 2, the use of an ICM offered a significant additional diagnostic yield in both groups. Remarkably, only a third of the diagnoses

TABLE 4 | Outcomes during follow-up.

Variable	Total ($n = 443$)	Men ($n = 278$)	Women ($n = 165$)	*P*
Median follow-up time (years)	3.4 [1.7–6.0]	3.4 [1.5–5.8]	3.2 [1.8–6.2]	0.845
Pacing requirements				
Total patients requiring pacing due to the syncope, *n* (%)	252 (58.2)	167 (60.7)	85 (53.8)	0.159
Devices implanted during admission, *n* (%)	198 (44.7)	134 (48.2)	64 (38.8)	0.054
Devices implanted during follow up, *n* (%)	54 (22.5)	33 (23.24)	21 (21.4)	0.741
Syncope recurrence				
Total syncope recurrence, *n* (%)	95 (21.4)	63 (22.7)	32 (19.4)	0.418
Syncope recurrence after diagnosis, *n* (%)	30 (8.9)	19 (8.9)	11 (8.9)	0.998
Mortality				
Total deaths, *n* (%)	111 (25.1)	81 (29.1)	30 (18.2)	0.010
Mortality rate, (x100 person-years)	6.3	7.3	4.5	0.009
Cause of death				
Cardiovascular death	26 (23.4)	18 (22.2)	8 (26.7)	0.686
Non-cardiovascular death	81 (73.0)	60 (74.1)	21 (70.0)	
Unknown	4 (3.6)	3 (3.7)	1 (3.3)	

TABLE 5 | Cox proportional hazards multivariate model to assess the association between sex and pacing needs.

Factor	HR	HR 95% CI	*p*-value
Unadjusted			
Women	**0.82**	**0.63–1.06**	**0.131**
Adjusted			
Women	**0.72**	**0.52–0.99**	**0.046**
Age>75 y.o	1.19	0.89–1.61	0.247
Hypertension	1.06	0.73–1.54	0.765
Diabetes	1.09	0.80–1.48	0.586
IHD	1.22	0.86–1.75	0.266
LVEF<45%	0.87	0.56–1.35	0.542
Atrial fibrillation	1.09	0.70–1.70	0.698
Recurrent syncope	1.20	0.89–1.61	0.236
LBBB	1.54	0.95–2.50	0.080
Isolated RBBB	0.30	0.12–0.68	0.005
RBBB and LAFH	1.05	0.65–1.69	0.846
Long PR interval	1.62	1.20–2.19	0.002

CI, confidence interval; HR, hazard ratio; y.o, years old; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block.

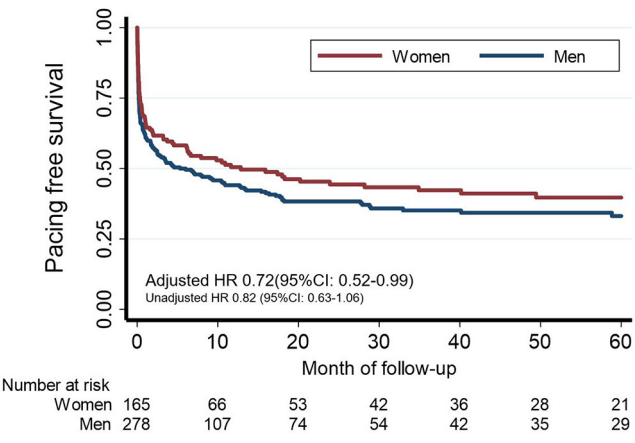


FIGURE 3 | Cardiac pacing. Kaplan-Meier pacemaker-free survival estimates curves for women and men.

reached in Step 3 was due to aAVB. This finding supports the systematic use of an ICM in patients where EPS is not diagnostic.

Another key finding of the present study is that women have a lower risk of requiring a permanent pacemaker compared to men [adjusted HR 0.72 (95% CI 0.52–0.99)]. From the clinical point of view, this finding is especially relevant since pacemakers are useful to treat not only syncope due to aAVB/sCD but also due to other types of bradyarrhythmias and some cases of cardioinhibitory reflex syncope. Even though some of these bradyarrhythmias, such as sinus node dysfunction, seem to be more common in women, the overall risk of needing pacing is lower in women compared to men. Ahmed et al. investigated the predictors of pacemaker implantation in patients with syncope receiving an ICM (19). They found that female sex was an independent predictive factor for bradycardia necessitating pacemaker implantation. However, several differences are evident compared to our study. Firstly, only a quarter of the patients included had a BBB and EPS was not routinely performed. Second, less than of half of pacemakers were implanted due to AVB. SND was the most common indication for pacing and as has been commented previously, it seems to be more prevalent in women. Indeed, in the general population, pacemaker implantation is more common in men (9, 15, 29, 30). In a German registry of more than 17,000 patients with primary pacemaker implantation, 53% were men (29). In this large-scale patient cohort, it was found that male patients had more AV blocks when compared with women and less sick sinus syndrome and atrial fibrillation with bradycardia.

Although it was not the aim of the present study, it is remarkable that our results confirm that a systematic stepwise approach to evaluate syncope in patients with BBB, which was initially evaluated in the B4 study (3) and detailed in the ESC guidelines (1), is safe and achieves a high rate of etiological diagnosis allowing to select specific treatment and avoiding the implantation of unnecessary pacemakers. In the present study, once the diagnosis was reached and appropriately treated, only a few patients (8.9%) experienced a syncopal recurrence, most of them due to a vagal or orthostatic mechanism. This finding suggests that the diagnoses were specific. We also found that, compared to men, women had nearly half the mortality rate, probably in relation to a lower comorbidity burden (14).

The optimal management of patients with unexplained syncope and BBB is still controversial (1–4, 8, 18). In fact, the 2017 American College of Cardiology/the American Heart Association (ACC/AHA) guidelines (2) suggest empirical direct pacemaker implantation after exclusion of other syncope etiologies while ESC guidelines (1) recommend opting for a stepwise approach. In light of our results, gender may be an additional factor to be taken into account in the workup of patients with syncope and BBB. A stepwise approach seems reasonable to avoid unnecessary pacemaker implantation, especially in women, given that only half of them will require pacing because of the syncope. Nonetheless, randomized controlled trials are warranted to better answer this important question.

LIMITATIONS

This study has certain limitations. It is an observational study carried out at a single high-volume center with a dedicated syncope clinic. To minimize potential biases inherent to the study's design, the patients were included consecutively, and possible confounding factors were analyzed. No genetic testing was done systematically to identify certain inherit heart disease that present a higher prevalence of sCD, however, the prevalence of these diseases is low. One aspect worth mentioning is that in our series, the prevalence of reflex/orthostatic syncope was low. It should be noted that some of these episodes were usually diagnosed in Step 1 of the protocol, prior to the patients' inclusion in the study. As such, this series refers not to the global etiology of syncope in this population, rather it focuses on those patients lacking an evident initial diagnosis. The study population was not ethnically diverse. All patients included in the study were from Caucasian or Latin, so the results observed may not be directly extrapolable to other ethnicities. Also, the tilt-test was not used in the workup protocol due to its low specificity in this population (1). However, in selected patients, tilt-test could have revealed an indication for pacing (1). Moreover, the study was not designed to assess predictors of pacemaker implantation in both groups.

CONCLUSIONS

In this cohort study evaluating sex-specific differences in patients with unexplained syncope and BBB, we found that compared to men, women are at lower risk of having aAVB/sCD and of requiring cardiac pacing. A stepwise diagnostic approach based on EPS and long-term cardiac monitoring have similar diagnostic yield in both sexes and it seems appropriate to guide treatment and avoid unnecessary pacemaker implantation, especially in women.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitè d'Etica de Vall d'Hebron. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JF-P prepared the concept, design the study, performed statistical analysis, and draft and editing of the manuscript. NR-G participate in the study design, data review, and manuscript editing. IR-L prepared the clinical database and reviewed the study design. MB-O, CB-M, and MM-B recorded clinical data and revised data in the database. All authors contributed to design the manuscript, patients selection, manuscript review, and agreed with the content of its final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.838473/full#supplementary-material

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Sex Differences in Incidence and Outcome of Out-of-Hospital Cardiac Arrest Within a Local Health Network

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Introduction: Sex and gender differences in presentation and characteristics of out-of-hospital cardiac arrest (OHCA) are established in cohorts with presumed cardiac aetiology but not non-cardiac etiology. This study investigated the effect of sex on incidence and outcome of OHCA according to presumed and adjudicated aetiology within a local health network.

Methods: Population-based observational cohort study of emergency medical services (EMS) attended OHCAs within an Australian local health network. Cases identified from an EMS registry between 2012-2016 were linked to a hospital registry. Age-standardised incidence and baseline characteristics were stratified by sex for EMS-treated OHCA, non-EMS witnessed presumed cardiac and obvious non-cardiac sub-cohorts, and hospitalised cases. Logistic regression was used to explore the primary outcome of survival to hospital discharge.

Results: We identified 2,024 EMS-attended and 780 EMS-treated OHCAs. The non-EMS witnessed sub-cohorts comprised 504 presumed cardiac and 168 obvious non-cardiac OHCAs. Adjudicated aetiology was recorded in 123 hospitalised cases. Age-standardised incidence for women was almost half that of men across all groups. Across cohorts, women were generally older and arrested with a non-shockable initial rhythm in an area of low socioeconomic status. There was no sex difference in the primary outcome for the main EMS-treated cohort or in the non-cardiac sub-cohorts. The sex difference in outcome in the presumed cardiac sub-cohort was not present after multivariable adjustment.

Conclusions: There are sex differences in incidence and outcome of EMS-treated OHCA that appear to be driven by differences in susceptibility to cardiac arrhythmias and underlying etiology, rather than treatment delays or disparities.

Keywords: out-of-hospital cardiac arrest, sex, gender, outcomes - health care, aetiology (etiology), socioeconomic status, epidemiology

INTRODUCTION

Incidence, characteristics, and outcomes of out-of-hospital cardiac arrest (OHCA) differ according to sex. Women represent around 40% of the OHCA population attended by emergency medical services (EMS) but present with fewer established predictors of survival including increased age, unwitnessed arrest, arrest within a private residence, and non-shockable initial rhythm compared with men (1, 2). Precipitating non-cardiac aetiology leading to OHCA, as confirmed by diagnostic testing or autopsy, is also more common in women than men, and is associated with fewer survival predictors, such as shockable initial rhythm, and poor overall survival (3–9). Nonetheless, sex differences in outcomes have not been investigated according to adjudicated cardiac and non-cardiac etiology. Recent meta-analyses found that adult women were up to 50% less likely to survive to hospital discharge or 30 days after OHCA compared with men (2, 10). Adjusting for known survival predictors fully accounts for observed sex differences in survival to hospital discharge in Australian and international populations (1, 11–14). It is likely that the high rates of non-cardiac aetiology and associated non-shockable initial rhythm in women play a key role in driving the relationship with poor outcome after OHCA, but this area remains under-researched. Socioeconomic status (SES) is another important determinant of cardiovascular health, particularly in women (15, 16). Low SES is associated with a high incidence of OHCA and poor survival (17); however, limited studies suggest that low SES is associated with poor survival in men but not women (18, 19).

The primary study objective was to investigate the effect of sex on survival to discharge in a cohort of EMS-treated OHCAs and sub-cohorts of non-EMS-witnessed presumed cardiac and obvious non-cardiac cases. The secondary objectives were to report incidence stratified by age and sex, explore the effect of SES on survival according to sex, and to investigate sex differences in adjudicated aetiology in the sub-cohort transported to hospital.

METHODS

Study Design

This was a retrospective observational study of all adult OHCAs within the Northern Adelaide Local Health Network (NALHN), South Australia. The study cohorts were generated by linking an EMS-based and a hospital-based OHCA registry for all cases occurring within a NALHN catchment as defined by postcode. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (20) were followed and the Central Adelaide Local Health Network Human Research Ethics Committee approved the study [HREC/15/TQEH/89].

Study Setting

The SA Ambulance Service (SAAS) provides a two-tier EMS where patients are treated by paramedics on scene across the state of South Australia (SA). NALHN comprises two public hospitals that service a population of 395,000 across 631 km^2 within the northern metropolitan area of Adelaide, SA. Compared with the rest of Australia, both SA and NALHN are characterised by low SES and are ranked in the 37th and 19th percentiles according to the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD), respectively (21). SAAS and NALHN hospitals follow the ANZCOR resuscitation guidelines (22). Cardiac catheterisation and targeted temperature management are performed at the discretion of treating clinicians according to local guidelines.

Data Sources and Definitions

The SAAS Cardiac Arrest Registry (SAAS-CAR), described previously (23), was searched from 2012–16 for all cases aged ≥18 years within NALHN using the postcode associated with arrest location. Patients without attempted resuscitation by EMS had high rates of missing data (85 missing for initial rhythm, 63 witness status, 63% bystander CPR) and were included for incidence rate calculations only. The main cohort comprised all EMS-treated OHCAs including obvious non-cardiac aetiologies such as trauma, asphyxia, exsanguination, overdose etc., while the sub-cohorts comprised EMS-treated, non-EMS-witnessed OHCA with (presumed cardiac) or without obvious non-cardiac cause. Attempted resuscitation was defined as any chest compressions or any defibrillation by paramedics. Arrest location (e.g., private residence) and response times were not available due to limitations in data capture within the study period. The primary outcome of survival to hospital discharge was extracted for cases transported to non-NALHN hospitals.

The Northern Adelaide Local Health Network (NALHN) OHCA registry is a hospital-based quality assurance initiative (24). Variables are obtained from linkage with existing clinical registries and abstraction from the hospital medical record. Ethnicity was frequently documented as unknown and therefore excluded from this analysis. The hospitalised sub-cohort was formed by manually linking cases with the NALHN OHCA registry using age, sex, arrest date, and time of call.

The 2011 IRSAD was generated from census data by the Australian Bureau of Statistics (abs.gov.au) according to postal area code (POA) and linked to postcode of arrest. Although residential postcodes better reflect individual SES, they were not available for analysis. Higher national deciles indicate low levels of disadvantage and high levels of advantage.

Outcomes

The primary outcome was survival to hospital discharge. Secondary outcomes included incidence per 100,000 person-years, whether the patient was transported to hospital (excluding patients transferred for certification of death), and survival with good neurological recovery (cerebral performance category, CPC, 1-2) in hospitalised patients.

Statistical Analysis

Crude and age-standardised incidence rates per 100,000 person-years were explored according to sex for EMS-attended OHCAs with attempted resuscitation aged ≤20 years, to match with available population data. To account for dynamic changes in the at-risk population over the study period, enumerated NALHN population data (Australian Bureau of Statistics, compiled and presented by.id) was averaged between data available for

2011 and 2016 (25). Adjusted rates were calculated using the direct method across 5-year age groups from 20 to >85 years and applied to the 2001 Australian standard population. Age was missing, presumed at random, in eight cases so an inflation factor was calculated as the percentage of missing data and applied to both crude and age-adjusted incidence rates (**Supplementary Table 1**).

Descriptive statistics were used to explore differences between males and females in all cohorts. Comparisons between sexes were performed using Wilcoxon Sum Rank Tests, Chi-Squared Tests or Fisher's Exact Tests as appropriate for skewed continuous and categorical variables.

Exploratory binary logistic regressions investigated the association between sex and survival to hospital discharge for both the main cohort and presumed cardiac sub-cohort, while adjusting for available survival predictors (age, witness status, bystander CPR, and shockable rhythm). The obvious non-cardiac sub-cohort was too small and survival rate too low to permit multivariable analysis. Interactions between sex and each covariate were tested in the adjusted models and removed if insignificant. Odds ratios (OR), 95% confidence intervals (95%CI), and comparison and global *P*-value are presented.

P-values less than or equal to 0.05 were regarded as significant and adjustments were not made for multiple comparisons. Analyses were performed using SPSS 26 (IBM SPSS Statistics, Armonk, NY, USA).

RESULTS

There were 9,026 EMS-attended cardiac arrests aged ≥18 years identified from SAAS-CAR between 2012–16, of which 2,024 (23%) occurred within a NALHN postcode and 780 were EMS-treated (**Figure 1**). There was no difference in proportion of males vs. females receiving attempted resuscitation (38% vs. 39% of all attended arrests, $p > 0.05$). In the sub-cohorts of non-EMS witnessed cases, 504 were of presumed cardiac origin and 168 were of obvious non-cardiac origin. The hospitalised sub-cohort consisted of 123 cases with adjudicated aetiology documented in the NALHN OHCA registry, excluding 24 with unknown etiology.

Crude and age-adjusted incidence rates of OHCAs aged ≥20 years according to sex are presented in **Table 1**. Incidence in women was similar to that of men 10–20 years younger for EMS-attended and EMS-treated OHCAs (**Figure 2**).

EMS-Treated Cohorts

Sex differences in characteristics of the main adult EMS-treated OHCA cohort and sub-cohorts are presented in **Table 2**. Women represented 35% of the main cohort, 33% of the presumed cardiac sub-cohort, and 38% of the non-cardiac sub-cohort, were a median 4–6 years older than men on presentation, and had similar rates of presumed cardiac diagnosis as men. Women in the main cohort and presumed cardiac sub-cohort, but not the obvious non-cardiac sub-cohort were less likely to present with VF/VT and more likely to present with asystole than men. OHCA was more likely to occur in an area associated with higher levels of disadvantage (lowest 5 deciles) in women than men in the presumed cardiac sub-cohort, but this difference was not observed for the main or non-cardiac cohorts.

There was no significant sex difference in unadjusted survival to hospital discharge observed in the main cohort (9% women vs. 13% men; OR: 0.66, 95% CI: 0.40-1.08, $p = 0.099$). Exploratory analyses were performed and an interaction between sex and shockable rhythm, but not sex and age, SES, or other predictors, was observed. On multivariable analysis, higher odds of survival were associated with shockable rhythm in both males and females, decreasing age, bystander witness, and EMS witness, as well as IRSAD deciles, such that for every increase in IRSAD decile the odds of survival increased by 11% (**Table 3**). There was no difference in survival from hospital arrival to discharge in all cases transported to hospital, including non-NALHN hospitals (women 29% vs. men 42%, $p = 0.14$).

In unadjusted analyses of the presumed cardiac sub-cohort, women were less likely than men to survive to hospital discharge (7% women vs. 15% men; OR: 0.45, 95%CI 0.23–0.87, $p = 0.018$). No interactions were observed between sex and age, SES, or other predictors. Multivariable analysis revealed that sex was not associated with higher odds of survival to hospital discharge (OR: 0.76, 95% CI 0.35–1.64, $p = 0.48$), nor was bystander CPR (OR: 1.02, 95% CI 0.49-2.11, $p = 0.96$). Decreasing age (OR: 0.97, 95% CI 0.95–0.99, $p = 0.013$), bystander witness (OR: 3.04, 95% CI 1.47–6.27, $p = 0.003$), shockable rhythm (OR: 16.1, 95% CI 6.99-37.0, $p < 0.001$), and increasing IRSAD deciles (OR: 1.13, 95%CI: 1.00, 1.28, $p = 0.046$) were associated with higher odds of survival to hospital discharge.

Hospital-Treated Sub-cohort

Sex differences in survival to hospital discharge were explored according to adjudicated aetiology (cardiac vs. non-cardiac, excluding unknown) in a small sub-cohort of non-EMS witnessed OHCAs transported to NALHN hospitals (**Table 4**). Cardiac aetiology represented 68% of known adjudicated diagnoses (57% including unknown diagnoses) and was significantly more prevalent in men than women (76% vs. 50%, $p = 0.01$). Women with cardiac aetiology were younger than men, but there were no other statistically significant sex differences in arrest characteristics or outcomes within groups. In cases with a pre-hospital presumed cardiac diagnosis, precipitating aetiology was confirmed as cardiac in fewer women than men when cases with unknown diagnoses were included (53% vs. 75%, $p = 0.029$).

DISCUSSION

We report sex differences in incidence and outcome of consecutive EMS-attended and -treated OHCA within a local health network. Within these populations, women were almost half as likely to experience OHCA compared with men after age-standardisation. Although women in the sub-cohort with non-EMS-witnessed presumed cardiac OHCA were less likely to survive to hospital discharge than men in unadjusted analyses, this association was not present in the adjusted model. Exploratory

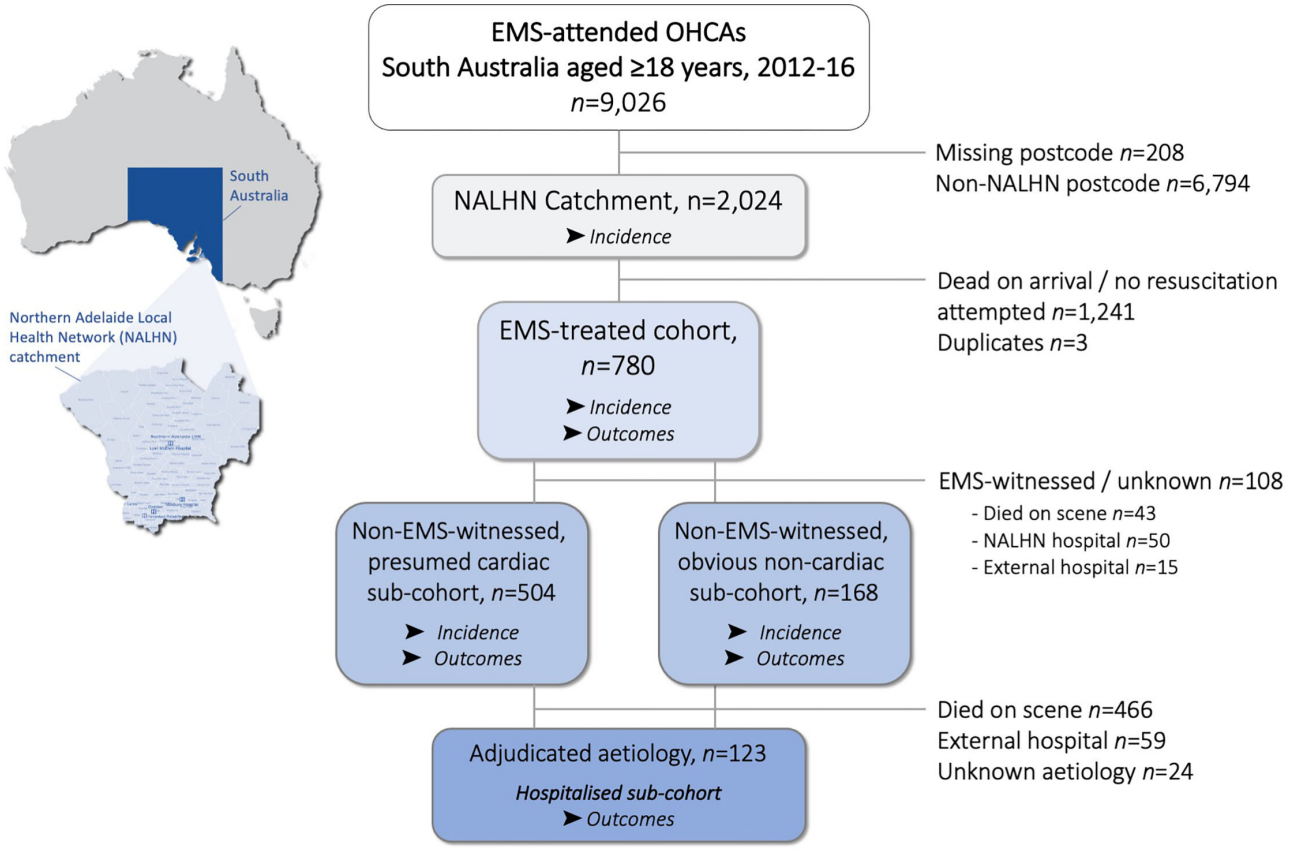

FIGURE 1 | Flowchart of out-of-hospital cardiac arrests (OHCA) aged ≥18 years occurring within the Northern Adelaide Local Health Network (NALHN) catchment area in South Australia, Australia from 2012–2016.

TABLE 1 | Incidence of OHCA aged ≥20 years within NALHN according to sex, 2012–2016.

	Total	Females	Male
EMS-attended*	***n* = 1,970**	***n* = 691**	***n* = 1,279**
Crude	148.7	100.3	199.6
Age-standardised	139.9	96.0	184.3
EMS-treated cohort*	***n* = 772**	***n* = 273**	***n* = 499**
Crude	57.3	39.2	76.4
Age-standardised	54.6	38.1	71.8
Non-EMS witnessed presumed cardiac sub-cohort	***n* = 501**	***n* = 163**	***n* = 338**
Crude	36.8	23.4	50.9
Age-standardised	34.7	22.8	47.2
Non-EMS witnessed obvious non-cardiac sub-cohort*	***n* = 161**	***n* = 63**	***n* = 98**
Crude	12.3	9.0	15.8
Age-standardised	12.2	9.0	15.6

*Data is presented per 100,000 person-years. *Inflation factor applied to crude and age-standardised incidence rates, excepting female EMS-treated rates and non-EMS witnessed obvious non-cardiac rates for females.*

analyses highlighted the discrepancy between presumed and adjudicated aetiologies and pointed to a survival advantage for hospitalised women with adjudicated non-cardiac aetiology.

Sex Differences in Incidence

Few studies have reported sex differences in age-standardised incidence of EMS-attended and EMS-treated adult OHCAs, irrespective of etiology. Unadjusted and age-adjusted

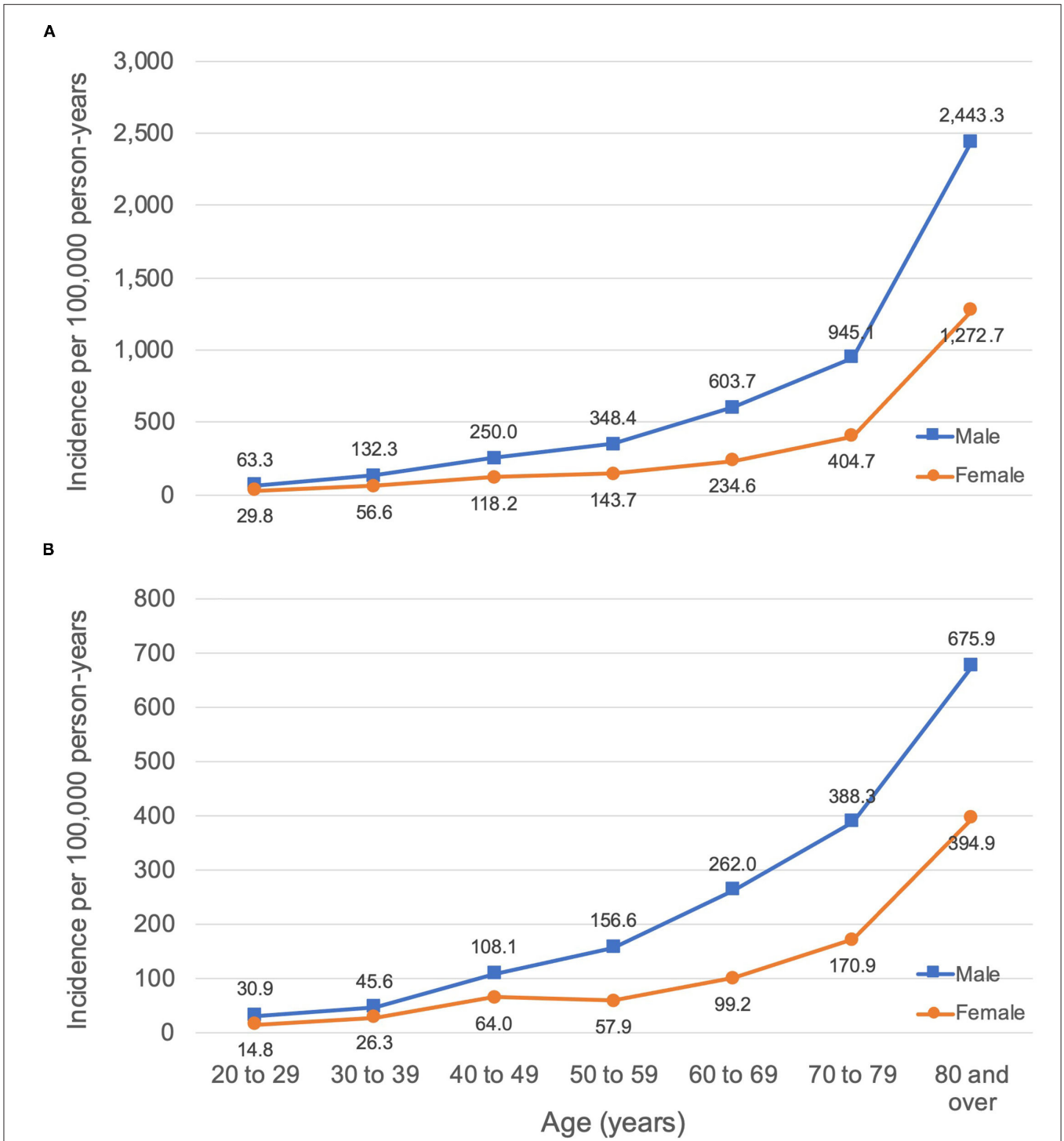

FIGURE 2 | Incidence of OHCA per 100,000 person-years according to age and sex within a local health network in **(A)** EMS-attended OHCA, **(B)** EMS-treated OHCA.

rates stratified by sex were consistent with comparable previous studies, confirming that men consistently experience OHCA at a rate more than double that of women (13, 26–28). Similar to the delayed onset of cardiovascular disease in women, our data and that of others suggests that the incidence of OHCA in women of any given age group is similar to that of men 10 years younger (27–29).

TABLE 2 | Characteristics of EMS-treated OHCAs within NALHN according to sex.

Characteristics	EMS-treated cohort $n = 780$			Non-EMS witnessed sub-cohorts					
				Presumed cardiac $n = 504$			Obvious non-cardiac $n = 168$		
	Sex		Missing	Sex		Missing	Sex		Missing
	Female $n = 273$	Male $n = 507$		Female $n = 165$	Male $n = 339$		Female $n = 63$	Male $n = 105$	
Age	68 [49–82]	64 [50–76]*	8 (1%)	72 [53-82]	67 [56-77]	–	53 [42-71]	47 [35-65]	–
IRSAD decile ≤5	205 (75%)	377 (74%)	–	134 (81%)	247 (73%)*	–	43 (67%)	83 (79%)	–
Witnessed			4 (0.5%)			–			–
EMS-witnessed	42 (15%)	61 (12%)	–	–	–	–	–	–	–
Bystander	102 (38%)	221 (44%)	–	77 (47%)	117 (52%)	–	25 (39%)	44 (42%)	–
Unwitnessed	127 (47%)	223 (44%)	–	88 (53%)	222 (48%)	–	39 (61%)	61 (58%)	–
Bystander CPR	148 (56%)	291 (59%)	28 (3.7%)	107 (66%)	217 (65%)	7 (1.4%)	39 (61%)	71 (69%)	
Initial rhythm			8 (1%)			3 (0.6%)			1 (0.6%)
VF/VT	50 (19%)	158 (32%)*	–	33 (21%)	137 (41%)*		5 (8%)	5 (5%)	–
PEA	79 (29%)	220 (44%)	–	38 (23%)	61 (18%)		21 (33%)	31 (30%)	–
Asystole	139 (52%)	126 (25%)*	–	92 (56%)	140 (41%)*		37 (59%)	68 (65%)	–
Presumed cardiac	192 (71%)	385 (76%)	1 (0.1%)	165 (100%)	339 (100%)	–	0 (0%)	0 (0%)	–
NALHN Hospital	71/92 (77%)	126/178 (71%)		34/42 (81%)	87/119 (73%)	–	13/20 (65%)	13/25 (52%)	–
Transported to hospital	92 (34%)	178 (35%)		42 (25%)	119 (35%)*	–	20 (31%)	25 (24%)	–
Survived to discharge	24 (9%)	65 (13%)	8 (1%)	12 (7%)	50 (15%)*	1 (0.2%)	4 (6%)	3 (3%)	2 (1.2%)

*Data presented as median [interquartile range] and number (percentage). *P-value <0.05; p-values reflect data that excludes missing values. CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IRSAD, Index of relative social advantage and disadvantage; NALHN, Northern Adelaide Local Health Network; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.*

TABLE 3 | Multivariable logistic regression model: predictors of survival to hospital discharge after EMS-treated OHCA (main cohort), $n = 751$.

Characteristics	Comparison	Odds Ratio (95% CI)	*p*-value
Female sex	Shockable vs. non-shockable	1.26 (1.09–1.46)*	0.001
Male sex	Shockable vs. non-shockable	1.46 (1.30–1.65)	<0.001
Age, per *y*		0.98 (0.96-1.00)	0.012
IRSAD decile		1.11 (1.00–1.23)	0.041
Bystander witnessed vs. unwitnessed		3.00 (1.56–5.77)	<0.001
EMS witnessed vs. unwitnessed		6.77 (2.97–15.5)	<0.001
Presumed cardiac cause		0.83 (0.39–1.76)	0.621

**Interaction p < 0.05. EMS, emergency medical services; IRSAD, Index of relative social advantage and disadvantage.*

Sex Differences in Survival

Women in the presumed cardiac sub-cohort were 55% less likely to survive to hospital discharge than men in unadjusted analyses. Once adjusted for available predictors of survival that differ between males and females (age, SES, witness status, and initial rhythm) the sex difference in outcome disappeared. It is likely that a smaller magnitude of difference in outcome between sexes exists for the main cohort of EMS-treated OHCAs, but the sample may not have been sufficiently powered. Only a few studies have reported sex differences in outcome of all-cause OHCA with the survival rate for men ranging from 1 to 5.5% higher than women (13, 30–32). Attenuation of the magnitude of difference in outcome between sexes may be due to the inclusion of obvious non-cardiac etiologies such as asphyxia, exsanguination, and overdose, the outcomes of which may not differ between males and females. Although we found that outcomes were similar between sexes in the small non-cardiac sub-cohort, this hypothesis has only been investigated in one other study of patients presenting with shockable rhythm and requires further validation (33). Previous reports of sex differences in survival appear contradictory; however, all of the larger OHCA registries ($n > 10{,}000$) report unadjusted survival and favourable neurological prognosis at hospital discharge as consistently higher in men than women, with no difference (1, 11–14, 30) or even a favouring of women (34) after adjustment, irrespective of differences in population subsets. The observed sex differences in survival across our cohorts were explained by the older age of women, their higher rate of arrest in a low SES

TABLE 4 | Characteristics of EMS-treated, non-EMS witnessed OHCAs treated at NALHN hospital according to adjudicated aetiology and sex, $n = 123$.

	Cardiac $n = 84$		Non-cardiac $n = 39$	
Characteristics	**Female $n = 18$**	**Male $n = 66$**	**Female $n = 18$**	**Male $n = 21$**
Age	51 [41–65]	65 [54–72]*	53 [43–70]	50 [34–67]
IRSAD decile ≤5	14 (78%)	47 (71%)	11 (61%)	15 (71%)
Bystander witnessed	11 (61%)	53 (80%)	8 (44%)	11 (52%)
Bystander CPR	15 (83%)	47 (71%)	13 (72%)	16 (76%)
Initial rhythm				
VF/VT	14 (78%)	56 (85%)	1 (6%)	2 (10%)
PEA	0 (0%)	3 (5%)	7 (39%)	5 (24%)
Asystole	4 (22%)	7 (11%)	10 (56%)	14 (67%)
Pre-hospital presumed cardiac diagnosis	18 (100%)	65 (98%)	7 (39%)	12 (57%)
GCS 3 on arrival	15 (83%)	49/64 (77%)	16 (89%)	20 (95%)
Sustained ROSC	16 (89%)	61 (92%)	18 (100%)	20 (95%)
ST-elevation	6/16 (38%)	25/60 (42%)	1/16 (6%)	4/19 (21%)
Inpatient admission	16 (89%)	59 (89%)	15 (83%)	19 (90%)
Survived to discharge	7 (39%)	37 (56%)	4 (22%)	1 (5%)
Neurological recovery (CPC 1-2) at discharge	7 (39%)	35/65 (54%)	4 (22%)	1 (5%)
12-month survival	7 (39%)	35 (53%)	4 (22%)	1 (5%)

*Data presented as median [interquartile range] and number (percentage). *P-value < 0.05; p-values reflect data that excludes missing values. CPR, cardiopulmonary resuscitation; EMS, emergency medical services; IRSAD, Index of relative social advantage and disadvantage; NALHN, Northern Adelaide Local Health Network; PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia.*

area with an initial non-shockable rhythm, and lower likelihood of a confirmed cardiac aetiology than men. Our results confirm a different distribution of risk factors, such as age and SES, and precipitating etiologies between sexes rather than a male survival advantage.

Interaction Between Sex and Established Predictors of Survival

There were no significant interactions in adjusted models between sex and age, bystander witness, or bystander CPR, respectively. Similar to Bray et al. (1) our findings did not show increased survival in younger Australian women. We did not observe any sex differences in pre-hospital treatment such as bystander CPR or EMS resuscitation, which is in contrast to some previous studies (1, 35). In the main EMS-treated cohort, but not the presumed cardiac sub-cohort, we observed a significant interaction between sex and initial rhythm where the relationship between shockable rhythm and survival was stronger in men than women. Although women are 50% less likely to present with a shockable rhythm after adjustment for established predictors of survival, (27, 30, 36) we again confirm that non-shockable initial rhythm predicts poor outcome regardless of sex (1, 12, 30, 34, 37). Poor survival in women is therefore directly related to their lower incidence of shockable initial rhythm, which, in our population, is likely due to sex differences in susceptibility to cardiac arrhythmias and underlying aetiology (38, 39), rather than treatment delays or disparities.

Effect of Socioeconomic Status on Survival

Consistent with international studies, we found that SES was a predictor of survival after OHCA in adjusted analyses (40, 41). Each increase in SES decile (more advantaged) was associated with an 11% increase in odds of survival to hospital discharge after EMS-treated OHCA (adjusted OR: 1.11, 95% CI 1.00–1.23). Women with a presumed cardiac OHCA were more likely to arrest in a postcode associated with low SES but this was not the case for the full cohort that included obvious non-cardiac etiologies such as asphyxia, exsanguination, and overdose. However, the interaction between sex and SES was not significant and differences in survival rate across low and high SES did not vary between men and women. Wells et al. (18) found no interaction between sex and individual-level education or occupation in a cohort of EMS-treated non-traumatic OHCAs with shockable initial rhythm. Similarly, Jonsson et al. (19) reported no interaction between sex and area-level income and area-level education in all EMS-treated OHCAs, excluding EMS-witnessed. These findings are somewhat surprising given that a stronger association between low SES risk of cardiac arrest and sudden cardiac death has been observed in women compared with men, even after adjustment for traditional risk factors (42). Importantly, our results should be considered as hypothesis-generating only as the study population is biased and over-representative of low SES (IRSAD ≤5 in 75% of the study population). The importance of SES in determining outcome of OHCA has been highlighted in this study and should be explored in larger state-wide and national analyses.

Sex Differences According to Adjudicated Etiology

Cause of arrest documented by EMS providers does not reflect true aetiology in many cases and these discrepancies may contribute to observed differences in outcome between sexes

(43). We performed an in-depth exploration of aetiology as documented in the hospital medical record or autopsy report for the hospitalised sub-cohort. The sample was underpowered to detect a significant difference in outcome and should be considered as hypothesis generating only. The results suggest that survival after adjudicated cardiac OHCA is higher in men, whereas survival after non-cardiac OHCA is higher in women. Only 53% of hospitalised women with a pre-hospital presumed cardiac diagnosis were confirmed as cardiac, which highlights the importance of investigating and recording the aetiology as confirmed in the medical record or by autopsy.

Limitations

This is a small retrospective study conducted within a local health network in Australia and care should be taken when generalising the findings. Crude and age-adjusted incidence calculations were made using enumerated population data that was averaged between 2011 and 2016 to account for dynamic population changes and may not accurately reflect the true at-risk population. OHCA incidence calculations may be underestimated due to missing cases within SAAS-CAR during the study period (24). Arrest location and EMS response times are important predictors of survival that may have influenced outcome but were not available within SAAS-CAR during the study period. Arrest postcode was used as a surrogate for patient SES but may not reflect the patient's true level of advantage and disadvantage. Finally, investigation of sex differences in outcome of EMS-treated OHCA was limited due to small sample size and the findings should be confirmed in a larger sample. Nonetheless, this study provides important findings on sex differences in incidence and outcome of OHCA according to both presumed and confirmed cardiac and non-cardiac etiology.

CONCLUSIONS

Women were less than half as likely to experience OHCA than men and the incidence of OHCA in women of any given age group was similar to that of men 10 years younger within a local health network. The effect of sex on survival to discharge after EMS-treated OHCA was influenced by precipitating etiology. Women with non-EMS witnessed presumed cardiac OHCA were more likely to present with unfavourable predictors of survival and were more likely to arrest in location associated with low SES, but there was no sex difference in adjusted survival. Analysis of adjudicated aetiology in the hospitalised sub-cohort suggests that survival after non-cardiac OHCA may be higher in women than men, but this finding requires further validation.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because access to participant identifiable data is subject to relevant institutional approval(s). Requests to access the datasets should be directed to MW, melanie.wittwer@adelaide.edu.au.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MW: conceptualisation, methodology, investigation, formal analysis, and writing—original draft. EA: conceptualisation and writing—original draft. CH: data curation, writing—review, and editing. MT: data curation, writing—review, and editing. CZ: supervision, writing—review, and editing. JB: supervision, writing—review, and editing. MA: conceptualisation, supervision, writing—review, and editing. All authors take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read, critically reviewed, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.870696/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW
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Brugada Syndrome in Women: What Do We Know After 30 Years?

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Brugada syndrome (BrS) was initially described in 1992 by Josep and Pedro Brugada as an arrhythmogenic disease characterized by ST segment elevation in the right precordial leads and increased risk of sudden cardiac death (SCD). Alterations in the *SCN5A* gene are responsible for approximately 30% of cases of BrS, following an autosomal dominant pattern of inheritance. However, despite its autosomal transmission, sex-related differences are widely accepted. BrS is more prevalent in males than in females (8–10 times), with males having a 5.5-fold higher risk of SCD. There are also differences in clinical presentation, with females being more frequently asymptomatic and older than males at the time of diagnosis. Some factors have been identified that could explain these differences, among which testosterone seems to play an important role. However, only 30% of the available publications on the syndrome include sex-related information. Therefore, current findings on BrS are based on studies conducted mainly in male population, despite the wide acceptance of gender differences. The inclusion of complete clinical and demographic information in future publications would allow a better understanding of the phenotypic variability of BrS in different age and sex groups helping to improve the diagnosis, management and risk management of SCD.

Keywords: brugada syndrome, women, arrhythmias, sudden cardiac death, gender

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INTRODUCTION

Thirty years ago, Josep and Pedro Brugada reported a new clinical entity characterized by "*Right bundle branch block, persistent ST segment elevation and sudden cardiac death*." In this first report, two of eight patients described were females, suggesting potential gender differences (1). In 1996, Japanese researchers coined the term Brugada syndrome (BrS) when referring to this syndrome (2). Two years later, the first genetic alteration to cause this condition was reported in *SCN5A*, following an autosomal dominant pattern of inheritance. This gene encodes the α subunit of the cardiac sodium channel protein (Nav1.5) responsible for the initial upstroke of the action

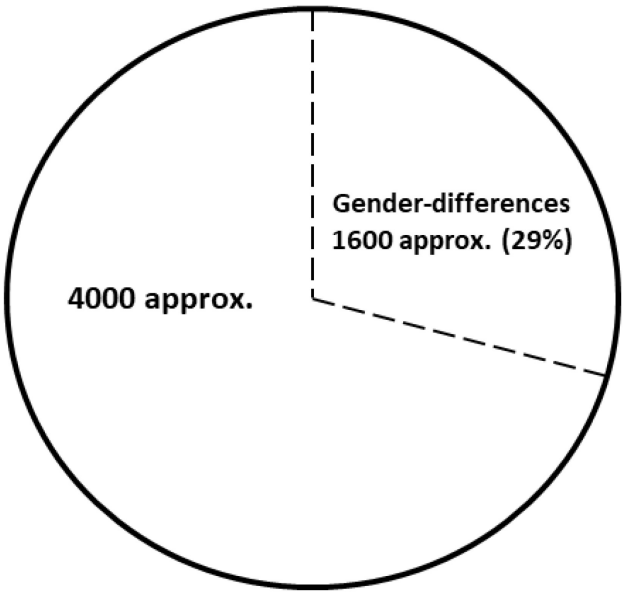

FIGURE 1 | Publications focused on Brugada Syndrome (BrS) (PubMed, January 2022). Of approximate 5,600 publications about BrS near 29% (1,600 publications) included any data concerning female/women or gender/sex differences.

potential (3). Current guidelines define BrS as "a trait inherited in an autosomal dominant manner and showing sex- and age-related penetrance and variable expressivity." Clinical manifestations are more common in adults, and eightfold more frequent in males than in females (4, 5). Therefore, 30 years after the first description of BrS, gender differences are widely accepted, but its underlying causality remains unclear and further research is needed. To date, only about 1,600 (approx. 29%) of around 5,600 papers focused on BrS (PubMed, January 2022) include any data concerning female/women or gender/sex differences (**Figure 1**). It is also important to remark that, despite the extensively accepted differences between genders and the increasing number of publications up to 2014, publications including any data regarding gender differences has progressively decreased in recent years (**Figure 2**).

CLINICAL FINDINGS

In 1992, the first report of BrS included six males and two females, suggesting potential gender differences despite the low number of cases and inclusion of infants (1). In 1997, nearly fifty patients were reported worldwide to have BrS (only three were women) (6). Two years later, the number of reported BrS patients increased to one hundred and 60 (13 were female) (7). At that time, gender differences were widely accepted in BrS, but no explanation was reported.

After ten years, BrS was phenotypically and genetically known as sudden unexpected death syndrome (SUDS), known for many years in southern Asia and characterized by a disproportionate number of men died suddenly, usually sleeping (8). Also in 2002, the first BrS consensus was published, focusing on diagnostic criteria and reporting a male predominance (8:1 ratio) (9). At the clinical level, males showed easier inducibility of BrS pattern on ECG and a higher number of events on follow-up compared to females (10, 11). In 2005, the second consensus conference was published, and stated that male sex was a 5.5-fold greater risk factor for SCD than female sex, although no data concerning the cellular mechanisms involved were included, mainly due to lack of conclusive mechanistic/physiopathologic evidence (12). In 2008, a study reported that women with the BrS resuscitated from cardiac arrest or with appropriate ICD shocks exhibit a different ECG pattern than men, suggesting that it may be more difficult to identify women with BrS who are at risk for SCD (13).

In 2013 HRS/EHRA/APHRS expert consensus statement declared that "*BrS is 8-10 times more prevalent in men than in women*" and "*Male sex has consistently been shown to be associated with more arrhythmic events*" (14). However, no further reference to gender differences was mentioned. In 2015, ESC/AEPC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD were published (4). BrS was listed but no reference to gender differences were included, despite mention of male predominance. In 2017, J Wave Syndrome Consensus Conference report stated a male predominance in BrS, potentially due to "*Testosterone modulation of ion currents underlying the epicardial AP notch*" (15). No other reference to gender differences in BrS was mentioned. Similar data concerning gender differences were included in AHA/ACC/HRS Guidelines (5). In 2018, the Shanghai Score System was proposed focused on diagnosis and risk stratification of BrS patients but, the cohort included more than 90% men, probably as a result of the male predominance in BrS. No inclusion of any additional data concerning gender differences was reported, despite its wide acceptance (16).

Hence, although few data concerning clinical translation of BrS gender differences published so far, it is accepted that women with BrS are more frequently asymptomatic at the time of diagnosis and older than men both at the time of diagnosis and with the first arrhythmic event (17, 18). In addition, women with BrS show a spontaneous type 1 Brugada ECG pattern or ventricular arrhythmia inducibility less frequently than men (19, 20). Furthermore, women diagnosed with BrS are less likely to experience arrhythmic events (syncope, aborted cardiac arrest, and documented ventricular fibrillation) (18, 19). Following similar data, BrS ECG patterns are not uncommon in elderly women, but are not associated with an increased risk of mortality (21, 22). Recently, a new study demonstrated that women with BrS less frequently presented with a type 1 ECG pattern, had a higher rate of family history of SCD, and had less sustained ventricular arrhythmias on electrophysiological study, despite not constituting a risk-free group. Concerning the risk of malignant events, only atrial fibrillation and positive genetic test were found as risk factors for further arrhythmic events. Neither clinical risk factors nor electrophysiological study predicts future arrhythmic episodes in women, making correct risk stratification difficult (23).

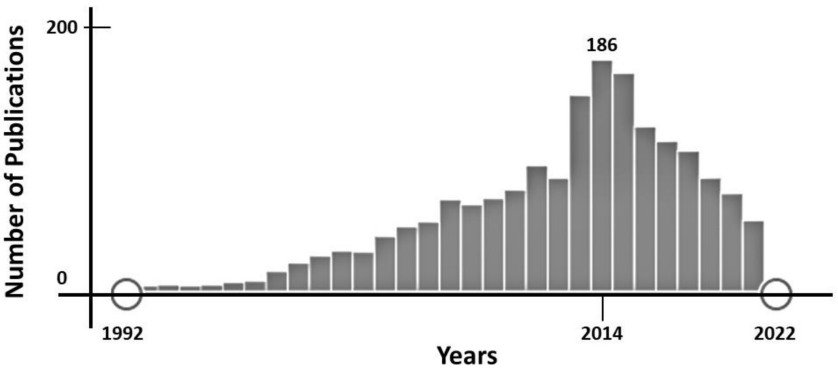

FIGURE 2 | Time-line of publications focused on Brugada Syndrome (BrS) (PubMed, January 2022). Since 2014, the number of publications including any data concerning female/women or gender/sex differences has decreased progressively.

AGE DIFFERENCES IN WOMEN

The aforementioned data were performed on young-adult and adults women diagnosed with BrS. Regarding early years, few studies contain diagnosed children, despite the first report already included two pediatric-aged female (1). In large cohorts of asymptomatic children, the characteristic ECG pattern was identified in 0.01–0.02%; it suggests that BrS exist in children but becomes clinically unmasked with increasing age (24, 25). The incidence rate of life-threatening arrhythmias in the pediatric population was showed to be around 10%, with fever as trigger for ventricular arrhythmias (26, 27). In addition, there is at most a mild male predominance of BrS in the pediatric population compared to adults. And women show a higher rate of arrhythmic events in the pediatric age group than at an older age (17). Curiously, almost 25% of asymptomatic children who were first-degree relatives of BrS patients showed characteristic BrS ECG on ajmaline test after puberty, despite showing normal ECG also on ajmaline test before adolescence (28); it reinforces the role of hormones in BrS (29). Therefore, pediatric cases are rare and are usually identified during familial screening, but children often have a more severe form of the disease, which manifests as a quickly progressive manner and lead to malignant arrhythmias and SCD (26, 30–32). Patients showing an ECG type I and a history of syncope or aborted SCD should receive an ICD implantation (class I indication). Contrarywise, ICD implantation is not indicated in asymptomatic patients without risk factors (33).

Concerning elderly BrS patients, scattered data have been published to date, showing that BrS ECG patterns are less frequent than in adults, with similar episodes in both genders and a reduced risk of life-threatening arrhythmias (22). There is no strong evidence that levels of testosterone decrease during aging, thus/thereby reducing the risk of malignant events. Although decreased testosterone levels are associated with comorbidities, it is important to remark that the treatment of these comorbidities includes many drugs that should be avoided in BrS[1] (34). The device-guided management should be personalized. A personalized approach should be done before ICD implantation. At our acknowledgement, the first and only study focused on elderly BrS women was published in 2020, showing a not infrequent BrS pattern in the ECG but associated with a lower risk of malignant arrhythmias and SCD (21).

PREGNANCY

Following the lack of data on BrS in women, few studies focusing on pregnancy in BrS diagnosed women have been published to date. First studies emphasized the role of hormonal changes during pregnancy as trigger for arrhythmic events (35) but typical ECG changes of BrS may be linked to sodium channel blockers used as anesthetics (36). The first large serie was published in 2014, showing that serious events were not more frequent during pregnancy or the peripartum period (37). Finally, women with BrS might have an overall low tendency to malignant arrhythmias during pregnancy (38) and obstetrical management should include a multidisciplinary follow-up carried out in a close collaboration between gynecologists, pediatricians, cardiologists and anesthesiologists.

CELLULAR BASIS

Since the first report in 1992, gender differences were widely accepted in BrS, nevertheless no explanation was published in 2002. Di Diego et al. demonstrated a more prominent transient outward current (Ito) in males than in females in right ventricular epicardium of dogs (39). Therefore, gender differences in BrS due to intrinsic differences in the ventricular action potential between genders were suggested. One year on, in 2003, sex hormones were also proposed as another factor contributing to the male predominance in BrS. Especially testosterone that may accentuate ST-segment elevation by increasing outward currents (Ito, IKr, IK1. . .) or decreasing inward currents (ICa-L, INa. . .) at the end of phase 1 of the action potential (40, 41). In 2005, a potential role for gonadal steroids in gender-related differences

[1] www.BrugadaDrugs.org

in cardiac repolarization and BrS susceptibility was suggested (42, 43). In 2007, Shimizu et al. reported higher testosterone levels, serum sodium, potassium and chloride levels, as well as a significantly lower body-mass index in males diagnosed with BrS (44). In the same year, Eckardt reviewed all published studies concerning patients with BrS (more than 1,200 up to 2.006) and observed that 80% were males. Authors suggested that gonadal steroids seem to be an unlikely single explanation for gender differences in BrS. Therefore, BrS differences may be due to a complex interaction between gender- and age-dependent genetic and other triggering and/or modulating factors such as circadian variations of vagal balance, hormones, and metabolic factors, among others (45, 46).

Focusing on mechanistic pathways, it is currently accepted that transmural voltage gradient created by an imbalance in the cardiac ion currents involved in phase 1 of the action potential is the cause of the typical Brugada-type ST segment elevation observed mainly in men; it is due to a loss of function of the sodium or calcium inward depolarization current and a gain of function of the transient outward potassium current (Ito) (47). Ito is higher in males and may facilitate the presence of the BrS ECG pattern and arrhythmias. In addition, testosterone may increase outward repolarizing currents, leading to loss of the AP dome (48). In line with this hypothesis, the delayed right ventricular ejection, more frequently observed in males than in females, could contribute to an increase risk of malignant events in BrS (49). In concordance to this fact, in 2019 a case report of a female living as a transgender male was reported, in which testosterone supplementation unmasked the BrS ECG pattern (50).

GENETICS

In 1998, the first genetic alteration associated with BrS was reported, confirming genetic basis as cause of BrS already suggested in 1992 (1). The first genetic alteration was reported in *SCN5A*, following an autosomal dominant pattern of inheritance. Then, two hallmarks of BrS were identified: incomplete penetrance and variable expressivity. Pathogenic alterations in this gene leads to loss of function in the α subunit of the cardiac sodium channel protein (Nav1.5). To date, more than 150 deleterious alterations in *SCN5A* have been associated with BrS and underlie nearly 30% of all BrS cases (49, 51). Although several genetic alterations located in more than 20 genes have been reported as potentially cause of BrS (52) recent evidence-based reappraisal of gene-disease validity disputed the causality of main part of these genes, leaving *SCN5A* as the only gene with definite causality in BrS (53). In addition, a recent study suggested few minor genes as high potential cause of BrS (*SLMAP*, *SEMA3A*, *SCNN1A*, and *SCN2B*) (54). Due to low genetic yield after a comprehensive genetic analysis, other patterns of inheritance have been also suggested for BrS families (51). Nowadays, it is widely accepted an 8–10-fold male BrS predominance despite equal genetic transmission. Hence, carriers of a deleterious variant in the *SCN5A* gene showed more aggressive arrhythmias (55). However, in recent years a higher prevalence of pathogenic variants in *SCN5A* has been published in asymptomatic female patients with BrS compared with male patients and an even high prevalence in female patients with BrS with arrhythmic events (20) suggesting that female patients carrying a pathogenic variant in *SCN5A*, may be a marker of increased risk (56).

CONCLUSION

Nowadays, the existence of sex-attributable differences in the prevalence, risk profile and clinical course of BrS is widely accepted. Current knowledge supports that such differences are not exclusively due to the influence of sex hormones, but may be the result of a complex interplay of gender- and age-dependent genetic factors and other variables that modulate the expression and function of cardiac ion channels. However, further studies are still needed to elucidate the pathophysiological mechanisms underlying these gender differences. In general, women have a lower prevalence of BrS, a lower risk of arrhythmic events, and are more frequently asymptomatic and older at the time of diagnosis than their male counterparts. Despite this, the female sex does not represent a risk-free group and the fact that they present less frequently with the ECG BrS pattern in the electrophysiological study could hinder its diagnosis. Nevertheless, current expert guidelines on the management and risk stratification of BrS patients do not differ in their recommendations according to sex, probably due to the low number of published data on female patients. Although current studies in young, pregnant and menopausal women with BrS predict a low risk of events and lethality, data are scarce. More in-depth evaluation of the influence of female hormonal changes on the BrS phenotype, as well as the cellular mechanisms involved, is needed. We recommend including as complete as possible clinical and phenotypic information on BrS patients in future publications. A more detailed knowledge of the course of the syndrome in different age and sex groups would allow adapting clinical recommendations toward individualized care in the diagnosis, management and risk stratification of women with BrS.

AUTHOR CONTRIBUTIONS

GS-B, OC, EA, JB, and RB developed the concept and supervised the study. EM-B, EA, SC, JC, VF, ND-E, CH, and GS-B acquired, pre-processed, and analyzed the data. EM-B, EA, OC, and GS-B prepared the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Influence of Sex-Based Differences in Cardiac Phenotype on Atrial Fibrillation Recurrence in Patients Undergoing Pulmonary Vein Isolation

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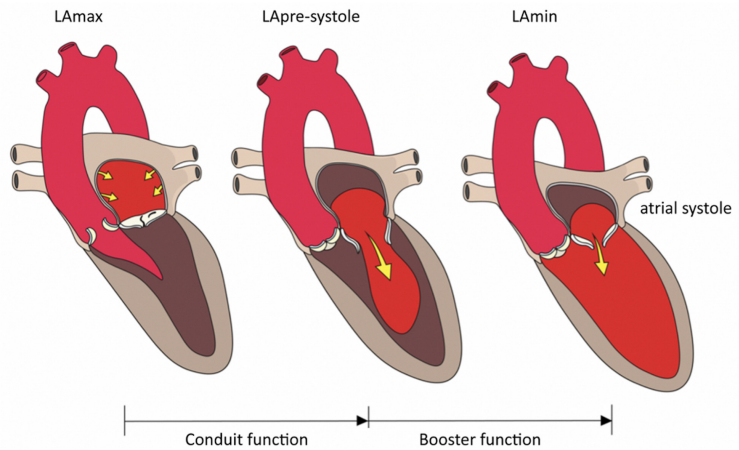
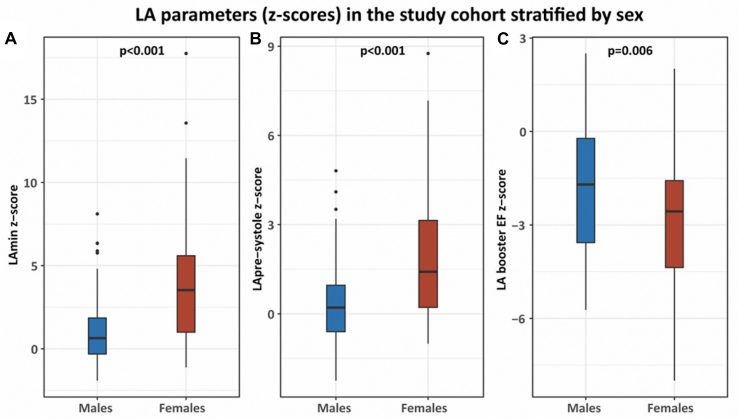
Background: Pulmonary vein isolation (PVI) is a commonly engaged therapy for symptomatic atrial fibrillation (AF). Prior studies have documented elevated AF recurrence rates among females vs. males. Sex-specific mechanisms underlying this phenomenon are poorly understood. This prospective cohort study aimed to evaluate the sex-based differences in cardiac phenotype and their influence on (AF) recurrence following first-time PVI.

Methods: A total of 204 consecutive patients referred for first-time PVI and 101 healthy subjects were prospectively studied by cardiovascular magnetic resonance (CMR) imaging. Multi-chamber volumetric and functional measures were assessed by sex-corrected Z-score analyses vs. healthy subjects. Patients were followed for a median of 2.6 years for the primary outcome of clinical AF recurrence. Multivariable analyses adjusting for age and comorbidities were performed to identify independent predictors of AF recurrence.

Results: AF recurrence following first PVI occurred in 41% of males and 59% of females (p = 0.03). Females were older with higher prevalence of hypertension and thyroid disorders. Z-score-based analyses revealed significantly reduced ventricular volumes, greater left atrial (LA) volumes, and reduced LA contractility in females vs. males. Multivariable analysis revealed each of LA minimum and pre-systolic volumes and booster EF Z-scores to be independently associated with AF recurrence, providing respective hazard ratios of 1.10, 1.19, and 0.89 (p = 0.001, 0.03, and 0.01).

Conclusion: Among patients referred for first time PVI, females were older and demonstrated significantly poorer LA contractile health vs. males, the latter





Hazard ratios for AF recurrence by z-score threshold

LA min > 4.9	LA pre-sys > 2.8	LA booster EF ≤ -3.6
3.2 (p<0.001)	2.4 (p=0.002)	1.8 (p=0.03)

GRAPHICAL ABSTRACT | This cohort study examined sex-based differences in cardiac phenotype and atrial fibrillation (AF) recurrence following pulmonary vein isolation (PVI). Two-hundred-four patients and 101 healthy volunteers were studied by cardiac MRI to determine z-score based measures of chamber volumes and function. Following a median 932 days of follow-up, AF recurrence occurred in 41% of males and 59% of females (p = 0.03). Markers of left atrial contractile health were significantly reduced in females vs. males, and were found to be independent predictors of AF recurrence.

independently associated with AF recurrence. Assessment of LA contractile health may therefore be of value to identify female patients at elevated risk of AF recurrence. Factors influencing female patient referral for PVI at more advanced stages of atrial disease warrant focused investigation.

Keywords: atrial fibrillation, pulmonary vein isolation, cardiovascular magnetic resonance imaging, left atrial function, gender differences, women cardiovascular health, left atrial volume, left atrial booster pump function

INTRODUCTION

Atrial Fibrillation (AF) is the most common arrhythmia encountered in contemporary practice, estimated to affect over 30 million people worldwide (1). With rising prevalence over the past two decades (2), AF is recognized as an important contributor to cardiovascular hospitalization and healthcare expenditure (3). Pulmonary vein isolation (PVI) is a common invasive therapy for the treatment of symptomatic AF. Despite providing value for the improvement of symptom burden and

quality of life (4, 5), AF recurrence remains common and occurs in up to 43% of patients by 1-year (6, 7), this decreasing to 20–35% at 3–5 years following the engagement of repeat interventions (8–10). Despite contributing to 43% of community reported AF, females currently represent 27% of PVI procedures (11). Among these female patients, higher rates of AF recurrence have been consistently reported vs. males (12–19). Phenotypic sex differences related to these important discrepancies have not been previously explored.

Cardiovascular magnetic resonance (CMR) imaging provides accurate and reproducible quantification of the cardiovascular phenotype in patients referred for PVI, inclusive of vascular anatomy and cardiac chamber volumetry (20). This presents unique opportunities to comprehensively study phenotypic differences between women and men that may contribute to post-PVI AF recurrence.

In this study we prospectively recruited a consecutive series of patients clinically referred for pre-procedural CMR prior to first-time PVI. We simultaneously recruited a healthy reference cohort to permit sex-matched comparisons of cardiac chamber remodeling and alterations in contractile health through use of Z-score based analysis. Respective associations for CMR-derived phenotypic markers and AF recurrence were then explored with multivariable adjustment for known confounders.

MATERIALS AND METHODS

Study Design and Population

This was a prospective observational cohort study of patients referred for pre-procedural CMR prior to first time PVI, being a pre-defined study of the Cardiovascular Imaging Registry of Calgary (CIROC) (NCT04367220). CIROC is a prospective clinical-outcomes-based registry of the Libin Cardiovascular Institute. All patients undergo standardized capture of baseline social and clinical demographics, co-morbid illnesses, and Quality of Life (EQ-5D-3L and EQ-VAS) using a tablet-based questionnaire followed by capture of quantitative and qualitative imaging variables using commercial software (cardioDI™, Cohesic Inc., Calgary, Alberta). Automated data matching of historic and prospective laboratory, pharmacy, ECG, Holter and ICD-10 coded admission and procedural data is then executed from institutional data warehouses for a period of 10 years.

Patients were recruited between March 2015 and September 2018 and followed for a median of 2.6 years for AF recurrence. Patients were excluded if they had complex congenital heart disease, severe valvular heart disease (severe stenosis or regurgitation), or prior cardiac surgery involving the atrioventricular valves. Patients were classified by AF type in accordance with contemporary Canadian Cardiovascular Society guidelines (2).

One hundred and one healthy volunteers (HV) were prospectively recruited to establish healthy reference values for non-contrast phenotypic markers. HV were recruited from the local community and required to have no history of cardiovascular disease and no moderate or severe obesity (BMI $\geq$ 35 kg/m^2), hypertension, diabetes mellitus, kidney, or collagen vascular disease.

The study was approved by the Conjoint Health Research Ethics Board at University of Calgary (REB 13-0902) and all subjects provided written informed consent. All research activities were performed in accordance with the Declaration of Helsinki.

Cardiovascular Magnetic Resonance Imaging and Analysis Protocols

CMR imaging was performed using 3 Tesla clinical scanners (Prisma or Skyra, Siemens Healthineers, Erlangen, Germany). All underwent a standardized protocol inclusive of routine cine imaging in standard 2, 3, and 4-chamber long axis views and sequential short-axis slices, 3D magnetic resonance angiography (MRA) of the pulmonary veins using a 3D gradient-echo pulse sequence followed by a volumetric interpolated breath-hold examination (VIBE). MRA was performed using a bolus of 0.2 mmol/kg Gadovist (Bayer Inc., Canada) followed by a 30cc saline flush.

Blinded analyses were performed using standardized operating procedures (SOPs) adherent to published Society of Cardiovascular Magnetic Resonance (SCMR) recommendations (20). All analyses were performed using commercially available software (cvi**42**; Circle Cardiovascular Imaging Inc., Calgary, Canada).

Ventricular volumetric analyses were performed on short axis cine images to obtain end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and left ventricular (LV) mass. Left atrial (LA) volumes were measured at maximal (LAmax) and minimal (LAmin) volume, respectively obtained prior to atrio-ventricular valve opening and following atrial contraction using the bi-plane area-length method. LA volume was also measured prior to atrial systole (LApre-systole) for the calculation of LA booster function, a measure of active LA emptying due to atrial contraction. LA function parameters were reported as LA global, conduit, and booster EF, as previously described (21). Right atrial (RA) volumes were obtained from the 4-chamber view. All measures were indexed to body surface area (BSA) using the Mosteller formula, as appropriate. Sex-based Z-score values were calculated as the standard deviation from mean reference values of sex-matched healthy volunteers, ensuring reported differences in cardiac phenotype were independent of known sex-dependencies. Pulmonary vein and artery dimensions were measured from 3D MRA using multi-plane reconstruction (MPR) with ostial cross-sectional

Abbreviations: AF, Atrial fibrillation; BSA, Body surface area; CIROC, Cardiovascular Imaging Registry of Calgary; CMR, Cardiovascular magnetic resonance imaging; DAD, Discharge Abstract Database; EF, Ejection fraction; GFR, Glomerular filtration rate; HV, Healthy volunteers; ICD-10, International Classification of Diseases, Tenth Revision; NACRS, National Ambulatory Care Reporting System; LAmax, Maximum left atrial volume; LAmin, Minimum left atrial volume; LApre-systole, Left atrial volume prior to LA systole; LV, Left ventricle; NCT, ClinicalTrials.gov Identifier; NYHA, New York Heart Association; PA, Pulmonary artery; PVI, Pulmonary vein isolation.

dimensions performed for each pulmonary vein, measured 10 mm from the atrial junction. Pulmonary artery (PA) measurements were performed for the main PA and for each branch PA at 15 mm from the main PA bifurcation.

Pulmonary Vein Isolation Procedures

All PVI procedures were performed by percutaneous radiofrequency ablation using irrigated, contact force sensing catheters or, in a small minority, using a multielectrode pulmonary vein ablation catheter (PVAC®, Medtronic Inc., Minneapolis, MN, United States). Prior to ablation, 3D surface rendered models of LA anatomy were generated from CMR MRA datasets using EnsiteNavX® Velocity (St Jude Medical, St. Paul, MN, United States) or Carto3® system (Biosense Webster, Baldwin Park, CA, United States), providing intra-procedural guidance. The LA was catheterized under fluoroscopic guidance by femoral access followed by transseptal puncture. In all patients, the targeted procedural endpoint was complete PVI using wide antral circumferential ablation, with demonstration of bidirectional block. 3D electroanatomic mapping was performed in all cases with mapping density and intra-procedural use of this data left at the discretion of each physician. Complete isolation of the PVs was defined as elimination or dissociation of PV potentials by way of Lasso catheter. Additional LA linear ablations, most commonly a left atrial roof line, could be performed at operator discretion. Ablation of the cavotricuspid isthmus was incrementally performed for patients with a history of atrial flutter.

Primary Clinical Outcome

The primary clinical outcome was defined as time in days to first AF recurrence following index PVI procedure. Patients were assessed at 3-months with 12-lead ECG and 24-h Holter monitoring. Clinical follow-up was subsequently performed at 6- and 12-months in out-patient clinics with 12-lead ECG and Holter monitoring ordered for patients describing palpitations. In addition, a detailed review of all 12-lead ECG's and Holters ordered outside these visits was performed and administrative health data used to identify all emergency room or hospital visits related to AF recurrence across the Province of Alberta. The latter used ICD-10 coding from the National Ambulatory Care Reporting System (NACRS) and Discharge Abstract Database (DAD). A 1-month blanking period following PVI was applied in accordance with prior recommendations (22).

Statistical Analysis

Continuous variables were expressed as mean ± SD or median (Q1, Q3); categorical variables as counts (percentage). We compared males and females using two-sample *t*-test/Mann-Whitney test or Chi-square/Fisher exact test for continuous and categorical variables, respectively.

Univariable and multivariable Cox proportional hazards models were constructed to investigate the relationship between predictors (demographic, procedural, and CMR variables) and AF recurrence; results were expressed as hazard ratios (HR) and 95% confidence intervals (CI). Time to event was calculated as time from first PVI procedure until first AF recurrence. Patients who did not develop recurrence were considered censored at the time of last follow-up. The assumptions of proportional hazards and linearity were verified using plots of scaled Schoenfeld and martingale residuals, respectively. We applied restricted cubic spline (RCS) transformations for variables not linearly related to the log hazard (Z-scores for LA volumes and EF), placing three pre-defined knots at the 0.05, 0.5, and 0.95 quantiles based on the number of events. HRs and 95% CI for all numerical variables were presented per one unit increase except for RCS transformed ones that were presented as partial effect plots of relative HRs against Z-scores, followed by point estimates of HRs comparing a Z-score of 2.0 vs. 1.0.

Receiver Operator Characteristic (ROC) curve analysis was used to establish an optimal univariable cut-point for Z-scores for LAmin, LApre-systole, and LA booster EF, using the maximally selected rank statistics from the "maxstat" R package (23). Kaplan-Meier curves were constructed to compare patients above and below this cut-point, with significance established by log-rank test.

Multivariable models for the overall PVI cohort were constructed to test associations of LA parameters (Z-scores) with AF recurrence, adjusting for pre-specified age, diabetes, hypertension, alcohol consumption, and pre-procedural anti-arrhythmic medication use. Z-score covariates with a p-value < 0.1 in univariable analysis were considered eligible for entry to multivariable models.

Analyses were conducted using R version 3.6.2, with two-tailed p-value < 0.05 indicating statistical significance. Survival analysis was performed using R packages "survival" version 3.1-12, "rms" version 6.0-1, and "survminer" version 0.4.9.

RESULTS

Baseline Clinical Characteristics

A total of 204 patients and 101 HV were enrolled. Baseline clinical characteristics for patients, stratified by sex, are provided in **Table 1**; those for HV provided in **Supplementary Table 1**.

The mean age of patients was 60.2 ± 9.1 years (range 32–80 years), with 25% being female. A total of 132 (65%) patients had paroxysmal AF with the remaining having persistent AF. Forty-two patients (21%) had a concurrent history of atrial flutter. As shown in **Table 1**, female patients were significantly older (mean difference 5.3 years), with a higher proportion having hypertension (39 vs. 24%, $p = 0.03$), hypothyroidism (31 vs. 7%, $p < 0.001$), or hyperthyroidism (8 vs. 1%, $p = 0.01$) vs. males. A similar prevalence of diabetes, hyperlipidemia, and obesity was seen. Patient survey responses yielded lower rates of regular ($\geq$ 1 per day) caffeine consumption among females (53 vs. 68%, $p = 0.009$) but similar smoking and alcohol intake.

Baseline medication use was similar between sexes except for increased loop diuretic use in females (20 vs. 8%; $p = 0.02$). Anti-arrhythmic therapy was being used at time of CMR imaging in 71% of subjects, with no difference between sexes. Compared to males, females had a lower mean GFR and higher overall prevalence of chronic kidney disease, defined as GFR < 60 ml/kg/m^2 (24 vs. 4%, $p < 0.001$).

TABLE 1 | Baseline non-imaging characteristics of the total study cohort, stratified by sex.

Characteristic	Overall *N* = 204	Males *N* = 153 (75%)	Females *N* = 51 (25%)	*P*-value
Age	60.2 ± 9.1	58.9 ± 8.9	64.2 ± 8.7	**<0.001***
Body surface area (BSA, m^2)	2.1 ± 0.2	2.2 ± 0.2	1.9 ± 0.2	**<0.001***
Body mass index (BMI, kg/m^2)	28.8 ± 4.8	28.9 ± 4.3	28.4 ± 5.9	0.60
Obesity (BMI ≥30 kg/m^2)	66 (32%)	51 (33%)	15 (29%)	0.60
Heart rate, bpm	58.0 (52.0, 70.0)	57.0 (51.0, 68.2)	60.0 (55.5, 72.0)	**0.039***
Systolic BP, mmHg	115.9 ± 14.0	115.3 ± 12.7	117.8 ± 17.3	0.6
Diastolic BP, mmHg	70.0 ± 9.7	70.5 ± 9.3	68.5 ± 10.8	0.24
Dyspnea (NYHA class II-IV)	66 (34%)	46 (32%)	20 (43%)	0.17
Diabetes mellitus†	10 (4.9%)	7 (4.6%)	3 (5.9%)	0.71
Hypertension	56 (27%)	36 (24%)	20 (39%)	**0.030***
Hyperlipidemia‡	141 (69%)	105 (69%)	36 (71%)	0.79
Hypothyroidism	27 (13%)	11 (7%)	16 (31%)	**<0.001***
Hyperthyroidism	5 (2%)	1 (1%)	4 (8%)	**0.014***
CKD§	18 (9%)	6 (4%)	12 (24%)	**<0.001***
Smoking				0.96
Never	150 (78%)	112 (77%)	38 (81%)	
Current	22 (11%)	17 (12%)	5 (11%)	
Former	20 (10%)	16 (11%)	4 (9%)	
Alcohol consumption				0.67
None	24 (12%)	17 (11%)	7 (14%)	
Occasional (<1 drink/day)	139 (68%)	103 (68%)	36 (71%)	
Regular (at least 1 drink/day)	40 (20%)	32 (21%)	8 (16%)	
Caffeine consumption				**0.009***
None	9 (4.7%)	3 (2.1%)	6 (13%)	
Occasional (<1 drink/day)	59 (31%)	43 (29%)	16 (34%)	
Regular (at least 1 drink/day)	125 (65%)	100 (68%)	25 (53%)	
QoL (rating on 0–100 scale)	80.0 (70.0, 85.0)	80.0 (70.0, 85.0)	77.5 (70.0, 85.0)	0.79
Medications				
Aspirin	25 (12%)	21 (14%)	4 (8%)	0.27
Beta-blocker	136 (67%)	100 (65%)	36 (71%)	0.49
ACEi/ARB	64 (31%)	47 (31%)	17 (33%)	0.73
Calcium channel blocker	46 (23%)	33 (22%)	13 (25%)	0.56
Anti-coagulant	190 (93%)	142 (93%)	48 (94%)	0.999
Anti-arrhythmic	145 (71%)	112 (73%)	33 (65%)	0.25
Digoxin	12 (6%)	9 (6%)	3 (6%)	0.999
Loop diuretic	22 (11%)	12 (7.8%)	10 (20%)	**0.019***
Lipid lowering	67 (33%)	52 (34%)	15 (29%)	0.55
Atrial fibrillation type Paroxysmal (vs. persistent)	132 (65%)	98 (64%)	34 (67%)	0.74
Labs				
Hemoglobin, g/L	148.6 ± 12.6	151.9 ± 11.0	138.6 ± 11.6	**<0.001***
GFR, ml/min/1.73 m^2	89.3 (73.4, 105.7)	94.9 (77.3, 113.9)	77.5 (61.0, 94.1)	**<0.001***

Values are mean ± SD, median (IQR), or number (%). NYHA indicates New York Heart Association; CKD, chronic kidney disease; QoL, quality of life; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; and GFR, glomerular filtration rate.
Bold values indicate p < 0.05.
**p < 0.05.*
†*Coded as present if the patient was receiving oral hypoglycemics or insulin or had a HbA1C ≥ 6.5% within 3 years prior to or 4 months following index CMR.*
‡*Coded as present if the patient was receiving lipid-lowering therapy or had an LDL-C ≥ 3.5 mmol/L or triglycerides ≥ 1.7 mmol/L within 3 years prior to or 4 months following index CMR.*
§*Defined as GFR < 60 ml/kg/m^2.*

Pulmonary Vein Isolation Procedural Details

Median duration from CMR to first PVI was 24.5 (8.3, 53.0) days with no differences between sexes. **Table 2** summarizes all relevant intra-procedural variables. Complete electrical pulmonary vein isolation was achieved in 100% of females and 93% of males. There were no observed differences between sexes in any procedural variable.

Sex-Based Differences in Cardiovascular MRI Phenotype

All patients completed CMR imaging. Despite active rhythm control strategies, AF was present at time of CMR in 25 (12%) patients, preventing quantification of atrial function in these subjects. A single male patient had mild to moderate aortic and mitral regurgitation.

Baseline chamber volumes, mass, and EF stratified by sex, are shown in **Table 3**, and displayed according to both non-Z-score

TABLE 2 | Catheter ablation procedure details for the overall cohort and stratified by sex.

Characteristic	Overall *N* = 204	Males *N* = 153 (75%)	Females *N* = 51 (25%)	*p*-value
Sinus rhythm at onset of procedure	123 (61%)	90 (59%)	33 (67%)	0.31
Ablation count	55.0 (44.0, 75.0)	55.5 (44.2, 74.8)	55.0 (39.0, 75.0)	0.341
Total ablation time, s	2809.0 (2291.5, 3562.5)	2864.0 (2343.0, 3618.0)	2713.0 (2198.5, 3294.5)	0.11
Maximum power, watts	30.0 (25.0, 31.0)	30.0 (25.0, 31.0)	30.0 (25.0, 31.0)	0.73
Complete electrical PVI achieved	194 (95%)	143 (93%)	51 (100%)	0.069
Concurrent Atrial flutter ablation	37 (18%)	25 (16%)	12 (24%)	0.25
LA roof line	12 (5.9%)	6 (3.9%)	6 (12%)	0.077
Posterior isolation/posterior box	3 (1.5%)	3 (2.0%)	0 (0%)	0.57
PVAC catheter used	4 (2.0%)	3 (2.0%)	1 (2.0%)	0.999
3D mapping system used	202 (99%)	151 (99%)	51 (100%)	0.999

Values are mean ± SD, median (IQR), or number (%).
AF indicates atrial fibrillation; PVI, pulmonary vein isolation; and LA, left atrium.

TABLE 3 | Baseline CMR chamber volumes and ejection fraction of the overall cohort and stratified by sex.

CMR variables	Overall *N* = 204	Males *N* = 153 (75%)	Females *N* = 51 (25%)	*p*-value
Non-Z-score values				
LV EDV, ml/m^2	78.9 ± 15.1	82.1 ± 14.5	69.6 ± 12.8	**<0.001***
LVESV, ml/m^2	32.0 ± 10.2	33.8 ± 10.9	26.9 ± 5.1	**<0.001***
LVEF,%	59.2 ± 9.0	58.8 ± 9.3	60.6 ± 7.9	0.18
LV mass, g/m^2	52.8 ± 11.5	55.8 ± 10.5	44.0 ± 9.8	**<0.001***
RVEDV, ml/m^2	85.5 ± 18.9	90.5 ± 17.3	70.7 ± 15.6	**<0.001***
RVESV, ml/m^2	39.4 ± 11.1	42.7 ± 9.9	29.7 ± 8.4	**<0.001***
RVEF,%	53.9 ± 7.9	52.6 ± 7.6	58.0 ± 7.4	**<0.001***
LAmax, ml	83.0 (67.9, 102.7)	84.4 (69.5, 105.0)	73.8 (65.6, 97.0)	0.17
LAmax, ml/m^2	39.4 (32.4, 48.0)	39.4 (30.5, 46.7)	39.3 (34.7, 51.4)	0.094
LAmin, ml	41.6 (29.7, 58.5)	41.6 (29.7, 58.6)	41.7 (29.7, 55.1)	0.75
LAmin, ml/m^2	20.1 (14.5, 27.0)	18.9 (13.6, 25.7)	23.9 (16.3, 30.1)	**0.023***
LApre-systole, ml	60.3 (47.0, 77.3)	62.8 (47.0, 77.0)	60.0 (47.3, 77.5)	0.80
LApre-systole, ml/m^2	29.3 (22.5, 35.8)	27.9 (21.3, 34.0)	31.1 (24.5, 40.5)	**0.017***
LA global EF,%	48.1 (36.2, 57.5)	51.0 (37.2, 59.1)	43.5 (32.9, 54.2)	**0.017***
LA booster EF,%	29.7 (17.7, 39.8)	29.7 (16.0, 40.7)	28.9 (19.3, 34.2)	0.40
LA conduit EF,%	24.9 (17.2, 31.7)	26.1 (18.6, 33.3)	23.6 (13.1, 29.0)	**0.018***
Z-score values by sex†				
LV EDV	–0.4 ± 1.2	–0.2 ± 1.2	–0.7 ± 1.1	**0.011***
LV ESV	0.2 ± 1.6	0.4 ± 1.8	–0.1 ± 0.8	**0.012***
LV EF	–1.1 ± 2.3	–1.1 ± 2.5	–0.8 ± 1.6	0.35
LV mass	–0.1 (–0.8, 0.5)	–0.2 (–0.7, 0.4)	0.1 (–0.9, 1.3)	0.17
RV EDV	–0.6 ± 1.3	–0.4 ± 1.3	–1.0 ± 1.2	**0.009***
RV ESV	–0.2 ± 1.2	0.0 ± 1.3	–0.6 ± 1.1	**0.002***
RV EF	–0.6 ± 1.7	–0.7 ± 1.7	–0.2 ± 1.5	0.061
LAmax	0.3 (–0.6, 1.3)	0.2 (–0.8, 0.9)	0.5 (–0.2, 2.2)	**0.003***
LAmin	1.1 (–0.1, 2.7)	0.6 (–0.3, 1.9)	3.5 (1.0, 5.6)	**<0.001***
LApre-systole	0.5 (–0.4, 1.5)	0.2 (–0.6, 1.0)	1.4 (0.2, 3.1)	**<0.001***
LAglobal EF	–1.9 (–3.7, –0.5)	–1.3 (–3.3, –0.2)	–3.2 (–4.9, –1.4)	**<0.001***
LAbooster EF	–2.0 (–3.9, –0.4)	–1.7 (–3.6, –0.2)	–2.6 (–4.4, –1.6)	**0.006***
LA conduit EF	–0.8 (–1.6, 0.0)	–0.5 (–1.3, 0.2)	–1.2 (–2.2, –0.6)	**<0.001***

Values are mean ± SD or median (IQR). LV indicates left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; RV, right ventricle; LA, left atrium; LAmax, maximum LA volume; LAmin, minimum LA volume; and LApre-systole, LA volume pre-atrial systole.
Bold values indicate p < 0.05.
**p < 0.05.*
†Z-score values calculated from sex-stratified reference values (BSA-adjusted for all volume and mass measures) from a healthy reference cohort (n = 101).

and Z-score-based values. Non-Z-score values showed females to have smaller BSA-indexed LV volumes and mass, similar LV EF, smaller RV volumes, and relatively higher RV EF (58.0 vs. 52.6%, $p < 0.001$) vs. males. BSA-indexed LAmax volume was similar between sexes. Of 179 patients in sinus rhythm at time of CMR, BSA-indexed LApre-systole and LAmin measurements were 11 and 26% higher in females, respectively ($p = 0.02$ for each). LA function was significantly lower in females by both LA global and conduit EF measures. Z-score correction demonstrated a further reduction in all LA function parameters in women vs. men when compared to sex-matched controls, with LA booster EF becoming highly significant ($p = 0.006$).

Observed differences in RA volumes, pulmonary venous and arterial measurements are provided in **Supplementary Table 2**.

TABLE 4 | Univariable associations of non-imaging variables with the primary clinical outcome in the overall cohort (both sexes).

Characteristic	HR (95% CI)	*p*-value
Age, per 1 year	0.9995 (0.977–1.023)	0.963
Female sex	**1.633 (1.057–2.524)**	**0.027***
Dyspnea (NYHA class II-IV)	1.149 (0.748–1.764)	0.53
Diabetes mellitus	0.545 (0.173–1.724)	0.30
Hypertension	1.085 (0.693–1.698)	0.72
Hyperlipidemia	0.802 (0.523–1.230)	0.31
Hypothyroidism	1.475 (0.860–2.531)	0.16
Hyperthyroidism	0.733 (0.181–2.978)	0.66
Chronic kidney disease	1.443 (0.748–2.784)	0.27
Smoking		
Never	Reference category	
Current	1.003 (0.516–1.950)	0.99
Former	1.054 (0.542–2.049)	0.88
Regular alcohol consumption (at least 1 drink/day)†	0.575 (0.320–1.033)	0.064
Caffeine consumption		
None	Reference category	
Occasional (< 1 drink/day)	0.660 (0.270–1.610)	0.36
Regular (at least 1 drink/day)	0.676 (0.290–1.576)	0.37
QoL (rating on 0–100 scale)	0.998 (0.986–1.011)	0.80
Baseline medications		
Aspirin	1.139 (0.633–2.047)	0.66
Beta-blocker	1.058 (0.685–1.634)	0.80
ACEi/ARB	1.07 (0.695–1.647)	0.76
Calcium channel blocker	1.290 (0.810–2.054)	0.28
Anti-coagulant	1.147 (0.501–2.628)	0.75
Anti-arrhythmic	**0.602 (0.394–0.919)**	**0.019***
Digoxin	0.451 (0.142–1.427)	0.18
Loop diuretic	1.422 (0.791–2.556)	0.24
Lipid-lowering	0.746 (0.476–1.167)	0.20
Body surface area, per m^2	0.662 (0.275–1.596)	0.36
BMI, per 1 kg/m^2	0.989 (0.947–1.033)	0.63
Obesity (BMI $\geq$30 kg/m^2)	0.977 (0.633–1.510)	0.92
Heart rate, per 1 bpm	1.008 (0.999–1.018)	0.095
Systolic blood pressure, per 1 mmHg	1.013 (0.998–1.028)	0.098
Diastolic blood pressure, per 1 mmHg	1.005 (0.983–1.027)	0.68
Atrial fibrillation type—non-paroxysmal (vs. paroxysmal)	1.300 (0.856–1.973)	0.22
Labs		
Hemoglobin, per 1 g/L	0.993 (0.978–1.009)	0.38
GFR, per 1 ml/min/1.73 m^2	1.001 (0.993–1.008)	0.87
Ablation procedure		
Sinus rhythm at onset of procedure	0.755 (0.499–1.144)	0.18
Ablation count	0.998 (0.990–1.006)	0.66
Total ablation time, per 1 s	0.999 (0.999–0.999)	0.54
Maximum power, per 1 watt	0.990 (0.924–1.061)	0.78
Left atrial roof line	1.983 (0.960–4.099)	0.065
Posterior isolation/posterior box	1.525 (0.375–6.199)	0.56
PVAC catheter used	1.007 (0.248–4.091)	0.99
3D mapping system used	1.054 (0.147–7.566)	0.96
Complete pulmonary vein isolation achieved	0.875 (0.355–2.157)	0.77

HR indicates hazard ratio; CI, confidence interval; NYHA, New York Heart Association; CKD, chronic kidney disease; QoL, quality of life; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; and GFR, glomerular filtration rate.
Bold values indicate p < 0.05.
**p < 0.05.*
†*Among regular drinkers, only 3 male patients were heavy drinkers (3–4 drinks/day), all remaining patients reported 1–2 drinks/day.*

BSA-indexed RAmax and RAmin volumes were smaller in females vs. males (p = 0.02 and p = 0.008, respectively). 3D-MRA derived cross-sectional areas of pulmonary vein ostia were similar between sexes except for the right superior pulmonary vein which was smaller in females (p = 0.03). A similar prevalence of a left common trunk and separate right middle pulmonary vein was observed between sexes. No differences in main or left PA cross-sectional areas were

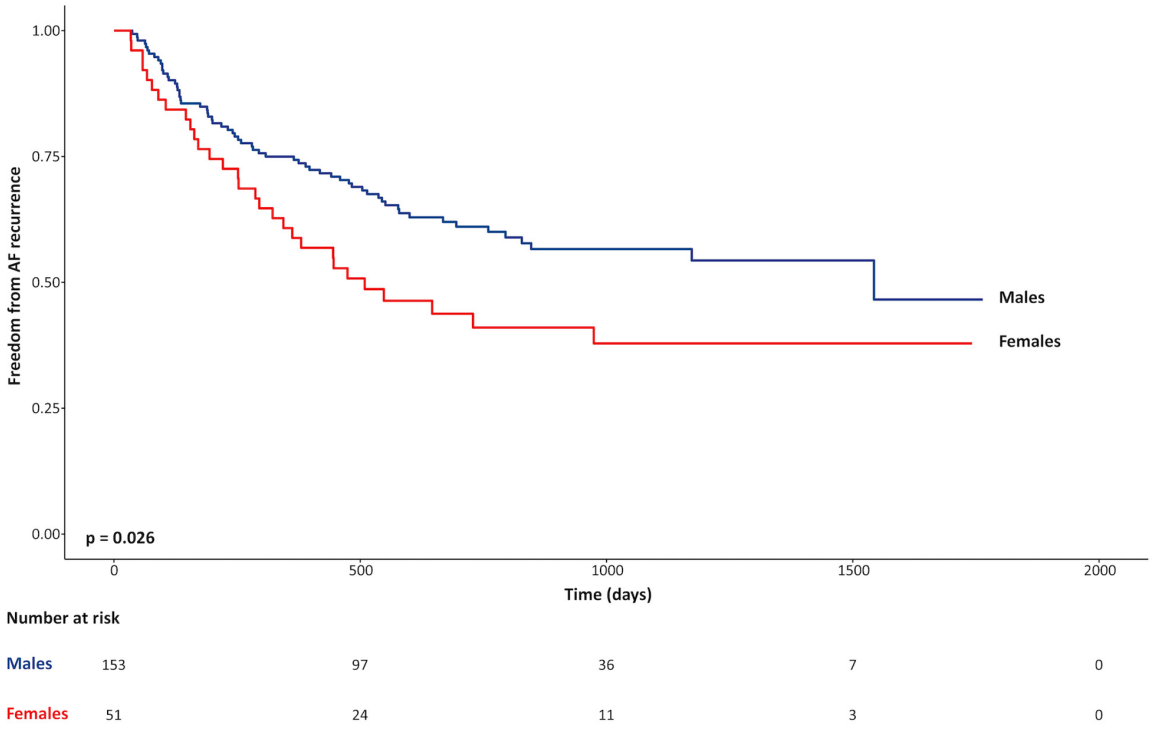


FIGURE 1 | Kaplan-Meier curves for freedom from recurrence of atrial fibrillation for females vs. males.

identified, while females had modestly smaller right PAs ($p = 0.02$).

Influence of Baseline Clinical Characteristics on Atrial Fibrillation Recurrence

Overall, 93 patients (46%) met criteria for AF recurrence over a median follow up period of 932 days (Q1-Q3 671–1,300). The 1-year cumulative incidence rate of AF recurrence was 29%. AF recurrence over the study period was significantly more common in females (59%) vs. males (41%, $p = 0.03$). Of the 93 patients with AF recurrence, 60 (16 females and 44 males) subsequently underwent a repeat PVI procedure. A single patient was lost to follow-up at 245 days with no documented AF recurrence, and another died at 63 days without documented AF recurrence and no cause of death being identified. Both were classified as negative with respect to AF recurrence.

Univariable associations of non-imaging parameters with the primary clinical outcome are shown in the **Table 4**. Female sex was the only clinical variable positively associated with the primary outcome (unadjusted HR 1.6, $p = 0.03$). Kaplan-Meier curves, shown in **Figure 1**, illustrate the influence of female sex on freedom from AF recurrence in the study population. Use of pre-procedural anti-arrhythmic medications at the time of CMR was the only clinical variable showing a significant protective association with AF recurrence (HR 0.6; $p = 0.02$). Regular alcohol consumption showed a protective trend (HR 0.6; $p = 0.06$). Of note, among regular alcohol drinkers, only 3 male patients described heavy drinking ($\geq$ 3 drinks/day); all remaining patients reporting an intake of 1–2 drinks/day.

Influence of Sex-Corrected Phenotype Markers on Atrial Fibrillation Recurrence

Univariable associations for Z-score reported (corrected for sex-specific reference values) chamber volumes, EF, and LV mass with the primary outcome are shown in **Table 5** and **Figure 2**. Z-score measures for LA booster EF were inversely associated with the primary outcome (HR 0.98 for a Z-score of 2.0 vs. 1.0; $p = 0.03$). LAmin was similarly associated with the primary outcome, demonstrating a HR of 1.07 for a Z-score of 2.0 vs. 1.0 ($p = 0.004$), where-as LApre-systole volume showed a trend with HR 1.15 ($p = 0.09$). RA volumes, pulmonary venous, and PA ostial dimensions were not associated with the primary outcome (**Supplementary Table 3**).

ROC curve analysis was performed to identify optimal Z-score thresholds for LAmin, LApre-systole, and LA booster EF for prediction of AF recurrence. Patients with a Z-score booster EF less than or equal to a threshold of –3.6 experienced an 1.76-fold risk of AF recurrence ($p = 0.03$); those with Z-score LAmin or LApre-systole above 4.9 and 2.8 experienced respective 3.22-fold ($p < 0.001$) and 2.4-fold ($p = 0.002$) increased risk of AF recurrence, as illustrated in **Figure 3**.

Multivariable models were constructed to identify independent associations between Z-score (sex-corrected) phenotype markers and future AF recurrence. Separate models were constructed assessing the influence of LA booster EF,

TABLE 5 | Univariable associations of Z-score values for CMR chamber volumes and ejection fraction with the primary clinical outcome in the overall cohort (both sexes).

CMR variables	HR (95% CI)*	*p*-value
LV EDV	1.115 (0.939–1.325)	0.21
LV ESV	1.038 (0.913–1.180)	0.57
LV EF	1.020 (0.932–1.117)	0.66
LV mass	1.138 (0.945–1.371)	0.17
RV EDV	1.079 (0.925–1.259)	0.34
RV ESV	1.046 (0.886–1.236)	0.59
RV EF	1.033 (0.912–1.170)	0.61
LAmax†	1.026 (0.859–1.225)	0.54
LAmin†	**1.073 (0.953–1.208)**	**0.004**‡
LApre-systole†	1.147 (1.014–1.298)	0.093
LA global EF†	0.916 (0.833–1.006)	0.19
LA booster EF†	**0.979 (0.763–1.256)**	**0.026**‡
LA conduit EF†	0.899 (0.692–1.167)	0.89

HR indicates hazard ratio; CI, confidence interval; LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; RV, right ventricle; LA, left atrium; LAmax, maximum LA volume; LAmin, minimum LA volume; and LApre-systole, LA volume pre-atrial systole.
Bold values indicate p < 0.05.
**Calculated per 1 unit increase in Z-score for all variables, except for restricted cubic spline (RCS) transformed ones calculated for a Z-score of 2.0 vs. 1.0.*
†RCS transformation used, with HR and 95% CI calculated for a Z-score of 2.0 vs. 1.0.
‡p < 0.05.

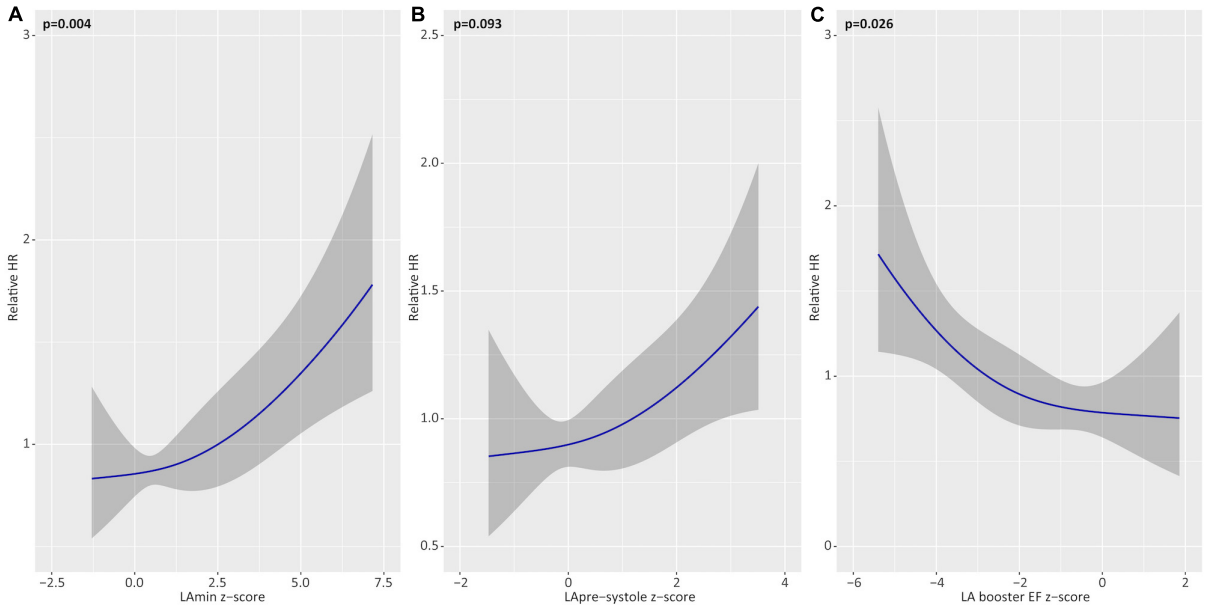


FIGURE 2 | Univariable associations of left atrial (LA) parameters with the primary outcome. Unadjusted hazards of atrial fibrillation recurrence for Z-score based deviations (relative to healthy reference values) for minimum LA volume (LAmin; **A**), pre-systole LA volume (LApre-systole; **B**), and LA booster ejection fraction (EF; **C**). Relative hazard ratios plotted across the range of restricted cubic spline-transformed variables.

LAmin, and LApre-systole on the primary outcome, adjusted for age, diabetes, hypertension, regular alcohol consumption, and pre-procedural anti-arrhythmic medication use (**Table 6**). In these models, LA booster EF was found to be independently protective for the primary outcome, providing a HR 0.89 for a Z-score of 2.0 vs. 1.0 (p = 0.01). Similarly, Z-score LAmin and LApre-systole were independently associated with the primary outcome with respective HR of 1.10 and 1.19 for Z-scores of 2.0 vs. 1.0 (respective p = 0.001 and 0.03). In all models, regular alcohol consumption and anti-arrhythmic medication use remained independently protective from the primary outcome. **Figure 4** provides adjusted relative hazard ratios for each of the studied LA parameters according to sex-based Z-scores. Similar results were obtained on repeat multivariable analysis adjusting separately for each of hyperthyroidism and hypothyroidism, in addition to age, diabetes, hypertension, regular alcohol consumption, and pre-procedural anti-arrhythmic medication use.

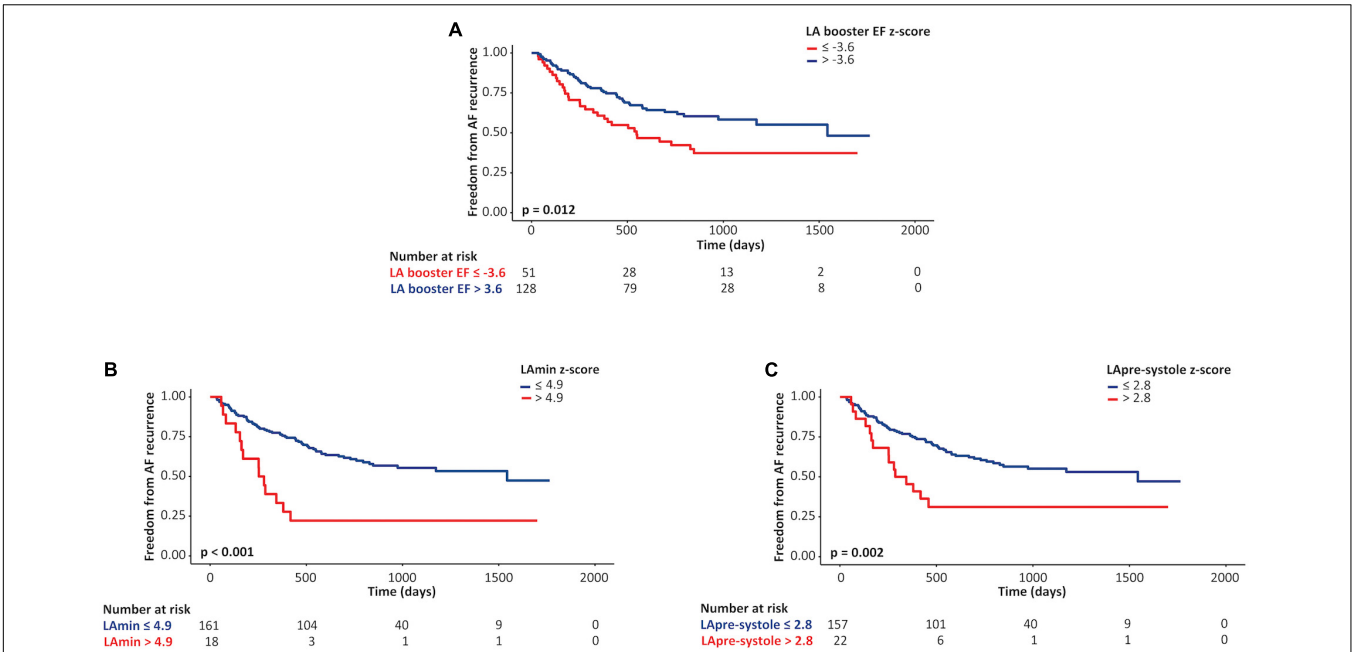


FIGURE 3 | Kaplan-Meier curves for left atrial (LA) parameters as predictors of AF recurrence. Unadjusted Kaplan-Meier curves describing associations between lower vs. higher Z-scores of LA booster ejection fraction (EF; **A**), minimum LA volume (LAmin; **B**), and pre-systole LA volume (LApre-systole; **C**) values and freedom from atrial fibrillation recurrence following pulmonary vein ablation.

TABLE 6 | Multivariable models for associations of Z-scores for left atrial CMR parameters with the primary clinical outcome in overall cohort (both sexes).

Parameter	HR (95% CI)*	*p*-value
Model 1. LAmin		
Age, per 1 year	0.967 (0.966–1.242)	0.45
Diabetes	0.525 (0.158–1.742)	0.29
Hypertension	1.341 (0.809–2.223)	0.25
Regular alcohol consumption (at least 1 drink/day)†	**0.498 (0.262–0.949)**	**0.034**‡
Pre-procedural anti-arrhythmic medication	**0.500 (0.312–0.801)**	**0.004**‡
LAmin§	**1.096 (0.967–1.242)**	**0.001**‡
Model 2. LApre-systole		
Age, per 1 year	0.993 (0.968–1.019)	0.60
Diabetes	0.575 (0.175–1.891)	0.36
Hypertension	1.309 (0.793–2.159)	0.29
Regular alcohol consumption (at least 1 drink/day)†	**0.513 (0.270–0.973)**	**0.041**‡
Pre-procedural anti-arrhythmic medication	**0.511 (0.314–0.829)**	**0.007**‡
LApre-systole§	**1.185 (1.046–1.342)**	**0.027**‡
Model 3. LA booster EF		
Age, per 1 year	1.001 (0.977–1.026)	0.92
Diabetes	0.580 (0.176–1.912)	0.37
Hypertension	1.428 (0.848–2.403)	0.18
Regular alcohol consumption (at least 1 drink/day)†	**0.495 (0.260–0.940)**	**0.032**‡
Pre-procedural anti-arrhythmic medication	**0.498 (0.311–0.798)**	**0.004**‡
LA booster EF§	**0.885 (0.681–1.152)**	**0.013**‡

HR indicates hazard ratio; CI, confidence interval; LA, left atrium; LAmin, minimum LA volume; and LApre-systole, LA volume pre-atrial systole; LApre-systole, LA volume pre-atrial systole; and EF, ejection fraction.
Bold values indicate p < 0.05.
**Calculated per 1 unit increase for all numerical variables, except for restricted cubic spline (RCS) transformed ones calculated for a Z-score of 2.0 vs. 1.0.*
†*Among regular drinkers, only 3 male patients were heavy drinkers (3–4 drinks/day), all remaining patients reported 1–2 drinks/day.*
‡*p < 0.05.*
§*RCS transformation used, with HR and 95% CI calculated for a Z-score of 2.0 vs. 1.0.*

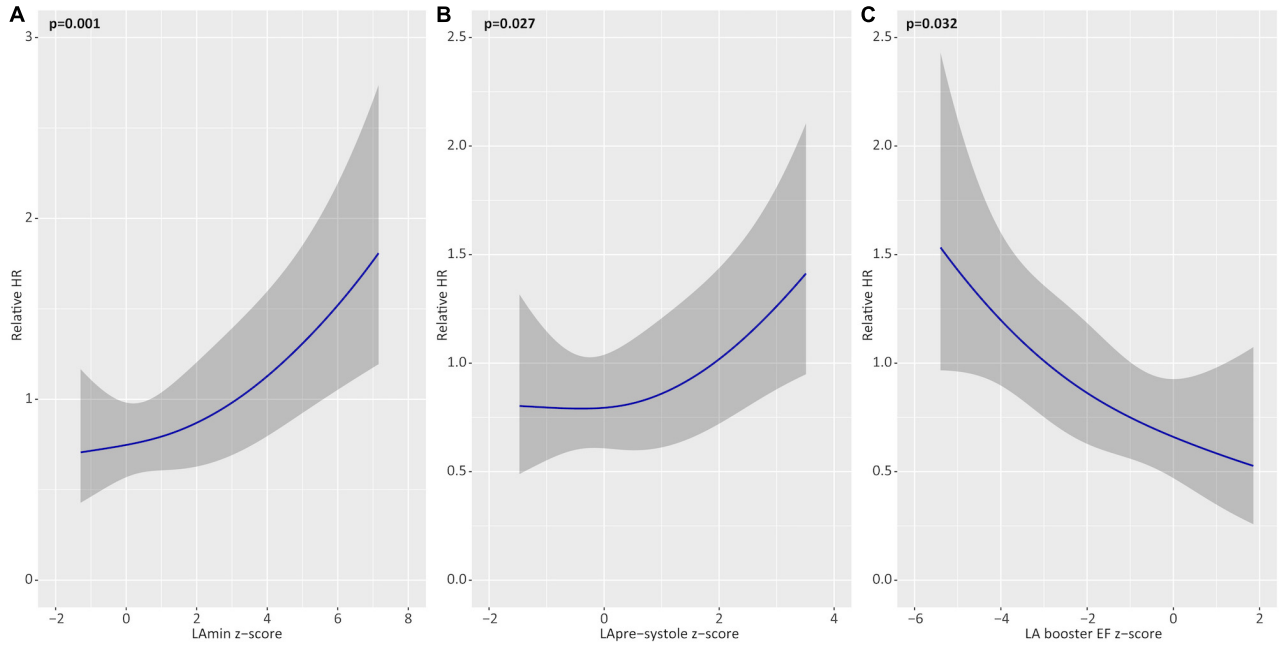


FIGURE 4 | Multivariable associations of left atrial (LA) parameters with the primary outcome. Adjusted hazards of atrial fibrillation recurrence for Z-score based deviations (relative to healthy reference values) for minimum LA volume (LAmin; **A**), pre-systole LA volume (LApre-systole; **B**), and LA booster ejection fraction (EF; **C**). Shown as partial effect plots for multivariable associations with relative hazard ratios plotted across the range of restricted cubic spline-transformed variables. All models are adjusted for age, hypertension, diabetes, alcohol consumption, and pre-procedural anti-arrhythmic medication use.

Sensitivity Analysis

Of 93 total AF recurrence events, all but 6 were based on documented AF using an available ECG or Holter recording, these available for all local hospitals. The incremental use of ICD-10 coded AF hospitalization across the Province of Alberta, this used to identify events beyond the local ECG data repository, yielded an additional 6 events. Sensitivity analysis removing these administratively only coded events did not alter the results of analysis, as detailed in **Supplementary Tables 4–6** and **Supplementary Figures 1**, **2**.

DISCUSSION

This is the first prospective study dedicated to identifying sex-based differences in cardiac phenotype and their related influence on AF recurrence in patients undergoing first time PVI. Our study identified an 18% absolute increase in the incidence of AF recurrence in females vs. males during the study period, this strongly associated with reductions in left atrial contractile health. Versus male patients, females showed significantly higher LAmin and LApre-systole volumes and lower LA booster function relative to sex-matched reference values, these markers being independently associated with AF recurrence following multivariable adjustment. These observations provide unique insights into sex-related differences among patients referred for PVI, and offer support for a greater severity of atrial myopathy that contributes to the higher observed incidence of AF recurrence in females.

Elevated rates of AF recurrence in females following PVI have been reliably observed in numerous studies (12–19). Over a decade ago, a landmark study by Patel et al. demonstrated that, among 3,265 consecutively studied patients undergoing PVI, women experienced significantly lower freedom from AF recurrence compared to men (68.5 vs. 77.5% $<$ 0.001) over a median follow-up of 24 months (14). Following this, a subgroup analysis of the Fire and Ice trial showed female gender to be associated with a 37% increased risk in AF recurrence (HR 1.37; 95% CI, 1.08–1.73; p = 0.010) (24), findings that have since been replicated in CABANA trial (25).

Our current study provides strong support for greater relative reductions in LA contractile health in females vs. males at time of referral to PVI. While no prior study has focused on identifying sex-based differences in cardiac phenotype in this referral population, one prior study by Yu et al., identified surrogate evidence of reduced LA contractile health in females using TEE-based LA appendage Doppler interrogation. In this study females experienced a significantly higher rate of AF recurrence vs. males (39 vs. 27%, $p < 0.001$) and demonstrated significantly lower LA appendage emptying velocities (13).

Without targeted focus on sex phenotypic differences, several prior echocardiography studies have identified population level associations between LA contractile function and AF recurrence (26–31). Similar studies leveraging CMR markers of LA contractile health have also shown population wide associations. Several CMR-based studies have replicated these

findings, using both volumetric and strain-based analyses (32–35). Collectively, these studies have provided a foundation for establishing LA health, as assessed by contractile performance, to be of central importance for the maintenance of sinus rhythm following PVI. Our current study expands on these observations by identifying important sex-related differences in atrial contractile health, identifying females to have a greater relative reduction in these markers at time of PVI referral vs. males, and that this is associated with elevation in rates of AF recurrence.

While associations between atrial contractile performance and fibrosis burden by MRI have shown poor correlation (36), reductions in atrial contractility are anticipated to accompany the adverse atrial remodeling (i.e., fibrosis) observed in chronic AF populations (37–39), the latter is strongly associated with AF recurrence (36, 39). However, to our knowledge, no study has examined sex-related differences in atrial remodeling or contractile function in AF referral populations. Both animal models (40) and population MRI-based investigations (41) have, however, suggested sex-related differences in remodeling that occurs at the ventricular level.

LIMITATIONS

As a single center study with potential for referral bias, our study findings would benefit from external validation. We observed that females in our referral cohort showed a higher mean age than males, this potentially reflecting referral bias toward later stage referral of females to PVI procedures in clinical practice. Z-scores for the LA metrics were stratified for sex but not for age. Despite efforts to recruit healthy volunteers of similar age, challenges were experienced in identifying qualifying healthy subjects aged $>$ 60 years. However, observed sex differences in event rates were maintained following adjustment for age. We also ensured that the predictive utility of LAmin, LApre-systole, and booster EF, demonstrated to be higher among females, was maintained following adjustment for age and all other relevant covariates. As with all clinical observational studies evaluating AF recurrence, lack of continuous ambulatory surveillance limits the capture of asymptomatic or brief AF episodes. Accordingly, such episodes may be missed, providing a potential limitation to the study design. We also acknowledge the inability to execute a time-dependency analysis of the influence of anti-arrhythmic medication prescription at different time-points following ablation. Finally, while of interest, our CMR imaging protocol was not designed to directly evaluate measures of LA fibrosis by advanced 3D acquisition techniques, and therefore correlation to this marker was not permitted.

CONCLUSION

Female patients experience higher rates of AF recurrence following first time PVI for the treatment of paroxysmal or persistent AF. Using pre-procedural CMR-based phenotyping with z-score correction to sex-matched controls, we observed females to have significantly greater reductions in LA contractile health at time of PVI referral compared to males. This finding was strongly associated with future AF recurrence. Our findings support that female patients have more advanced atrial myopathy at time of referral to PVI, providing pathophysiologic substrate for the higher observed rate of AF recurrence in this population. Efforts to improve access to PVI for female patients at earlier stages of AF care may be of importance to improve procedural outcomes in this population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available from the corresponding author, on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Conjoint Health Research Ethics Board at University of Calgary (REB 13-0902). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AY performed patient data collection, image analysis, and manuscript authorship. JW was senior author and conceived, designed, edited, and finalized manuscript content. DL performed statistical analysis and manuscript revision. SD, YM, AS, and JF structured related data collection, data analysis, and manuscript review. PF performed image acquisition. SR performed patient recruitment and data collection. AH, CL, FQ, and SW participated in patient recruitment and manuscript revision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.894592/full#supplementary-material

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Cardiac magnetic resonance defines mechanisms of sex-based differences in outcomes following cardiac resynchronization therapy

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Background: Mechanisms of sex-based differences in outcomes following cardiac resynchronization therapy (CRT) are poorly understood.

Objective: To use cardiac magnetic resonance (CMR) to define mechanisms of sex-based differences in outcomes after CRT and describe distinct CMR-based phenotypes of CRT candidates based on sex and non-ischemic/ischemic cardiomyopathy type.

Materials and methods: In a prospective study, sex-based differences in three short-term CRT response measures [fractional change in left ventricular end-systolic volume index 6 months after CRT (LVESVI-FC), B-type natriuretic peptide (BNP) 6 months after CRT, change in peak VO_2 6 months after CRT], and long-term survival were evaluated with respect to 39 baseline parameters from CMR, exercise testing, laboratory testing, electrocardiograms, comorbid conditions, and other sources. CMR was also used to quantify the degree of left-ventricular mechanical dyssynchrony by deriving the circumferential uniformity ratio estimate (CURE-SVD) parameter from displacement encoding with stimulated echoes (DENSE) strain imaging. Statistical methods included multivariable linear regression with evaluation of interaction effects associated with sex and cardiomyopathy type (ischemic and non-ischemic cardiomyopathy) and survival analysis.

Results: Among 200 patients, the 54 female patients (27%) pre-CRT had a smaller CMR-based LVEDVI (p = 0.04), more mechanical dyssynchrony based

on the validated CMR CURE-SVD parameter (p = 0.04), a lower frequency of both late gadolinium enhancement (LGE) and ischemic cardiomyopathy (p < 0.0001), a greater RVEF (p = 0.02), and a greater frequency of LBBB (p = 0.01). After categorization of patients into four groups based on cardiomyopathy type (ischemic/non-ischemic cardiomyopathy) and sex, female patients with non-ischemic cardiomyopathy had the lowest CURE-SVD (p = 0.003), the lowest pre-CRT BNP levels (p = 0.01), the lowest post-CRT BNP levels (p = 0.05), and the most favorable LVESVI-FC (p = 0.001). Overall, female patients had better 3-year survival before adjustment for cardiomyopathy type (p = 0.007, HR = 0.45) and after adjustment for cardiomyopathy type (p = 0.009, HR = 0.67).

Conclusion: CMR identifies distinct phenotypes of female CRT patients with non-ischemic and ischemic cardiomyopathy relative to male patients stratified by cardiomyopathy type. The more favorable short-term response and long-term survival outcomes in female heart failure patients with CRT were associated with lower indexed CMR-based LV volumes, decreased presence of scar associated with prior myocardial infarction and ICM, and greater CMR-based dyssynchrony with the CURE-SVD.

KEYWORDS

sex differences, magnetic resonance imaging, heart failure, cardiac resynchronization therapy, implantable cardioverter defibrillator

Introduction

Cardiac resynchronization therapy (CRT), a pacing therapy used to treat chronic systolic heart failure (HF) and wide QRS complexes (1, 2), has been shown to improve left ventricular function, New York Heart Association (NYHA) functional class, HF hospitalization rates, and overall survival (3–8); however, non-response to CRT is a significant challenge, as 30–50% of patients do not meet standard response criteria for this therapy (9). Prior studies have noted differences in cardiac structural characteristics of male and female heart failure patients undergoing CRT such as left ventricular (LV) size (10–14) with demonstration, for example, of better clinical outcomes in the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study (15) and a sub-study of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) (16). An important limitation of prior work in this area is that the studies have been based largely on echocardiography. In this regard, analyses based on well-curated datasets with cardiac magnetic resonance (CMR) data, response findings based on exercise peak VO_2 data (17, 18) and laboratory data such as B-type natriuretic peptide (BNP) (19), and long-term clinical outcomes are needed to provide a better understanding of the mechanisms associated with heart failure response in men and women.

In the present study, we hypothesized that scar presence associated with prior myocardial infarction, LV/RV size and function by CMR cine imaging, and the validated CURE-SVD CMR strain parameter (20) calculated using cine displacement encoding with stimulated echoes (DENSE) would be among the key explanatory parameters from CMR to provide an understanding of sex-based differences in CRT response. Furthermore, we hypothesized that cardiomyopathy etiology (non-ischemic versus ischemic) would also be important in defining mechanistic differences in female and male patients not only on the basis of the prevalence of each etiology in men and women, but also in relation to differences in each cardiomyopathy type in women versus men. In this sense, we also aimed to define CMR phenotypes among CRT candidates for female non-ischemic cardiomyopathy, male non-ischemic cardiomyopathy, female ischemic cardiomyopathy, and male ischemic cardiomyopathy. These hypotheses and aims were addressed using a single-center dataset with all the features described above.

Materials and methods

Study design, cohort selection, and informed consent

This research was approved by the Institutional Review Board for Human Subjects Research at the University of Virginia (UVA) and conducted over a 10-year period from 2011 to 2021

during which all patients provided informed consent. Inclusion criteria were LVEF 35% or less, New York Heart Association (NYHA) functional class II-IV, QRS > 120 ms, and a class I or class II indication for CRT based on AHA/ACC/HRS guidelines. Additionally, all patients received CRT defibrillators except for one who received a CRT pacemaker. The flow diagram that represents the design of the observational study is shown in **Figure 1**.

Baseline patient characteristics

Before CRT implantation at the UVA Health System, patients completed intake forms to document their demographic characteristics, comorbid conditions, and medications; these data were confirmed by cross-checking electronic medical records. Baseline characteristics included age, sex, race, and comorbid conditions (in addition to heart failure). These comorbid conditions included hypertension, atrial fibrillation, chronic kidney disease, diabetes mellitus, prior coronary artery bypass grafting surgery, and ischemic cardiomyopathy (ICM). In this study, ICM was defined as cardiomyopathy associated with prior myocardial infarction and significant contribution of ischemic heart disease to LV dysfunction. Prior infarction was also assessed with late gadolinium enhancement (LGE) on CMR. In the majority of cases, LGE was in an ischemic distribution. Prescribed medications at the time of CRT implantation, including beta-blockers, ACE inhibitor/angiotensin receptor blockers, loop diuretic usage and dosage, digoxin, and statins, were also extracted from the electronic health record. Patients received laboratory studies (including BNP, creatinine, sodium, and hemoglobin), blood pressure assessments, and exercise testing before the CRT procedure. Electrocardiographic data such as QRS duration and bundle branch block morphology were documented from 12-lead ECGs prior to CRT.

Features recorded at baseline and 6 months after cardiac resynchronization therapy

Cardiopulmonary exercise testing was performed at baseline and again 6 months after CRT for patients able to exercise. The peak VO_2, VE/VCO_2 slope, and respiratory exchange ratio were recorded. Echocardiography with standard 2D echocardiographic images were obtained for all patients at baseline and 6 months after CRT, and volumetric measurements indexed for body surface area were calculated using standard methodology (21). CMR examinations were performed for all patients before CRT and for 38% of patients 6 months after CRT. The CMR protocol included steady-state free precession cine imaging, cine DENSE, and LGE. Circumferential strain from cine DENSE was calculated semiautomatically to determine CURE-SVD (range, 0–1, 1 = greatest synchrony). In patients with CMR performed 6 months after CRT, CMR cine imaging was used to calculate the change in LV function, while echocardiographic measurement before and after CRT were used for this purpose in other patients.

Post-cardiac resynchronization therapy response measures

As CRT response can be assessed in several ways, three different measures of CRT response were recorded at 6 months based on LV function, the neurohormonal axis, and exercise capacity, respectively. With respect to LV function, the fractional change in the LVESVI (LVESVI-FC) was defined as the (post-CRT LVESVI – baseline LVESVI)/baseline LVESVI, such that a more negative number reflected smaller (more favorable) post-CRT LV volumes. Pre-CRT and post-CRT MRIs were used to determine the LVESVI-FC in the 38% of patients who received post-CRT MRIs, while pre-CRT and post-CRT echocardiograms were used to determine the LVESVI-FC in the remaining 62% of patients.

With respect to the neurohormonal axis, the BNP post-CRT was log-transformed and used instead of the absolute BNP levels because it was considered a more meaningful parameter, as BNP values can range from less than 100 to over 5,000 pg/mL. The post-CRT BNP was used rather than a ratio measure based on prior analyses demonstrating the importance of the post-CRT value of the BNP relative to any ratio measure. With respect to exercise capacity, the change in peak oxygen output (Δ peak VO_2 = VO_2 post-CRT – VO_2 pre-CRT) was calculated. These response measures were calculated and reviewed by the data analysts without knowledge of patient outcomes.

Statistical analysis

Missing data

Only 2% of the imaging-based parameters (CURE-SVD and ventricular volumes) gathered before the CRT procedure were missing and were imputed using their respective median values. The change in peak VO_2 was missing in 20% of patients since some patients had difficulty exercising both before and after CRT. The expectation maximation (EM) algorithm for matrix completion was used to impute these missing measures (22). The **Supplementary material** describes this imputation technique in more detail.

Statistical tests and linear regression with interaction term

With the complete data set, the cohort was stratified into males and females, and statistical tests were performed to identify the sex-based differences in clinical parameters and CMR findings in patients undergoing CRT. Chi-square tests

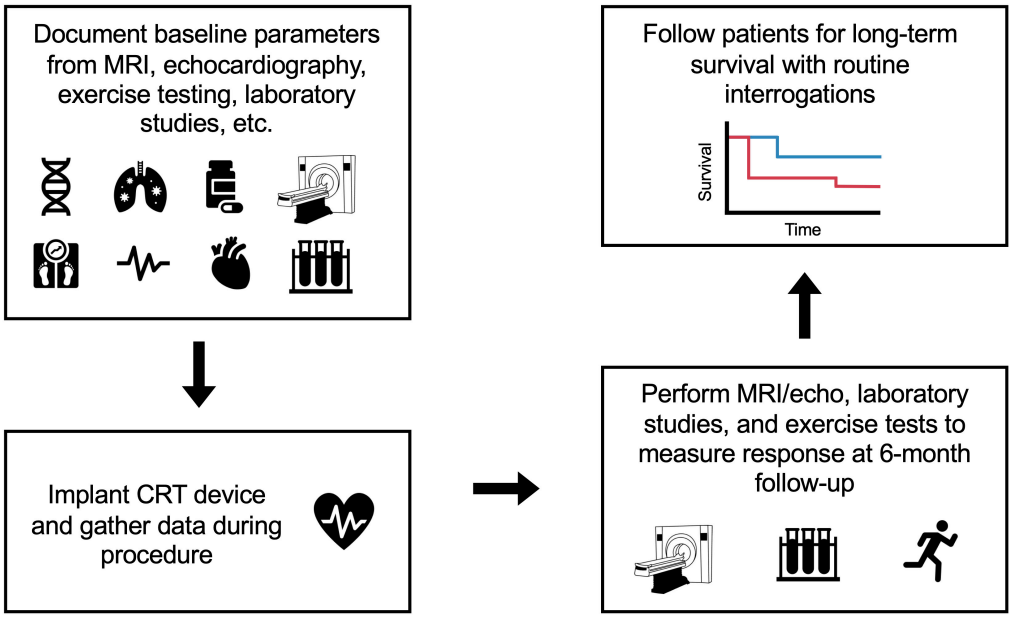

FIGURE 1
Flow diagram of the study design. Patients were enrolled over approximately a 10-year period from 2011 to 2021. Before CRT device implantation, the baseline parameters of the patients were recorded based on findings from MRI, echocardiography, electrocardiograms, exercise testing, and laboratory studies. Additional parameters (such as QLV which indicates late activation of LV pacing cite) were gathered during the CRT procedure. Six months after CRT, patients received follow-up MRI/echocardiograms, laboratory studies, and exercise testing to calculate response measures. Finally, patients were followed for long-term survival with routine interrogations.

were used to compare discrete variables between the two groups, while *t*-tests were used for comparisons of continuous variables. To assess the effect of sex, cardiomyopathy type, and their interaction on CRT response measures and survival, multivariable linear regression models were constructed with an interaction term. Linear regression models for CURE-SVD along with the three response measures were implemented using the *statsmodels* package in Python.

Survival analysis and exploring mechanisms of response

Kaplan–Meier analysis was used to construct survival curves of three stratifications of the data: males vs. females, males with ICM vs. females with ICM, and males with NICM vs. females with NICM. Log-rank tests were used to determine the *p*-values for the differences in survival among the groups, and Cox proportional hazards regression was used to calculate hazard ratios (HRs). The Kaplan–Meier analyses, log-rank tests, and Cox regression were performed using the *lifelines* package in Python. Finally, the data was split into four groups (males with ICM, females with ICM, males with NICM, and females with NICM), and intergroup differences among CURE-SVD, LVEDVI, RVEF, log-transformed pre-CRT BNP, LVESVI-FC, and log-transformed post-CRT BNP were calculated using ANOVA. Tukey tests were run to compare group means following a significant ANOVA.

Results

Baseline characteristics of entire cohort

Baseline characteristics for the 200 patients (age 66.1 ± 11.4 years; 27.0% female) are shown in **Table 1**. The median change in the LVESVI-FC following CRT was −0.18 (interquartile range −0.33 to −0.01). In terms of response, 56.0% of patients had 15% or greater reduction in the LVESVI post-CRT (LVESVI-FC ≤ -0.15). In the entire cohort, the median log-transformed post-CRT BNP level was 2.25 (IQR 1.77–2.77), and the median change in the peak VO_2 was 0.0 mL/kg/min (IQR −1.0–1.2). During a median follow-up of 3 years, 28 (14.0%) patients died.

Sex-based differences in clinical parameters, cardiac magnetic resonance findings, and cardiac resynchronization therapy outcomes

Significant differences among males (N = 146, 73.0%) and females (N = 54, 27.0%) were observed for the following baseline clinical parameters and CMR measures: weight ($p < 0.0001$), hemoglobin ($p < 0.0001$), presence of ischemic cardiomyopathy

TABLE 1 Baseline characteristics and CRT response measures of patient cohort and male vs. female.

	Cohort (N = 200)	Male (N = 146)	Female (N = 54)	P-value
Demographics				
Age, years	67.4 (58.0–74.0)	68.0 (59.9–75.0)	65.9 (56.0–72.0)	0.2
BMI	28.9 (25.4–33.7)	29.3 (25.8–32.9)	28.0 (23.3–36.4)	0.6
Weight (kg)	89.4 (75.1–103.0)	91.6 (80.7–105.2)	75.0 (58.4–95.8)	< 0.0001
Female	54 (27.0)			
NYHA heart failure class				0.5
II	73 (36.5)	56 (38.4)	17 (31.5)	
III	126 (63.0)	89 (61.0)	37 (68.5)	
IV	1 (0.50)	1 (0.6)	0 (0)	
Race				0.02
Black	27 (13.5)	14 (9.6)	13 (24.1)	
White/other	173 (86.5)	132 (90.4)	41 (75.9)	
Comorbid conditions				
Ischemic cardiomyopathy	87 (43.5)	77 (52.7)	10 (18.5)	< 0.0001
Hypertension	115 (57.5)	87 (59.6)	28 (51.9)	0.4
Atrial fibrillation	52 (26.0)	41 (28.1)	11 (20.4)	0.07
Chronic kidney disease	62 (31.0)	42 (28.8)	20 (37.0)	0.3
Diabetes mellitus	73 (36.5)	55 (37.7)	18 (33.3)	0.7
Prior CABG	35 (17.5)	33 (22.6)	2 (3.7)	0.004
Medications				
Beta-blocker	191 (95.5)	140 (95.9)	51 (94.4)	0.9
ACE inhibitor or ARB	175 (87.5)	127 (87.0)	48 (88.9)	0.9
Loop diuretic dose, mg				0.9
0	58 (29.0)	42 (28.8)	16 (29.6)	
20–40	90 (45.0)	67 (45.9)	23 (42.6)	
60–80	34 (17.0)	25 (17.1)	9 (16.7)	
> 100	18 (9.0)	12 (8.2)	6 (11.1)	
Digoxin	17 (8.5)	12 (8.2)	5 (9.3)	0.9
Statin	120 (60.0)	95 (65.1)	25 (46.3)	0.02
Laboratory studies, vital signs and exercise testing				
Systolic BP, mm Hg	118.0 (104.0–130.0)	120.0 (104.0–130.0)	114.0 (102.8–131.8)	0.7
Sodium, mEq/L	138.0 (137.0 –140.0)	138.0 (137.0–140.0)	138.0 (136.0–140.0)	0.2
Creatinine, mg/dL	1.1 (0.9–1.3)	1.1 (0.91–1.4)	1.0 (0.8–1.2)	0.001
Hemoglobin, g/dL	13.3 (12.3–14.7)	13.9 (12.6–14.9)	12.5 (11.5–13.7)	< 0.0001
GFR, mL/min/1.72 m^2	67.2 (54.1–84.1)	70.4 (57.7–85.0)	62.5 (52.2–76.0)	0.1
Log(BNP)	2.43 (2.11–28.0)	2.43 (2.19–2.79)	23.1 (1.96–2.83)	0.7
Peak VO_2, mL/kg/min	14.4 (12.5–15.7)	14.4 (12.8–16.5)	13.9 (11.5–15.0)	0.01
CMR and echocardiography assessment parameters				
LVEF, %	24.0 (17.7–30.5)	24.0 (17.6–29.0)	25.1 (18.7–33.1)	0.3
LVEDVI, mL/m^2	126.3 (102.5–157.0)	128.7 (105.3–162.1)	116.0 (98.4–135.7)	0.04
LVESVI, mL/m^2	93.7 (73.7–123.6)	95.9 (77.1–127.0)	86.7 (67.2–111.6)	0.06
RVEF, %	37.5 (25.8–45.6)	36.5 (25.7–44.1)	39.3 (25.9–55.1)	0.02
RVEDVI, mL/m^2	65.8 (52.9–83.1)	66.8 (54.8–83.1)	63.8 (48.0–81.2)	0.1
RVESVI, mL/m^2	38.8 (29.9–55.5)	39.7 (31.8–56.4)	37.3 (21.2–51.6)	0.05
LGE presence	95 (47.5)	87 (59.6)	8 (14.8)	< 0.0001
CURE-SVD	0.59 (0.45–0.76)	0.61 (0.47–0.77)	0.52 (0.40–0.72)	0.04
ECG parameters				
QRS, ms	158 (142–175)	160.0 (140.5–177.5)	155.0 (144.0–164.8)	0.2

(Continued)

TABLE 1 (Continued)

	Cohort (N = 200)	Male (N = 146)	Female (N = 54)	P-value
QLV, ms	120.0 (87.0–149.3)	110.0 (84.3–145.0)	130.0 (100.0–150.0)	0.3
LBBB	151 (75.5)	103 (70.5)	48 (88.9)	0.01
RBBB	22 (11.0)	21 (14.4)	1 (1.9)	0.02
Paced Rhythm	28 (14.0)	22 (15.1)	6 (11.1)	0.6
Upgrade or new device				0.1
De novo device	153 (76.5)	107 (73.3)	46 (85.2)	
Upgrade device	47 (23.5)	39 (26.7)	8 (14.8)	
Response measures at 6-months post-CRT				
Fractional change in LVESVI	−0.18 (−0.33 —0.01)	−0.17 (−0.31–0.015)	−0.23 (−0.41—0.07)	0.08
Log(BNP)	2.25 (1.77–2.77)	2.29 (1.80–2.78)	2.14 (1.75–2.58)	0.2
Change in Peak VO_2, mL/kg/min	0.0 (−1.0–1.2)	−0.025 (−1.4–1.3)	0.11 (−0.54–1.1)	0.6
Survival status at 3 years				0.02
Alive	172 (86.0)	120 (82.2)	52 (96.3)	
Dead	28 (14.0)	26 (17.8)	2 (3.7)	

Values are median (interquartile range) or n (%). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft; CURE-SVD, circumferential uniformity ratio estimate with singular value decomposition; GFR, glomerular filtration rate; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; NYHA, New York Heart Association; QLV, QRS-LV electrogram time; RBBB, right bundle branch block; RVEDVI, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end-systolic volume index.

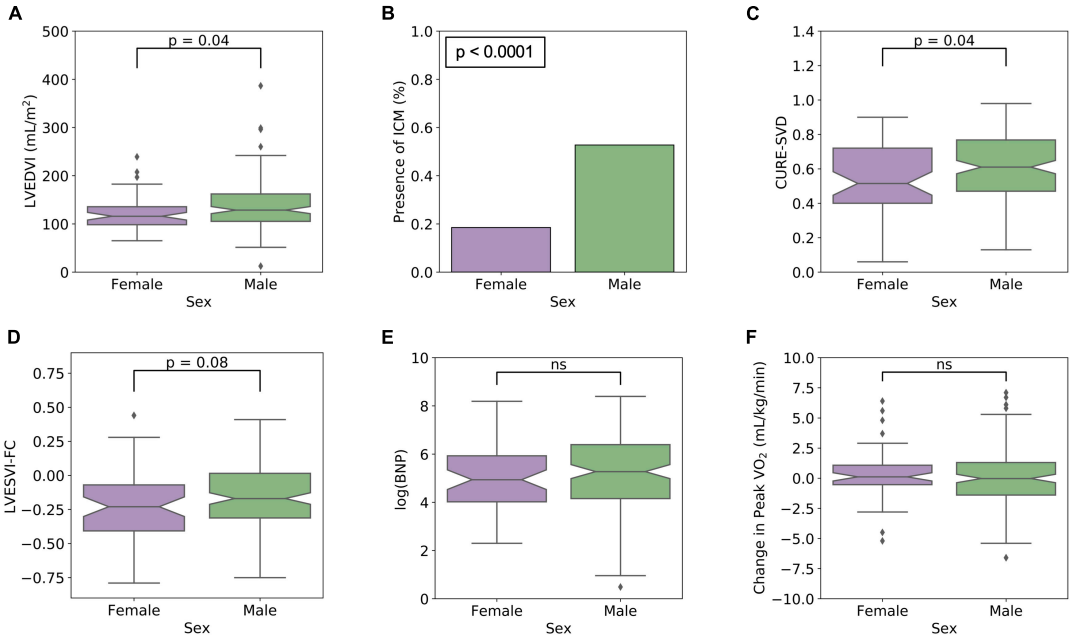

FIGURE 2
Significant pre-CRT CMR findings and post-CRT response measures stratified only by sex. **(A)** LVEDVI (p < 0.04), **(B)** ICM presence (p 0.0001), **(C)** CURE-SVD (p = 0.04) are highlighted as these parameters were found to be significantly different between males and females. Compared with males, females were more likely to have smaller LVEDVI, less frequency of ICM, and lower CURE-SVD. In **(D–F)**, the response measures stratified by sex only (as opposed to sex and cardiomyopathy type in **Figure 4**) are shown to be similar by group.

(p < 0.0001), presence of LGE (p < 0.0001), creatinine (p = 0.001), prior CABG (p = 0.004), peak VO_2 (p = 0.01), presence of LBBB and RBBB (p = 0.01, p = 0.02, respectively), RVEF (p = 0.02), African-American race (p = 0.02), the usage of a statin (p = 0.02), LVEDVI (p = 0.04), CURE-SVD (p = 0.04), and RVESVI (p = 0.05). Notched Box and Whisker plots (for LVEDVI and CURE-SVD) are shown in **Figures 2A,C** and a histogram (for ICM presence) is shown in

Figure 2B. Females demonstrated greater RVEF, smaller CMR-based LVEDVI, and more mechanical dyssynchrony based on CURE-SVD; they also had a lower frequency of both LGE and ischemic cardiomyopathy and a higher frequency of LBBB. The three CRT response measures stratified by sex only (as opposed to sex and cardiomyopathy type, as described later) are shown in Figures 2D–F. Median values of the response parameters were more favorable in females (more negative LVESVI-FC, lower post-CRT BNP levels, and higher Δ peak VO_2), but statistical tests for differences were not apparent without stratification by cardiomyopathy type. A statistically significant difference in time to survival during 3 years of follow-up was present with stratification by sex (p = 0.02) as 26 out of the 146 male patients (17.8%) died, but only 2 of the 54 female patients (3.7%) died.

Linear regression and the interaction of sex and ischemic cardiomyopathy on cardiac resynchronization therapy response measures

The results of the linear regression models are summarized in Table 2. The term representing the interaction of sex and ICM was significant for each of three different models with the following respective dependent variables: CURE-SVD (p = 0.004), LVESVI-FC (p = 0.008), and log(post-CRT BNP) (p = 0.02). The following two observations are highlighted based on these models.

1. In the CURE-SVD model, the effect of being male (sex = 1) decreased CURE-SVD by 0.23 [coefficient of interaction term = -0.23 (CI: −0.39 to −0.076)] when ICM was present, though the ICM coefficient [0.23 (CI: 0.09–0.37)] nearly negated this effect; therefore, for males with ICM (sex = 1, ICM = 1), the only term in the regression model was that of sex [0.11 (CI: 0.03–0.19)] along with the intercept [0.50 (0.44–0.56)]. When ICM was not present in males, a similar relationship was found as the only term remaining in the model was for sex [0.11 (CI: 0.03–0.19)]. Furthermore, the larger effect was observed in females since the female sex (sex = 0) offset both the sex-only term and interaction term, leaving only the ICM term [0.23 (CI: 0.09–0.37)] and intercept. This indicated that females without ICM expressed the lowest CURE-SVD scores.
2. These relationships were similar in the regression models for LVESVI-FC and log(post-CRT BNP). The effect of the female sex drove LVESVI-FC and log(post-CRT BNP) lower, which are both favorable responses, with NICM females having smaller predicted values compared to ICM females; on the other hand, being male resulted in greater predicted LVESVI-FC and log(post-CRT BNP) values regardless of the presence of ICM.

TABLE 2 Linear regression models with interaction term.

Model variable	Model coefficient (95% CI)	*P*-value
(A) CURE-SVD		
Intercept	0.50 (0.44 to 0.56)	$p < 0.0001$
Sex	0.11 (0.03 to 0.19)	0.006
ICM	0.23 (0.09 to 0.37)	0.001
Sex × ICM	−0.23 (−0.39 to −0.076)	0.004
(B) LVESVI-FC		
Intercept	−0.28 (−0.35 to −0.21)	$p < 0.0001$
Sex	0.097 (0.0071 to 0.19)	0.03
ICM	0.30 (0.14 to 0.46)	0.0004
Sex × ICM	−0.25 (−0.43 to −0.067)	0.008
(C) Log(post-CRT BNP)		
Intercept	4.7 (4.2 to 5.2)	$p < 0.0001$
Sex	0.60 (−0.017 to 1.2)	0.06
ICM	1.4 (0.33 to 2.6)	0.01
Sex × ICM	−1.5 (−2.7 to −0.25)	0.02
(D) Δ Peak VO_2		
Intercept	0.53 (−0.17 to 1.2)	0.1
Sex	−0.66 (−1.6 to 0.23)	0.1
ICM	−1.4 (−3.0 to 0.21)	0.09
Sex × ICM	1.7 (−0.039 to 3.6)	0.06

Response measures and survival with stratification by sex and cardiomyopathy type

Figures 3A–F show results for CURE-SVD, pre-CRT LVEDVI, RVEF, log(pre-CRT BNP), LVESVI-FC, and log(post-CRT BNP) with the patients stratified by sex and cardiomyopathy type, effectively dividing the cohort into four groups (ICM males, ICM females, NICM males, and NICM females). Intergroup differences were significant among CURE-SVD (Figure 3A, p = 0.003), log-transformed pre-CRT BNP (Figure 3D, p = 0.01), LVESVI-FC (Figure 3E, p = 0.0006), and log-transformed post-CRT BNP (Figure 3F, p = 0.05). The Tukey *post hoc* analysis demonstrated that the CURE-SVD scores of NICM females were lower than those for ICM females along with ICM and NICM males ($p < 0.05$, Figure 3A). The log(pre-CRT BNP) was lower in NICM females compared with that in ICM females and ICM males ($p < 0.05$, Figure 3D). The LVESVI-FC was lower in NICM females compared with that in ICM females and ICM males ($p < 0.05$, Figure 3E). The log(post-CRT BNP) was lower in NICM females compared with that in ICM males (p = 0.05, Figure 3F).

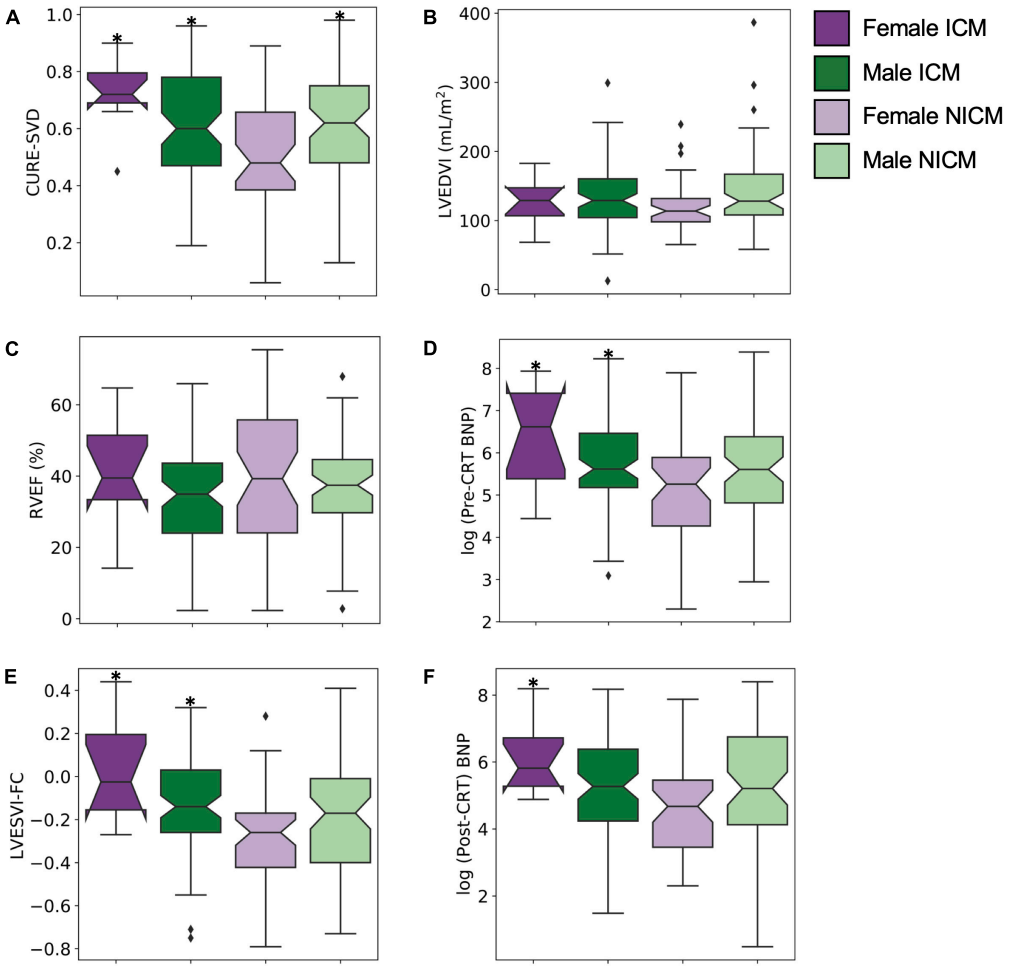

FIGURE 3
Differences in dyssynchrony, LV size, RV function, hormonal activity, and CRT response measures among cohort stratified by sex and cardiomyopathy type. **(A)** CURE-SVD, **(B)** pre-CRT LVEDVI, **(C)** RVEF, **(D)** log(pre-CRT BNP), **(E)** LVESVI-FC, and **(F)** log(post-CRT BNP) were compared among the four different groups (females with ICM, males with ICM, females with NICM, and males with NICM) using ANOVA. Significant differences between group means were noted for **(A)** CURE-SVD (p = 0.003), **(D)** log(pre-CRT BNP) (p = 0.01), **(E)** LVESVI-FC (p = 0.0006), and **(F)** log(post-CRT BNP) (p = 0.05). The Tukey *post hoc* analysis demonstrated differences for pairwise comparisons with *$p < 0.05$ with the NICM female group as the reference.

Greater QRS duration was associated with improved LVESVI-FC (p = 0.008) but not after adjustment for CURE-SVD; QRS duration was not associated with post-CRT BNP levels or change in peak VO_2 after CRT. Additionally, QRS duration was not significantly different between males and females or among the four phenotypes. RBBB (p = 0.03) was associated with suboptimal LVESVI-FC.

The Kaplan–Meier survival curves for three stratifications of the data [(**A**) males vs. females, (**B**) males with ICM vs. females with ICM, and (**C**) males with NICM vs. females with NICM] are shown in Figure 4. Overall, females had better survival than males over 3 years of follow-up with p = 0.007 and HR = 0.45 (Figure 4A). While the Cox proportional hazards analysis showed just a borderline improvement in survival for females with ICM relative to males with ICM (p = 0.17, HR = 0.91, Figure 4B), females with NICM had a more marked improvement in survival relative to males with NICM (p = 0.009, HR = 0.67, Figure 4C).

Figure 5 presents the possible mechanisms underlying sex-differences in CRT outcomes by illustrating the relationship between the significant pre-CRT parameters and post-CRT response measures. Figure 5A shows a scatterplot of CURE-SVD versus LVESVI-FC, and the points are colored and shaded based on their one of four group assignments. There is a greater proportion of dark purple versus light purple points in the highlighted appear in the highlighted upper right-hand corner (larger CURE-SVD and positive, unfavorable LVESVI-FC), while there is a greater proportion of light purple versus dark purple points in the highlighted lower left-hand corner (lower CURE-SVD and negative, favorable LVESVI-FC). This

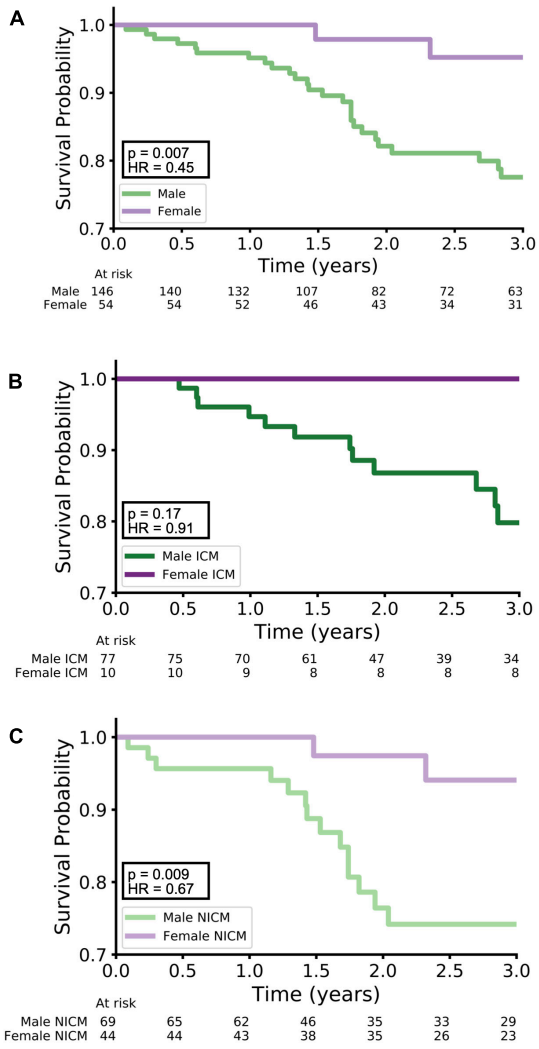

FIGURE 4
Kaplan–Meier survival curves. Kaplan–Meier curves for survival are shown with stratification by: **(A)** males vs. females, **(B)** males with ICM vs. females with NICM, and **(C)** males vs. NICM versus females with NICM. Females had better survival than males (**A**, p = 0.007, HR = 0.45), and females with NICM had better survival than males with NICM (**C**, p = 0.009, HR = 0.67). There was no significant difference in survival between females with ICM and males with ICM (**B**, p = 0.17, HR = 0.91).

indicates that ICM played a role in LVESVI-FC. Furthermore, many of the green points appear in the highlighted upper right-hand corner while many of the purple points appear in the highlighted lower left-hand corner; this demonstrates the role of sex in LVESVI-FC and suggests that the mechanism for more favorable responses in females is their smaller CURE-SVD scores. The scatterplot of log-transformed pre-CRT BNP levels versus log-transformed post-CRT BNP levels shown in **Figure 5B** exhibited similar trends. This graph suggested that sex plays a role in post-CRT BNP levels and that the mechanism for more favorable responses in females is their smaller pre-CRT BNP levels.

Discussion

Summary of differences in outcomes after cardiac resynchronization therapy by sex

The analysis based on an observational study with CMR provides novel insights into possible mechanisms previously unexplored with respect to CRT outcomes in males versus females.

1. Females had smaller CMR-based left ventricular end-diastolic volume indices and more dyssynchrony based on the CURE-SVD determined with DENSE.
2. Females were less likely to have ischemic cardiomyopathy and had less LGE compared with males.
3. Females had more favorable right ventricular ejection fractions and were more likely to have LBBB.
4. Females had greater improvements in LV function after CRT.
5. Females had a better 3-year survival probability.

Cardiac magnetic resonance-derived CURE-SVD and B-type natriuretic peptide explain sex-differences in cardiac resynchronization therapy outcomes

The CURE-SVD measures the extent of simultaneous contraction (negative circumferential strain) and stretch (positive circumferential strain) in LV segments using CMR (23). It ranges between 0 and 1, and values closer to 0 indicate greater dyssynchrony. In our present study, females generally had lower CURE-SVD (and thus more dyssynchrony) than males while the female NICM group had the lowest CURE-SVD among all the groups. Our group has previously demonstrated the effectiveness of CURE-SVD in predicting LV functional improvement (LVESVI-FC) in CRT within prior cohorts and has shown that a lower CURE-SVD correlates with a more favorable LVESVI-FC (23–27); however, CURE-SVD's association with female sex is a new finding. This association provides a possible mechanistic insight as to why females are more likely to have more beneficial outcomes after CRT – they have greater degrees of dyssynchrony and consequently experience more favorable changes in LV functional improvement from ventricular resynchronization. Additionally, in the NICM female group, an even more favorable LVESVI-FC was observed due to both a lower CURE-SVD and the absence of scar from prior myocardial infarction. Our group

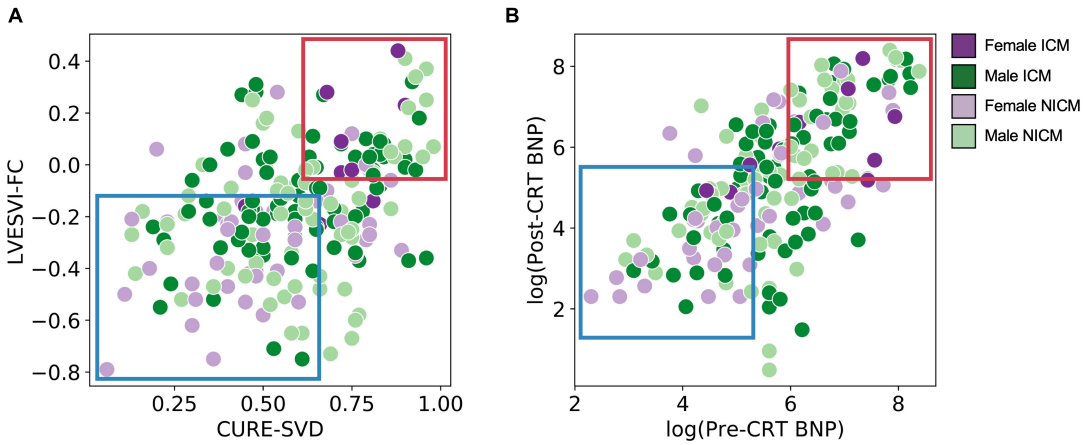

FIGURE 5
Scatter plots of pre-CRT parameters versus post-CRT response measures for stratified cohort. **(A)** CURE-SVD versus LVESVI-FC for all patients is shown with color and shade based on grouping. Many of the darker points (ICM) appear in the highlighted upper right-hand corner (larger CURE-SVD and positive, unfavorable LVESVI-FC) while many of the lighter points (NICM) appear in the highlighted lower left-hand corner (lower CURE-SVD and negative, favorable LVESVI-FC). Many of the green points (male) appear in the highlighted upper right-hand corner while many of the purple points (female) appear in the highlighted lower left-hand corner. **(B)** log(pre-CRT BNP) versus log(post-CRT BNP) is shown and exhibits similar trends. The plot in panel **(A)** demonstrates clustering of LVESVI-FC and CURE-SVD by sex/cardiomyopathy group, while the plot in panel **(B)** demonstrates differences in BNP by sex/cardiomyopathy group.

has previously shown that ICM decreases the success of CRT as non-conductive scar from prior myocardial infarction hinders travel of the paced electrical impulses. Therefore, because females are more likely to have a lower CURE-SVD and less likely to have ICM, they respond better to CRT.

Another interesting finding concerned neurohormonal activity measured as the logarithm of serum BNP levels before CRT implantation. In our current study, we report that the female NICM group had lower levels of pre-CRT BNP compared with the male ICM and female ICM groups. This is rather striking as other studies in non-CRT cohorts have shown that BNP levels are lower in males than in females and increase with age (28, 29). Incidentally, age was not different between the male and female groups within our cohort. Furthermore, obesity, renal disease and kidney dysfunction are known to influence BNP levels (30, 31), yet these parameters were not significant among sex within our cohort. We along with others have shown that lower levels of BNP are correlated with better CRT response (19, 27), and since in our current cohort, and as the NICM females in our cohort had the lowest BNP levels, this measure may mechanistically explain the better outcomes of NICM females. Still, our findings of lower BNP levels in females with no difference in age or kidney function coupled with favorable outcomes warrant further investigation.

Cardiac magnetic resonance phenotypes for female non-ischemic and ischemic cardiomyopathies

These findings lead to interesting observations regarding the underlying mechanisms of the observed sex-based differences in CMR findings and CRT response measures in this study. In particular, we have shown that a particular phenotype of female non-ischemic cardiomyopathy was characterized by a more favorable CURE-SVD (more dyssynchrony) at baseline and lower baseline pre-CRT BNP levels. We also showed that this phenotype exhibited more favorable responses to CRT with a more favorable LVESVI-FC and lower log(post-CRT BNP). Taken together, these findings suggest that sex-related differences in CMR-derived CURE-SVD and BNP serum levels define distinct female ischemic and non-ischemic cardiomyopathy phenotypes and may explain differences in survival and outcome, although these findings must be interpreted in the context of the observational study design, which establishes associations rather than causal relationships.

Furthermore, the CURE-SVD parameter has proven to be a robust tool in predicting CRT response and may be worth considering during patient selection for the therapy, as we have shown that it reliably predicts response, survival, and arrhythmia risk in patients undergoing CRT implants, even after adjustment for clinical risk models (23–25). A primer for DENSE and CURE-SVD for cardiologists is also available as Supplementary material in a recent publication (24).

Importance of sex in cardiac resynchronization therapy guidelines and future clinical trials

The results of this study highlight the importance of considering the impact of a patient's sex and cardiomyopathy etiology when evaluating the patient for CRT. After adjustment by cardiomyopathy etiology, male patients had

less favorable outcomes and lower, which may be an important consideration in the timely allocation of evidence-based medical therapies in patients with heart failure undergoing CRT. Our study also underscores the need for the inclusion of more females in CRT research studies and clinical trials; females evidently differ in their response to CRT, and more information may be helpful in further specifying CRT treatment based on sex in the context of cardiomyopathy etiology.

Limitations

Our study cohort included 54 females out of a total of 200 patients (27.0%), and only 10 of those females had ICM. A larger number of females may strengthen the connections that we observed between sex, CMR finding, and CRT outcomes. We also acknowledge that medical therapy for heart failure continues to evolve (i.e., more patients are being prescribed sodium-glucose cotransporter-2 inhibitors and angiotensin-neprilysin inhibitors). Longitudinal studies of outcomes for devices in heart failure with long-term follow-up may lag behind adoption of novel medical therapies, and sex-based differences in outcomes may change as medical therapies change. For example, angiotensin-neprilysin inhibitors have been shown to increase BNP expression (32). We acknowledge the potential for bias in any cohort study. In this study, we wanted to minimize that chance that analysis of response measures would be influenced by a knowledge of patient outcomes. We did this by ensuring that response measures were determined independently without knowledge of patient outcomes. Finally, our cohort underwent traditional CRT implants with defibrillators, and we did not consider patients with conduction system pacing; however, an evaluation of sex-related differences in parameters of interest in a cohort of patients with conduction system pacing is planned in the future.

Data availability statement

The datasets presented in this article are not readily available because use of the dataset is restricted to users at the author's institution. Requests to access the datasets should be directed to KB, bilchick@virginia.edu.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Virginia Institutional Review Board for Human Subjects Research. The patients/participants provided their written informed consent to participate in this study.

Author contributions

DB and KB contributed to the study conception, data analysis, and writing of the manuscript. ST, MA, PO, and XG contributed to the data analysis and a critical review of the manuscript. RM, AD, OM, JM, and PM contributed to the study conception and enrollment of patients. SM, MS, CK, FE, and JH contributed to the critical review of the manuscript. PO and FE contributed to the study conception. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1007806/full#supplementary-material

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Sex, Rhythm & Death: The effect of sexual activity on cardiac arrhythmias and sudden cardiac death

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Arrhythmias and sudden cardiac death with sexual activity are rare. However, the demographics are changing regarding the cardiovascular patients at risk for these events. Recent studies have highlighted that the individuals having cardiac events during sexual activity are becoming younger, with a higher proportion of female decedents than previously described. There needs to be an open dialog between the cardiovascular team and the cardiac patient to provide the education and reassurance necessary for cardiovascular patients to participate in sexual intercourse safely. This paper reviews how sexual activity can lead to an increase in cardiac arrhythmias and sudden cardiac arrest in patients that are not medically optimized or are unaware of their underlying cardiac condition. The most common cardiovascular diseases associated with sexually induced arrhythmias and arrest are discussed regarding their potential risk and the psychosocial impact of this risk on these patients. Finally, cardiovascular medications and implantable cardioverter-defibrillators (ICDs) are addressed by reviewing the literature on the safety profile of these cardiac interventions in this patient population. Overall, sexual activity is safe for most cardiac patients, and providing proper education to the patient and their partner can improve the safety profile for patients with higher risk cardiovascular conditions. To give the appropriate education and reassurance necessary, cardiovascular team members need an understanding of the pathophysiology of how sexual activity can provoke arrhythmias and sudden cardiac arrest. Healthcare providers also need to build comfort in speaking to all patients and ensure that sexual partners, female patients, and those in the LGBTQIA + community receive the same access to counseling but tailored to their individual needs.

KEYWORDS

arrhythmias, sudden cardiac death, sudden cardiac arrest, sex, sexual activity

Introduction

Although it is rare, there is considerable trepidation regarding cardiac arrhythmias and sudden cardiac death with sexual activity. This apprehension is not only present in patients with cardiovascular disease but also patients with no known risk factors for arrhythmias or sudden cardiac death. In a recently published study in JAMA, when reviewing 6,847 sudden cardiac deaths across twenty-six years in London, the risk of death during or within an hour of sex was rare (0.2%). However, this study differed from previous studies due to the lower average age of patients at risk and the higher proportion of female decedents (1). While this study was reassuring, it highlights the changing demographic and phenotype of the cardiovascular patient at risk for cardiac arrhythmias and sudden death during sex.

In 2012, the American Heart Association (AHA) published a scientific statement paper on sexual activity and cardiovascular disease (CVD) (2). Despite the overall change in the profile of the cardiovascular patient at risk for arrhythmias and sudden cardiac death during sexual activity, there has not been an AHA update, and this topic is rarely discussed in guidelines (3, 4). As we improve our ability to treat heart disease to decrease morbidity and mortality, we also need to improve awareness and education about how our interventions impact sexual activity in patients at risk for arrhythmias and sudden cardiac death. Sexual activity is a vital component of a patient's social environment and greatly impacts overall quality of life. Patients with cardiovascular disease and their partners often have questions regarding sexual activity. When these issues are not adequately addressed, depression and anxiety can ensue, which can indirectly worsen clinical outcomes. Clinicians need more knowledge and specific practical training in providing information on sexual matters and counseling patients with various cardiovascular diseases (5–7).

Patients and their partners can have various concerns ranging from sexual performance to concerns about exacerbation of their disease process, which can decrease the frequency of sexual activity or lead to the complete cessation of sexual activity due to fear and anxiety. To explore sexual counseling needs, sexual concerns, and sexual activity of patients with heart failure, a survey study of 45 patients showed that the majority (77%) did not discuss sexual concerns with a health care professional. Sexual concerns included erectile problems (74%), partner overprotectiveness (63%), orgasmic difficulties (51%), lack of sexual interest (42%), and partner fear of sex (36%) (8).

The taboo regarding arrhythmias and sudden cardiac death during sex can extend past the patient and their partner and can also impact clinicians. Health care professionals often feel uncomfortable discussing sexual activity with their patients, particularly female patients and those in the LGBTQIA + community. In a small study of women postmyocardial infarction, many resumed sexual activity without guidance from their physicians. And when a discussion was held about resuming sexual activity the patients usually initiated the conversation (9).

This paper reviews the prevalence and physiology of arrhythmias and sudden cardiac death with sexual activity, and the steps healthcare professionals need to take to provide reassurance while maintaining safety in patients at risk for arrhythmias and sudden cardiac death.

The pathophysiology of arrhythmias and sudden death during sex

Arrhythmias induced during sexual activity is postulated to occur due to increased sympathetic activation or ischemia due to increased myocardial oxygen demand related to increased physical activity. Patients with channelopathies and inherited cardiomyopathies are more at risk for arrhythmias due to increased sympathetic activation. Whereas those with ischemic heart disease are at increased risk of arrhythmias due to increased myocardial demand during physical activity.

In individuals with channelopathies the pathophysiology on how sympathetic activation precipitates sudden cardiac death varies greatly. In people with Brugada syndrome (BrS) there are multiple theories on the role of the sympathetic nervous system as a potential precipitant of sudden cardiac arrest. These people tend to have reduced cAMP and norepinephrine concentrations found in endomyocardial biopsies, ECG fluctuations with autonomic modulation and a higher incidence of cardiac arrest at night suggesting that cardiac vagal tone may have a significant contribution to arrhythmias in people with BrS (10). Whereas as individuals with Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) have polymorphic VT from adrenergic stimulation from physical or emotional stressors from an inherited dysfunction in the handling of calcium ions by the sarcoplasmic reticulum in myocardial cells (11). Conversely, Long QT syndrome (LQTS) is a heterogenous group of channelopathies that have genetic mutations associated with cardiac repolarization leading to prolongation of the QT on the surface electrogram that can lead to sudden cardiac death from Torsades de Pointes (TdP). Although there are many precipitants for TdP in patients with LQTS the patients at the greatest risk from risk of SCD with sexual activity are those with LQT1 and LQT2 which can be triggered by physical activity or emotional stress respectively (12).

Inherited cardiomyopathies such as Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) and Hypertrophic Cardiomyopathy (HCM) can have varied risk profiles in regards to sudden cardiac death based on phenotypic expression, predominant genetic mutation and progression of disease over

time. ARVC is an inherited cardiomyopathy that is characterized by the fibrofatty infiltration of the right ventricle but can also infiltrate the left ventricle (13). As this disease progresses patients are at a greater risk for ventricular arrhythmias that can lead to sudden cardiac death. These ventricular arrhythmias are often precipitated by physical exertion and emotional stress. HCM can have a similar clinical presentation with physical activity as a trigger for ventricular arrhythmias and sudden cardiac death, but this cardiomyopathy arises from mutations of the sarcomeric proteins manifesting phenotypically as left ventricular hypertrophy (14).

Finally, ischemic heart disease whether from atherosclerotic heart disease, coronary vasospasm, myocardial bridging or anomalous coronary arteries can cause acute ischemia when there is an increased metabolic demand placed on the heart due to physical activity such as sex which often manifests as chest pain but can rarely present as ventricular fibrillation or polymorphic ventricular tachycardia.

Sex as a metabolic equivalent and its risk of arrhythmias or sudden cardiac death

Sexual activity is considered to require a low to moderate metabolic equivalent of task (MET), but even mild physical activity in a de-conditioned patient with cardiovascular disease while trying to achieve an orgasm during coitus can precipitate arrhythmias or sudden cardiac death (**Figure 1**).

When counseling cardiovascular patients, prior to the patient participating in sexual activity, the clinician should ensure that the patient can perform between three to five METs of activity without symptoms. This number is derived from a trial measuring metabolic expenditure in 10 healthy married couples aged 25–43 engaged in foreplay to orgasm and performing various sexual activities and positions during coital and non-coital stimulation by their partner or through self-stimulation (15). If the clinician is unsure from a patient's history, exercise stress testing can be performed to assess if the patient can achieve three to five METs without symptoms or arrhythmias. Although most patients do not have arrhythmias during sex, in one study, 71% of patients who did experience arrhythmias during near-maximal exercise testing also had arrhythmias during sexual intercourse (15, 16). However, the risk of lethal or hemodynamically significant arrhythmias is rare, with the most reported arrhythmia during sexual activity being ectopic ventricular depolarizations (15, 16).

Most patients with cardiovascular disease can have sex safely without clinical arrhythmias or sudden cardiac death. Even in patients with a known diagnosis of supraventricular tachyarrhythmias, sexual activity is safe and reasonable in well-controlled patients (2). Despite the rare incidence of arrhythmias and sudden cardiac death during sex, some conditions have a higher likelihood of arrhythmias or sudden cardiac death during coitus. This information should be disclosed to the patient and their partner in a reassuring manner that improves safety but diminishes anxiety. The demographic most likely patient to experience sudden cardiac death during coitus is a middle-aged man engaging with a younger partner during an extramarital affair in an unfamiliar setting with a preponderance of ischemic heart disease (17, 18). However, these are not the only patients that benefit from counseling regarding sexual activity. As we improve outcomes in patients with congenital heart disease, channelopathies, non-ischemic structural heart disease and inherited cardiovascular syndromes; counseling regarding sexual activity impacts decreases the likelihood of a rare cardiac in addition to giving these patient the reassurance needed to improve their quality of life and decrease anxiety about childbearing.

Cardiovascular syndromes at risk for arrhythmias and sudden cardiac death during sex

Ischemic heart disease

Arrhythmias associated with ischemic heart disease include supraventricular arrhythmias (such as atrial fibrillation) and sudden cardiac death due to ventricular tachycardia and fibrillation. Patients with ischemic heart disease often receive counseling about safely resuming sexual activity to prevent recurrent angina or myocardial infarction; although counseling regarding arrhythmias and the importance of bystander cardiopulmonary resuscitation (CPR) for their partner, while important, is rarely provided. Although sex-associated death is rare and nearly universally witnessed, there is almost a five-fold lower survival rate due to the low rate of bystander CPR (18). Educating a partner on bystander CPR not only has the potential to save the patient's life but can also decrease fear and anxiety associated with sex and increase the frequency of sexual activity. A review of sexual activity in women after a myocardial infarction showed a reduced desire and decreased frequency of sexual activity due to fear of death during sexual activity (19).

Patients with ischemic heart disease should also be counseled on using recreational sexual enhancers due to their ability to potentiate arrhythmias. **Figure 2** is a tracing of an ICD interrogation of our patient with ischemic heart disease. He used amyl nitrite, also known as "poppers," which is sometimes used due to its dilatory effects but can also markedly increase heart rate and AV node conduction in these patients leading to tachyarrhythmias such as atrial fibrillation with rapid ventricular rates that can cause pre-syncope or angina during

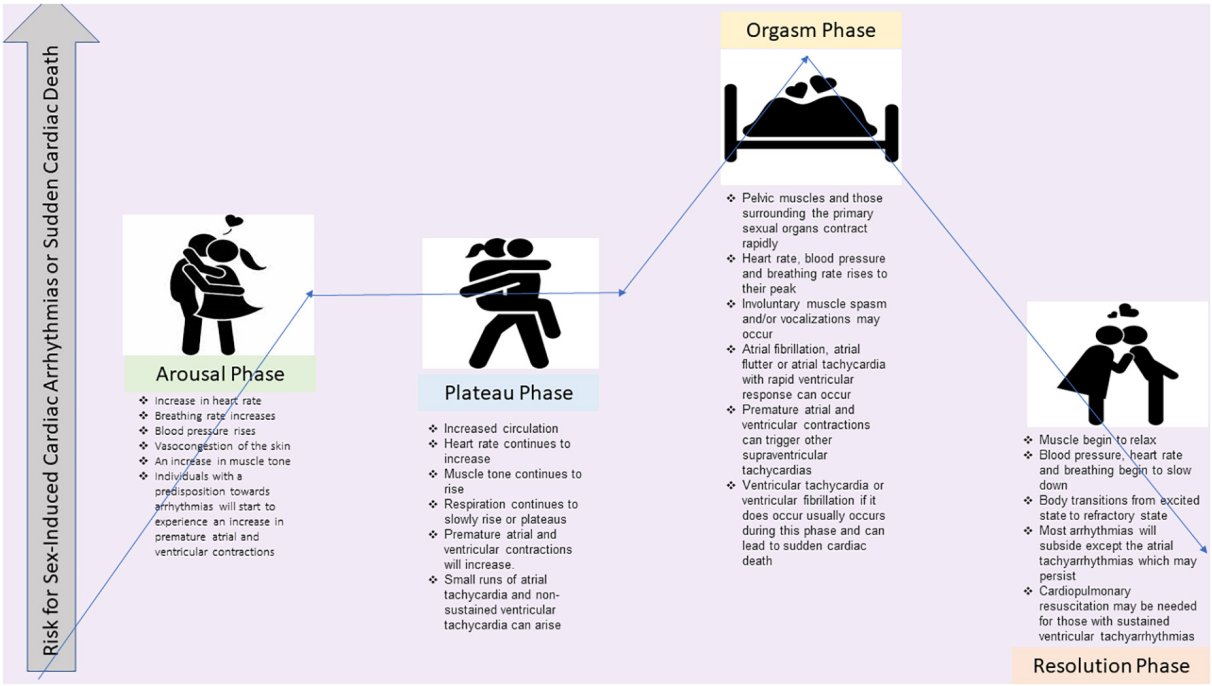

FIGURE 1
The illustration shows the four phases of sexual intercourse and the potential risk for sex-induced cardiac arrhythmias or sudden cardiac death for each phase. References are Bohlen et al. (15) and Masters and Johnson (16).

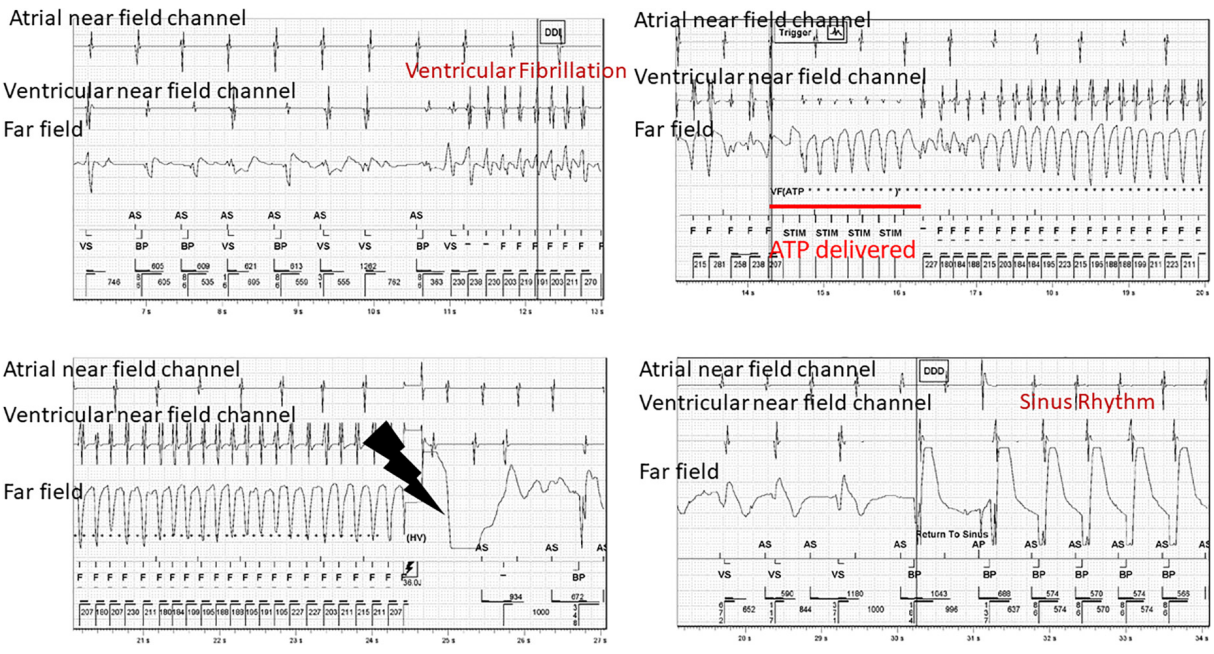

FIGURE 2
Device tracings of a 70 year old male with ischemic heart disease and prior myocardial infarction who experienced ventricular fibrillation that resulted in delivery of anti-tachycardia pacing and then eventually defibrillation. This event occurred during sexual activity. AS, atrial sensing; VS, ventricular sensing, F, fibrillation zone; STIM, anti-tachycardia pacing.

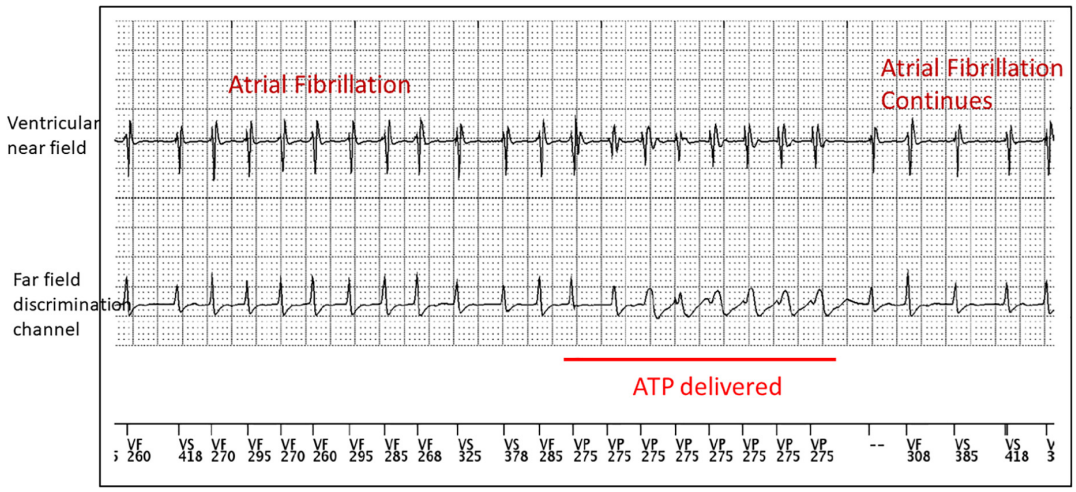

FIGURE 3
Device tracings of a 50 year old male with non-ischemic heart disease who experienced episodes of atrial fibrillation with rapid AV conduction into his ventricular fibrillation zone that resulted in the delivery of anti-tachycardia pacing. This event occurred while taking amyl nitrite during sexual activity. ATP, anti-tachycardia pacing.

sexual intercourse that can be disconcerting for both the patient and their partner. The tracing shows that his heart rate increased to a heart rate that triggered anti-tachycardia pacing.

Non-ischemic heart disease and inherited cardiovascular syndromes

Arrhythmias and sudden cardiac death can also occur in patients with non-ischemic structural heart disease or structurally normal hearts, such as those with channelopathies and other inherited cardiovascular syndromes. Non-ischemic structural heart diseases, such as Hypertrophic Cardiomyopathy (HCM), Arrhythmogenic Ventricular Cardiomyopathy (AVC), idiopathic fibrosis, and aortic dissection have been described through registry data and case reports (20). The risk of death during sex in patients with non-ischemic structural heart disease can cause anxiety and depression in these patients and their partners.

In a recent study by Finocchiaro, sex-associated sudden cardiac death was rare and occurred in 17 out of 6,847 cases (0.2%), with 8 of these patients having non-ischemic structural heart disease (1). Similarly, the Paris-SDEC registry (Paris Sudden Cardiac Death Expertise Center) reported that sudden cardiac death due to sex was rare (<1%), but non-ischemic structural heart disease accounted for 12.5% of the sex-related sudden cardiac arrests (18). Overall, patients with non-ischemic heart disease have a very low risk of arrhythmia-related death during sex and can safely participate in sexual activity. Patients and their partners should be made aware of the low risk of arrhythmias and sudden cardiac death during sex but reassured by their cardiologists that these events are rare.

Long QT Syndrome (LQTS) and Catecholaminergic Polymorphic Ventricular Tachycardiac (CPVT) are channelopathies that can lead to arrhythmias such as torsade de pointes (TdP) or polymorphic ventricular tachycardia (PMVT) which can deteriorate into ventricular fibrillation. In an electronic medical review of patients seen by the Genetic Heart Rhythm Clinic, sex-induced cardiac events were more likely in CPVT than in LQTS. Sex-induced cardiac events occurred in two out of forty-three patients (4.7%) with CPVT but in none of the patients with LQTS (21). Despite the low occurrence of sex-related arrhythmias or sudden cardiac death in patients with LQTS, orgasm induced torsades de pointes has been reported in a Long QT Syndrome type 2 (LQT2) patient with a mutation (c.361del) in the KCNH2 gene (chromosome 7q36) (22). Treatment with beta-blockers in these patients can decrease the likelihood of deadly arrhythmias. Proper counseling regarding the safety profile of sex in patients with channelopathies who are well controlled on medications can provide reassurance to the patient and their sexual partner.

Sex in patients with cardiomyopathies with implantable cardioverter-defibrillators and on goal directed medical therapy

ICDs are implanted in patients as either primary or secondary prevention of life-threatening arrhythmias (ventricular tachycardia and fibrillation). Although ICDs are life-saving devices for at-risk patients, receiving a shock

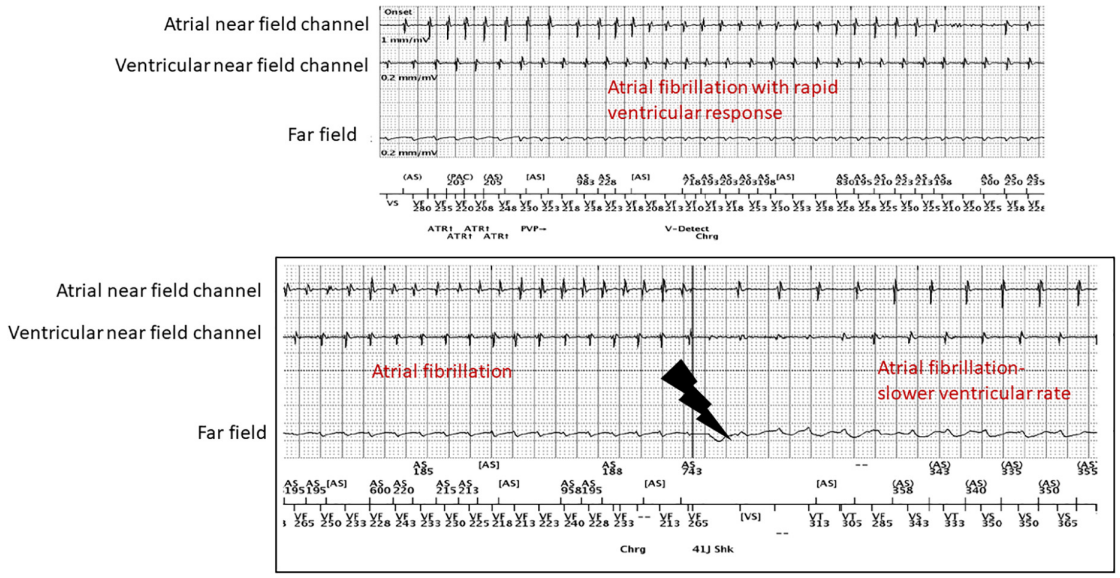

FIGURE 4
Patient with atrial fibrillation with rapid ventricular response with an inappropriate shock after stopping his beta-blocker due to concerns for erectile dysfunction.

during sexual activity or fear that their partner might receive an ICD shock is a frequent concern of patients and their partners. It causes significant anxiety and fear of sexual activity (23, 24). Counseling before and after device implantation can decrease the anxiety in patients requiring ICDs. According to the AHA Scientific Statement on Sexual Activity and Cardiovascular Disease, sexual activity is reasonable in patients with ICDs for primary prevention and in those requiring secondary prevention that can perform three to five METs without precipitating VT or VF. Sexual activity should be deferred in patients who have received multiple shocks until the causative arrhythmia has been stabilized and they can safely perform three to five METs without arrhythmias (2).

Optimizing patients so that they can perform three to five METs so that they can participate in sexual activity can be achieved through cardiac rehab. A recent meta-analysis of fourteen trials showed that cardiac rehabilitation could improve sexual function (25). In addition to cardiac rehabilitation, improving the arrhythmia burden through ablations and goal-directed medical therapy can also help patients improve their physical activity levels. Unfortunately, despite best medical practices, sexual dysfunction can still arise due to a patient's underlying disease process and the prescribed cardiovascular medications.

Cardiovascular medications can cause erectile dysfunction, decreased sex drive, and decreased vaginal lubrication due to their mechanism of action and the nocebo effect (26, 27). This can contribute to patients discontinuing their cardiac medications without disclosing to their provider due to embarrassment, leading to poorly controlled cardiac arrhythmias and inappropriate shocks (**Figure 3**) and in the worst-case scenario sudden cardiac death.

Counseling, education, and shared decision-making can improve patient adherence to cardiac medications. If the patient continues to have significant issues regarding sex drive, erectile dysfunction, or vaginal dryness, alternate but equivalent medications can be prescribed. For patients with cardiovascular disease and erectile dysfunction, phosphodiesterase type 5 inhibitors can be prescribed in patients not taking long-acting nitrates. Vaginal dryness can be safely treated with topical estrogens to decrease pain with sexual intercourse (26, 27). Finally, individual and couple's therapy can also be an effective adjunct to improving sex drive for patients with cardiomyopathies and ICDs.

Conclusion

Sex is a salient part of life and procreation that contributes to overall wellness and quality of life. In most individuals, sex can occur safely without risk of death or arrhythmias. But it is devastating when arrhythmias or sudden cardiac death do occur during sexual activity. Patients and their partners should be given reassurance that sex is reasonable and safe in most situations. However, they should also receive personalized counseling and education on the likelihood of arrhythmias or sudden cardiac death as it applies to their disease process and how to minimize these events with medication adherence, avoiding non-FDA-approved sexual enhancers, and the importance of bystander CPR.

Medical providers can improve outcomes in patients at risk for arrhythmias and sudden cardiac death by initiating a conversation about sexual activity with their at-risk patients. During these counseling sessions, the provider should listen to the patient's concerns regarding sexual activity and make shared decisions regarding cardiovascular medications and devices while abiding by current medical guidelines. Cardiovascular specialists can help stratify patients at risk for arrhythmias and sudden cardiac death by utilizing exercise stress tests and improve outcomes by enrolling patients in cardiac rehabilitation to improve aerobic conditioning when appropriate. Health care professionals also need to be aware of potential disparities in healthcare and ensure that sexual partners, female patients, and those in the LGBTQIA + community receive the same access to counseling but tailored to their individual needs.

Author contributions

CD and AV created the outline, wrote sections, and edited the entire manuscript. CD created **Figure 1**. CD, TL, and JM created **Figures 2–4**. EE and SS wrote several sections. TL edited the entire manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Assessment of absolute risk of life-threatening cardiac events in long QT syndrome patients

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Background: Risk stratification in long QT syndrome (LQTS) patients is important for optimizing patient care and informing clinical decision making. We developed a risk prediction algorithm with prediction of 5-year absolute risk of the first life-threatening arrhythmic event [defined as aborted cardiac arrest, sudden cardiac death, or appropriate implantable cardioverter defibrillator (ICD) shock] in LQTS patients, accounting for individual risk factors and their changes over time.

Methods: Rochester-based LQTS Registry included the phenotypic cohort consisting of 1,509 LQTS patients with a QTc $\geq$ 470 ms, and the genotypic cohort including 1,288 patients with single LQT1, LQT2, or LQT3 mutation. We developed two separate risk prediction models which included pre-specified time-dependent covariates of beta-blocker use, syncope (never, syncope while off beta blockers, and syncope while on beta blockers), and sex by age $<$ and $\geq$13 years, baseline QTc, and genotype (for the genotypic cohort only). Follow-up started from enrollment in the registry and was censored at patients' 50s birthday, date of death due to reasons other than sudden cardiac death, or last contact, whichever occurred first. The predictive models were externally validated in an independent cohort of 1,481 LQTS patients from Pavia, Italy.

Results: In Rochester dataset, there were 77 endpoints in the phenotypic cohort during a median follow-up of 9.0 years, and 47 endpoints in

the genotypic cohort during a median follow-up of 9.8 years. The time-dependent extension of Harrell's generalized C-statistics for the phenotypic model and genotypic model were 0.784 (95% CI: 0.740–0.827) and 0.785 (95% CI: 0.721–0.849), respectively, in the Rochester cohort. The C-statistics obtained from external validation in the Pavia cohort were 0.700 (95% CI: 0.610–0.790) and 0.711 (95% CI: 0.631–0.792) for the two models, respectively. Based on the above models, an online risk calculator estimating a 5-year risk of life-threatening arrhythmic events was developed.

Conclusion: This study developed two risk prediction algorithms for phenotype and genotype positive LQTS patients separately. The estimated 5-year absolute risk can be used to quantify a LQTS patient's risk of developing life-threatening arrhythmic events and thus assisting in clinical decision making regarding prophylactic ICD therapy.

KEYWORDS

long QT syndrome, risk prediction, sex, syncope, beta blocker, cardiac arrest, implantable cardioverter defibrillator

Introduction

Congenital long QT syndrome (LQTS) is a genetic channelopathy manifested by QT prolongation on the electrocardiogram and an increased risk of ventricular tachyarrhythmia and sudden cardiac death (SCD) (1, 2). It is a major cause of SCD in young subjects without structural heart disease (3). To date, disease-causing mutations have been identified in 17 genes (4), with three genes (KCNQ1, KCNH2, and SCN5A) accounting for over 90% of genotype-positive patients (5), Risk stratification in LQTS patients is important for optimizing patient care and clinical decision regarding treatment, especially the decision to implant implantable cardioverter defibrillators (ICD) in young patients with lifetime risk of complications (6, 7). Previous studies have identified several risk factors including prolonged heart rate corrected QT interval (QTc, (7–13) history of syncope, (8–10, 13, 14) male sex before adolescence, (9, 12, 15, 16) female sex after adolescence, (9, 12, 15, 16) protective beta-blocker treatment, (12, 17) and genotype (1, 7, 13). However, there is a need for a risk stratification algorithm able to integrate all individual risk factors and predict a patient's absolute risk of developing a life-threatening arrhythmic event in a given time window. A recent study by Mazzanti et al. (4) developed an algorithm for LQTS patients with calculations of absolute risk of cardiac events based on QTc and genotype.

We developed a risk prediction algorithm with prediction of 5-year absolute risk of life-threatening arrhythmic events [aborted cardiac arrest, sudden cardiac death (SCD), or appropriate ICD shocks] in LQTS patients, accounting for individual risk factors (age, sex, QTc, syncope, beta-blocker use) and their changes over time, using data from the Rochester LQTS Registry. At first, an assessment of the risk can be based on the abovementioned clinical variables since genetic testing results (if test performed) usually are available several weeks later. When genetic test results become available, they could be used to further refine estimation of individual risk. Given that genotype data were not available for about one-third of patients in the Registry and some patients with prolonged QTc were tested negative, we developed two algorithms for two cohorts separately: (1) a clinical algorithm that only included clinical risk factors (QTc, age, sex, history of syncope, use of beta-blockers) for patients with QTc prolongation, regardless of genotype or with unknown yet genotype (*phenotypic cohort*); (2) and a genetic algorithm that included all abovementioned clinical risk factors plus genotype for LQTS genotype positive patients, regardless of a patient's QTc duration (*genotypic cohort*). This manuscript describes development of these models and subsequent external validation in a large LQTS registry cohort followed in Pavia, Italy, and proposes an on-line calculator estimating the risk of life-threatening cardiac events in LQTS patients.

Materials and methods

Study population

LQTS patients included in the study were from the Rochester LQTS Registry (18), which is the US

portion of the International LQTS Registry established in 1979 (18), Participants in the Registry are LQTS patients and their family members enrolled across the United States. Patients included in the present study were enrolled before December 21, 2016. The phenotypic cohort included 1,509 patients with a QTc $\geq$ 470 ms, regardless of their genotype (i.e., these patients could be genotype positive or negative), and the genotypic cohort included 1,288 patients with a single mutation in KCNQ1 (LQT1), KCNH2 (LQT2), or SCN5A (LQT3) genes and whose QTc was available (regardless of the specific value of QTc). There were 698 patients who had both QTc $\geq$ 470 and a single mutation in KCNQ1, KCNH2, or SCN5A that were included in both cohorts. Patients who developed life-threatening arrhythmias (definition provided below) before registry enrollment were excluded from the study. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board at the University of Rochester Medical Center.

Follow-up and assessment of the endpoint

Participants in the Registry were followed annually using mailed questionnaires since enrollment. For probands, annual follow-up with patients' physicians was also performed. The endpoint was the first occurrence of a life-threatening arrhythmic event, defined as a composite endpoint of aborted cardiac arrest, SCD, or appropriate ICD shock. Aborted cardiac arrest was defined as abrupt onset of loss of consciousness that requires external defibrillation as part of the resuscitation (8). It was assessed by patients' self-report at enrollment and at each annual follow-up and verified by medical records whenever possible. Mortality was assessed by contact with relatives of the deceased using available medical documentation. SCD was defined as death abrupt in onset without evident cause if witnessed or death that was not explained by any other cause if it occurred in a non-witnessed setting such as sleep (8). SCDs were adjudicated by LQTS investigators based on a description of the circumstances around the time of death and medical records when available. Appropriate ICD shocks were defined as shocks delivered for torsade de pointes or polymorphic ventricular tachycardia or ventricular fibrillation. The type of arrhythmia that triggered a shock and the appropriateness of the shock were ascertained by an event adjudication committee based on all available information including reports from the patient's electrophysiologist.

Assessment of clinical risk factors and genotype

A 12-lead electrocardiogram (ECG) was obtained at Registry enrollment for all subjects included in the study. ECGs were read centrally by the study physicians at the University of Rochester Medical Center. QTc was calculated using Bazett's formula. For probands, QTc was measured from the first ECG received and read by the reading center showing a qualifying QTc of >440 ms. For family members, QTc was measured from the earliest ECG available. History of syncope and beta-blocker use were self-reported by the study subject at enrollment and at each annual follow-up. In the presence of a self-reported arrhythmic event, the patient's physician was contacted to verify the information. Genetic testing results reported to the Registry came from research or commercial laboratories. A patient may have undergone comprehensive testing for all known LQTS genes or just targeted mutation-specific genes. The registry only documented genetic testing results that had been reported by genetic testing laboratories or patient's physicians. Assessments of these clinical risk factors and genotype used in risk prediction were performed without knowledge of a patient's outcome status since they were assessed prior to outcome occurrence.

Statistical analysis

Multivariable models

We used time-dependent Cox models, including pre-specified LQTS prognostic factors, to estimate the 5-year absolute risk of developing a life-threatening arrhythmic event. Robust sandwich estimates of standard errors were used to account for clustering of events within the same family. Follow-up started at enrollment and was censored on the date of subjects' 50th birthday, date of death due to reasons other than SCD, or date of last registry contact, whichever occurred first.

Pre-specified factors in the model for the phenotypic cohort included QTc, age at enrollment, an interaction term between sex and time-dependent age $<$ and $\geq$13 years (to account for the sex risk-reversal occurring around the time of adolescence), time-dependent beta-blocker use (yes vs. no), and time-dependent history of syncope (no syncope, syncope that occurred while off beta-blockers, and syncope that occurred while on beta-blockers). For the genotypic cohort, in addition to these clinical factors, genotype (LQT1, LQT2, and LQT3) was also included in the model. We further examined interactions among genotype, age, and sex; no significant interactions were found.

We checked the assumption of linear functional form for QTc using cumulative martingale residuals and no significant violations were found in either cohort. Therefore, QTc was

analyzed as a linear term. When checking the assumption of linear functional form for age at enrollment using the same approach, violations were found. Therefore, we categorized age into five groups with 10 years as interval length (i.e., 0– < 10, 10– < 20, 20– < 30, 30– < 40 and 40–50 years). Given that the effect estimates for age groups 20– < 30, 30– < 40 and 40–50 years compared to 0– < 10 years were similar in both cohorts, and there is a biological basis of human development (childhood, adolescence, and adulthood), we combined the age groups of 20– < 30, 30– < 40 and 40–50 years. Thus, age at enrollment was analyzed as a three-level categorical variable (i.e., 0– < 10 years, 10– < 20 years, and 20–50 years) in the final models for both cohorts. The three groups of time-dependent history of syncope were mutually exclusive at any given time point, with "no syncope" as the reference group. If a patient had both histories of syncope on beta-blockers and syncope off beta-blockers, he/she was classified in the group of syncope on beta blockers (i.e., the group expected to have a higher risk). Only syncopal events that occurred prior to ICD implantation were counted. Proportional hazard assumptions were tested via interactions between each risk factor and log (time), and no violations were found.

Estimation of 5-year risk

Assuming that the covariate pattern (and thus risk score z) will remain fixed for t years, the event-free survival from time 0 to time t for an individual patient can be predicted using the following equation, derived from the Cox model:

$$S(t|z = risk\ score) = S_0(t)^{\exp(\text{risk score} - \text{reference risk score})},$$

where the risk score is the linear combination of all log hazard ratios (regression coefficients) relevant to the covariate pattern of the patient (i.e., risk score $= \sum_{i=1}^{p} \beta_i x_i$, where β is the regression coefficient and x is the level for each risk factor). $S_0(t)$ is the cumulative event-free survival probability from time 0 (i.e., enrollment) to time t (e.g., $t = 5$ years) for an individual with the reference risk score, estimated via Breslow's estimator of the baseline cumulative hazard function (19).

Since it is necessary to hypothesize some reasonable 5-year future covariate trajectory when forecasting risk using a time-dependent Cox model, we assumed that the covariate pattern will remain fixed for the 5-year prediction window since enrollment. Therefore, in most cases when predicting 5-year risk for a patient, only the baseline risk score (i.e., at enrollment) of that patient was used. However, one exception was to predict risk for female patients whose age at enrollment was between 8 and 13 years (i.e., 8 years < age at enrollment < 13 years). Given that the 5-year prediction window for these patients included 13 years, and based on the model the effect estimate for female vs. male before age 13 was different from that after age 13, it would not be appropriate to still assume a fixed risk score over the 5 years. The **Supplementary material** provide a detailed description of how to compute predicted risk when the 5-year prediction window for a female includes age 13. Briefly, we divided the 5-year prediction window into two intervals: starting age to year 13, and age 13 to ending age (starting age+5). We first computed the event-free survival probability using the risk score at the starting age for the first interval, then computed the event-free survival probability using the risk score at age 13 years (assuming the level of each risk factor remains the same as it is at the starting age) for the second interval.

Assessment of model performance

For each of the two models, we first assessed apparent model discrimination (i.e., discrimination performance estimated directly from the dataset that was also used to develop the prediction model) using time-dependent extension of Harrell's generalized C-statistic proposed by Kremers (20). Furthermore, both models were externally validated in an Italian cohort of 1,481 individuals younger than 50 years at enrollment and carriers of a single mutation in one of the three major LQTS genes (KCNQ1, KCNH2, or SCN5A) who were followed-up prospectively at the Molecular Cardiology clinic of the IRCCS ICS Maugeri in Pavia, Italy. The model for the phenotypic cohort was validated in a subsample of 681 patients with QTc $\geq$ 470 ms, while the model for the genotypic cohort was validated in all 1,481 patients. For each model, a time-dependent risk score was calculated for each patient in the Italian cohort, using the parameters estimated from the training dataset (the Rochester cohort). The risk score was then included in a time-dependent Cox model as the only covariate. The C-statistic, calibration coefficient (i.e., beta coefficient of the risk score), and their 95% confidence intervals obtained from this model were reported. All analyses were performed using SAS software (version 9.4; SAS Institute Inc.).

Results

Clinical characteristics of long QT syndrome patients

Clinical characteristics of patients included in the Rochester phenotypic and genotypic cohorts are shown in **Table 1**. There were 698 patients included in both cohorts. Females accounted for 60.2% in the phenotypic cohort and 56.2% in the genotypic cohort. Average age at enrollment was 20 years in both cohorts. Prevalence of syncope at enrollment was higher in the phenotypic cohort compared to the genotypic cohort (39.5% vs. 29.7%). Prevalence of a history of beta blocker use (phenotypic vs. genotypic: 74.5% vs. 78.0%) and prevalence of a history of ICD implantation (21.0% vs. 21.1%) were similar between the two cohorts. In the phenotypic cohort, 49.8% patients were genotype positive, 9.5% were negative for the mutations tested, and 40.8% were either not tested or had missing data on genotype. In the genotypic cohort, 45.8% patients were mutation carriers with a QTc < 470 ms.

TABLE 1 Patients characteristics at enrollment in the Rochester phenotypic and genotypic cohort.

Characteristics	Phenotypic cohort (N = 1,509)	Genotypic cohort (N = 1,288)
Females	908 (60.2)	724 (56.2)
Age at enrollment, years		
<10	430 (28.5)	412 (32.0)
10– < 20	434 (28.8)	293 (22.7)
20– < 50	645 (42.7)	583 (45.3)
Mean age	20 ± 15	20 ± 16
QTc. ms		
<470	0 (0)	590 (45.8)
470– < 500	820 (54.3)	342 (26.6)
500– < 550	459 (30.4)	242 (18.8)
≥550	230 (15.2)	114 (8.9)
Mean QTc, ms	507 ± 44	477 ± 50
Heart rate, bpm	83 ± 26	82 ± 28
Age at ECG, year	18.7 ± 14.7	18.8 ± 15.6
History of syncope*		
No syncope	913 (60.5)	906 (70.3)
Syncope while off beta blockers	498 (33.0)	327 (25.4)
Syncope while on beta blockers	98 (6.5)	55 (4.3)
History of treatment		
Beta-blockers	1,124 (74.5)	1,005 (78.0)
Sodium channel blockers	72 (4.8)	46 (3.6)
Left cardiac sympathetic denervation	27 (1.8)	13 (1.0)
Pacemaker	146 (9.7)	82 (6.4)
ICD	317 (21.0)	272 (21.1)
Genotype		
LQT1 (single mutation)	334 (22.1)	582 (45.2)
LQT2 (single mutation)	291 (19.3)	549 (42.6)
LQT3 (single mutation)	73 (4.8)	157 (12.2)
Others (single mutation)	12 (0.8)	0 (0)
Multiple mutations	41 (2.7)	0 (0)
Negative for mutations tested	143 (9.5)	0 (0)
Not tested/unknown	615 (40.8)	0 (0)
No. of life-threatening events	77	47
SCD	30	14
ACA	14	7
Appropriate ICD shocks	33	26
Follow-up: Total person-years	15,505	14,221
Median (years)	9.0	9.8
Interquartile range (years)	4.4–15.1	5.3–15.9
Incidence rate of the endpoint (No. of events/100 person-years)	0.50	0.33

Data are mean ± SD or N (%). *If a patient experienced both syncope while on beta blockers and syncope while off beta blockers, the patient was classified in the group of syncope while on beta blockers (i.e., the group with a presumed higher risk).

Endpoints during follow-up

In the Rochester phenotypic cohort, during a follow-up of 15,505 person-years (median: 9.0 years) 77 patients developed the endpoint (30 SCD, 14 aborted cardiac arrest, and 33 appropriate ICD shocks, Table 1). The incidence rate of the first life-threatening arrhythmic event was 0.5 per 100 person-years. In the Rochester genotypic cohort, during a follow-up of 14,221 person years (median: 9.8 years) 47 patients developed the endpoint (14 SCD, 7 aborted cardiac arrest, and 26 appropriate ICD shocks). The incidence rate of the first life-threatening arrhythmic event was 0.33 per 100 person-years.

Prediction models

The risk prediction model for the phenotypic cohort is shown in Table 2. QTc and time-dependent history of syncope and beta-blocker use were all significantly associated with the risk of life-threatening arrhythmic events. Compared to patients who were younger than 10 years at enrollment, those aged 10– < 20 years had a non-significant 31% decrease in the risk (HR = 0.69, 95% CI: 0.38–1.25, P = 0.221), and those aged 20–50 years had a significant 69% decrease in the risk (HR = 0.31, 95% CI: 0.16–0.62, P = 0.001). Although not significant, before age 13 years, females had a 64% lower risk of life-threatening arrhythmic events than males (HR = 0.36, 95% CI: 0.11–1.22, P = 0.102), whereas from 13 years onward, females had a 45% higher risk than males (HR = 1.45, 95% CI: 0.84–2.50, P = 0.185). There was a significant interaction between sex and time-dependent age < 13 vs. ≥13 years (P = 0.038). Figure 1 shows the predicted 5-year risk since enrollment for some example covariate patterns.

The risk prediction model for the genotypic cohort is shown in Table 3. Similar to the model for the phenotypic cohort, time-dependent history of syncope and beta-blocker use were significantly associated with the risk of life-threatening arrhythmic events. However, the effect size of QTc was smaller and non-significant (HR = 1.02, 95%CI: 0.96–1.09, P = 0.442). In sensitivity analysis, QTc was analyzed using a piecewise linear spline with a knot at 470 ms to allow different slopes for the QTc- arrhythmia risk association in the two QTc ranges (<470 ms and ≥470 ms), but there was insufficient evidence of such nonlinearity (p = 0.885 and Schwartz's Bayesian Information Criterion increased from 597.7 to 601.6). The pattern of association for age at enrollment and sex by time-dependent age (<13 vs. ≥13 years) was similar to that of the phenotypic model. Compared to LQT1 patients, LQT2 patients had a non-significant 44% higher risk of life-threatening arrhythmic events (HR = 1.44, 95% CI: 0.75–2.77, P = 0.279), and LQT3 patients had a significantly over threefold higher risk (HR = 3.75, 95% CI: 1.74–8.07, P = 0.001). Figure 2 shows the predicted 5-year risk since enrollment for some example covariate patterns. For both

TABLE 2 Model predicting ACA, SCD, or appropriate ICD shock after enrollment in 1,509 LQTS patients with QTc ≥ 470 ms (No. of events = 77, 30 SCD, 14 ACA, and 33 shock).

Variables in the model	β	HR	95% CI		*P*
QTc, per 10 ms increase	0.08	1.09	1.05	1.13	<0.001
Age at enrollment (Ref: 0– < 10 years)					
10– < 20 years	-0.37	0.69	0.38	1.25	0.221
20–50 years	-1.16	0.31	0.16	0.62	0.001
Time-dependent syncope (Ref: No syncope)					
Syncope while off BB	1.14	3.12	1.59	6.11	0.001
Syncope while on BB	1.77	5.87	2.89	11.90	<001
Time-dependent beta-blocker (yes vs. no)	-0.58	0.56	0.34	0.93	0.024
Sex by time-dependent age (female vs. male)					
<13 years	-1.01	0.36	0.11	1.22	0.102
≥13 years	0.37	1.45	0.84	2.50	0.185
C statistic	0.784 (0.740–0.827)				

Robust sandwich estimates of standard errors were used. *P*-value for interaction between time-dependent age and sex: 0.038.

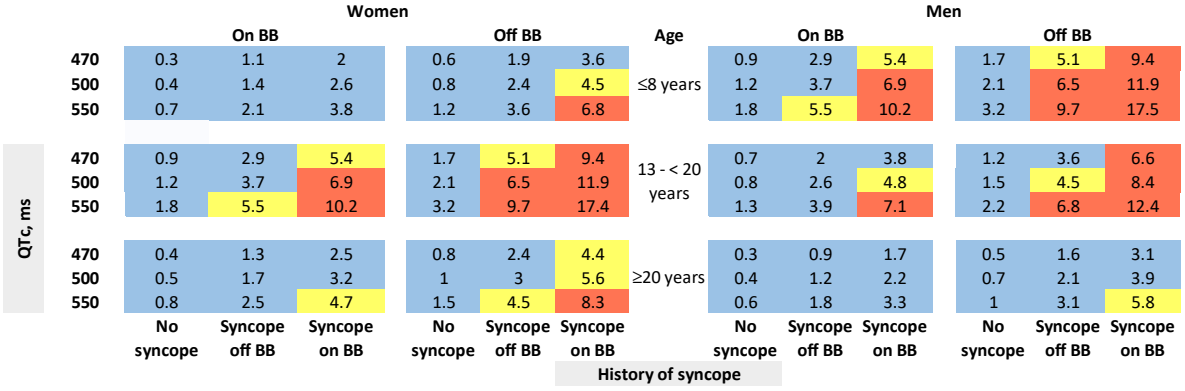

FIGURE 1
Predicted 5-year risk of life-threatening arrhythmic events (aborted cardiac arrest, sudden cardiac death, or appropriate ICD shocks) for some example risk factor combinations for patients with a QTc ≥ 470 ms. Blue color indicates a predicted 5-year risk of < 4%, yellow color indicates a predicted 5-year risk of 4– < 6%, and red color indicates a predicted 5-year risk of ≥6%. Numbers in this figure are percentage. BB: beta-blockers. We chose three QTc values (470, 500, and 550 ms) and three age groups at baseline (≤8 years, 13– < 20 years, and ≥20 years) as examples. We did not show the age group of 8–13 years. Given that the 5-year risk prediction interval includes age 13 for patients aged 8–13 years at baseline, in this age group each unique age has a unique predicted risk. Thus, graphical presentation can be cumbersome. The online risk calculator can compute predicted risk for any age points.

the phenotypic and genotypic cohorts, formulae with examples of risk calculations were given in **Supplementary material**. An online risk calculator is shown in **Figure 3** and can be accessed via the following link: LQTS Risk Calculator[1].

Validation of model performance

Patient characteristics of the genotypic cohort from Pavia, Italy, has been described previously showing similar clinical characteristics to Rochester genotypic cohort including 52% (vs. 56%) of females, mean QTc of 471 ± 45 ms (vs. 477 ± 50 ms), similar proportions of LQTS genotypes, follow-up duration and event rates of 0.47% (vs. 0.33%) events per year (4).

In the Italian cohort (N = 1,481, all patients had a single mutation in LQT1, LQT2, or LQT3), during a follow-up of 12,616 person-years 57 patients developed the endpoint with an incidence rate of 0.45 per 100 person-years. Of the 1,481 patients, 681 had a QTc ≥ 470 ms. During a follow-up of 6,193 person-years, 50 of the 681 patients developed the endpoint with an incidence rate of 0.81 per 100 person-years.

The time-dependent extension of Harrell's generalized C-statistics for the phenotypic model and genotypic model were 0.784 (95% CI: 0.740–0.827, p < 0.001) and 0.785 (95% CI: 0.721–0.849, p < 0.001), respectively, in the Rochester cohort. The C-statistics obtained from external validation in

1 https://www.urmc.rochester.edu/clinical-cardiovascular-research/lqts-registry/lqts-registry.aspx

TABLE 3 Model predicting ACA, SCD, or appropriate ICD shock after enrollment in 1,288 LQTS patients with singe LQT1, LQT2, or LQT3 mutation (No. of events = 47, 14 SCD, 7 ACA, and 26 shock).

Variables in the model	β	HR	95% CI		*P*
QTc, per 10 ms increase	0.02	1.02	0.96	1.09	0.442
Age at enrollment (Ref: 0–10 years)					
10–20 years	-0.60	0.55	0.26	1.15	0.112
20–50 years	-1.40	0.25	0.11	0.56	0.001
Time-dependent syncope (Ref: No syncope)					
Syncope while off BB	0.87	2.38	1.10	5.16	0.028
Syncope while on BB	1.88	6.54	2.91	14.65	<001
Time-dependent beta-blocker (yes vs. no)	-0.73	0.48	0.25	0.91	0.025
Sex by time-dependent age (female vs. male)					
<13 years	-1.92	0.15	0.02	1.13	0.066
≥13 years	0.58	1.79	0.91	3.51	0.090
Genotype (Ref: LQT1)					
LQT2	0.36	1.44	0.75	2.77	0.279
LQT3	1.32	3.75	1.74	8.07	0.001
C statistic	0.785 (0.721–0.849)				

Robust sandwich estimates of standard errors were used. *P*-value for interaction between time-dependent age and sex: 0.018.

the Italian cohort were 0.700 (95% CI: 0.610–0.790, $p < 0.001$) and 0.711 (95% CI: 0.631–0.792, $p < 0.001$) for the two models, respectively. The calibration coefficient (beta) obtained from external validation for the phenotypic model was 0.822 (95% CI: 0.513–1.131), with $p < 0.001$ for the null hypothesis of beta = 0 (implying significant discrimination) and a $p = 0.259$ for the null hypothesis of beta = 1 (insufficient evidence of miscalibration). The calibration coefficient for the genotypic model was 0.744 (95% CI: 0.491–0.997), with $p < 0.001$ (significant discrimination) and $p = 0.048$ (significant miscalibration) for the two hypotheses, respectively.

Discussion

The risk prediction algorithms for life-threatening arrhythmic events in LQTS patients proposed by the present study integrate several risk factors including age, sex, QTc, history of syncope, beta-blocker treatment, and genotype. The algorithm for the phenotypic cohort could be applied to patients with unknown yet genotype or patients who test negative for currently known LQTS mutations. The algorithm that included genotype could be applied to patients with a single mutation in LQT1, LQT2, or LQT3. Both algorithms demonstrated good discrimination in external validation (C-statistics ≥0.70 with >97.5% confidence that C-statistics ≥0.61 and $p < 0.001$). These algorithms with prediction of 5-year absolute risk of life-threatening cardiac events including aborted cardiac arrest, sudden cardiac death or appropriate ICD shock may be used in clinical practice to help identify high-risk patients requiring ICD therapy.

Different from the traditional approach that only uses baseline data when developing a risk prediction model, we included time-dependent covariates, accounting for changes in risk factors (i.e., beta blockers and syncope) over time. We believe this approach more accurately quantified the effect of each risk factor on the risk of life-threatening arrhythmic events compared to approaches that only use covariate status at baseline. We proposed a novel yet simple and familiar looking method to predict individual survival functions based on the time-dependent Cox model. Our approach assumes that a patient's risk profile will remain fixed over the prediction time interval (e.g., 5-years), while placing no restrictions or assumptions on the time-dependent covariate trajectory outside that interval (for details, see **Supplementary Methods**). When interpreting the predicted risk, this assumption of fixed risk profile should be considered. Once a patient's risk profile changes, the patient needs to be re-evaluated.

The risk stratification method used by current clinical practice guidelines for LQTS is based on a crude combination of individual risk factors, primarily QTc and the presence or absence of symptoms (21), failing to account for the difference in the strength of associations between each individual factor and the risk of life-threatening arrhythmic events. By contrast, the algorithm developed by the present study integrates individual risk factors by assigning each factor a weight of its effect size, and it is able to quantify a patient's absolute risk. Furthermore, the algorithm can estimate risk for both patients under beta-blocker treatment and patients who cannot take beta-blockers due to intolerance or contraindication. Multivariable risk assessment avoids overlooking patients with multiple marginal risk factors and over-treating patients with only one isolated risk factor such as syncope history (22). Our risk stratification algorithm suggests that some patients without a history of syncope may have a higher risk of life-threatening arrhythmic events than patients with a history of syncope. For example, a LQT3

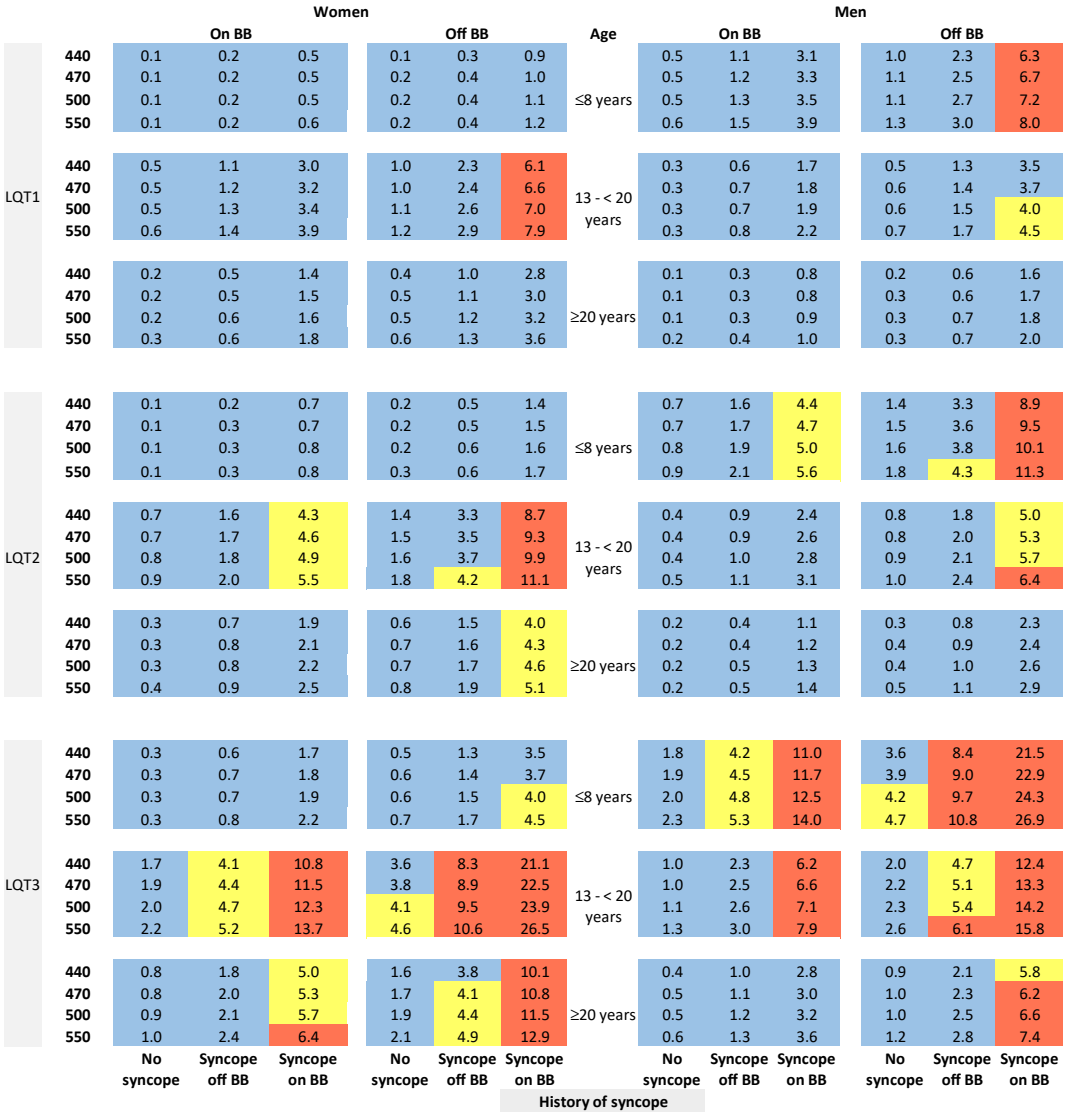

FIGURE 2
Predicted 5-year risk of life-threatening arrhythmic events (aborted cardiac arrest, sudden cardiac death, or appropriate ICD shocks) for some example risk factor combinations for patients with a single mutation in LQT1, LQT2, or LQT3. Blue color indicates a predicted 5-year risk of <4%, yellow color indicates a predicted 5-year risk of 4% to < 6%, and red color indicates a predicted 5-year risk of ≥ 6%. Numbers in this figure are percentage. BB, beta-blockers.

boy younger than 8 years with a QTc of 550 ms who never experienced syncope and will be continuously treated by beta blockers has a predicted 5-year risk of 2.3%, which is higher than the 5-year predicted risk for a LQT1 male adult with the same QTc (i.e., 550 ms) and a history of syncope while on beta blockers who will be continuously treated by beta blockers (predicted risk = 1.0%). However, it should be noted that syncopal events in LQTS patients may be due to reasons other than arrhythmias such as vasovagal syncope and orthostatic hypotension, and the Registry data were not able to differentiate different types of syncope. This may also be the case in real world clinical settings when the exact reason for a syncopal event cannot be determined (e.g., a patient came to see a physician after experiencing a syncopal event). The nature of syncope and the likelihood that it is arrhythmic should be carefully evaluated and considered when estimating a patient's risk and making treatment decisions.

The approach presented in the manuscript reflects real-world scenario when patients suspected for or diagnosed with LQTS are evaluated first without genetic testing available. The risk stratification approach proposed in this manuscript allows physicians to use existing clinical information without knowledge of genetic results at first. When genetic testing becomes available, the risk stratification model allows the use

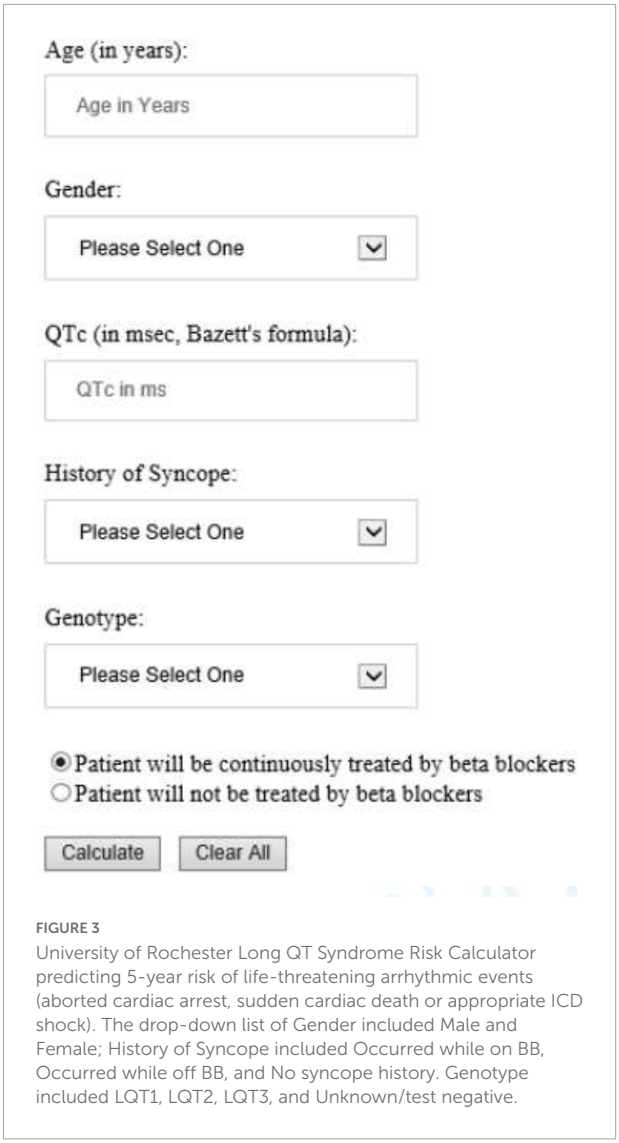

FIGURE 3
University of Rochester Long QT Syndrome Risk Calculator predicting 5-year risk of life-threatening arrhythmic events (aborted cardiac arrest, sudden cardiac death or appropriate ICD shock). The drop-down list of Gender included Male and Female; History of Syncope included Occurred while on BB, Occurred while off BB, and No syncope history. Genotype included LQT1, LQT2, LQT3, and Unknown/test negative.

of risk calculator that accounts for genetic results. Furthermore, the risk could be re-evaluated at different age or at the time when new clinical information is available (i.e., new syncopal episode on beta-blocker).

A recent study by Mazzanti et al. also developed a risk stratification algorithm with calculations of 5-year absolute risk of life-threatening arrhythmic events in LQTS patients with a QTc >460 ms while not taking beta-blockers (4). However, the algorithm only considered two risk factors QTc and genotype. In our study, we included QTc, age at enrollment, sex by time-dependent age, and time-dependent history of syncope and beta-blocker use in the phenotypic model and additionally LQTS genotype in the genotypic model. Both models demonstrated good discrimination as suggested by an external validation C-statistic of ≥0.70. For the phenotypic model, the calibration coefficient (0.822, 95% CI: 0.513–1.131) was not significantly different from 1 (P = 0.259), thus providing insufficient evidence of miscalibration. However, for the genotypic model, the calibration coefficient (0.744, 95% CI: 0.491–0.997) was significantly different from 1 (P = 0.048), indicating evidence of miscalibration. Nevertheless, given that the point estimate of the calibration coefficient was as large as 0.744 and different from 0 ($p < 0.001$), the risk score was still capable of discrimination in the validation cohort and the magnitude of miscalibration was not large.

It is worth noting that the aim of this risk prediction tool is to provide objective data on prognosis to facilitate the clinical decision-making of treatment, especially ICD implantation, rather than to simply categorize patients into high or low risk groups using arbitrary thresholds. As already noted by others (23), there is no universal consensus on the level of absolute risk that justifies ICD therapy. The risk of life-threatening arrhythmic events should be interpreted as a continuum. When making decisions regarding ICD implantation for the primary prevention of life-threatening events, patients and physicians need to weigh the risks and benefits of the device in the context of the patient's clinical condition and preference. Nevertheless, current guidelines for other cardiac diseases have made recommendations regarding the risk cut-off that warrants ICD implantation. For example, based on the 2014 European Society of Cardiology Guidelines on Diagnosis and Management for Hypertrophic Cardiomyopathy, a 5-year risk of ≥6% could be used as the risk category for ICD recommendation (24).

The long-term prospective follow-up (median follow-up was 9.0 and 9.8 years for the phenotypic and genotypic cohort, respectively) was a major strength of the present study. By using enrollment as baseline, recall bias was minimized and the study population was more representative of concurrent patients under medical care. Additionally, we proposed a novel method to predict absolute risk based on time-dependent Cox models, which enabled us to include time-dependent syncope and beta blockers in our risk prediction models and thus account for changes in risk factors over time. However, several limitations of our study should be considered when interpreting our findings. First, the majority of our study population were females (60.2% in the phenotypic cohort and 56.2% in the genotypic cohort). It is known that the risk pattern of life-threatening arrhythmic events between males and females throughout their lifetimes is very different, and females have their distinct risk factors such as the post-partum high risk period (25), probably due to the influence of sex hormones (25–29). Although it would be ideal to build different models for males and females separately, our sample was not sufficiently large to perform this sex-specific analysis. Second, Caucasian non-Hispanic white (93.8% in the phenotypic cohorts and 96.7% in the genotypic cohorts) predominated in our cohorts. Therefore, our findings may not be generalizable to patients of other racial and ethnic origins. Third, to avoid informative censoring and to account for the fact that patients were still at risk of life-threatening arrhythmic events after

ICD implantation, we included appropriate ICD shocks in the composite endpoint. However, appropriate ICD shock is not a perfect surrogate of life-threatening arrhythmic events. Data on detailed ICD programming (e.g., programmed delay of ICD therapy) were not available for every patient. Thus, we were not able to perform analyses focusing on prolonged ventricular tachycardia or fibrillation. In fact, given that it is impossible to know what would happen to a patient who experienced an appropriate ICD shock had the shock not been delivered, there is no way to ascertain life-threatening arrhythmic events with absolute accuracy after ICD implantation, even if details about ICD programming are available. Some syncopal events may be due to non-arrhythmic causes and our study was not able to differentiate arrhythmic vs. non-arrhythmic syncope. However, given the strong effect estimates for syncope variables in our models, most syncopal events documented in the registry should be arrhythmic. In future studies, the incremental predictive value of provocation testing and more detailed genetic information such as mutation locations and functions of genetic variants as well as pathogenicity should be evaluated in larger combined cohorts.

Conclusion

This study proposed two risk stratification algorithms of the first life-threatening arrhythmic event, separately for patients with unknown and known genotype. Model performance was satisfying in an external cohort for both algorithms. Although genetic testing is increasingly used, it is not easily accessible in many parts of the world and initially physicians need to evaluate risk while waiting for genetic test results. We integrated individual risk factors including age, sex, QTc, history of syncope, beta-blocker treatment, and genotype (for genotype positive patients only). The estimated 5-year absolute risk can be used to quantify a patient's risk and thus assist clinicians in decision making regarding prophylactic ICD therapy.

Data availability statement

The datasets presented in this article are not readily available because the datasets are restricted to investigators and collaborating groups. Requests to access the datasets should be directed to WZ, wojciech.zareba@heart.rochester.edu.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Subject Review Board, University of Rochester Medical Center, Rochester, NY. Written informed consent to participate in this study was provided by the participants or the participants' legal guardian/next of kin.

Author contributions

MW, DP, DR, CS, VK, IG, and WZ contributed to the concept and design of the study. MW drafted the manuscript. MW, DP, SM, BP, and WZ contributed to acquisition, analysis, or interpretation of data. MW and EP performed statistical analyses. All authors contributed to critical revision of the manuscript for important intellectual content.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.988951/full#supplementary-material

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Temporal trends of arrhythmias at delivery hospitalizations in the United States: Analysis from the National Inpatient Sample, 2009–2019

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Background: Cardiac arrhythmias are associated with increased maternal morbidity. There are limited data on trends of arrhythmias among women hospitalized for delivery.

Materials and methods: We used the National Inpatient Sample (NIS) database to identify delivery hospitalizations for individuals aged 18–49 years between 2009 to 2019 and utilized coding data from the 9th and 10th editions of the *International Classification of Diseases* to identify supraventricular tachycardias (SVT), atrial fibrillation (AF), atrial flutter, ventricular tachycardia (VT), and ventricular fibrillation (VF). Arrhythmia trends were analyzed by age, race-ethnicity, hospital setting, and hospital geographic regions. Multivariable logistic regression was used to evaluate the association of demographic, clinical, and socioeconomic characteristics with arrhythmias.

Results: Among 41,576,442 delivery hospitalizations, the most common arrhythmia was SVT (53%), followed by AF (31%) and VT (13%). The prevalence of arrhythmia among delivery hospitalizations increased between 2009 and 2019. Age > 35 years and Black race were associated with a higher arrhythmia burden. Factors associated with an increased risk of arrhythmias included valvular disease (OR: 12.77; 95% C1:1.98–13.61), heart failure (OR:7.13; 95% CI: 6.49–7.83), prior myocardial infarction (OR: 5.41, 95% CI: 4.01–7.30), peripheral vascular disease (OR: 3.19, 95% CI: 2.51–4.06), hypertension (OR: 2.18; 95% CI: 2.07–2.28), and obesity (OR 1.69; 95% CI: 1.63–1.76). Delivery hospitalizations complicated by arrhythmias compared with those with no

arrhythmias had a higher proportion of all-cause in-hospital mortality (0.95% vs. 0.01%), cardiogenic shock (0.48% vs. 0.00%), preeclampsia (6.96% vs. 3.58%), and preterm labor (2.95% vs. 2.41%) (all $p < 0.0001$).

Conclusion: Pregnant individuals with age > 35 years, obesity, hypertension, valvular heart disease, or severe pulmonary disease are more likely to have an arrhythmia history or an arrhythmia during a delivery hospitalization. Delivery hospitalizations with a history of arrhythmia are more likely to be complicated by all-cause in-hospital mortality, cardiovascular, and adverse pregnancy outcomes (APOs). These data highlight the increased risk associated with pregnancies among individuals with arrhythmias.

KEYWORDS

trends, arrhythmia, pregnancy, predictors, outcomes

Introduction

Maternal morbidity and mortality have risen steadily in the United States (1–3). In particular, limited data suggest an increased incidence of pregnancy-related arrhythmias, including supraventricular tachycardia (SVT), atrial fibrillation (AF), atrial flutter, and ventricular tachycardia (VT) (4, 5). Although many arrhythmias during pregnancy have been considered benign, there is also limited data suggesting a relationship with in-hospital death. There is also little data associating arrhythmias with comorbidities and risk factors (4). Many cardiovascular risk factors, including preexisting diabetes, obesity, and hypertension increase the risk of adverse pregnancy outcomes (APOs), including preeclampsia and preterm labor, which then contribute to later cardiovascular diseases (6–9). However, the association between arrhythmias before or during delivery and APOs and other cardiovascular outcomes, including cardiogenic shock and cardiac arrest, is poorly understood. It is crucial to recognize comorbidities and risk factors associated with arrhythmias during pregnancy early, particularly if associated with APOs and other cardiovascular outcomes, as it could help guide further risk mitigation (10). The purpose of this paper is threefold: (1) To provide a contemporary analysis of the prevalence of arrhythmias in delivery hospitalizations, (2) To identify outcomes associated with arrhythmias during delivery hospitalizations, and (3) To identify risk factors associated with arrhythmias during delivery hospitalization.

Abbreviations: AF, Atrial fibrillation; APO, Adverse Pregnancy Outcomes; CVD, Cardiovascular Disease; ICD, International Classification of Diseases; IQR, Interquartile Range; NIS, National Inpatient Sample; SVT, Supraventricular Tachycardia; VF, Ventricular Fibrillation; VT, Ventricular Tachycardia.

Materials and methods

Data source

The study population was derived from the National Inpatient Sample (NIS) dataset (2009–2019), a part of the Healthcare Cost and Utilization Project (HCUP), organized and supported by the Agency for Healthcare Research and Quality (AHRQ) (11). The NIS is the largest all-payer publicly accessible healthcare database in the United States of inpatient encounters. It incorporates a stratified sample of 20% non-federal US community hospitals representing nearly 95% of the US population. It comprises roughly 7 million unweighted records, and about 35 million weighted hospital encounters annually. Weighted data allow us to measure national estimates. The NIS uses de-identified hospital discharges as samples with prior ethical committee approval, therefore, Institutional Review Board (IRB) was not required for this study.

Study cohort

We used International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9 and 10-CM) codes to identify pregnant patients aged 18 years or older hospitalized for delivery. A delivery admission was defined by delivery code (ICD-9 cesarean delivery procedural codes 74 and diagnosis codes 72, 73, 75, v27, or diagnostic codes 650–659 for vaginal delivery; ICD-10 cesarean delivery procedure codes 10D00Z0, 10D00Z1, 10D00Z2, and diagnosis code O82, or vaginal delivery diagnosis codes 060-077, 080, Z37, Z38). Patients were classified into 2 groups based on whether they had prevalent or incident arrhythmia during the same hospitalization (**Figure 1**). The study cohort was further divided into different age groups (18–24, 25–30, 31–35, 36–40, 41–45, and > 46 years),

race/ethnicity groups (White, Black, Hispanic, Asian, Native American, and other), urban or rural settings, and hospital regions (Northeast, Midwest, South, and West). In addition, data on the demographic details, comorbidities, procedure details, and clinical presentation were studied. Specific ICD-9 and ICD-10 codes used to identify comorbidities and outcomes are listed in **Supplementary Tables 2, 3**.

Study endpoints

Maternal arrhythmias were characterized according to the various subtypes such as SVT (ICD-9, 427.0; ICD-10, I47.1), AF (ICD-9, 427.31; ICD-10, I48.0, I48.1, I48.2, I48.91), Atrial flutter (ICD-9, 427.32; ICD-10, I48.3, I48.4, I48.92), VT (ICD-9, 427.1; ICD-10, I47.2), and Ventricular fibrillation (VF) (ICD-9, 427.41; ICD-10, I49.01). The primary endpoint was all-cause in-hospital mortality. Secondary endpoints included APOs such as preterm labor, preeclampsia, gestational diabetes, placenta previa; adverse fetal outcomes such as fetal death; mode of delivery such as cesarean section; cerebrovascular outcomes such as ischemic stroke, intracranial hemorrhage; and cardiovascular outcomes such as cardiogenic shock, cardiac arrest, complete heart block and pacemaker implantation, and acute heart failure.

Data analysis and statistics

As recommended, survey procedures using discharge weights provided with the HCUP-NIS database were used

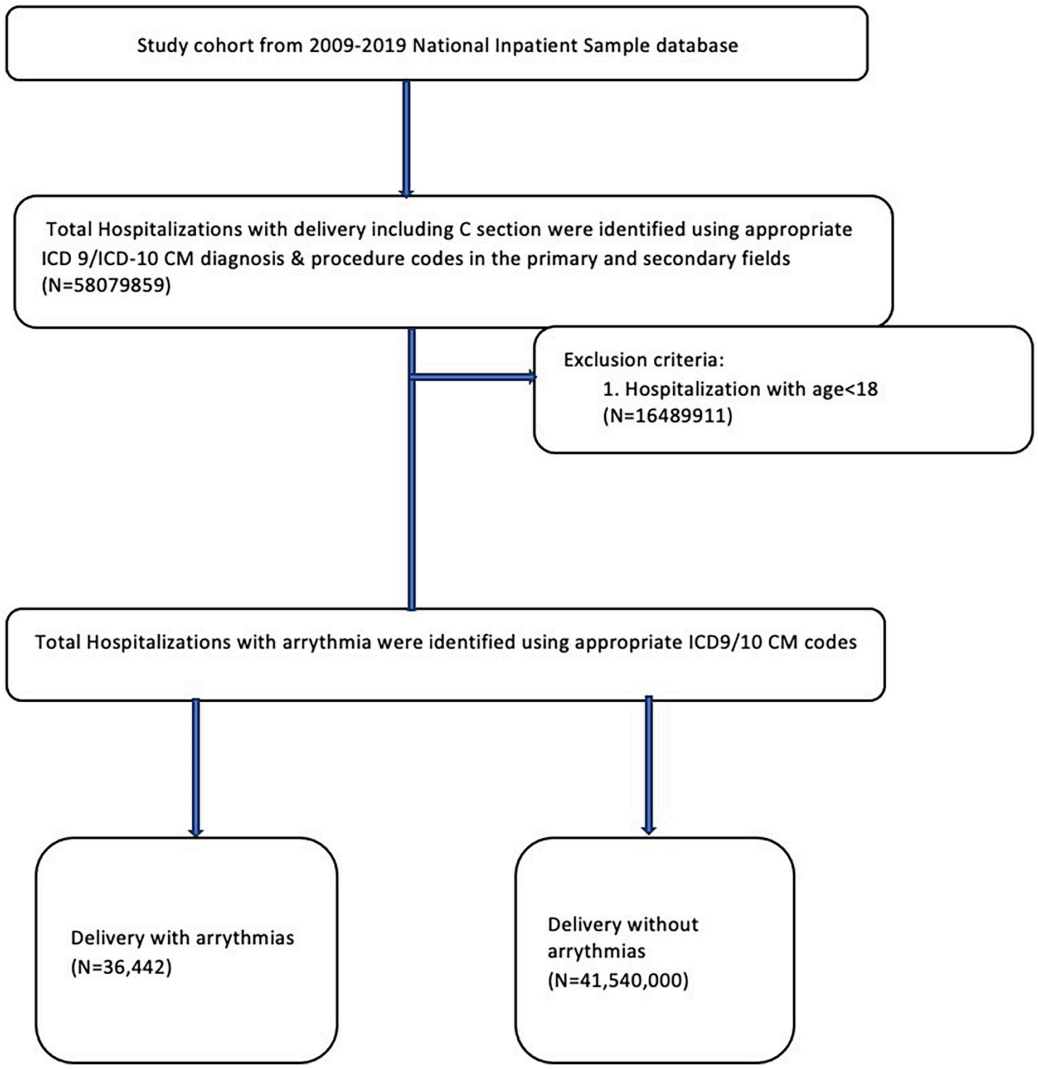

FIGURE 1
Study population selection algorithm from the National Inpatient Sample database from 2009 to 2019.

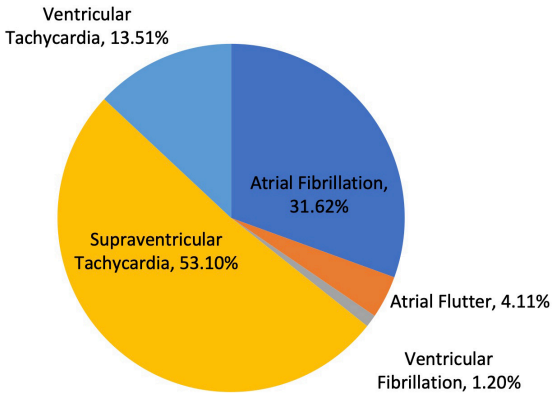

FIGURE 2
Frequency of arrhythmia subtypes in all delivery hospitalizations; specifically atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular tachycardia, and ventricular fibrillation.

to generate national estimates. Descriptive statistics were used to analyze the demographic and comorbidity data. Most hospital-level characteristics were directly obtained as provided in the NIS, whereas the Elixhauser Comorbidity Index was used to identify co-morbid disorders (12). Categorical variables were compared using the Chi-square test and are presented as numbers and percentages. Continuous variables were compared using the Wilcoxon test and are presented as the median and interquartile range (IQR). A two-tailed p-value of < 0.05 was used to determine the statistical significance. We performed multivariable logistic regression to look for risk factors associated with arrhythmia in delivery hospitalization. Furthermore, the Jonckheere-Terpstra trend test was used to analyze various trends, including the overall frequency of arrhythmia, frequency of arrhythmia stratified by age group, ethnicity, hospital setting, and hospital geographic regions in delivery hospitalizations from 2009 to 2019. All analyses were performed using SAS, version 9.4 (SAS Institute Inc.).

Results

Overall delivery hospitalizations with arrhythmia

During the study period from 2009 to 2019, there were a total of 41,576,442 delivery hospitalizations. Among delivery hospitalizations, there were 36,442 hospitalizations associated with any diagnosis of arrhythmia either during or prior to the delivery hospitalizations. The most common arrhythmia diagnosis was SVT (53%), followed by AF (31%) and VT (13%) (**Figure 2**).

Demographic data

The baseline demographics of delivery hospitalizations with and without an arrhythmia are shown in **Table 1**. Delivery hospitalizations with an arrhythmia were more likely in older age groups than those without an arrhythmia (31–35 years: 26.58% vs. 23.71; 36–40 years: 15.15% vs. 10.86%; 41–45years: 4.27% vs. 2.07%, all $p < 0.0001$). There were also significant differences in race/ethnicity in delivery hospitalizations with an arrhythmia compared with those without. (White: 60.13% vs. 52.82%; Black: 20.44% vs. 14.77%; Hispanic: 11.35% vs. 21.13%; Asian: 3.94% vs. 5.76, all $p < 0.0001$). Additionally, there were rural and urban differences in delivery hospitalizations associated with arrhythmias, where 73.66% of delivery hospitalizations with an arrhythmia occurred in urban teaching hospitals. In comparison, 59.29% without arrhythmia occurred in urban teaching hospitals ($p < 0.0001$). In addition, delivery hospitalizations with arrhythmia had a higher proportion of private insurance status (54.89% vs. 50.79%, $p < 0.001$) compared with those with no arrhythmia.

Comorbidities

The clinical comorbidities and complications of delivery hospitalizations with and without arrhythmia are detailed in **Table 2**. Individuals with delivery hospitalizations with an arrhythmia were more likely to have cardiovascular risk factors including obesity (16.95% vs. 8.31%), hypertension (6.19% vs. 1.53%), type II diabetes (1.39% vs. 0.64%), previous myocardial infarction (0.22% vs. 0.01%), peripheral vascular disease (0.23% vs. 0.01%), and hyperlipidemia (0.35% vs. 0.06%) compared with those without arrhythmias (all $p < 0.001$). Individuals with arrhythmias, compared with those without, had a higher prevalence of risk behaviors such as tobacco use (2.15% vs. 1.36%) and other substance abuse (2.17% vs. 1.38%) (all $p < 0.0001$). Additionally, delivery hospitalizations were more likely to have comorbidities such as heart failure (3.02% vs. 0.04%), valvular disease (4.09% vs. 0.13%), chronic obstructive pulmonary disease (7.41% vs. 2.84%), fluid and electrolyte disorders (5.03% vs. 0.34%), hypothyroidism (4.02% vs. 2.06%), and coagulopathy (4.14% vs. 1.37%) as compared to those who did not have any arrhythmias (all $p < 0.0001$).

Temporal trends in prevalence and baseline characteristics of hospitalizations with arrhythmia

In 2009, the prevalence of arrhythmias was 48.67 per 1,000,000 in delivery hospitalizations, which increased to 148.17 per 1,000,000 (**Figure 3**). From 2009 to 2019, SVT

TABLE 1 Demographics and baseline characteristics of delivery hospitalizations.

	Arrhythmia ($N = 36,442$)	No arrhythmia ($N = 41,540,000$)	*P*-value
Age groups			<0.0001
18–24	17.25%	25.10%	
25–30	36.74%	38.26%	
31–35	26.58%	23.71%	
36–40	15.15%	10.86%	
41–45	4.27%	2.07%	
>46	–	–	
Race			<0.0001
White	60.13%	52.82%	
Black	20.44%	14.77%	
Hispanic	11.35%	21.13%	
Asians	3.94%	5.76%	
Native Americans	0.65%	0.79%	
Others	3.50%	4.74%	
Type of admission			<0.0001
Elective	45.18%	49.39%	
Non-elective	54.82%	50.61%	
Primary payer			<0.0001
Medicare	2.32%	0.71%	
Medicaid	37.58%	42.81%	
Private insurance	54.89%	50.69%	
Other/Self-pay	5.21%	5.79%	
Median income (quartile)			0.0002
0–25th percentile	26.69%	27.61%	
26–50th percentile	24.94%	25.02%	
51–75th percentile	25.33%	25.00%	
76–100th percentile	23.04%	22.37%	
Hospital bedside			<0.0001
Small	11.90%	14.81%	
Medium	24.90%	29.05%	
Large	63.20%	56.14%	
Hospital region			<0.0001
Northeast	16.97%	16.06%	
Midwest	21.14%	21.14%	
South	38.25%	38.54%	
West	24.25%	24.26%	
Hospital location and teaching status			<0.0001
Rural	6.97%	9.99%	
Urban non-teaching	19.37%	30.72%	
Urban teaching	73.66%	59.29%	

Comparisons were made by chi-squared for categorical variables. Statistical significance set at $p < 0.05$; SD, Standard deviation.

TABLE 2 Comorbidities and complications of women with and without arrhythmia at delivery hospitalization.

	Arrhythmia ($n = 36,442$)	No arrhythmia ($n = 41,540,000$)	*P*-value
CV risk factors			
Obesity	16.95%	8.31%	<0.0001
Hypertension	6.91%	1.54%	<0.0001
Hyperlipidemia	0.35%	0.06%	<0.0001
Type 2 DM	1.39%	0.64%	<0.0001
Previous MI	0.22%	0.01%	<0.0001
Peripheral vascular disease	0.23%	0.01%	<0.0001
Risk behaviors			
Tobacco use	2.15%	1.36%	<0.0001
Alcohol abuse	0.10%	0.07%	0.04
Substance abuse	2.17%	1.38%	<0.0001
CV comorbidities			
Heart failure	3.02%	0.04%	<0.0001
Valvular heart disease	4.09%	0.13%	<0.0001
Extracardiac comorbidities			
COPD	7.41%	2.84%	<0.0001
Renal failure	0.44%	0.05%	<0.0001
Hypothyroidism	4.02%	2.06%	<0.0001
Fluid and electrolyte disorders	5.03%	0.36%	<0.0001
Coagulopathy	4.14%	1.37%	<0.0001
Pulmonary circulation disease	0.58%	0.01%	<0.0001

Comparisons were made by ANOVA for continuous variables and a chi-squared for categorical variables. Statistical significance set at $p < 0.05$. COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DM, diabetes mellitus; MI, myocardial infarction.

increased the most from 18.13 to 100.84 per 1,000,000 delivery hospitalizations. Patients in the oldest age groups (36–40 and 41–45) had the highest prevalence of an arrhythmia compared to women in younger age groups (18–24, 25–30, and 31–35) (Figure 4). For almost every year, Black women had the highest prevalence of arrhythmia per 1,000,000 delivery hospitalizations compared to other races (Figure 5). Hospitals in urban settings had a higher prevalence of arrhythmia per 1,000,000 delivery hospitalizations across the entire study period compared to hospitals in rural settings (Figure 6).

Outcomes of patients with arrhythmia

Delivery hospitalizations in women with a history of arrhythmia had a significantly higher proportion of all-cause in-hospital mortality (0.95% vs. 0.01%, $p < 0.0001$) as well as other poor clinical outcomes (Table 3). There was also a

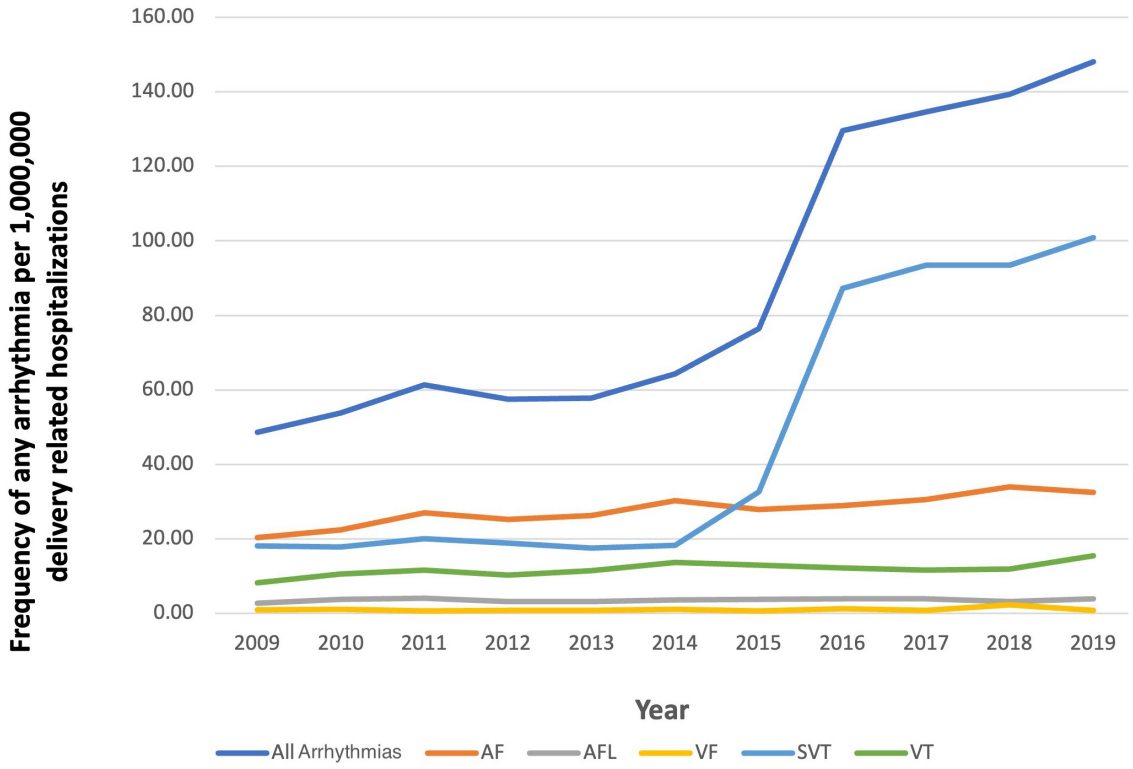

FIGURE 3
Frequency of any arrhythmia per 1,000,000 delivery related hospitalizations from 2009 to 2019, stratified by type of arrhythmia.

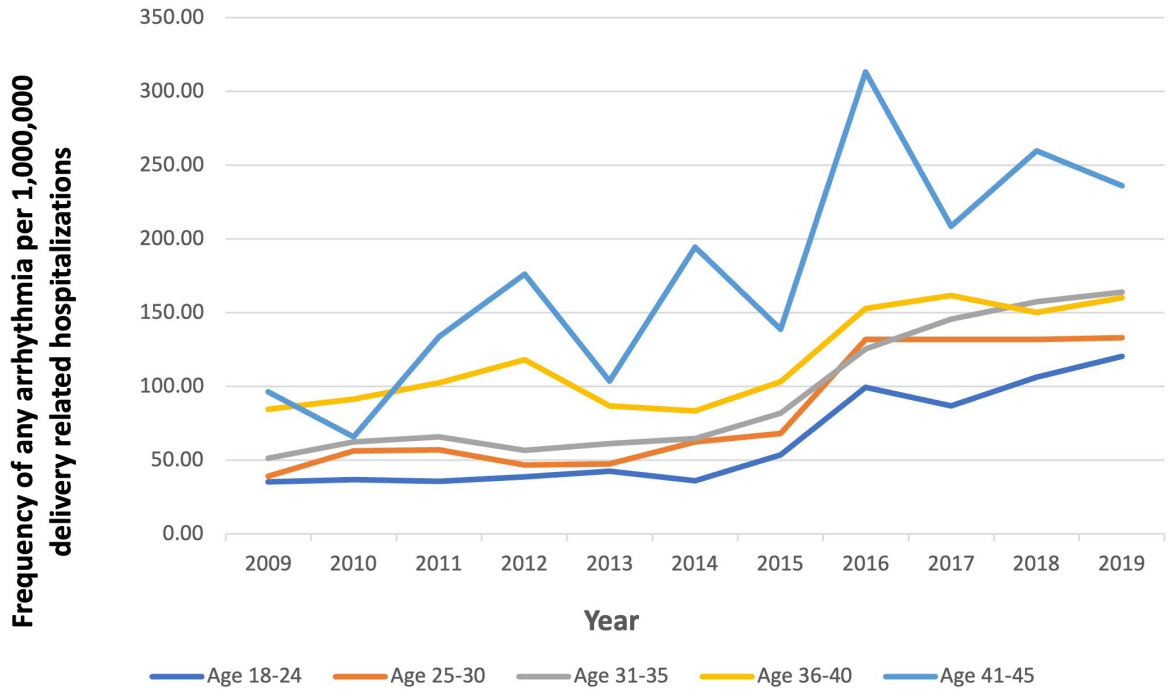

FIGURE 4
Frequency of any arrhythmia per 1,000,000 delivery related hospitalizations from 2009 to 2019, stratified by age.

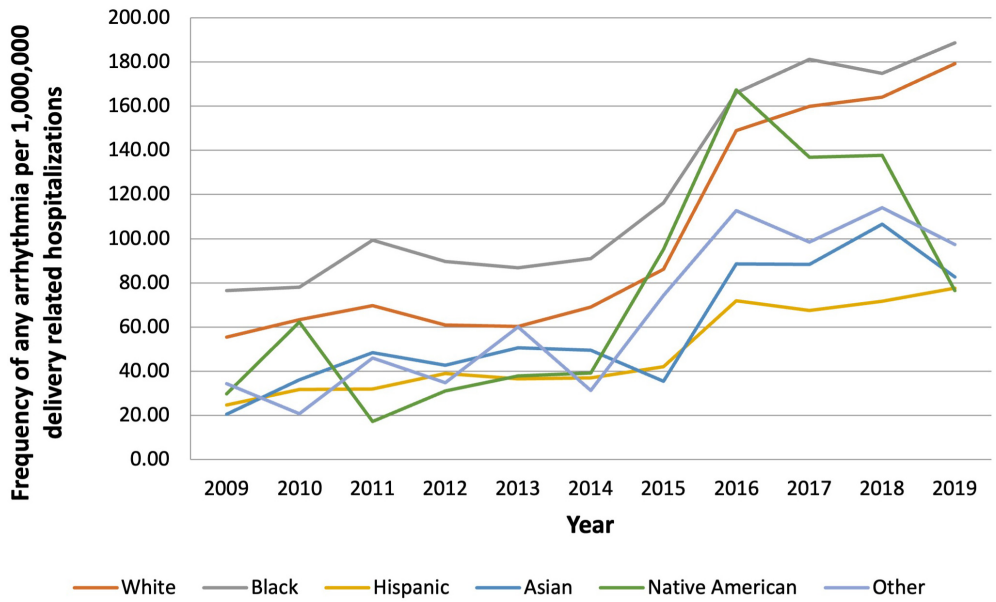

FIGURE 5
Frequency of any arrhythmia per 1,000,000 delivery related hospitalizations from 2009 to 2019, stratified by race.

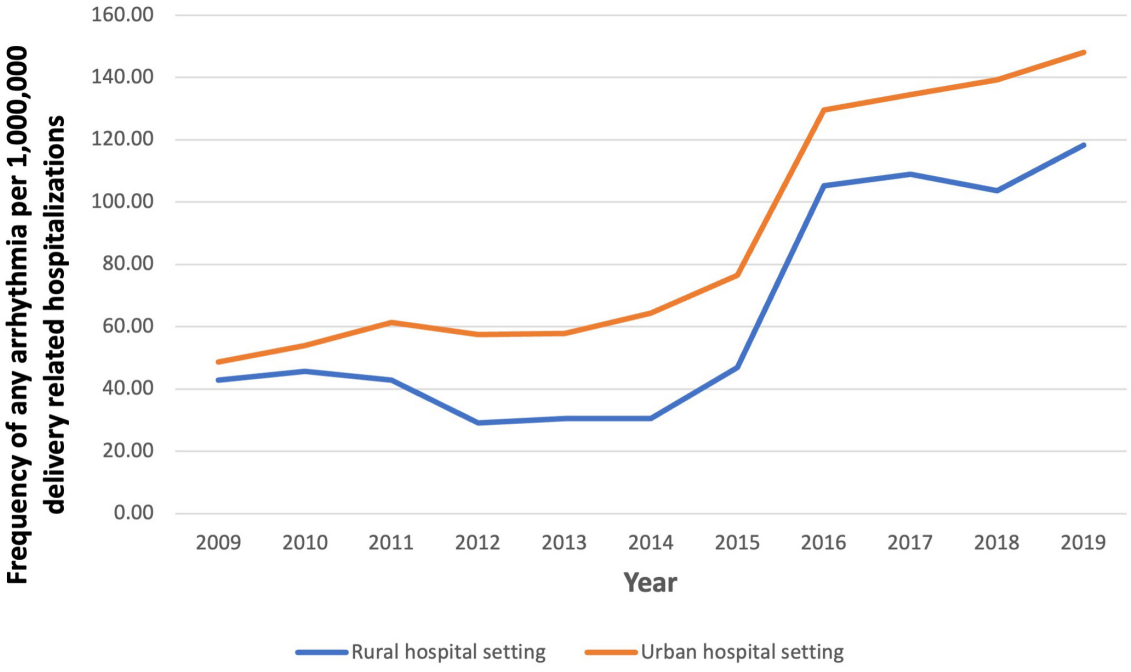

FIGURE 6
Frequency of any arrhythmia per 1,000,000 delivery related hospitalizations from 2009 to 2019, stratified by hospital setting.

higher prevalence of various APOs: preeclampsia (6.96% vs. 3.58%), preterm labor (2.95% vs. 2.41%), placental abruption (0.67% vs. 0.26%), placenta previa (0.33% vs. 0.11%) (all $p < 0.001$) and gestational diabetes mellitus (3.69% vs. 1.74%; $p = 0.04$) compared with those with no arrhythmia. The delivery hospitalizations with a history of arrhythmia were more associated with cesarean section (43.48% vs. 31.97%), fetal death (0.21% vs. 0.04%), cardiac arrest (1.32% vs. 0.00%), and cardiogenic shock (0.48% vs. 0.0%) ($p < 0.0001$).

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TABLE 3 Outcomes in delivery hospitalizations with and without arrhythmias.

	Arrhythmia ($n = 36,442$)	No arrhythmia ($n = 41,540,000$)	*P*-value
All-cause in-hospital mortality	0.95%	0.01%	<0.0001
Adverse pregnancy outcomes			
Gestational diabetes mellitus	3.69%	1.74%	0.04
Preterm labor	2.95%	2.41%	<0.0001
Preeclampsia	6.96%	3.58%	<0.0001
Placental abruption	0.67%	0.26%	<0.0001
Placenta previa	0.33%	0.11%	<0.0001
Fetal death	0.21%	0.04%	<0.0001
Obstetrics outcomes			
Cesarean section	43.48%	31.97%	<0.0001
CV outcomes			
Ischemic stroke	0.08%	0.00%	<0.0001
Cardiogenic shock	0.48%	0.00%	<0.0001
Cardiac arrest	1.32%	0.00%	<0.0001
Acute heart failure	1.55%	0.01%	<0.0001
Other			
ICH	0.05%	0.00%	<0.0001

Comparisons were made by ANOVA for continuous variables and a chi-squared for categorical variables. Statistical significance set at $p < 0.05$. OR, Odds Ratio; CI, Confidence Interval; CV, Cardiovascular; CM, Cardiomyopathy; ICH, Intracranial hemorrhage.

TABLE 4 Comparisons were made by ANOVA for continuous variables and a chi-squared for categorical variables.

	OR [95% CI]
Age	1.04 [1.03–1.04]
Type of admission	
Elective	0.86 [0.83–0.88]
Race	
Hispanic	Reference
Black	2.05 [1.95–2.15]
White	1.91 [1.83–1.99]
Asian	1.15 [1.07–1.24]
Native American	1.60 [1.36–1.87]
Others	1.37 [1.27–1.48]
Payee status	
Self-pay/other	Reference
Medicare	1.51 [1.42–1.61]
Medicaid	0.96 [0.93–1.00]
Private insurance	0.98 [0.95–1.01]
Median household income (percentile)	
0–25th	Reference
25th–50th	1.05 [1.01–1.09]
50th-75th	1.02 [0.98–1.06]
75th–100	1.02 [0.98–1.07]
Comorbidities	
Obesity	1.69 [1.63–1.76]
Hypertension	2.18 [2.07–2.28]
Hyperlipidemia	1.50 [1.20–1.87]
Diabetes mellitus	0.92 [0.84–1.02]
Hypothyroidism	1.50 [1.42–1.58]
CHF	7.13 [6.49–7.83]
Chronic pulmonary disease	1.92 [1.84–2.00]
Renal failure	1.26 [1.05–1.50]
Pulmonary embolus	1.55 [1.30–1.85]
Tobacco use	1.12 [1.03–1.23]
Alcohol abuse	0.75 [0.53–1.05]
Drug abuse	1.07 [0.99–1.16]
Valvular disease	12.77 [11.98–13.61]
Fluid and electrolyte disorders	6.57 [6.21–6.96]
Coagulopathy	1.94 [1.83–2.05]
Peripheral vascular disease	3.19 [2.51–4.06]
Old myocardial infarction	5.41 [4.01–7.30]

Statistical significance set at $p < 0.05$. CHF, Heart failure; OR, Odds Ratio; CI, Confidence Interval; ICH, intracranial hemorrhage.

Factors associated with delivery hospitalizations complicated with arrhythmias

Multivariable logistic regression for the presence of arrhythmia during delivery hospitalization is shown in Table 4. Inspecting demographic predictors of arrhythmias showed that per each 1-year increase in age, the odds of an arrhythmia increased by 4% (OR: 1.04; 95% CI: 1.03–1.04). When controlled for other risk factors, Black women had 2.05 times greater odds (95% CI: 1.95–2.12) of an arrhythmia than Hispanic women, and White women had 1.91 times greater odds (95% CI: 1.82–1.99) of an arrhythmia than Hispanic women.

Cardiovascular comorbidities, including valvular disease and heart failure, significantly increased the odds of an arrhythmia during pregnancy by 12.77 (95% CI: 11.98–13.61) and 7.13 (95% CI 6.49 –7.83), respectively. In addition, the presence of cardiovascular risk factors, including obesity (OR: 1.69; 95% CI: 1.63–1.76), hypertension (OR: 2.18; 95% CI: 2.07–2.28), previous MI (OR: 5.41, 95% CI: 4.01–7.30), and peripheral vascular disease (OR: 3.19, 95% CI: 2.51–4.06), also increased the odds of reported arrhythmias though to a slightly lesser degree.

Regarding socioeconomic factors, women with Medicare status were 1.5 times more likely to have arrhythmias (OR 1.51, 95% CI 1.423–1.61) than those who self-pay. There was no association of arrhythmia with median household income or substance abuse.

Discussion

In this large nationally represented sample of delivery hospitalizations from 2009 to 2019, we report the overall prevalence and incidence and temporal trends of arrhythmia frequency in pregnancy-related hospitalizations. Our major conclusions from this analysis show: (1) the overall combined prevalence and incidence of arrhythmias increased by ∼200% from 48.67/1,000,000 to 148.14/1,000,000 from 2009 to 2019, (2) there was an increased APO frequency, cardiovascular and obstetric complications, and slightly higher in-hospital mortality, among women with preexisting or incident arrhythmias, (3) there was a higher association of arrhythmias with older age, non-Hispanic race, and certain cardiovascular conditions and obstetric conditions.

These findings build upon previously published studies, which have all shown an increased frequency of arrhythmias in pregnant women since the 1990s (4, 5). Our findings demonstrate a similar increase in arrhythmias from 2009 to 2019. The measured rise in prevalence of arrhythmias during pregnancy is likely multifactorial. While the increased prevalence could be partially the result of a rise in risk factors, such an increase could be also be due to greater use of electronic medical records, remote monitoring, and overall shifts in monitoring and recording practices. Additionally, many health systems shifted from ICD-9 and ICD-10 over the examined time frame which may have also contributed to a shift in identification and coding thus leading to a perceived increase in arrhythmias from 2009 to 2019. In another report of pregnancy hospitalizations from 2000 to 2012 AF was the most frequent arrhythmia in pregnancy; however, our results show that SVT is more common, which is also the most significant contributor to the rise in overall arrhythmias from 2009 to 2019. Our findings are most similar to a cohort of pregnant women with congenital heart disease, where SVT was also the most commonly reported arrhythmia (13).

This study highlights that presence of any arrhythmia is associated with a slightly greater risk of in-hospital mortality among women hospitalized for delivery. Arrhythmias were also associated with increased obstetric complications, including increased likelihood of Cesarean section, cardiovascular complications, including cardiac arrest, and APOs, specifically preeclampsia and preterm labor. Such adverse outcomes have their own health consequences and are not self-limited, leading to increased risk for short-term and long-term maternal morbidity (14–17). This analysis was unable to elucidate if one specific arrhythmia was more associated with in-hospital mortality or specific negative outcomes. However, further studies examining contribution of SVT, which is thought to be more benign, in comparison to VT, VF, or AF, with regards to mortality would provide great clinical significance for providers as they attempt to risk stratify their patients in real time. As maternal morbidity rises globally, early recognition of risk factors becomes more crucial to preventing APOs and downstream complications.(1, 18, 19) At the very least, the presence of an arrhythmia might help identify a higher risk group that will benefit from addressing cardiovascular health during pregnancy and in the post-partum time frame.

Since arrhythmias are markers for poor maternal outcomes, identifying sociodemographic and clinical risk factors that increase arrhythmia risk are crucial for risk mitigation. Our analysis shows that older pregnant individuals hospitalized for delivery, particularly those of advanced maternal age (age > 35), had a higher frequency of prevalent and incident arrhythmia. This is not unexpected, as aging in the general population has been associated with increased prevalence and severity of arrhythmias.(20) Also, increased maternal age is associated with cardiovascular comorbidities such as diabetes, hypertension, dyslipidemia, and obesity, which may partly contribute to the increased risk of arrhythmia. As the mean age of mothers continues to rise, it is essential to recognize the increased risk of arrhythmias in this population when counseling before and during pregnancy (21). Notably, our analysis was primarily focused on acquired risk factors. The specific contribution of having a history of congenital heart disease or inherited arrhythmogenic conditions—both of which have known correlation with increased risk of arrhythmia—were not elucidated in this study (22, 23). However, the considerable contribution of such history should not be forgotten and must be included in clinical practice when working with pregnant populations.

Beyond demographics, general cardiovascular risk factors such as obesity, hypertension, and known coronary artery disease with prior myocardial infarction further increased risk a woman's risk for arrhythmia among delivery hospitalizations. Individuals who are contemplating pregnancy or are pregnant with these risk factors should undergo aggressive risk factor modification and lifestyle modification. Our data also emphasize that those with known history of structural cardiac disease have an increased risk for arrhythmia and maternal morbidity—with a seven times greater risk for those with heart failure and 12 times greater risk for those with valvular disease. In addition, there are important differences in risk depending on race and ethnic status. Overall arrhythmias are highest in White pregnant individuals compared to other races; however, Black individuals had the highest yearly prevalence of arrhythmia. During the study time period, the prevalence of arrhythmia increased greatly for both Black and White pregnant individuals from 76.59/100,000 to 188.70/100,000 for Black (a 146% increase) and 55.49/100,000 to 179.19/100,000 for White (a 225% increase). Our results are in line with other NIS studies which have shown that Black pregnant individuals face a disproportionate burden of preeclampsia, peripartum cardiomyopathy, and severe maternal morbidity (24–26).

Socioeconomic factors may also be associated with differences in arrhythmia prevalence. Individuals on Medicare

are at increased risk of arrhythmia compared to those with private insurance. Since almost all patients in their peripartum years are younger than the typical year of eligibility for Medicare, it is likely that these patients have renal failure, end-stage renal failure, or other serious that qualify them for this coverage antenatally. In contrast, there is no association between arrhythmias and median household income. While other studies evaluating members of the general population reveal a lower risk of AF for those with a higher socioeconomic status than their age and race-matched counterparts (27), our study did not demonstrate the same trends. However, our population is different, as it includes only women who were hospitalized for delivery, who are younger than other study populations. Thus, the cascading downstream impact of social determinants of health may not yet have manifested clinically.

All women with known CVD or at increased CVD risk benefit from multidisciplinary care and preventive cardiology intervention prior to pregnancy and antenatally. As more individuals with simple or complex cardiovascular history are becoming pregnant, interdisciplinary cardio-obstetric collaboration has been shown to reduce cardiac maternal morbidity.(10, 28–30) Management of arrhythmia must occur at every stage of pregnancy, from prevention to early recognition of complications during delivery. Current risk scores for cardiovascular maternal morbidity, such as ZAHARA (Zwangerschap bij vrouwen met een Aangeboren HARtAfwijking-II) and CARPREG II (Cardiac Disease in Pregnancy II) already include history of prior cardiac events or arrhythmias in their score (31–33). Implementing interventions on cardiovascular comorbidities of pregnant women are necessary to reduce the growing morbidity and mortality of arrhythmia.

Study limitations

As with other studies which utilize the NIS, our study does face several limitations. First, in this deidentified NIS sample, we are unable to differentiate between pregnant individuals who may have had multiple admissions during the study period. Second, large databases are at risk of errors in coding, and we are unable to validate arrhythmia categorization, electrocardiogram analysis, causes of death, pregnancy outcomes, and long-term-follow up and other arrhythmia monitoring practices. Third, the database is not able to differentiate between new arrhythmias during the delivery hospitalization vs. a prior history of arrhythmia earlier in the patient's life. Fourth, we were unable to fully characterize patients with multiple admissions prior to the delivery. Fifth, we are unable to determine long-term outcomes of delivery hospitalizations complicated with arrhythmias due to database limitations. Finally, the NIS database did not include all characteristics that we would hope to examine including, but not limited to, an analysis of outcomes from hospitals that offer high-risk obstetric care verses those that do not, parity of delivery, and outcomes from natural pregnancies verses those that occurred with the use of assisted reproductive therapies. Furthermore, this analysis does not specifically evaluate the contribution of congenital heart disease or inherited arrhythmia conditions, such as arrhythmogenic cardiomyopathy or catecholaminergic polymorphic VT, to arrhythmia during pregnancy. Despite these limitations, our study is one of the largest evaluating delivery hospitalizations associated with arrhythmias from data across the United States providing greater generalizability.

Conclusion

In conclusion, we note an increasing combined prevalence and incidence of arrhythmias among women hospitalized for pregnancy in recent years. Pregnant individuals with underlying comorbidities, such as obesity, hypertension, structural heart disease, and heart failure, are more likely to be associated with tachyarrhythmias. Additionally, those hospitalized for delivery with arrhythmias prior to or during their pregnancy are more likely to have APOs, such a preeclampsia, preterm birth, and cesarean sections. This study allows physicians and patients to recognize recent trends in arrhythmias and related complications for pregnant women.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: National Inpatient Sample Database, https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp.

Author contributions

AT substantially contributed to the conception and design of the work, interpreted the results, drafted the first version of the manuscript, substantially revised the manuscript, and approved the final manuscript. YK, HP, SD, and GS substantially contributed to the conception and design of the work, acquisition and analysis of the data, verification of the underlying data, interpretation of the results, revised the manuscript, and approved the final manuscript. AM, AV, NG, SZ, RB, KW, and JC substantially contributed to the conception and design of the work, interpreted the results, revised the manuscript, and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1000298/full#supplementary-material

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Sex-related differences in self-reported treatment burden in patients with atrial fibrillation

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Background: Treatment burden (TB) is defined as the patient's workload of healthcare and its impact on patient functioning and wellbeing. High TB can lead to non-adherence, a higher risk of adverse outcomes and lower quality of life (QoL). We have previously reported a higher TB in patients with atrial fibrillation (AF) vs. those with other chronic conditions. In this analysis, we explored sex-related differences in self-reported TB in AF patients.

Materials and methods: A single-center, prospective study included consecutive patients with AF under drug treatment for at least 6 months before enrollment from April to June 2019. Patients were asked to voluntarily and anonymously answer the Treatment Burden Questionnaire (TBQ). All patients signed the written consent for participation.

Results: Of 331 patients (mean age 65.4 ± 10.3 years, mean total AF history 6.41 ± 6.62 years), 127 (38.4%) were females. The mean TB was significantly higher in females compared to males (53.7 vs. 42.6 out of 170 points, $p < 0.001$), and females more frequently reported TB ≥ 59 points than males (37.8% vs. 20.6%, $p = 0.001$). In females, on multivariable analysis of the highest TB quartile (TB ≥ 59), non-vitamin K Antagonist Oral Anticoagulant (NOAC) use [Odds Ratio (OR) 0.319; 95% Confidence Interval (CI) 0.12–0.83, $P = 0.019$], while in males, catheter ablation and/or ECV of AF (OR 0.383; 95% CI 0.18–0.81, $P = 0.012$) were negatively associated with the highest TB quartile.

Conclusion: Our study was the first to explore the sex-specific determinants of TB in AF patients. Females had significantly higher TB compared with males. Approximately 2 in 5 females and 1 in 5 males reported TB ≥ 59 points, previously shown to be an unacceptable burden of treatment for patients. Using a NOAC rather than vitamin K antagonist (VKA) in females and a rhythm control strategy in males could decrease TB to acceptable values.

KEYWORDS

atrial fibrillation, treatment burden, sex-related differences, quality of life, female sex

Introduction

Treatment burden (TB) is defined as the workload of healthcare (including time invested by a patient due to treatment and self-monitoring of chronic health conditions) and its impact on patient functioning and wellbeing (1). Patient capacity to endure treatment workload varies and depends on a variety of psychological, physical, and social factors (2, 3). One research showed that patients with three chronic health conditions spent a mean of 49.6–71.0 h on health-related activities and 1–6 visits to a healthcare giver per month, and a patient's workload increased with an increasing number of chronic health conditions (4). High TB can lead to patient non-adherence (5–7), exacerbation of chronic health conditions, higher hospitalization rate, and higher mortality, as well as lower quality of life (QoL) (8–10).

Treatment of chronic health conditions is time-consuming for both patients and physicians (11). The new concept of a minimally disruptive medicine approach aims to achieve the patient's goals in health and life while minimizing the patient's workload and suggests that care should move from the disease-centered to more patient-centered models of care (11, 12).

Several disease-specific and general tools have been developed and validated for the assessment of TB (13). Recently, a study in France (2,413 patients with one or more chronic conditions) reported a TBQ score cutoff of 59 points (out of 150 points) to be an unacceptably high burden of treatment for patients (14). In our main study, we assessed TB in patients with AF and found that approximately 1 in 4 patients with AF has TB $\geq$ 59 points; among others, the female sex was reported as an independent predictor of a TBQ score value of $\geq$59 points (15). Also, other studies showed that the female sex was associated with higher TB in patients with various chronic health conditions (16–18), but to our knowledge, there are no studies that address the sex differences in self-reported TB in patients with atrial fibrillation (AF).

In the present analysis, we explore sex differences in self-reported TB and the association of quality of life with TB in patients with AF.

Materials and methods

Study population

The detailed study protocol has been previously reported (15). Briefly, 514 consecutive adult in- or outpatients seen in the University Clinical Centre of Serbia from April to June 2019, who has been under treatment for at least 6 months before enrollment, were invited to voluntarily and anonymously answer the study questionnaires. Patients prescribed therapy within less than 6 months were excluded from the study to avoid under- or overestimation of the TB.

This exploratory analysis included the subset of patients with AF (n = 331) from the main study cohort, see **Figure 1** (15).

The study questionnaires included the modified Treatment Burden Questionnaire (TBQ, see **Supplementary Table 1**) and the EQ-5D questionnaire assessing QoL. The modification of TBQ in our study refers to the first four questions of the original TBQ addressing several aspects of taking medications, where we separately asked questions for oral anticoagulant therapy (OAC) and all other medication. The rationale for modifying the original TBQ was to elucidate specific treatment burden related to OAC. The remaining nine questions address the burden associated with laboratory testing, self-monitoring of health [e.g., measurements of blood

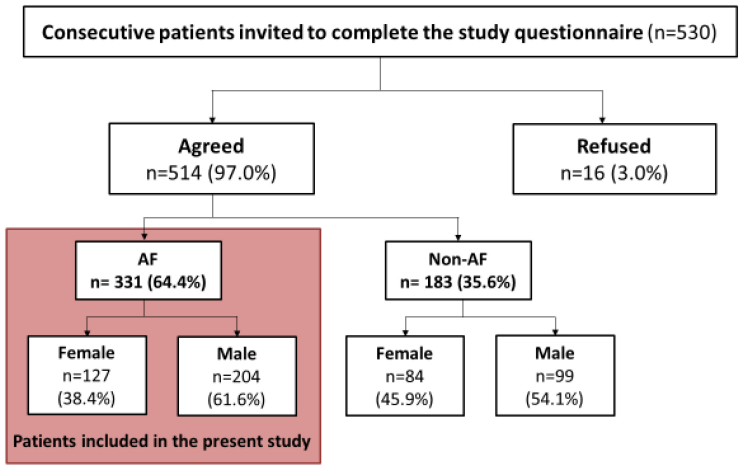

FIGURE 1
Study flowchart. AF, atrial fibrillation.

TABLE 1 Sex differences in socio-demographic characteristics of the study cohort, concomitant comorbidity and current medication in atrial fibrillation (AF) patients.

Variable	AF patients *n* = 331 (%)	Female *n* = 127 (38.4)	Male *n* = 204 (61.6)	*P*-value
Age (mean, ±SD)	65.42 ± 10.32	67.92 ± 8.74	63.86 ± 10.92	<0.001
Age ≤ 64	133 (40.2)	36 (28.3)	97 (47.5)	<0.001
Age 65–74	141 (42.6)	63 (49.6)	78 (38.2)	0.042
Age ≥ 75	57 (17.2)	28 (22.0)	29 (14.2)	0.074
Education degree				
Elementary	44 (13.3)	24 (18.9)	20 (9.8)	0.020
High school	165 (49.8)	63 (49.6)	102 (50.0)	1.000
College	47 (14.2)	18 (14.2)	29 (14.2)	1.000
University	75 (22.7)	22 (17.3)	53 (26.0)	0.079
Employment status				
Employed	83 (25.1)	14 (11.0)	69 (33.8)	<0.001
Unemployed	32 (9.7)	10 (7.9)	13 (6.4)	0.659
Retiree	49 (14.8)	103 (81.1)	122 (59.8)	<0.001
Marital status				
Married/living with a partner	250 (75.5)	85 (66.9)	165 (80.9)	0.006
Alone/divorced	32 (9.7)	9 (7.1)	23 (11.3)	0.253
Widow(er)	49 (14.8)	33 (26.0)	16 (7.8)	<0.001
Cigarette smoking				
Smoker	49 (14.8)	14 (11.0)	35 (17.2)	0.152
Former smoker	93 (28.1)	21 (16.5)	72 (35.3)	<0.001
Non-smoker	189 (57.1)	92 (72.4)	97 (47.5)	<0.001
Functional mobility[1]				
Fully mobile	313 (94.6)	118 (92.9)	195 (95.6)	0.325
Mobile with help	18 (5.4)	9 (7.1)	9 (4.4)	0.325
Comorbid conditions				
Hypertension	271 (81.9)	109 (85.8)	162 (79.4)	0.186
Heart failure	34 (10.3)	9 (7.1)	25 (12.3)	0.142
LVEF < 50%	50 (15.1)	6 (4.7)	44 (21.6)	<0.001
Ischemic heart disease	58 (17.5)	15 (11.8)	43 (21.1)	0.037
ACS	2 (0.6)	1 (0.8)	1 (0.5)	1.000
Prior MI	29 (8.8)	3 (2.4)	26 (12.7)	0.001
CAD	16 (4.8)	7 (5.5)	9 (4.4)	0.793
PCI/ballon angioplasty	30 (9.1)	6 (4.7)	24 (11.8)	0.031
CABG	8 (2.4)	0 (0.0)	8 (3.9)	0.026
Cardiomyopathy	30 (9.1)	7 (5.5)	23 (11.3)	0.080
Valvular disease	25 (7.6)	16 (12.6)	9 (4.4)	0.009
Supraventricular arrhythmias (SA + AFL)	52 (15.7)	18 (14.2)	34 (16.7)	0.642
Ventricular arrhythmias	30 (9.1)	9 (7.1)	21 (10.3)	0.431
CIEDs[2]	25 (7.6)	9 (7.1)	16 (7.8)	1.000
Peripheral artery disease	4 (4.1)	2 (1.6)	2 (1.0)	0.639
Diabetes mellitus type II	64 (19.3)	27 (21.3)	37 (18.1)	0.479
Prior stroke/TIA	13 (3.9)	7 (5.5)	6 (2.9)	0.257
Chronic kidney disease	28 (8.5)	8 (6.3)	20 (9.8)	0.314
COPD	24 (7.3)	9 (7.1)	15 (7.4)	1.000
Malignancy	24 (7.3)	7 (5.5)	10 (4.9)	0.803
Thyroid disfunction[3]	70 (21.2)	32 (26.0)	37 (18.1)	0.098
Hyperlipoproteinemia	114 (34.4)	43 (33.9)	71 (34.8)	0.906
Other diseases	46 (13.9)	17 (13.4)	29 (14.2)	0.872

(Continued)

TABLE 1 (Continued)

Variable	AF patients *n* = 331 (%)	Female *n* = 127 (38.4)	Male *n* = 204 (61.6)	*P*-value
CHA_2DS_2-VASc score (mean; range 0–7)	2.63 ± 1.50	3.38 ± 1.25	2.16 ± 1.45	<0.001
≥1 non-sex related CHA_2DS_2-VASc risk factors	300 (90.6)	121 (95.3)	179 (87.7)	0.031
AF characteristics				
Total AF history (yrs.)	6.41 ± 6.62	5.56 ± 5.60	6.91 ± 7.13	0.074
Permanent AF	97 (29.3)	37 (29.1)	60 (29.4)	1.000
Current medication				
OAC	299 (90.3)	113 (89.0)	186 (91.2)	0.568
VKA	189 (57.1)	70 (55.1)	119 (58.3)	0.570
NOAC	110 (33.2)	43 (33.9)	67 (32.8)	0.905
OAC treatment duration (yrs.)	3.69 ± 3.82	3.33 ± 3.38	3.90 ± 4.05	0.224
Aspirin	35 (10.6)	14 (11.0)	21 (10.3)	0.856
P2Y12 inhibitor	27 (8.2)	8 (6.3)	19 (9.3)	0.411
Beta blocker	264 (79.8)	99 (78.0)	165 (80.9)	0.574
Non-DHP Ca blocker	8 (2.4)	3 (2.4)	5 (2.5)	1.000
Digitalis	14 (4.2)	5 (3.9)	9 (4.4)	1.000
Antiarrhythmic drugs[4]	195 (58.9)	78 (61.4)	117 (57.4)	0.492
ACEI/ARB	232 (70.1)	87 (68.5)	145 (71.1)	0.624
Diuretics	188 (70.1)	77 (60.6)	111 (54.4)	0.305
Spironolactone	81 (24.5)	25 (19.7)	56 (27.5)	0.117
Statins	135 (40.8)	57 (44.9)	78 (38.2)	0.251
Sedative	35 (10.6)	13 (10.2)	22 (10.8)	1.000
PPI	95 (28.7)	32 (25.2)	63 (30.9)	0.318
Insulin	13 (3.9)	8 (6.3)	5 (2.5)	0.089
Oral antidiabetics	50 (15.1)	22 (17.3)	28 (13.7)	0.431
Other medications	127 (38.4)	55 (43.3)	72 (35.3)	0.164
Non-pharmacological treatment				
Ablation/ECV	136 (41.1)	39 (30.7)	97 (47.5)	0.003
ECV AF	96 (29.0)	24 (18.9)	72 (35.3)	0.002
AF Ablation	55 (16.5)	18 (14.2)	37 (18.1)	0.367
AFL Ablation	9 (2.7)	0 (0.0)	9 (4.4)	0.014
Multimorbidity and polypharmacy				
Patients with polypharmacy	237 (71.6)	96 (75.6)	141 (69.1)	0.213
N of drugs, mean (range)	6.18 ± 2.74 (1–15)	6.37 ± 2.68	6.07 ± 2.78	0.332
N of pills, mean (range)	7.21 ± 3.27 (1–20)	7.37 ± 3.05	7.11 ± 3.41	0.478
N of drugs without OAC, mean (range)	5.24 ± 2.63 (1–14)	5.42 ± 2.58	5.13 ± 2.66	0.338
N of pills without OAC, mean (range)	6.31 ± 3.21 (1–19)	6.48 ± 3.03	6.20 ± 3.33	0.433
Parenteral drug use	16 (4.8)	10 (7.9)	6 (2.9)	0.062
N of parenteral applications daily (range)	0.12 ± 0.59 (0–4)	0.20 ± 0.76	0.07 ± 0.44	0.068
N of comorbidities, mean (range)	3.70 ± 1.76 (1–14)	3.72 ± 1.78	3.68 ± 1.75	0.829
Patients with multimorbidity (without SA/VA)	313 (94.6)	123 (96.9)	190 (93.1)	0.213

AF, atrial fibrillation; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome; MI, myocardial infarction; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; AFL, atrial flutter; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; COPD, chronic obstructive pulmonary disease; OAC, oral anticoagulant therapy; VKA, vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; ASA, acetylsalicylic acid; DHP, dihydropyridine; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor inhibitor; PPI, proton pump inhibitor; ECV, electrical cardioversion; SA, supraventricular arrhythmias; VA, ventricular arrhythmias; N, number.

[1]There were no immobile patients in this cohort.

[2]CIED: cardiac implantable electronic devices (antybradicardia PM: *n* = 20, ICD: *n* = 7, CRT: *n* = 5).

[3]Thyroid disfunction: hypothyroidism, *n* = 65, hyperthyroidism, *n* = 29.

[4]Anthyarrhythmics: mexiletine, propafenone, flecanide, sotalol, amiodaron.

glucose, blood pressure or international normalized ratio (INR)], doctor visits, administrative tasks (e.g., arranging visit appointments, health-related paperwork), the effect(s) of diet restrictions/modification and physical exercise requirements and social impact of the treatment. The financial burden associated with healthcare was excluded

from the questionnaire because all Serbia citizens have a free national public health insurance program [however, specific drugs such as non-vitamin K antagonist oral anticoagulants (NOAC) are not reimbursed], which could have inflated the TB. Patient demographics, chronic health conditions (only confirmed diagnoses using International Classification of Diseases 10 were included), and current therapy were recorded by the study investigator. Multimorbidity was defined as the coexistence of two or more chronic health conditions (19) other than AF. Polypharmacy was defined as the concomitant use of five or more medications daily (20).

All patients signed the written consent for participation, and the Ethical Committee approved the study at the School of Medicine, Belgrade University.

Statistical analysis

Patients with AF were stratified and analyzed by sex. Continuous variables were shown as mean with standard deviation (SD) or median with interquartile range (IQR), while the nominal variables were shown as frequencies and percentages. Sex-specific differences in baseline demographics, comorbid conditions, characteristics of AF, and current treatment were analyzed using the Student's *t*-test for continuous variables or the Chi-Square test for categorical data.

Patients were instructed to grade each TB question from 1 (the lowest burden) to 10 (the highest burden) points. The total TB score value was calculated as a sum of question-specific points, and the maximum possible score value is 170 points. Therefore, an individual patient's TB score is expressed as a sum of points and a percentage of the maximum score value.

The self-reported TB was analyzed as a continuous variable with the Linear Regression method. In addition, TB was divided into quartiles and analyzed with the Binary Logistic Regression method. We examined the relationship of baseline variables listed in **Table 1** with total TB, the highest and lowest TB quartile on univariate analyses. Multivariate models with total TB and the highest/lowest TB quartile as independent variables were conducted using the statistically significant variables in univariate analyses.

The analyses of the EQ-5D questionnaire and QoL were conducted in the same manner as the analyses of TB. In addition, the relationship of the EQ-5D score with TB quartiles was analyzed using the Kruskal–Wallis H test.

The statistical software program IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA) was used for all analyses. All reported *P*-values in this study were two-sided, and the *P*-value of <0.05 was considered statistically significant.

Results

Study population

Of 331 patients with AF, 127 (38.4%) were females, and 204 (61.6%) were males. Sex differences in socio-demographic characteristics, concomitant comorbidities, and concomitant therapy are shown in **Table 1**.

The mean age was 65.4 ± 10.3 years, the mean CHA_2DS_2-VASc score was 2.63 ± 1.50, and the mean total history of AF was 6.41 ± 6.62 years (median 4.00 years, IQR 7.00 years). Permanent AF, multimorbidity, and polypharmacy were reported in 97 (29.3%), 313 (94.6%), and 237 (71.6%) patients, respectively.

Compared with males, females were more likely to be older and more frequently had valvular heart disease or ≥1 non-sex-related CHA_2DS_2-VASc score stroke risk factor (all $P \leq 0.05$). Males were more likely to have left ventricular ejection fraction <50% and ischemic heart disease and more frequently underwent catheter ablation and/or electrical cardioversion (ECV) of AF compared with females (all $P \leq 0.037$). There were no differences in concomitant therapy, a number of comorbidities, the prevalence of multimorbidity, and polypharmacy between the sexes (see **Table 1**).

Sex differences in self-reported treatment burden

The mean self-reported TB score was 46.9 points (27.6% of the maximum score value of 170 points). The mean TB score was significantly higher in females compared with males [53.7 (31.6% of 170 points) vs. 42.6 (25.1% of 170 points) points, $p < 0.001$]; also, females reported significantly more frequently TB ≥ 59 points compared with males (37.8% vs. 20.6%, $P = 0.001$), see **Figure 2** and **Table 2**.

Item-specific sex differences in self-reported treatment burden

Both females and males attributed the highest TB to administrative issues, including visit appointments and health-related paperwork, and diet modification requirements, see **Supplementary Table 1**.

In comparison to males, females reported significantly higher TB score values for questions about the frequency of drugs intake per day and specific conditions when drugs are taken, self-monitoring, doctor visits, diet modifications, physical activity requirements, and social aspects of TB score (all $P \leq 0.05$); see **Figure 3** and **Supplementary Table 1**.

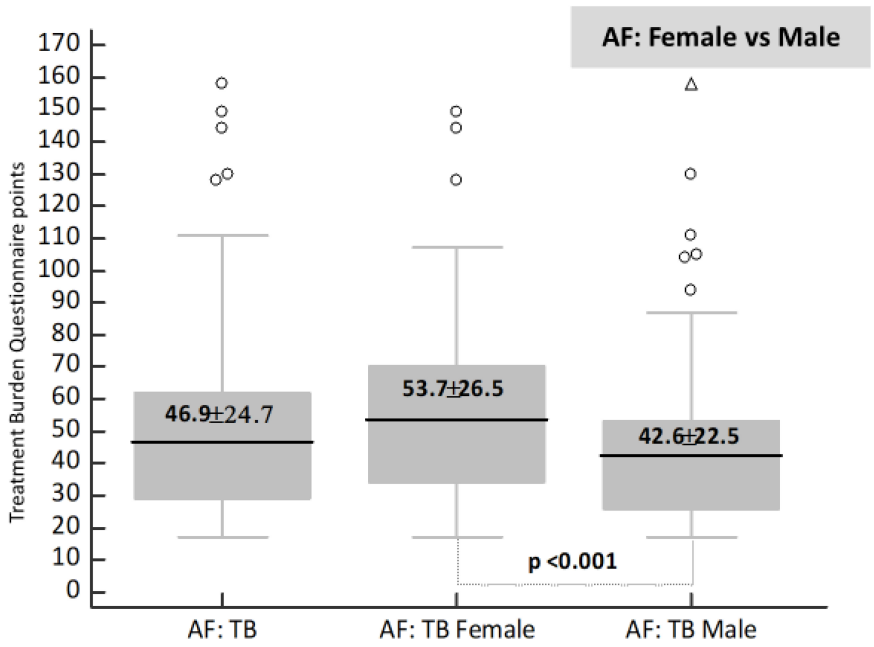

FIGURE 2
Sex difference in treatment burden in whole and atrial fibrillation (AF) study cohort. TB, treatment burden; AF, atrial fibrillation.

Sex-specific univariate and multivariable analysis of self-reported treatment burden

The univariate and multivariable analyses of self-reported TB are shown in **Table 3** and **Supplementary Tables 3–5**.

Oral anticoagulant treatment duration ranged from 0.5 to 21 years, there were no statistically significant differences in the mean duration of OAC treatment between sexes. On univariate analysis, OAC treatment duration as well as OAC treatment duration less than 1 year were not significantly associated with total TBQ score value, or the highest and the lowest TBQ score quartile in either sex, see **Supplementary Tables 3–5**. On multivariable linear regression analysis, VKA therapy was statistically significantly associated with higher TB (p = 0.001) in females, while diuretic therapy was a negative predictor of higher TB (p = 0.012). In males, ablation and/or ECV were negative predictors of higher TB, see **Table 3**.

On multivariable analysis of the highest TB quartile (TB ≥ 59), NOAC use [Odds Ratio (OR) 0.319; 95% Confidence Interval (CI) 0.12–0.83, P = 0.019], diuretic therapy (OR 0.318; 95% CI 0.13–0.76, P = 0.010), and CHA_2DS_2-VASc score (OR 0.700; 95% CI 0.49–0.99, P = 0.045) were negatively associated with the highest TB quartile, while proton pump inhibitor (OR 5.354; 95% CI 1.97–14.56, P = 0.001) was positively associated with the highest TB quartile, in females. In males, on a multivariable analysis of the highest TB quartile, catheter ablation and/or ECV of AF (OR 0.383; 95% CI 0.18–0.81, P = 0.012), and supraventricular arrhythmias (OR 0.222; 95% CI 0.05–0.98, P = 0047) were negatively associated with the highest TB quartile, see **Table 3**.

On multivariable analyses of the lowest TB quartile, there was a positive association with catheter ablation of AF (OR 2.753; 95% CI 1.26–6.01, P = 0.011) and a negative association with age ≤50 (OR 0.187; 95% CI 0.04–0.85, P = 0.030) in males, and a positive association with PCI/balloon angioplasty (OR 7.642; 95% CI 1.11–52.59, P = 0.039) in females, see **Table 3**.

On a multivariable sensitivity analysis restricted to patients taking a VKA [n = 189 patients, (57.1%)], the female sex was significantly associated with a higher TB score (Beta 0.187; 95% CI 2.4–18.5, P = 0.011), and the association was also present in the analysis restricted to 110 patients taking a NOAC (Beta 0.226; 95% CI 2.3–16.0, P = 0.009).

On a univariate sensitivity analysis restricted to AF patients without OAC therapy [n = 32 patients (9.7%)], there were no significant differences in self-reported TB between the sexes (Beta 0.201; 95% CI -7.3–25.2, P = 0.269).

Sex-related differences in self-reported quality of life and relations with treatment burden

The lowest QoL reflects the highest EQ-5D score of 20 points, whereas the highest QoL would reflect the lowest EQ-5D score of 0 points.

TABLE 2 The distribution of study cohort per quartiles of treatment burden in atrial fibrillation (AF).

Treatment burden	AF patients *N* (%)	Female *N* (%)	Male *N* (%)	*P*-value
Mean value	46.87	53.73	42.59	<0.001
95% CI	44.20–49.53	49.08–58.39	39.49–45.69	
Range	17–158	17–149	17–158	
SD	24.66	26.52	22.45	
Median	40.00	48.00	37.00	
IQR	33.00	36.00	27.00	
Proportion of the maximum 170 points	27.57%	31.61%	25.05%	
TB quartiles				
TB ≤ 26 points	73 (22.1)	21 (16.5)	52 (25.5)	0.058
TB 27–39 points	89 (26.9)	27 (21.3)	62 (30.4)	0.070
TB 40–58 points	79 (23.9)	31 (24.4)	48 (23.5)	0.855
TB ≥ 59 points	90 (27.2)	48 (37.8)	42 (20.6)	0.001
Total	331	127 (38.4)	204 (61.6)	

AF, atrial fibrillation; N, number; CI, confidence interval; SD, standard deviation; IQR, interquartile range: TB, treatment burden.

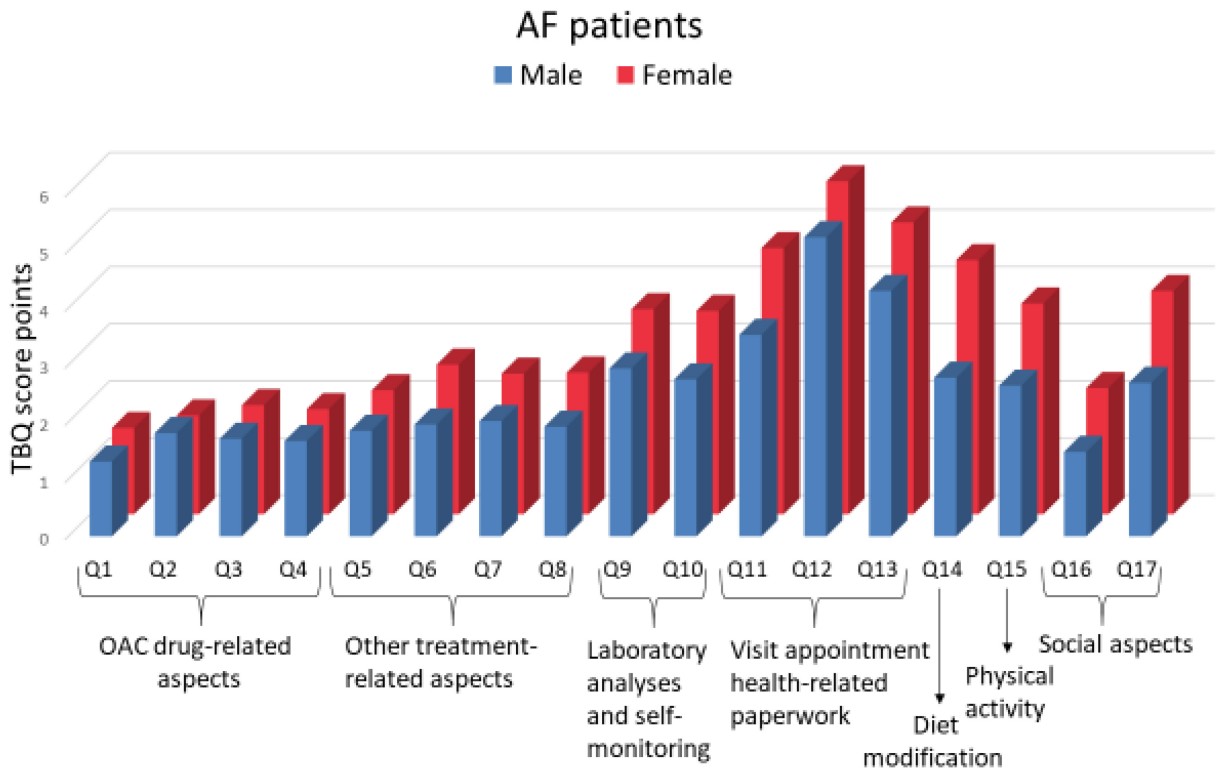

FIGURE 3
Sex difference in specific management aspect-related treatment burden. AF, atrial fibrillation; TBQ, treatment burden questionnaire; Q, question; OAC, oral anticoagulant.

Overall, the mean EQ-5D score value was 2.95 points (14.75% of the maximum 20 points). Females reported significantly higher EQ-5D score (i.e., lower QoL) compared with males (3.97 vs. 2.32 points, $P < 0.001$), Table 4. The EQ-5D item-specific sex differences are shown in Supplementary Table 2. Compared with males, female patients reported significantly higher EQ-5D score for mobility, pain/discomfort, and anxiety/depression (all $P \leq 0.002$); see Supplementary Table 2.

With increasing the TB mean score, the mean EQ-5D QOL score significantly increases (i.e., QoL was lower) in both sexes. In addition, the anxiety/depression question score was

TABLE 3 Multivariable linear regression and logistic regression analyses of treatment burden in atrial fibrillation (AF) patients.

	Variable	Beta	95% CI	*P*-value
Multivariable linear regression analysis				
Female	VKA therapy	0.192	1.19–19.24	0.027
	Diuretic therapy	−0.219	−21.05–(−2.67)	0.012
Male	Ablation and/or ECV	−0.179	−14.13–(−1.89)	0.011
Multivariable logistic regression analysis of the highest TB quartile (TB ≥ 59)				
Female	PPI therapy	5.354	1.97–14.56	0.001
	NOAC	0.319	0.12–0.83	0.019
	Diuretic therapy	0.318	0.13–0.76	0.010
	CHA_2DS_2-VASc score	0.700	0.49–0.99	0.045
Male	Ablation and/or ECV	0.383	0.18–0.81	0.012
	Supraventricular arrhythmias	0.222	0.05–0.98	0.047
Multivariable logistic regression analysis of the lowest TB quartile (TB ≤ 26)				
Female	PCI/balloon angioplasty	7.642	1.11–52.59	0.039
	Supraventricular arrhythmias	4.155	1.21–14.30	0.024
	Former smoker	3.752	1.15–12.21	0.028
Male	Ablation AF	2.753	1.26–6.01	0.011
	Age ≤ 50 years	0.187	0.04–0.85	0.030

VKA, vitamin K antagonist; ECV, electrical cardioversion; AF, atrial fibrillation; PPI, proton pump inhibitor; PCI, percutaneous coronary intervention; NOAC, non-vitamin K antagonist oral anticoagulant.

significantly increased with increasing TB among both sexes (see, **Figure 4**).

Univariate and multivariable analyses of the EQ-5D score are shown in **Supplementary Tables 6–9**. On multivariable analyses, the highest TB quartile (Beta 0.182; 95% CI 0.25–2.20, $P = 0.015$), question about physical activity requirements within TB (Beta 0.237, 95% CI 0.13–0.41, $P < 0.001$), age (Beta 0.156; 95% CI 0.01–0.11, $p = 0.032$), and mobility with help (Beta 0.149; 95% CI 0.06–3.73, $P = 0.043$) were associated with the lower QoL score in females, whereas number of comorbidities (Beta 0.160; 95% CI 0.09–0.473, $P = 0.004$), peripheral arterial disease (Beta 0.297; 95% CI 6.04–12.53, $P < 0.001$), physical activity requirements within TB (Beta 0.297; 95% CI 0.22–0.45, $P < 0.001$), and the social aspect of TB (Beta 0.186; 95% CI 0.16–0.56, $P = 0.001$) were associated with the lower QoL score in males, see **Supplementary Table 10**.

Overall self-rated health status

Females reported significantly lower self-estimated health status ratings than males (58.8 ± 19.72 vs. 64.0 ± 20.6, $p = 0.025$).

The self-estimated status rating decreased with increasing TB score in the entire study cohort [Beta 0.200; 95% CI -0.25–(-0.08), $P < 0.001$] and among males [Beta -0.224; 95% CI -0.33–(-0.08), $P = 0.001$], but not when the analysis was restricted to females (Beta -0.116; 95% CI -0.22–0.05, $P = 0.195$).

The highest TB quartile (≥59 points) was significantly associated with the lowest self-reported health status rating quartile in the whole cohort (OR 2.185; 95% CI 1.33–3.58, $P = 0.002$) and among females (OR 2.100; 95% CI 1.01–4.35, $P = 0.046$), but the association was of borderline significance on the analysis restricted to males (OR 1.962; 95% CI 0.98–3.93, $P = 0.057$); see **Supplementary Table 10**.

Discussion

To our knowledge, this study was the first to compare the TB, explore its significant determinants, and a TB impact on QoL between sexes in AF patients. The main findings were as

TABLE 4 The distribution of study cohort per quartiles of EQ-5D questionnaire in atrial fibrillation (AF).

	AF patients *N* (%)	Female *N* (%)	Male *N* (%)	*P*-value
EQ-5D questionnaire				
Mean value	2.95	3.97	2.32	<0.001
95% CI	2.60–3.31	3.39–4.54	1.90–2.75	
Range (minimum-maximum)	0–15	0–14	0–15	
SD	3.25	3.28	3.08	
Median	2.00	3.00	1.00	
IQR	5.00	5.00	3.00	
Proportion of the maximum 20 points	14.75%	19.85%	11.60%	
EQ-5D quartiles				
EQ-5D ≤ 1 point	150 (45.3)	36 (28.3)	114 (55.9)	0.094
EQ-5D = 2 points	39 (11.8)	17 (13.4)	22 (10.8)	<0.001
EQ-5D 3–5 points	83 (25.1)	38 (29.9)	45 (22.1)	<0.001
EQ-5D ≥ 6 points	59 (17.8)	36 (28.3)	23 (11.3)	<0.001
Total	331	127 (38.4)	204 (61.6)	

AF, atrial fibrillation; N, number; CI, confidence interval; SD, standard deviation; IQR, interquartile range.

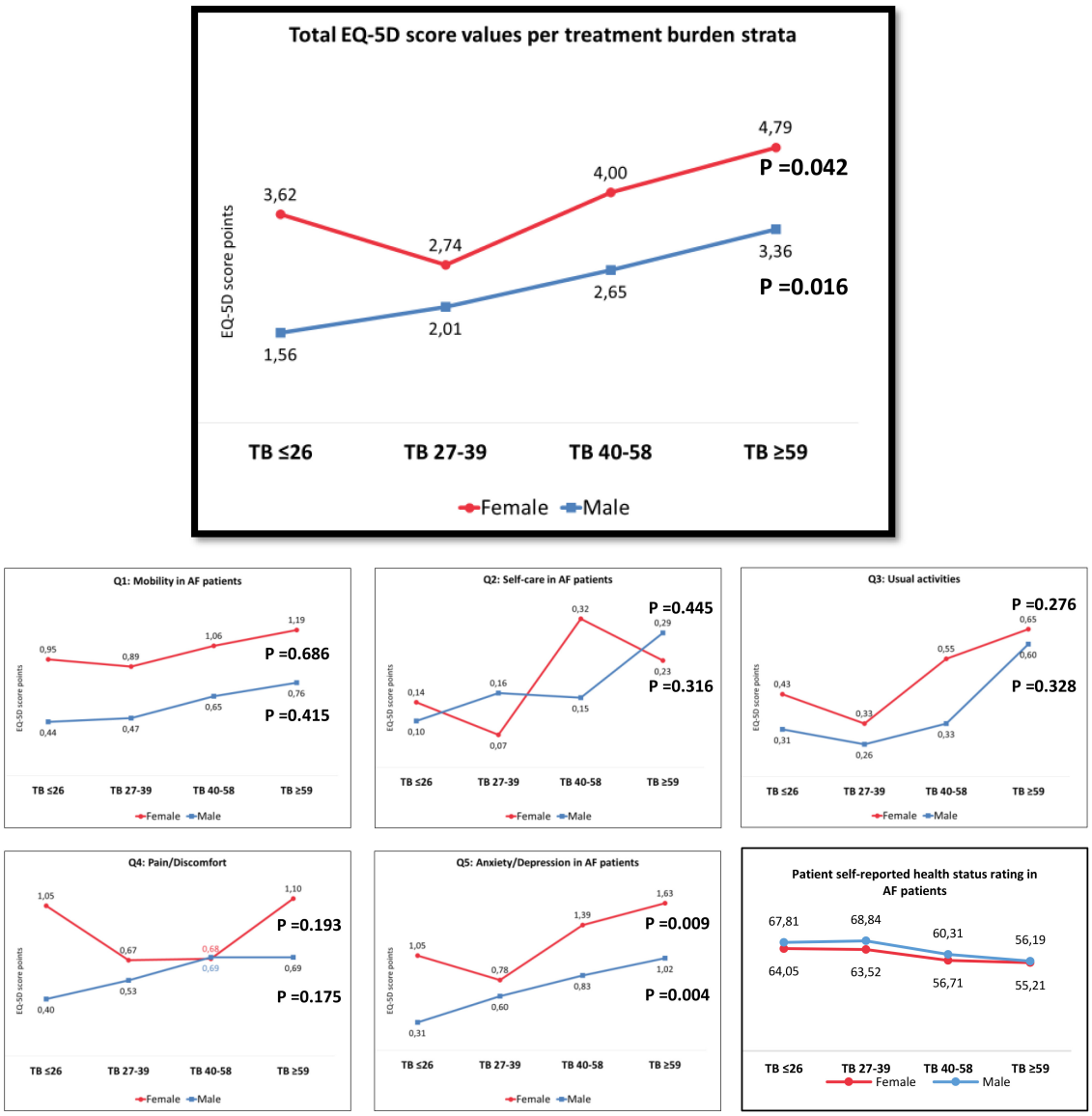

FIGURE 4
Sex difference in self-reported health rating and the EQ-5D score values across treatment burden quartiles.

follows: (i) females reported significantly higher TB compared to males; (ii) approximately 1 in 5 males and 2 in 5 females reported TB $\geq$ 59 points.

In detail, our analysis showed that: the most considerable share of self-reported TB in both sexes was attributed to administrative issues (e.g., visit appointments, health-related paperwork) and diet modification requirements; Compared with males, females reported significantly higher TB for questions about frequency of drugs intake per day and specific conditions drugs are taken, self-monitoring, doctor visits, diet modifications, physical activity requirements, and social aspects of TB score; Females who were taking VKA reported significantly higher TB than those without, while NOAC use in females was a negative predictor of the TB $\geq$ 59 points, such finding were not recorded in males; In males ablation of AF and in females PCI and/or balloon angioplasty were positive predictors of TB $\leq$ 26 points; The highest TB quartile ($\geq$59 points) and TB question about physical activity were significantly associated with lower QoL in females, while TB questions about physical activity and social aspects were significantly associated with lower QoL in males; Questions about a doctor visit appointment and recommended physical activity were associated with the highest EQ-5D quartile (score $\geq$ 6 points) in females, while question-related to recommended physical activity was significantly associated with the highest EQ-5D quartile; The highest TB quartile was

significantly associated with the lowest self-reported health status rating quartile in females, but the association was of borderline significance when the analysis was restricted to males.

Our analysis showed that females were significantly older than males, which aligns with previously published studies (21–23). Similarly, to other reports, females in our study underwent significantly less invasive procedures than males, also shown in several other studies (23–25).

A recent study of non-AF patients with various chronic health conditions reported that a TB of ≥59 points was unacceptably high for patients (14). In our main study, we determined that the highest quartile of TBQ among patients with AF was also ≥59 points and reported that 1 in 4 patients with AF has TB ≥ 59 points (15). In the current analysis, we showed that 2 in 5 females with AF reported a TB ≥ 59 points compared to 1 in 5 males, suggesting that females are more burdened by AF treatment than males. Furthermore, multivariable analysis restricted to non-AF patients showed no significant difference in TB among sexes, suggesting that the AF management burdened significantly more females than males. Similarly, the recent study which explored treatment burden among multimorbid patients using the Multimorbidity TBQ also showed a higher TB score among females (26).

The higher TB score in females may be influenced by a higher severity of symptoms, higher heart rate in AF, and longer durations of AF episodes, which occur more frequently in females compared to males, and thus requiring more frequent healthcare visits (23, 27). Females also underwent catheter ablation significantly less often and remained on antiarrhythmic drug therapy longer than males, which could also contribute to the higher TB (23).

Our main study findings suggest that it is essential to improve the healthcare system organization, as it may diminish TB in AF patients (15). Current analysis suggests that females may be more affected by TB than males, therefore, females may benefit more from better system organization.

Our findings also suggest that OAC use is more burdensome for females compared with males, and using a NOAC rather than a VKA in females could decrease TB below the unacceptable TB. Regarding males, a rhythm control strategy for AF management could significantly decrease TB.

Females reported significantly higher TB score on specific questions regarding self-monitoring, doctor visits, diet modifications, physical activity, and social aspects of TB. These particular areas may be the primary goal of developing sex-specific interventions and strategies to improve the healthcare system to reduce TB in females.

It has been previously reported that impaired QoL was associated with increased morbidity and mortality among patients with chronic cardiac health conditions (28). The recently published systematic review of sex differences in QoL in AF patients suggests that lower QoL in females may be explained by a more substantial effect of AF on females than on males (29). In line with other studies, we showed that females with AF have lower QoL than males with AF (30). In our main study, female sex, and TB were independent predictors of lower QoL in AF patients but not in non-AF patients, suggesting that AF may be more burdensome to females than males (15). Current analysis provides new insights regarding the impact of TB on quality of life. In females, TB ≥ 59 and TB question regarding recommended physical activity, while in males, recommended physical activity and social aspects of TB were independent drivers of the lower QOL. Thus, improving the burden of treatment or using a minimally disruptive medicine approach could lower TB and improve QoL, especially among females, but that needs further investigation.

In our study, females reported significantly lower self-reported health status than males. These sex differences in self-reported health status were also reported in an extensive global survey conducted in 59 countries and were attributed to possibly combined biological and social factors (31). We found that TB scores ≥59 points were an independent predictor of lower self-reported health status in AF patients, also when the analysis was restricted to females but not in males, implying that lowering TB using a minimally disruptive medicine approach may also lead to an improvement in self-reported health status.

Limitations

Single-center study results may not be generalizable to other AF cohorts. Nevertheless, the BALKAN-AF study, including Serbia, showed that the cardiovascular and AF-related risk profile of AF patients was broadly similar to AF patients in other European countries (32). We prospectively included consecutive patients with AF, but the relatively small cohort size may have influenced the results. In addition, in our study, we did not collect data on other factors that could influence TB, such as, for example, patient knowledge of AF, mental status, cognitive function, etc. Owing to the use of modified TBQ in this study, our findings may not be comparable to studies using originally reported TBQ. Nevertheless, the aim of our study was not a comparison to other chronic medical conditions, but the analysis of sex-related differences in self-reported TB among patients with AF. Also, our study did not investigate the financial burden of treatment because of the nationwide health insurance system used by all citizens in Serbia. Another limitation of our study is the lack of follow-up, as the treatment burden may change over time, but the follow-up in our study is ongoing.

Conclusion

Our study was the first to explore sex-specific determinants of TB in AF patients. Females reported significantly higher TB

compared with males. A TB of ≥59 points (i.e., unacceptably high TB) was reported by 2 out of 5 females and 1 out of 5 males with AF. Using a NOAC rather than VKA in females and a rhythm control strategy in males could decrease TB to acceptable values. More research is needed to confirm our findings in different AF cohorts and elucidate how to decrease TB in patients with AF.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the School of Medicine, Belgrade University, Ethical Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TP: study design, manuscript preparation, and critical intellectual impact. MMi: data acquirement and drafting of the manuscript. JS, MMa, VK, and AK: data acquirement and manuscript reviewing. NM: manuscript reviewing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

TP served as a consultant for Bayer and Pfizer with no personal fees.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1029730/full#supplementary-material

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Sex-related differences in incidence, phenotype and risk of sudden cardiac death in inherited arrhythmia syndromes

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Inherited Arrhythmia Syndromes (IAS) including long QT and Brugada Syndrome, are characterized by life-threatening arrhythmias in the absence of apparent structural heart disease and are caused by pathogenic variants in genes encoding cardiac ion channels or associated proteins. Studies of large pedigrees of families affected by IAS have demonstrated incomplete penetrance and variable expressivity. Biological sex is one of several factors that have been recognized to modulate disease severity in IAS. There is a growing body of evidence linking sex hormones to the susceptibility to arrhythmias, yet, many sex-specific disease aspects remain underrecognized as female sex and women with IAS are underinvestigated and findings from male-predominant cohorts are often generalized to both sexes with minimal to no consideration of relevant sex-associated differences in prevalence, disease manifestations and outcome. In this review, we highlight current knowledge of sex-related biological differences in normal cardiac electrophysiology and sex-associated factors that influence IAS phenotypes.

KEYWORDS

estrogen, progesterone, testosterone, long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, precision medicine

1. Introduction: The significance of sex differences in inherited cardiac arrhythmias

Inherited Arrhythmia Syndromes (IAS) can lead to sudden cardiac death (SCD) in the absence of apparent structural heart disease and are caused by pathogenic variants in genes encoding cardiac ion channels or associated proteins. Studies of large pedigrees of families affected by IAS have demonstrated incomplete penetrance and variable expressivity. Biological sex is one of several factors that have been recognized to modulate disease severity in IAS *via* the effect of steroid and non-steroid hormones on cardiac ion channels (1). In women, the risk of arrhythmias varies during different phases of the menstrual cycle, influenced by shifts in the balance of the steroid hormones estrogen and progesterone, while in men,

testosterone has been shown to regulate expression of critical myocardial ion channels (Figure 1). Herein, we will review evidence from basic research and clinical studies linking sex hormones to the susceptibility to arrhythmias in IAS. A better understanding of the role of sex-related differences in modulating clinical outcomes in IAS will lead to improvement in individualized risk prediction of SCD and clinical management of patients with IAS.

2. Sex differences in cardiac electrophysiology

Biological sex, among other factors, has been recognized as a modifier of cardiac electrical activity. In this respect, genetic differences and variations in sex hormones play an important role, while other aspects such as autonomic tone, hemodynamics, and non-steroid hormone levels may also contribute to sex-related differences but their roles are insufficiently studied. While males tend to have longer PR intervals, P-wave and QRS-durations, adult women have been shown to higher resting heart rate as well as longer heart-rate corrected QT intervals (QTc) (2). With the onset of puberty, males manifest QT shortening while females develop QT prolongation. Additionally, these apparent differences in QT intervals diminish in postmenopausal women, suggesting a prominent role of sex hormones in modulation of the QT interval (2–4). During the menstrual cycle, shorter QTc durations are observed in the luteal phase, considered an effect of higher progesterone levels (5). Furthermore, as the QT/RR slope is steeper in women, differences in QTc duration are more manifest at slow heart rates (6).

3. Long QT syndrome

Congenital Long QT Syndrome (LQTS) is a primary electrical disorder characterized by a prolonged repolarization phase of the cardiac action potential, reflected by a prolonged QT interval on the surface electrocardiogram (ECG). Clinically, LQTS leads to a predisposition to arrhythmias, including polymorphic ventricular tachycardia (torsades de pointes, TdP) and sudden cardiac death (7). Over the past 25 years, 17 genes have been reported in association with LQTS; however, a recent literature curation by an international expert group found only 6 genes –*KCNQ1, KCNH2, SCN5A,* and *CALM1-3* to have definitive evidence for causing LQTS (8). Variants in the LQT1-3 genes (*KCNQ1*, *KCNH2* and *SCN5A*, respectively) are responsible for ≈90% of all reported genotype-positive cases (9).

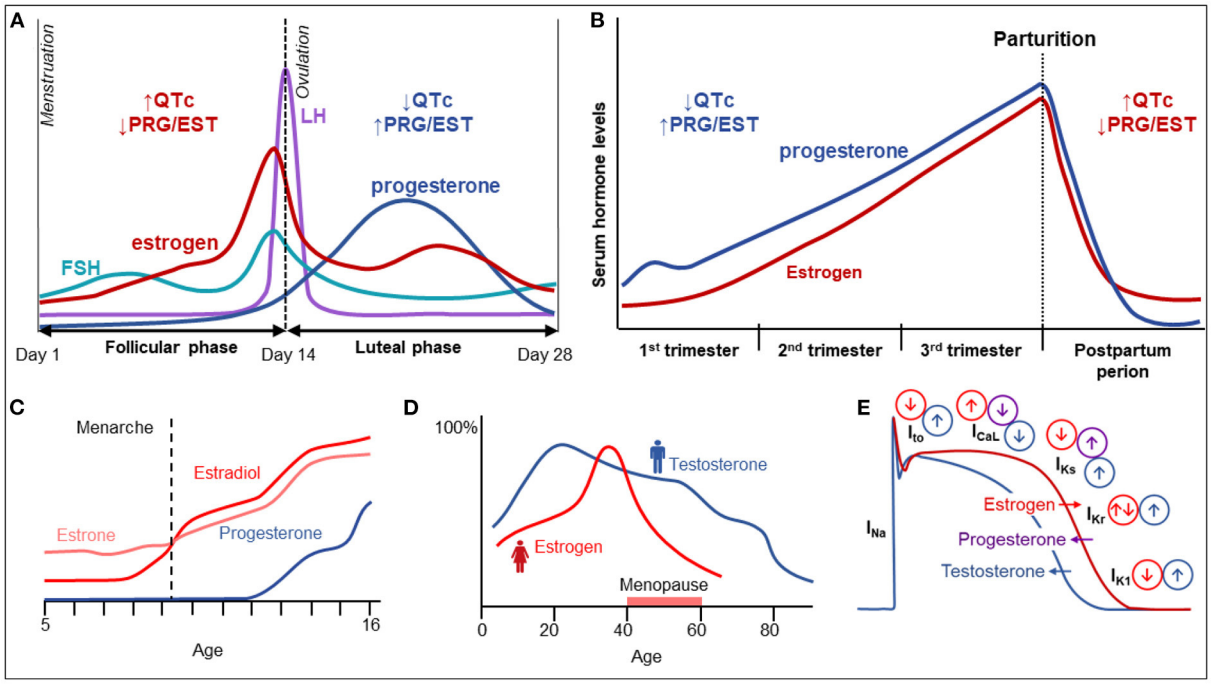

FIGURE 1
Sex hormones and their influence on cardiac electrophysiology. **(A)** Variation in female hormone levels during the menstrual cycle. **(B)** Variation in female sex hormones and electrical parameters during pregnancy and the postpartum period. **(C)** The increase of female sex hormones until adolescence. **(D)** The variation of female and male sex hormones with age. **(E)** The influence of various hormones on cardiac electrical currents and action potential duration.

As significant sex-related differences in the QT-interval exist, sex is considered an important factor in the management of LQTS patients (Table 1). QT intervals are generally longer in healthy women as compared to men; therefore, different cut-offs for prolonged QTc have been established—470 ms in men and 480 ms in women (10). Among patients with disease-causing variants in LQTS-associated genes, women have higher disease penetrance than men (11), and comprise around 56% of all LQTS cases (12, 13). Women with LQT1 and LQT2 have longer QTc than affected men (14). Women are more susceptible to developing prolongation of the QT at slower heart rates, making QTc duration at rest and during sleep critical markers of arrhythmic risk (14). The risk of TdP also varies during the lifespan with adult women with LQTS being at higher risk of TdP than males and pre-pubertal females (15).

In contrast, men with LQTS have a higher risk of a fatal presentation, while women often have recurrent, non-fatal events, such as syncopal episodes (11). Men suffering from LQT1 and LQT2 have clinical manifestations at a younger age than affected women (16). In childhood and prior to puberty, boys with LQT1 (but not LQT2 or LQT3) are at a higher risk for arrhythmic manifestations than girls (17), but the arrhythmic risk reverses after puberty with higher risk in females (11). The risk of arrhythmias is also higher in post-pubertal women with LQT2 compared to men (17), and it stays elevated at post-reproductive age (18). Among patients with LQT3, females in general, and particularly at 30–40 years age, are at higher risk for SCD (19).

3.1. Acquired long QT syndrome

Pathogenic variants in *KCNE1* and *KCNE2* genes have been reported in association with drug or electrolyte-provoked LQTS, referred to as acquired LQTS; certain *KCNE1* variants have also been implicated in congenital LQTS (8). Risk factors for drug-induced LQTS include underlying bradyarrhythmias or abrupt heart rate slowing (the "short–long–short" cycle length changes), female sex, hypokalemia and hypomagnesemia, the presence of advanced underlying structural heart disease, recent conversion from atrial fibrillation, previously unrecognized congenital LQTS, and polypharmacy, particularly, use of multiple QT-prolonging drugs (20, 21). Clinical studies have shown that female sex is associated with a 2–3-fold higher risk of developing drug-induced QT prolongation for both cardiovascular (22) and non-cardiovascular medications (23). This is also supported by the findings that females are prone to TdP at relatively shorter QTc intervals than their male counterparts (24). This higher susceptibility to drug-provoked QT prolongation is not fully explained by differences in plasma levels of sex hormones, but rather is attributed in part to female intrinsic sensitivity (25).

3.2. Clinical implications

β-blockers are the therapeutic cornerstone in congenital LQTS and recommended in both sexes (26). Therapy with β-blockers (preferably a non-selective beta blocker like nadolol) is most effective in LQT1, but also shows up to 70% efficacy in LQT2 (17). Response to β-blockers varies by sex and underlying genotype so that adult LQT1 men benefit most from β-blockade (27). Asymptomatic pre-adolescent boys with a QTc >500 ms are at >12-fold increased risk of life-threatening cardiac arrhythmias as compared to their female peers, highlighting the urgent need of therapy in these patients (28). Selected asymptomatic adult men with LQTS, particularly those with older age at diagnosis and QTc <470 ms, have the lowest arrhythmic risk, but may still benefit from low dose β-blocker therapy (11, 29), while the risk in females might be increased after puberty due to the influence of sex hormone on cardiac repolarization, requiring escalation of β-blocker therapy.

The evaluation of therapy in LQT3 is more difficult since these cases are less common. In one study, β-blockers resulted in 83% reduction in arrhythmic events in women but not in men with LQT3; men, however, had significantly fewer events (19). Patients with LQT3 and poor adherence to therapy with β-blockers may benefit from a left cardiac sympathetic denervation (LCSD) (30). In selected LQT3 patients, who remain symptomatic or have a QTc > 500 ms notwithstanding therapy with β-blockers, mexiletine can be considered (31, 32). Alternatively, flecainide may be used in LQT3, in the absence of flecainide-provoked Brugada ECG pattern, that is more frequently seen in males (33). Over the past years, the indications for ICD implantation have been revisited and currently only a small number of LQTS patients are eligible for ICD insertion; these primarily include survivors of cardiac arrest and patients at very high-risk for SCD who have recurrent syncope despite adequate therapy with β-blockers (26).

K^+ supplementation is a rational additional therapy in all LQTS patients and may be especially useful in LQT2 patients. Potassium-sparing diuretics may be used as an add-on therapy in patients with significant and frequent hypokalemia.

In women with LQTS, the probable QTc-prolonging effect of synthetic progesterone should be taken into account when making decisions regarding contraception (34). A recent retrospective study by Goldenberg et al. evaluated the arrhythmic risk of three types of oral contraceptives (progestin-only, estrogen-only, and the combination of progestin and estrogen) in 370 women with LQTS. In this study, progestin-only therapy was associated with an increased risk of arrhythmic events in LQTS (35), particularly in the absence of concomitant β-blocker therapy. Additionally, the authors found that LQT2 female patients had an increased risk of cardiac events when on oral contraceptives as compared with other LQTS genotypes, suggesting that oral contraceptives should be used with caution in LQT2 women without concomitant β-blocker therapy (35).

TABLE 1 Summary of sex-related differences in inherited arrhythmia syndromes.

IAS	Relevant sex-related differences	Reference(s)
LQTS*	Among patients with disease-causing LQTS gene variants, women have higher disease penetrance than men. Women with LQT1 and LQT2 have longer QTc than affected men.	(11, 14, 15, 17, 19)
	Women are more susceptible to developing prolongation of the QT at slower heart rates.	
	Adult women with LQTS have higher risk of TdP compared to males and females of pre-pubescent age.	
	Men with LQTS have a higher risk of fatal presentation, while women often have recurrent syncopal episodes.	
	In childhood and prior to puberty, males with LQT1 have an increased risk for arrhythmias compared to females, but the arrhythmic risk reverses after puberty with higher risk in females.	
	The risk of arrhythmias is also higher in post-pubertal women with LQT2 compared to men, and it stays elevated at post-reproductive age.	
	Among patients with LQT3, females in general, and particularly at 30–40 years age, are at higher risk for SCD. Women are more susceptible to developing drug-induced LQTS and can manifest TdP at relatively shorter QTc intervals.	
BrS	BrS phenotype is identified 8–10 times more frequently frequently in men, particularly in Southeast Asia.	(45–49, 59)
	Women with BrS are more frequently asymptomatic at the time of diagnosis, and 6–7 years older than men both at the time of diagnosis (49 vs. 43 years) and at the time of the first arrhythmic event (50 vs. 43 years).	
	Female BrS patients less frequently have a spontaneous type 1 Brugada ECG pattern (22–41 vs. 36–69%) or ventricular arrhythmia inducibility at electrophysiology study (27–36 vs. 42–66%).	
	Women are 3–4 times less likely to experience arrhythmic events, i.e., syncope, aborted cardiac arrest and documented VF, than men with BrS, except in the pediatric age group, where a spontaneous BrS ECG is associated with earlier onset of arrhythmic events.	
	Fragmented QRS and QRS prolongation (>120 ms) are important risk factors for arrhythmic events in women with BrS (HR 20.2 and 4.7, respectively).	
	Men with Brugada syndrome have been shown to have a larger arrhythmogenic substrate as compared to women.	
CPVT	The penetrance is high in both sexes and the risk of tachyarrhythmias appears to be mostly variant type/location dependent.	(68)
	The Canadian founder *RyR2*-p.R420W variant showed earlier mortality in affected men compared to women.	
SQTS	Nearly 70% of all patients diagnosed with SQTS are males, suggesting a sex-dependent penetrance.	(75, 76)
	No sex-related difference in QTc duration among those diagnosed with SQTS have been identified.	
	Affected men have a 3-fold higher risk of syncope at first presentation with a similar risk of SCD compared to females (24 vs. 25%).	
	No conclusions can be made regarding the risk of tachyarrhythmias as the available studies mostly include incomparable number of men and women with ICDs, which understandably results in differences in the VT/VF detection rates.	
ER pattern and ERS	The ER pattern is more often found in young men (>70% of cases) than in women, with reduced prevalence and diminished sex differences with increasing age.	(79–81)
	The ER pattern is more common in adolescents and athletes. In African Americans, an ER pattern has a prevalence of up to 25%, and has no association with tachyarrhythmias or SCD. Ethnicity may contribute to a higher arrhythmogenic risk with Caucasians being more susceptible.	
	Sex-differences in terms of risk have not been reported, but ischemia is known to provoke more arrhythmias in patients with ER pattern, and since men are more susceptible to coronary ischemia, they might be more susceptible to ER-related arrhythmias.	
IVF	Occurs in presumably healthy middle-aged individuals of either sex	(101–104)
	According to a meta-analysis of 23 studies, males comprise about 70% of all IVF patients.	
	Male sex, younger age, and presence of symptoms preceding the index event seem to be associated with multiple appropriate ICD shocks.	
	Affected men are more likely to receive a specific diagnosis during follow-up.	
	Among carriers of the DPP6 haplotype, men show higher rates of VF and lower survival than women (63 vs. 83 years).	

(Continued)

TABLE 1 (Continued)

IAS	Relevant sex-related differences	Reference(s)
PCCD	No sex-related differences have been described.	(108)
	As in other *SCN5A*-mediated diseases, PCCD seems to be more common among men, but robust data is lacking.	
	Data on risk during different reproductive phases does not exist.	
Familial ST-depression syndrome	While equal predisposition to the syndrome among men and women is expected given its autosomal dominant inheritance pattern, male patients appear to be more likely to develop AF or (aborted) SCD.	(110)
	The occurrence of left-ventricular systolic dysfunction is almost exclusively observed in men.	

BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; ER, early repolarization; ERS, early repolarization syndrome; IAS, inherited arrhythmia syndrome; LQTS, long QT-syndrome; PCCD, progressive cardiac conduction disease; SCD, sudden cardiac death; SQTS, short QT-syndrome; TdP, torsades de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia.
*Details regarding genotype-specific differences in phenotype and management are provided in the "Long QT syndrome" section of the manuscript.

Men with LQTS should be evaluated for low serum testosterone levels, androgen deprivation therapy exposure, and endocrine disorders associated with hypogonadism, since these factors have been associated with higher risk for drug-induced TdP (36, 37), and might represent modifiable risk factors in men with congenital LQTS. A recent small placebo-controlled study showed that transdermal testosterone attenuates the QT-prolonging effects of ibutilide in older men, suggesting that androgens might be useful to prevent or treat TdP in men with drug-induced LQTS (38). The applicability of these findings to congenital LQTS is unclear.

3.3. Pregnancy

Given the significant changes of sex hormones during pregnancy and the post-partum period, it is important to consider their modifier effect on the LQTS phenotype. Females, particularly those with LQT1, are at a lower risk for arrhythmias during the course of pregnancy (39). Arrhythmic risk is increased in the early post-partum period, particularly in patients with LQT2 (39) prior to returning to the pre-pregnancy baseline (39). β-blockers are effective in reducing the risk of arrhythmic events during pregnancy and are particularly essential at the post-partum period to prevent life-threatening manifestations (39). Non-selective β-blockers are preferred for women in the post-partum period, but metoprolol is the most studied in terms of fetal safety data (40). However, propranolol is safe in LQTS pregnancies (41) and may be preferred considering its higher efficacy in LQTS. If a non-selective β-blocker is used during pregnancy, consideration to switching to cardiac selective β-blocker like metoprolol in the third trimester should be given if childbirth by vaginal delivery is planned, as non-selective β-blockers can interfere with uterine contractions. Therapy with β-blockers is mostly well tolerated during pregnancy and the post-partum period though slightly lower fetal birth weights have been reported. Notably, β-blockers are secreted in breast milk, and rarely hypoglycemia and bradycardia may occur in breast-fed infants as a consequence of material β-blocker therapy.

4. Brugada syndrome

Brugada syndrome (BrS) is an IAS characterized by coved-type ST-segment elevation followed by a negative T-wave in the right precordial leads (V_1-V_3), either spontaneously or provoked by a sodium channel blocker, and increased susceptibility to SCD due to polymorphic ventricular tachycardia (VT) or VF (42). Over the past 25 years, 21 genes have been implicated in BrS (9) however, a recent evidence-based assessment of published literature found *SCN5A* to be the only gene definitely implicated causally in BrS (43). Pathogenic/likely pathogenic variants in the *SCN5A* gene are identified in around 20% of all BrS cases (44).

4.1. Sex-related differences in clinical phenotype

BrS primarily affects men; the BrS phenotype was recognized to be 8–10 times more common in Southeast Asian males than females (45). Because of this imbalance, there is paucity of studies analyzing the BrS phenotype and its consequences in females, and sex differences are underinvestigated. Registry data suggests that, women with BrS are more commonly asymptomatic, and on average 6 to 7 years older than men both at the time of diagnosis (49 vs. 43 years) and at the time of the first arrhythmic event (50 vs. 43 years) (46, 47). Female BrS patients less frequently have a spontaneous type 1 Brugada ECG pattern (22–41 vs. 36–69%) or ventricular arrhythmia inducibility at electrophysiology study (27–36 vs. 42–66%) (47, 48). Moreover, women are around 3–4-fold less likely to have syncope, aborted cardiac arrest and documented VF, than men with BrS (47, 49), except in the pediatric age group, where a spontaneous BrS ECG is associated with earlier

arrhythmia onset–particularly, provoked by fever–in females (48). Therefore, males show a normal distribution of first arrhythmic event, while females show a bi-modal distribution (46). Whether there are sex-related differences in susceptibility to atrial fibrillation in BrS, remains to be investigated.

The higher incidence of Brugada EKG pattern in adult men vs. women suggests that testosterone plays an important role in ventricular repolarization. This was supported by the clinical observation that the coved-type ST-segment elevation disappeared after orchiectomy (50) or after androgen-deprivation therapy (51) in patients with asymptomatic Brugada syndrome who underwent treatment for prostate cancer. An effect of testosterone on ventricular repolarization is also suggested by the lower J-point amplitude in men with secondary hypogonadotropic hypogonadism (52). Additionally, a higher incidence of prostate cancer has been reported in men with BrS (53), which seems to correlate to higher testosterone levels in men with BrS compared to control men (45).

4.2. Sex-specific risk factors for arrhythmic events

Risk assessment in BrS is challenging, especially in women, since most studies report almost exclusively men, and only recently, female sex in BrS has been the focus of investigation. Analysis of large cohort registry reports indicates that women comprise less than one third (28%) of all BrS patients (46, 47, 54). Fragmented QRS and QRS prolongation (>120 ms) have been shown to be important risk factors for arrhythmias in women with BrS (HR 20.2 and 4.7, respectively), allowing for risk assessment beyond traditional risk factors, such as proband status, syncope and family history of SCD (HR 10.15, 6.8 and 69.4, respectively) (47). Interestingly, one study reported a higher prevalence of disease-causing *SCN5A* variants in asymptomatic female vs. male patients with BrS (27 vs. 21%), and a further difference in the prevalence of pathogenic variants in those with arrhythmic events exists (48% in females vs. 28% in males) (48), indicating a potential role for a genetic basis of BrS in arrhythmic risk. Furthermore, longer PR intervals have been reported as a marker of arrhythmias in female BrS patients (HR 1.03 per each ms of increase) (49). Intriguingly, atrioventricular conduction disturbances are frequently seen in BrS and highlight its overlap with cardiac conduction disease, both attributed to loss-of-function *SCN5A* variants in certain genetic forms of both conditions. Interestingly, there are reports of variants that show sex-dependent phenotypes, such as Gly1406Arg, which results in BrS in men and cardiac conduction disease in women (55).

Sinus node dysfunction occurs in nearly 1% of BrS patients (47). Certain familial BrS-associated *SCN5A* variants produce almost exclusively VF/SCD in men, but predominantly sinus node dysfunction and rarely VF/SCD in women (56). Since VF in BrS patients occurs almost exclusively during sleep, one hypothesis suggests arrhythmias in BrS might be provoked by bradycardia. In this case, concomitant sinus node disease could contribute to increased arrhythmogenesis. Studies have reported inconsistent findings regarding sinus node disease as an arrhythmia predictor in female BrS patients (47, 54).

The ventricular arrhythmias in patients with BrS have been linked to an arrhythmogenic substrate in the right ventricular outflow tract (57). Electrophysiological mapping studies of predominantly male patients with BrS have demonstrated that ajmaline exposes its extent and distribution, which is correlated with the degree of coved ST-elevation (58). Men with BrS have been shown to have a larger arrhythmogenic substrate as compared to women (59). Additionally, in both sexes, the arrhythmogenic substrate was larger in patients with disease-causing *SCN5A* variants than in those without.

4.3. Management

Current data suggests that most BrS patients will not experience life-threatening cardiac arrhythmias during their lifetime. As the risk of VF in asymptomatic patients with spontaneous BrS Type 1 ECG is rather low (≈1%/year), Brugada lifestyle precautions are sufficient for low risk patients (60), and include aggressive and prompt treatment of fever and avoiding of arrhythmia-provoking medications (for details, see www.brugadadrugs.org). Contrary to historical approach with liberal criteria for primary prevention ICD implantation, ICDs are currently recommended almost exclusively only in patients with a history of arrhythmic syncope and in cardiac arrest survivors (42). Given the lower risk of arrhythmias in women (2 vs. 5% within 5 years of diagnosis), women are less likely to require an ICD (20 vs. 34%) (47). Quinidine has been effective in preventing arrhythmias in symptomatic patients with BrS (61, 62), and should be considered in BrS patients with recurrent syncope or VT/VF, atrial fibrillation or in those who are reluctant to undergo ICD implantation (42). Instead of, studies have demonstrated that elimination of arrhythmogenic electrophysiological substrate in the RVOT epicardium by radiofrequency ablation results in ECG normalization and VT/VF non-inducibility (58), and reduced recurrent VT/VF episodes (63), suggesting that substrate-based radiofrequency ablation might be useful in selected patients with BrS, particularly those with multiple episodes of VT/VF. Yet, the knowledge regarding the arrhythmogenic substrate in females is much less studied given the small proportion of women in studies.

4.4. Pregnancy

There is limited data regarding pregnancy in BrS patients. One retrospective single-center study of 104 BrS women with

219 deliveries, reported no malignant arrhythmias during the pregnancy or peripartum period (64).

5. Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an IAS characterized by polymorphic ventricular arrhythmias provoked by high adrenergic tone (65). Pathogenic/likely pathogenic variants in the *RYR2* gene, encoding for the ryanodine receptor 2, underlie around 65% of all CPVT cases (autosomal dominant transmission), whereas variants in the *CASQ2* gene, encoding cardiac calsequestrin, are found in 2–5% of cases (mainly autosomal recessive inheritance) (26).

5.1. Sex-related differences in clinical phenotype

CPVT appears to equally affect both men and women (66). While initial reports indicated that males with *RYR2*-CPVT might be at a higher risk for SCD (67), recent data did not confirm this finding. The arrhythmic risk in *RYR2*-CPVT seems to be influenced by variant type and location. In a Canadian population, the founder *RYR2*-p.R420W variant showed earlier mortality in affected men compared to women (68).

A study investigating the circadian variation of arrhythmic events in pediatric patients with CPVT found that ventricular arrhythmias are more likely to occur in the afternoon and evening hours (69).

5.2. Sex-specific risk factors for arrhythmic events

Prior investigations reported no sex-specific risk factors for arrhythmias and SCD in CPVT. The general predictors for cardiac and fatal or near-fatal events are younger age at the time of diagnosis and absence of β-blocker therapy.

5.3. Management

Thus, far, the management is similar in men and women with CPVT. β-Blockers are the mainstay of therapy (26). Nadolol is more effective than β1-selective blockers. Flecainide in addition to β-blocker provides better prevention of exercise-induced arrhythmias in comparison to β-blocker therapy alone (70). LCSD may be useful for patients with drug intolerance or arrhythmias despite medical therapy. ICD is recommended in survivors of cardiac arrest with CPVT (26), but recent studies indicate these may increase the risk of fatal VF storms due to inappropriate ICD therapies, suggesting that strict adherence to medications alone may be superior (71, 72).

5.4. Pregnancy

Data suggests that the arrhythmic risk is not elevated during pregnancy and the postpartum period in patients with CPVT, yet events can occur in the absence of adequate β-blocker therapy unrelated to pregnancy (73). Therefore, continuous therapy with preferably non-selective β-blockers is indicated during pregnancy and the post-partum period to reduce the arrhythmic risk in women with CPVT (74).

6. Short QT syndrome

Short-QT syndrome (SQTS) is a very rare IAS characterized by shortened QT interval (QTc $<$330 ms) and increased susceptibility to atrial and malignant ventricular arrhythmias and SCD in the first decades of life (75). In the presence of a pathogenic variant in SQTS genes, family history of SQTS or SCD at age $\leq$40, or survival of a cardiac arrest due to VF in the absence of other heart disease, the diagnosis of SQTS can be made in the presence of a QTc $<$360 ms (26). SQTS1-3 are associated with gain-of-function variants in *KCNH2, KCNQ1,* and *KCNJ2*, respectively, whereas SQTS4-6 are caused by loss-of-function variants in *CACNA1C, CACNB2, CACNA2D1*, respectively (9). Most SQTS patients are diagnosed before the age of 40 years and are symptomatic with dizziness, syncope or SCD (75).

Nearly 70% of all patients diagnosed with SQTS are males, suggesting a sex-dependent penetrance (76). This could be explained by the longer resting baseline QTc in females than males; yet, no sex-associated difference in QTc intervals have been identified in SQTS patients (75, 76). Men have higher rates of syncope at first presentation (24 vs. 7%), but the rates of SCD are similar between the two sexes (24 vs. 25%) (76). A composite endpoint of life-threatening cardiac arrhythmias was observed more often in females (48%) than males with SQTS (28%), partly attributable to higher detection rate of VF in women given that all had ICDs in comparison to only 1/3 of men (76).

Given the high SCD risk in patients with SQTS, ICDs are the mainstay of therapy. ICD implantation is recommended in patients with SQTS and sustained VF, and may be considered in SQTS patients with a family history of SCD (26). Quinidine has been reported to successfully reduce the rate of arrhythmic events and might, thus, be used in asymptomatic SQTS patients (77). Sotalol may also have beneficial effect, but there is very limited data available supporting its efficacy (26).

7. Early repolarization pattern and early repolarization syndrome

The diagnosis of early repolarization syndrome (ERS) can be established in patients presenting with otherwise unexplained aborted cardiac arrest, documented VF or polymorphic VT in the presence of an early repolarization (ER) pattern in the inferior and/or lateral ECG leads (42). The ECG ER pattern is considered present if a J-wave (end QRS notch) or slur on the downslope of a prominent R wave can be identified with a J-point elevation of $\geq$ 0.1 mV in 2 or more contiguous leads of the 12-lead ECG, excluding leads V1–V3 (42). The J wave can manifest as an end QRS notch or as a slur on the downslope of a prominent R wave.

ER patterns, however, are commonly seen in the general population, with described rates ranging from 3 to 25% (78, 79). The ER pattern is more often found in young men (>70% of cases) than in women (80), with reduced prevalence and diminished sex differences with increasing age (81). A longitudinal follow-up study has shown that while the pattern was present in 25% of probands at age 25, it was only seen in 7% at age 45 (79). The ER pattern is more common in adolescents and athletes, as well as in African-Americans with a prevalence of up to 25% (79). Exercise training significantly increases the prevalence of ER pattern, which is particularly prevalent in athletes with bradycardia (82).

Although an ER pattern is typically a benign finding, some ECG features are associated with an increased risk for SCD. Presence of the ER pattern in inferior leads carries a higher risk than J-point abnormalities in the lateral ECG leads (83). Additional risk is conferred by J-wave elevations $\geq$0.2 mV, bradycardia and by a horizontal or downsloping morphology of the ST-segment (84). While sex-differences in terms of risk have not been reported, ethnicity may contribute to a higher arrhythmogenic risk with Caucasians being more susceptible (79, 80). In Asians or African Americans, ER pattern was not associated with an increased risk for tachyarrhythmias or SCD.

The presence of the ER pattern appears to increase the vulnerability for malignant arrhythmias, particularly in the setting of myocardial ischemia (82). Both the prevalence of ER pattern and the incidence of acute myocardial infarction are higher in men, which together may increase the risk of arrhythmic death in men, compared to women. Current evidence suggests that ER is a modifier of phenotype in other IAS. A meta-analysis of 5 studies and a total of 1,375 patients with BrS concluded that ER pattern is associated with a high risk of arrhythmic events in patients with BrS (85). In particular, BrS patients with inferolateral ER (global ER pattern) displayed the highest arrhythmic risk. In a study by Watanabe et al., ER pattern was associated with arrhythmic events in SQTS patients (86). In a small study of 52 CPVT patients, ER pattern was present in an unexpected large proportion (45%) of patients; it was more common in symptomatic patients and was associated with an increased frequency of syncope (87). Studies showed contradicting results regarding the clinical significance of ER in LQTS, with association with symptoms in an early report (88) and lack thereof in a more recent study (89).

Animal experiments point to differences in various ion current densities resulting in imbalances between epi- and endocardial layers as the electrophysiological basis underlying the ER pattern (90). Pathogenic variants in *KCNJ8* (ERS) and *KCND2* (in an atypical J wave syndrome) resulting in augmented K_{ATP} and I_{to} currents, respectively (gain-of-function), and variants in *CACNA2D1, CACNA1C*, and *CACNB2* resulting in an attenuated $I_{Ca,}$ and in *SCN5A* predicted to result in an attenuation of $I_{Na.}$, have been implicated in ERS (90). In particular, a larger I_{to} and ATP-sensitive current (I_{KATP}) and a reduced I_{Na} and $I_{Ca,L}$ in the epicardium vs. the endocardium lead to a greater net outward current early during the myocardial AP. Testosterone levels are significantly higher among men with an ER pattern compared to those without. Furthermore, the benign ER pattern with rapidly ascending ST-segment seems to be the pattern most closely associated with testosterone levels (91). As outward K^+ currents are sensitive to testosterone levels, this may explain the higher prevalence of the ER pattern seen in men. A higher frequency of ER patterns in family members of probands with ER points, at least in part, toward a genetic basis (81, 92). While genetic findings are supportive of our current pathophysiological understanding (90), pathogenic variants have only been found in a minority of cases and our knowledge of disease heritability remains incomplete.

Management currently mainly depends on patient and family history; sex-specific differences in treatment algorithms have not been proposed (42). ICD implantation is recommended in ERS patients with documented VF. In the case of patient refusal, quinidine may be offered as an alternative therapy. ICD might also be considered in ERS patients with an arrhythmic syncope and high-risk ERS features or a strong family history of ERS-associated SCD at young age. If ERS patients present with electrical storm, both quinidine and isoproterenol have proven effective in stopping and preventing further arrhythmias (62). Both drugs reduce I_{to}, thereby restoring transmural AP homogeneity.

ER patterns during pregnancy and the postpartum period have not been investigated.

8. Idiopathic ventricular fibrillation

Approximately 12% of sudden cardiac arrest survivors have no structural heart disease (93). Comprehensive diagnostic testing allows identification of subclinical structural cardiac

abnormalities or IAS in up to half of these unexplained cardiac arrests (93, 94), whereas those with indeterminate cause of VF are referred to as idiopathic ventricular fibrillation (IVF) (95). IVF is estimated to account for 6.8% of all VFs (93), with prevalence increasing among older survivors. About 5–20% of IVF patients have a family history of SCD (96, 97), and in 9–17% genetic testing identifies potentially causal variants in genes mostly encoding cardiac ion channel subunits (98, 99), suggesting a significant overlap with the "concealed" forms of IAS. Because many IAS-related VFs were regarded as "IVF" prior to their discovery, advances in clinical recognition and genetic testing for IAS led to a decreased proportion of apparently unexplained cardiac arrests classified as IVF. The pathophysiology of IVF remains largely unclear. Few genes/variants have been clearly associated with IVF: *SCN5A*, Dutch *DPP6* risk haplotype, *CALM* genes, *RYR2*, and *IRX3* (99, 100).

IVF occurs in presumably healthy middle-aged individuals of either sex (average age ranging from 33 to 51 years) (101, 102). Clinical risk factors for IVF in the general population have not been established so far. A meta-analysis of 23 studies showed that males comprise about 70% of all IVF patients (101). Age at the time of the event appears to be comparable between men and women (103). Male sex, younger age, and presence of symptoms preceding the index event seem to be associated with multiple appropriate ICD shocks (103). Male patients are also more likely to receive a specific diagnosis during follow-up (103). Among carriers of the *DPP6* haplotype, men show higher rates of VF and lower survival than women (63 vs. 83 years) (104). The mechanisms underlying these disparities remain to be investigated.

About 30% of IVF patients experience recurrent VF within 5 years (101). Therefore, an ICD is recommended for secondary prevention of SCD in all IVF patients (26). In *DPP6* haplotype-positive individuals, the estimated risk of SCD is close to 50% by the age of 60 (104). Primary prevention ICD implantation or therapy with quinidine can be considered in this population. A subgroup of IVF patients has short-coupled premature ventricular complexes (scPVCs) from the specialized conduction system that can trigger so-called short-coupled TdP or VF (105). In those, mapping and ablation of scPVCs can prevent recurrent VFs and ICD shocks (105).

Complete evaluation of IVF patients including onset on ECG or ICD interrogation is critical for guiding clinical evaluation and cascade genetic testing in affected families, since relatives of survivors might be at similar risk for SCD (106). When a genetic origin is detected, functional characterization of the causal variant(s) might provide insight into the disease pathophysiology and help guide therapy for a selected subset of patients.

9. Progressive cardiac conduction disease

PCCD is a hereditary disease characterized by progressive and unexplained cardiac impulse conduction delay, with ensuing predisposition to complete AV block, syncope, and SCD (107). Familial forms of PCCD in the absence of structural heart disease are typically caused by variants in cardiac ion channel genes (108), with variants in *SCN5A* being the most common genetic substrate in isolated PCCD (108). However, the proportion of cases attributable to *SCN5A* remains unclear due to limited number of reports.

Sex-related differences in PCCD have not been investigated. As in other *SCN5A*-mediated diseases, the disease seems to be more common among men, but robust data is lacking. Because most reports on PCCD are limited to individual cases or families, data on risk during different reproductive phases does not exist.

10. Familial ST-depression syndrome

Familial ST-depression syndrome is an inherited disease characterized by persistent, non-ischemic concave ST-depressions in multiple leads, associated with an increased risk of atrial fibrillation, SCD and (in older persons) some degree of left ventricular dysfunction (109). Familial ST-depression syndrome is diagnosed in the presence of (1) unexplained concave-upward ST depression in at least 7 leads, 90 ms after J point, (2) ST-elevation in lead aVR $>$ 0.1 mV, (3) ECG findings persistent over time, and (4) autosomal dominant pattern of inheritance. The ST-segment depression develops in prepuberty, progress slowly, and are most pronounced in leads V_4, V_5, and II. Evaluation of the pedigrees indicated an autosomal dominant pattern of inheritance in all affected families. The genetic background of this syndrome is yet to be identified, as gene panels have not revealed a causative variant in known inherited heart disease associated genes. Based on the limited data available, the onset of complications does not appear to correlate with age in affected individuals.

The limited available data suggests strong sex-related differences in the arrhythmic phenotype of familial ST-segment depression syndrome. In a cohort of 40 individuals (43% men) from 14 apparently unrelated Danish families with $\geq$2 affected members, over a mean follow-up of 9 years, syncope occurred in 20%, atrial fibrillation was observed in 10 patients (25%, 7 men), (aborted) SCD in 5 patients (13%; 4 men), and left ventricular systolic dysfunction occurred in 10 patients (25%, 7 men) (110). The occurrence of ventricular arrhythmia and left-ventricular systolic dysfunction almost exclusively in men suggests a sex-specific natural history. The pathophysiological basis of these sex-specific events remains to be investigated.

11. Important considerations regarding pregnancy and the peripartum period

Pregnancy and the peripartum period are both associated with significant neurohumoral changes, which should be taken into account in patients with IAS. In particular, stressors, by increasing sympathetic tone, and drugs can provoke torsade de pointes and polymorphic VT, leading to syncope, seizures, or SCD in these patients (111). The balanced approach to pregnant women with IAS should consider the maternal and fetal risks related to the disease as well as antiarrhythmics used. Identification of known high-risk features, avoidance of specific arrhythmia triggers, preventive therapy when needed, and neonatal screening when available, are key to optimal medical care. Generally, children are at relatively low risk for arrhythmias during the first year of life (except those with *de novo* genetic disease); nevertheless, they should be screened appropriately given that 5–10% of all sudden infant death syndrome cases are attributed to IAS (112).

Generally, unassisted vaginal delivery may be performed in women with IAS (1). However, the delivery plan should be individualized according to the maternal risk profile, considering the history of any relevant arrhythmias. In high-risk patients, availability of a cardiologist or a cardiac electrophysiologist and use of maternal cardiac telemetry during labor are recommended. The choice of anesthetics should be made carefully taking into account the list of proarrhythmic medications to avoid drug-induced adverse reactions (e.g., drugs that interfere with cardiac repolarization and prolong the QT interval are strongly discouraged in patients with LQTS) (111). Limited evidence suggests, single bolus propofol may be used for induction of anesthesia in patients with BrS, but higher doses of propofol and longer infusions may potentially be associated with significant risk of arrhythmias and are presently not advisable (113).

Since IAS are rare diseases, only limited evidence exists regarding the outcome of pregnancies in women with IAS. Overall, arrhythmias seem to be very rare during labor. In patients with LQT1, LQT2, and CPVT, arrhythmic events are more likely to be provoked by increased heart rates, which are typically seen in the active pushing phase of labor. Notably, heart rate increases significantly in patients receiving intravenous oxytocin. Oxytocin also prolongs cardiac repolarization and may lead to TdP in those with LQTS (114) and thus, should be used with caution during labor.

12. Conclusions and future perspectives

A growing body of literature demonstrates substantial biological sex-related differences in the incidence and clinical phenotype of various IAS, most notably the higher prevalence of QT prolongation in women and male preponderance of BrS. Despite multiple basic and clinical studies showing an effect of sex hormones on outcomes in patients with IAS, many clinically relevant questions remain to be addressed. Thus, a precision medicine approach including the consideration of sex-specific characteristics should be integrated in the care of IAS patients. Further characterization and awareness of differences in symptom presentation, disease progression, outcomes and treatment response present new opportunities for improving patient care and for paving the way for precision medicine.

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BA and AB manuscript drafting and review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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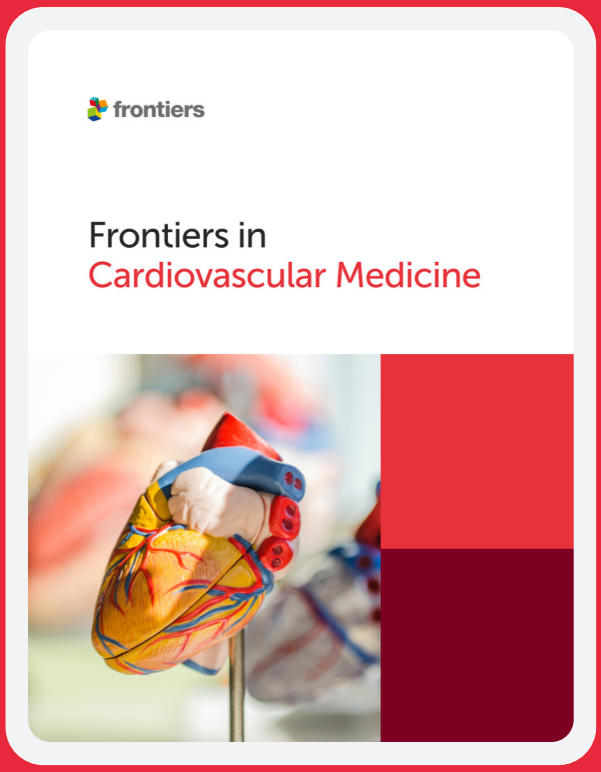

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