OUTCOMES AFTER CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES IN PATIENTS WITH CARDIAC SARCOIDOSIS AT A TERTIARY-CARE CENTRE IN SOUTH INDIA

DR. USNISH ADHIKARI

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A THESIS SUBMITTED BY

DR. USNISH ADHIKARI

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR

THE AWARD OF

PDF Cardiac Electrophysiology

YEAR: 2024-2025

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No part of this thesis has been submitted for the award of any other degree or diploma before this date.

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Submitted by

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7

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	ACE	Angiotensin Converting Enzyme
2	AICD	Automatic Implantable Cardioverter Defibrillator
3	ATP	Anti-Tachycardia Pacing
4	AVB	Atrio-Ventricular Block
5	CAG	Coronary Angiogram
6	CHB	Complete Heart Block
7	CMR	Cardiac Magnetic Resonance
8	CIED	Cardiac Implantable Electronic Device
9	CRT	Cardiac Resynchronisation Therapy
10	CS	Cardiac Sarcoidosis
11	DBP	Diastolic Blood Pressure
12	ECG	Electrocardiogram
13	EF	Ejection Fraction
14	ESR	Erythrocyte Sedimentation Rate

15	FAC	Fractional Area Change
16	FDG	Fluorodeoxyglucose
17	HF	Heart Failure
18.	HR	Heart Rate
19	ILR	Implantable Loop Recorder
20	LBBB	Left Bundle Branch Block
21	LGE	Late Gadolinium Enhancement
22	LOT	Left Bundle Optimised
23	LV	Left Ventricle
24	MACE	Major Adverse Cardiovascular Event
25	MRI	Magnetic Resonance Imaging
26	NYHA FC	New York Heart Association Functional Class
27	NT-pro BNP	N-Terminal prohormone of Brain Natriuretic Peptide
28	PET	Positron Emission Tomography
29	PVC	Premature Ventricular Complex
30	RBBB	Right Bundle Branch Block
31	RWMA	Regional Wall Motion Anomaly

32	SBP	Systolic Blood Pressure
33	SCD	Sudden Cardiac Death
34	SD	Standard Deviation
35	SPSS	Statistical Package for Social Sciences
36	VA	Ventricular Arrhythmia
37	VT	Ventricular Tachycardia
38	VF	Ventricular Fibrillation

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SYNOPSIS

- **Background & Objectives**: Sarcoidosis is a multisystem disorder that affects several organs of the body including the heart. Cardiac Sarcoidosis has a variable presentation including life-threatening ventricular arrhythmias, conduction defects and ventricular dysfunction, often requiring implantable electronic devices as a part of their management. Studies are limited in Indian population regarding the outcome after their implantation. The primary objective of this study was to determine the outcome of CIEDS in these patients- arrhythmia detection & therapy & adverse cardiovascular events, and factors affecting, thus providing information that may fill the knowledge gap and help in formulating guidelines.

- **Methods:** This is a single-centre retrospective study. All patients who were diagnosed with CS as per departmental diagnosis and underwent CIED implantation were included. Clinical data during initial presentation, device implantation, imaging findings, biochemical parameters, medication use and follow-up data during visits at device clinic, including device interrogation data and hospitalisations were collected from electronic medical records. Primary outcome was defined as a composite of clinically important arrhythmias (sustained ventricular arrhythmia/ appropriate AICD therapy), hospitalisation due to arrhythmia, heart failure & all-cause mortality. Secondary outcomes were time to first adverse event/ primary outcome and independent components of the primary outcome.

- **Results:** The study enrolled 45 patients- 8 with conventional permanent pacemakers, 3 with left bundle pacing, 19 AICD and 15 CRTs. The mean present age was 54.9±12.9 years with male predominance (71.1 %) with a mean follow-up of 56 months. The patients were found to have high event rate of primary outcome (44.4 %) on follow. Clinically important ventricular arrhythmias requiring device therapy or hospitalisation were seen in 28.9 %, HF hospitalisation in 15.6 % and mortality in 2.2% were noted. Higher heart rate and lower RV TAPSE at presentation and those with greater use of

antiarrhythmics predicted adverse events. No significant difference in event-free rate amongst primary and secondary prophylaxis AICD/CRT-D devices was noted.

- **Conclusion:** The most important finding in this study was the high event rate of the primary outcome in 44.4 % of the study cohort. Very few factors at presentation could predict adverse outcomes, with a non-significant difference in event-free survival among primary and secondary prophylaxis patients, thus making a decision for CIED implantation a challenge. Long-term prospective studies are needed.

INTRODUCTION

Sarcoidosis is a multisystem disorder that has unknown aetiology and is characterised by the presence of noncaseating granulomas. It can affect multiple organs, including the heart, lungs, liver, spleen, skin, eyes, and parotid gland and can mimic other conditions, making it difficult to diagnose. Approximately 25% of patients with systemic evidence of sarcoidosis have some form of cardiac involvement, based on imaging and autopsy finding (1). When it involves the heart, Cardiac Sarcoidosis (CS) presents as an infiltrative cardiomyopathy with a variable clinical presentation, thus making its diagnosis challenging(2). Even though it involves multiple organs in the body, cardiac involvement is associated with life-threatening complications, which requires a multidisciplinary approach for proper management. Cardiac involvement is associated with an increased risk of ventricular arrhythmias (VA), atrioventricular conduction blocks, and sudden cardiac death (SCD) along with ventricular dysfunction and heart failure. Initial involvement of the heart in CS is often silent clinically and thus it may go underrecognized. Additionally, no single diagnostic test is available for sarcoidosis, and although endomyocardial biopsy has a high specificity for diagnosis, it is invasive and insensitive in view of patchy involvement of the disease leading to poor yield on biopsy. Sometimes, it is considered a diagnosis of exclusion. Although imaging technology has improved the ability to detect CS, but it can still be challenging to confirm and requires high degree of clinical suspicion for its diagnosis. Screening for CS and risk stratification is often necessary when suspicion is high and substantiated with imaging, followed by the implantation of cardiac implantable electronic devices (CIEDs), if indicated. Although there are expert consensus criteria available for its diagnosis, and general recommendations regarding device implantation may be followed when indicated, less is known about the outcome of the patients post CIED implantation, regarding arrhythmia detection and therapy, and which subset of

patients are benefitted the most . Studies are lacking especially in Indian population regarding the same. This study plans to review the outcomes after CIED implantation, including arrhythmias detection, therapy and other adverse outcomes including mortality/ morbidity in such a cohort of patients.

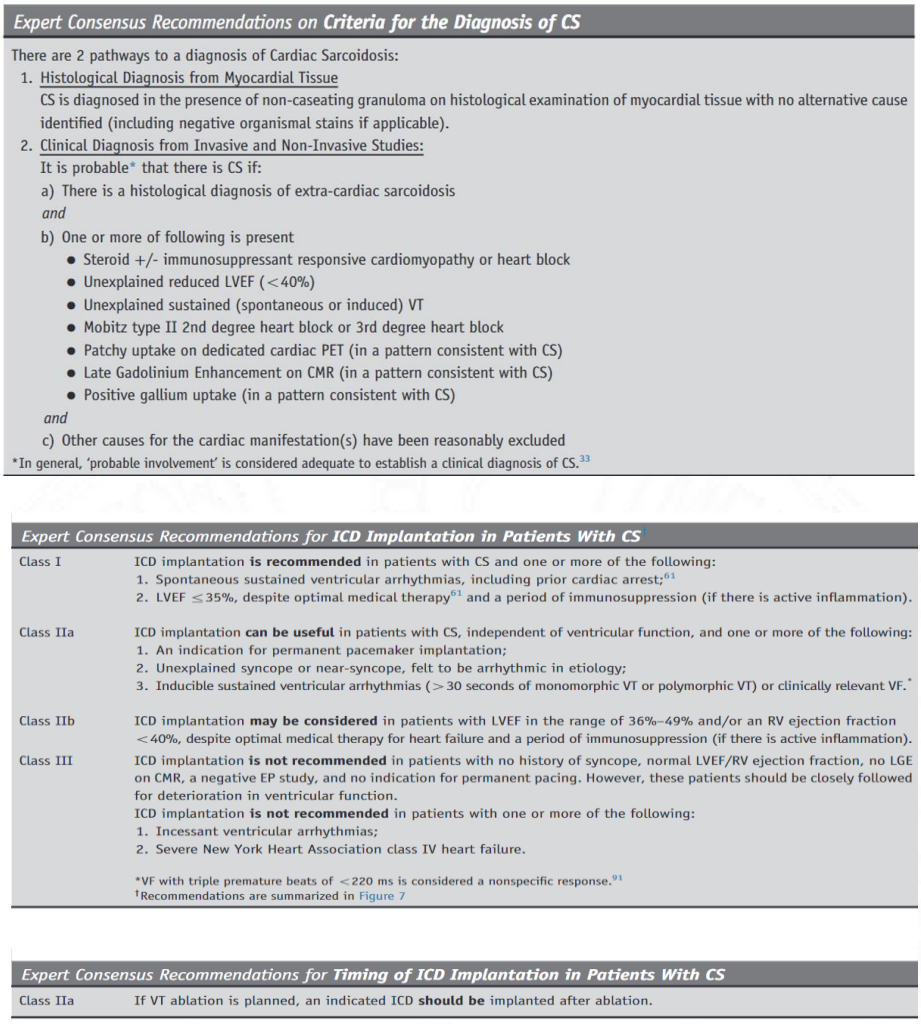
LITERATURE REVIEW

Even though the diagnosis of cardiac involvement has advanced significantly, there is still uncertainty regarding the best screening and risk-stratification approach as well as the additional diagnostic value of advanced imaging modalities. Autopsy studies show a prevalence of 20% to 30%, but only 5% to 10% of patients with sarcoidosis have clinically overt cardiac sarcoidosis The patchy distribution of myocardial infiltration and the absence of a highly sensitive and specific non-invasive test are the main causes of the diagnostic challenges in cardiac sarcoidosis(3). Traditional screening methods used in early studies, such as cardiac symptoms and electrocardiograms (ECG), are limited by low sensitivity and poor positive and negative predictive value, although they can give clues to diagnosis when clinical suspicion is high. Advanced imaging techniques like cardiac magnetic resonance (CMR) and positron emission tomography (PET) have identified cardiac involvement in sarcoidosis over the past 20 years; certain patterns on CMR and PET are thought to be extremely sensitive and specific(4). Treatment for CS is frequently multifactorial, including device placement, anti-granulomatous/ anti-inflammatory therapy,

medication for cardiac arrhythmias and/or HF and heart transplantation(1). According to certain studies, corticosteroid and immunosuppressant therapy may occasionally rectify AV blocks (AVB) in CS and enhance left ventricular performance. However, ventricular arrhythmias, which in CS are likely more associated with fibrotic regions that facilitate re-entry mechanisms, than with regions of myocardial oedema and active inflammation, may be unaffected by immunosuppression (5). Hence implantable defibrillators form an important part of management for these subsets of patients.

Clinicians frequently need to think about intracardiac device therapy in CS due to the high prevalence of AVB, the frequency of life-threatening VAs, the risk of SCD, and other factors. However, there are no clear-cut guidelines for the diagnosis and management of CS. The 2008 ACC/AHA/HRS (American College of Cardiology/ American Heart Association/Heart Rhythm Society) general device guideline recommended ICD implantation in CS as a Class IIa procedure(6), without much specifications. Despite the lack of evidence, domain experts believed it was reasonable to consider ICD implantation in all patients with CS, who had a meaningful expected survival because of the increased but difficult-to-stratify risk of SCD. The ACC/AHA/HRS consortium in 2018 and the HRS in 2014 both released more detailed recommendations. HRS has provided expert consensus criteria in 2014(7). These recommendations have not been validated and are based on expert opinion or observational studies. However, national guidelines published by the Japanese Circulation Society (8) are more stringent and were not used in this case. The use of CIED in CS patients is currently based on these recommendations along with the AHA/ACC/HRS criteria for implantation of AICD(2017) in ventricular arrhythmias(9).

Fig 1(7)



Expert Consensus Recommendations on ***Criteria for the Diagnosis of CS***

There are 2 pathways to a diagnosis of Cardiac Sarcoidosis:

1. Histological Diagnosis from Myocardial Tissue
   CS is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable).
2. Clinical Diagnosis from Invasive and Non-Invasive Studies:
   It is probable* that there is CS if:
   a) There is a histological diagnosis of extra-cardiac sarcoidosis
   and
   b) One or more of following is present
   - Steroid +/- immunosuppressant responsive cardiomyopathy or heart block
   - Unexplained reduced LVEF (<40%)
   - Unexplained sustained (spontaneous or induced) VT
   - Mobitz type II 2nd degree heart block or 3rd degree heart block
   - Patchy uptake on dedicated cardiac PET (in a pattern consistent with CS)
   - Late Gadolinium Enhancement on CMR (in a pattern consistent with CS)
   - Positive gallium uptake (in a pattern consistent with CS)

   and
   c) Other causes for the cardiac manifestation(s) have been reasonably excluded

*In general, 'probable involvement' is considered adequate to establish a clinical diagnosis of CS.[33]

Expert Consensus Recommendations for ***ICD Implantation in Patients With CS***†

Class I	ICD implantation **is recommended** in patients with CS and one or more of the following: 1. Spontaneous sustained ventricular arrhythmias, including prior cardiac arrest;[61] 2. LVEF ≤35%, despite optimal medical therapy[61] and a period of immunosuppression (if there is active inflammation).
Class IIa	ICD implantation **can be useful** in patients with CS, independent of ventricular function, and one or more of the following: 1. An indication for permanent pacemaker implantation; 2. Unexplained syncope or near-syncope, felt to be arrhythmic in etiology; 3. Inducible sustained ventricular arrhythmias (>30 seconds of monomorphic VT or polymorphic VT) or clinically relevant VF.*
Class IIb	ICD implantation **may be considered** in patients with LVEF in the range of 36%–49% and/or an RV ejection fraction <40%, despite optimal medical therapy for heart failure and a period of immunosuppression (if there is active inflammation).
Class III	ICD implantation **is not recommended** in patients with no history of syncope, normal LVEF/RV ejection fraction, no LGE on CMR, a negative EP study, and no indication for permanent pacing. However, these patients should be closely followed for deterioration in ventricular function. ICD implantation **is not recommended** in patients with one or more of the following: 1. Incessant ventricular arrhythmias; 2. Severe New York Heart Association class IV heart failure.

*VF with triple premature beats of <220 ms is considered a nonspecific response.[91]
†Recommendations are summarized in Figure 7

Expert Consensus Recommendations for ***Timing of ICD Implantation in Patients With CS***

Class IIa	If VT ablation is planned, an indicated ICD **should be** implanted after ablation.

Very few studies have reviewed the outcomes of these devices in monitoring of arrhythmias in CS patients and their role in reducing the mortality as well as morbidity. One of the prior studies, which have looked into the application of these guidelines in patients with CS has found out that, patients meeting class I recommendations for an ICD had an annualized event rate of 22.4%(9). They also identified an optimal late Gadolinium enhancement (LGE) cut-off of 5.7% for those with class IIa recommendation for ICD implantation and with LVEF>35%in CS(9). Kandolin et al as a part of MIDFIN Study Group (Myocardial Inflammatory Diseases in Finland) found out

that in young adults with CS, ≥25% of initially unexplained AVB had substantial adverse event rates and could be candidates for CIED implantation(10). Another study from Japan by Takaya et al found out that among 53 CS patients, 23 % underwent AICD & 17 % underwent CRT, 64% had an adverse major adverse cardiovascular event (MACE) on a median follow-up of thirty-four months, with patients with high-degree AVB having better outcomes than patients with ventricular tachycardias (VT)(11). A large multi-centre retrospective study by Kron et al involving 235 patients with CS who underwent AICD implantation, out of them 36.2% patients received an appropriate ICD therapy, 24.3% received inappropriate shocks with MACE occurring in 17.4% of patients over a mean follow-up of 4.2±4.0 years (12). Another large retrospective study by Nordenswan et al identified 143 CS patients - 75% received pacemakers, 24% received an AICD, and over a mean follow-up period of 4.1 years, 16.1% of patients suffered either fatal or aborted SCD(13). In another study by Bakker et al retrospectively analysed 105 patients with CS and classified them into high and low-risk subsets as per imaging and multi-disciplinary team analysis, 17 patients out of the high-risk group had been implanted with AICD, while 80 low-risk patients underwent implantable loop recorder (ILR). The study found an annualized overall event rate of 1.7% (10% in high-risk patients, 0.4% in low-risk patients)(14). Studies in Indian population are lacking. This study done in an Indian cohort will aid in formulating clear-cut guidelines for device use in CS patients and shed light on the long-term outcomes after their implantation.

AIMS & OBJECTIVES

Primary Objective: The primary objective of this study was to determine the outcome of CIEDS in CS patients- arrhythmia detection & therapy & adverse cardiovascular events

Secondary Objective: Secondary objective was to identify the risk factors that are associated with adverse outcome.

MATERIALS AND METHODS

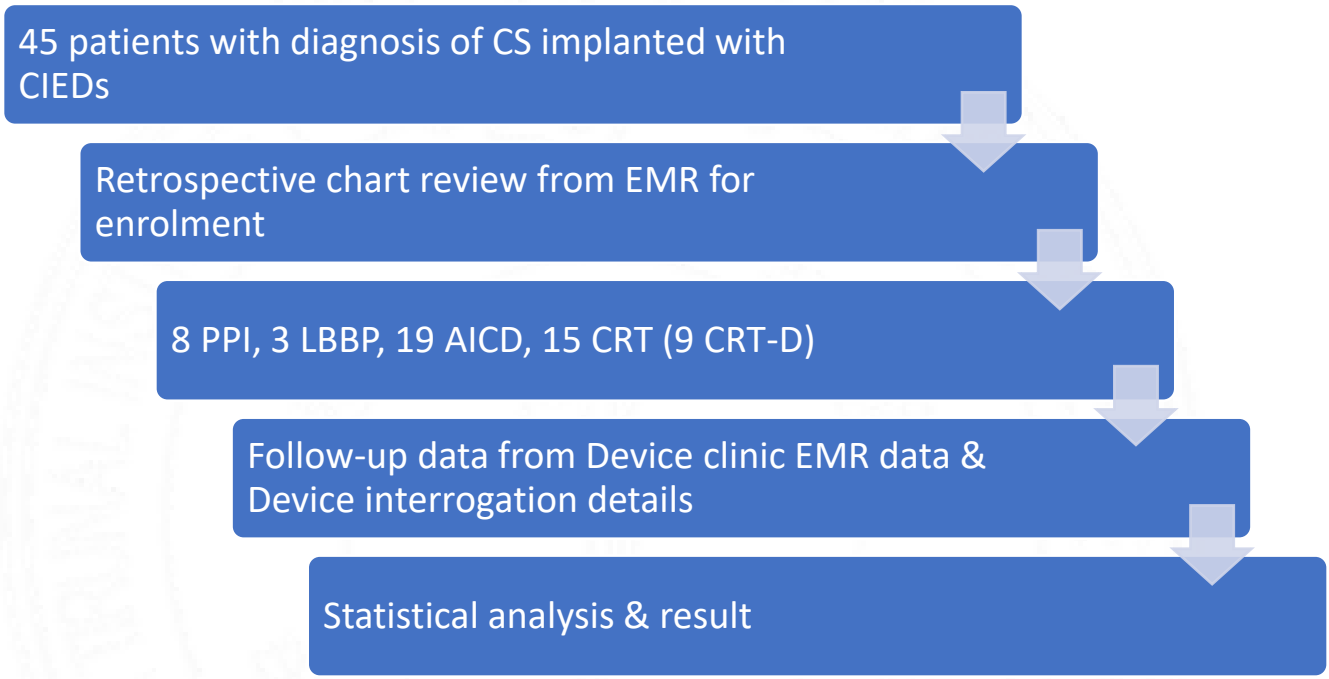
- Study Design: Retrospective single-centre study
- Study Period: December 2024
- Ethical clearance: Institutional Ethics Committee clearance was taken before conducting the study (SCT/IEC/2281).
- Sample Size: All consecutive patients diagnosed with cardiac sarcoidosis who underwent CIED implantation.
- Inclusion Criteria: All patients (>18 years of age) diagnosed with cardiac sarcoidosis (as per departmental diagnosis) and who underwent CIED implantation (Permanent Pacemaker/ AICD (Automatic Implantable Cardioverter Defibrillator)/ CRT-P/D (Cardiac Resynchronization Therapy)/ ILR (Implantable Loop Recorder) till the year 2024 and are under follow-up at SCTIMST device clinic will be included.
- Exclusion Criteria:
  - Lost to follow-up
  - Not willing

- Any other concomitant cardiac disease necessitating CIED

- Data Collection: Those who satisfied the inclusion criteria, data was collected from a retrospective chart review of the EMR (Electronic Medical Records)-
  - Demographic data, medical history, comorbidities,
  - Hospitalisation history
  - Imaging data:
    - ECG
    - Echocardiogram
    - Cardiac MRI (if available)
    - FDG PET (if available)
  - Extra-cardiac status
  - CIED Implantation details- PPI/ AICD/CRT-P/D/ ILR : Immediate post-implantation status & success (from admission chart review)
  - Indication: Primary/ Secondary prophylaxis
  - Blood Investigations (if available)
  - Medical Treatment Received: Immunosuppressive treatment
  - Device interrogation details: Device parameters, duration of follow-up, clinically significant arrhythmias, therapy received- appropriate/ inappropriate (from device clinic follow-up data)
  - EP Study/ Catheter Ablation if any
  - Clinical status at last follow-up in Device clinic
  - Current Medications

- Outcome: The primary outcome was a composite of clinically important arrhythmias (sustained ventricular arrhythmia/ appropriate ICD therapy), hospitalisation due to arrhythmia, heart failure & all-cause mortality. Secondary outcomes were time to first adverse event/ primary outcome and independent components of the primary outcome.

FIG 2. STUDY DESIGN FLOW CHART



STATISTICAL ANALYSIS

Continuous variables were conveyed as mean and standard deviation (SD) if they were normally distributed. Continuous variables which did not have normal distribution, were expressed as median and interquartile-range (IQR). Categorical variables were expressed in the form of frequency and percentage. Comparison of normally distributed continuous variables between two

groups were analysed using independent sample t-test and those that were not normally distributed were analysed using Mann-Whitney U-test. Association between the categorical variables was analysed by chi-square test. For nonparametric distribution, Wilcoxon rank sum tests was used for group comparisons. A p value <0.05 was considered as statistically significant. Data analysis was performed using SPSS version 24. To identify factors associated with adverse outcome a multivariate logistic regression model was used. Kaplan Meier survival analysis was used to evaluate the occurrence of primary and secondary outcomes with the distribution of time to first event and censored observations. Comparison of survival curves was done using the Log rank test and hazard ratio.

RESULTS

This study is a retrospective single-centre study conducted at SCTIMST. In total, 45 patients with CS underwent CIED implantation and were included in this study. Table 1 lists the baseline characteristics of these patients. The mean present age of the study population was 54.9±12.9 years with male predominance (32, 71.1 %)(Fig2). The mean age of device implantation was 50.5±12.9 years, with a mean duration of 56 months post-device implantation at the last follow-up. The initial presentation to our centre was that of conduction system disease, arrhythmia and heart failure or LV dysfunction in 14(31.8%), 19 (43.2%) and 11 (25%) respectively (Fig 3) with 10 (22%) presenting with symptoms of palpitation, 13 (28.9 %) with syncope, 4 (8.9 %) with presyncope, 10 (22.2%) with breathlessness, 1 (2.2%) with fatigue and 7 (15.6%) with history of resuscitated cardiac arrest respectively (Fig4, Table2). The NYHA functional classification indicated that most participants were in class II (62.2%), followed by class I (13.3%), and a smaller proportion in classes III (22.2%) and IV (2.2%) at presentation (Fig 5).

Table 1 Baseline characteristics		Total (N=45)
Current Age (in years)		
	Mean (SD)	54.9 (12.9)
	Range	27.0 - 75.0
Sex		
	Male	32 (71.1%)
	Female	13 (28.9%)
Age at Implantation (in years)		
	Mean (SD)	50.5 (12.9)
	Range	19.0 - 73.0
Duration after implantation (days)	Mean (SD)	1695.8 (1361.0)
	Range	115.0 - 5148.0

Fig 3

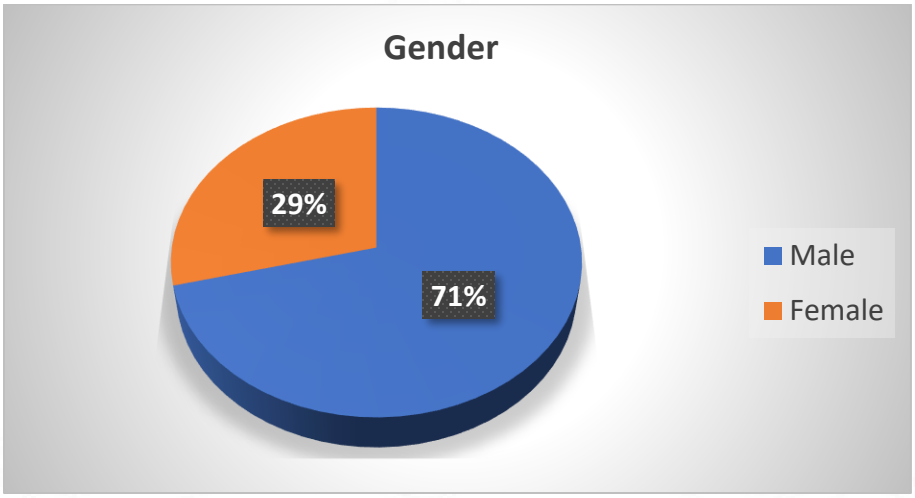


Table 2 (n=45)

Symptoms		
	Palpitation	10 (22.2%)
	Syncope	13 (28.9%)
	Presyncope	4 (8.9%)
\		
	Dyspnea	10 (22.2%)
	Fatigue	1 (2.2%)
	Resuscitated Cardiac arrest	7 (15.6%)
Presentation		
	Conduction system disease	14 (31.8%)
	Arrhythmia	19 (43.2%)
	Heart failure/ LV dysfunction	11 (25.0%)

Fig. 4

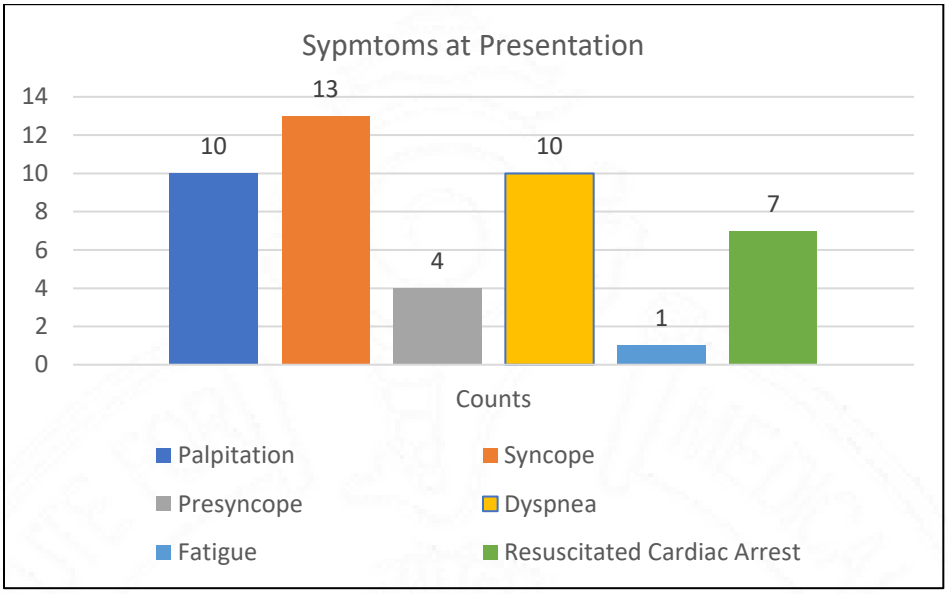

Sypmtoms at Presentation
14
12
10
8
6
4
2
0
10
13
4
10
1
7
Counts
Palpitation
Syncope
Presyncope
Dyspnea
Fatigue
Resuscitated Cardiac Arrest

Fig. 5

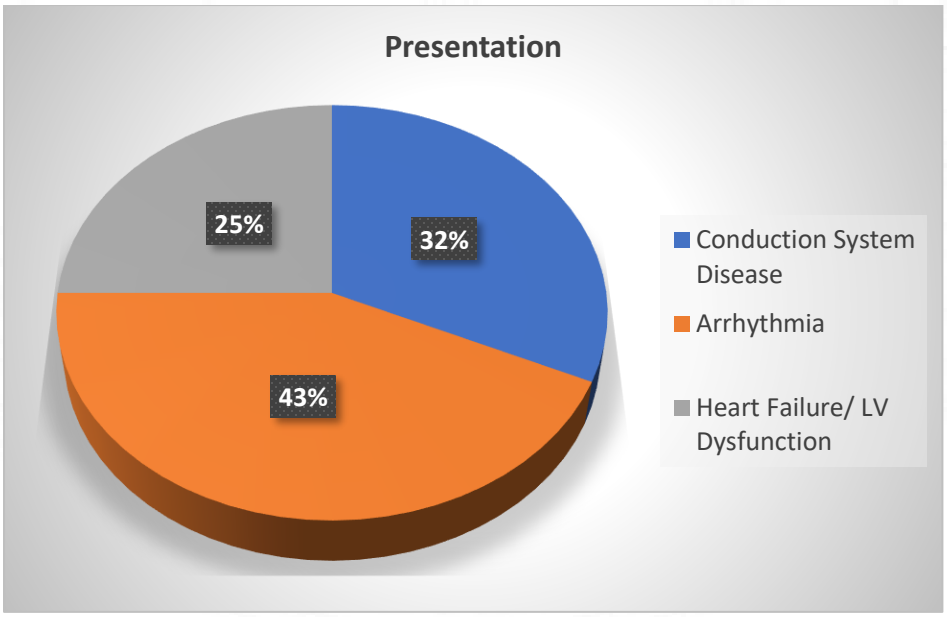
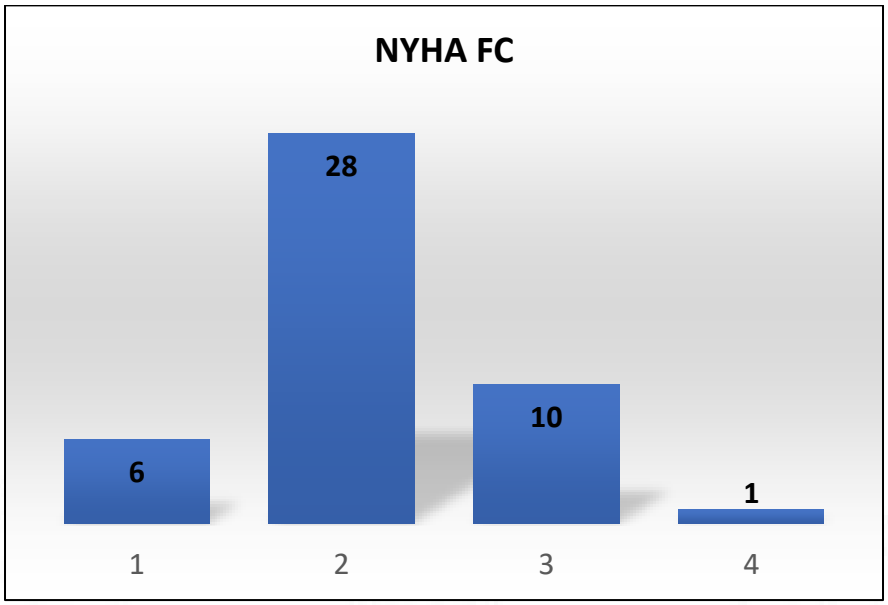

Presentation
25%
32%
43%
Conduction System Disease
Arrhythmia
Heart Failure/ LV Dysfunction

Fig. 6



The mean heart rate at presentation was 73±28.7bpm, and blood pressure (SBP/DBP) was 121.6±19.3/74.6±12.0 mm Hg respectively (Table 3). Baseline ECG findings at presentation showed the mean PR interval was 187.7±49.4 ms (among those with sinus rhythm), mean QRS duration was 122±34.4 ms, 7(15.6%) had left-bundle branch block, 8(17.8%) had right bundle branch block while 4 (8.9%) had non-specific intraventricular conduction defect. 19 (42.2%) had a documented sustained VT in ECG or Holter, 3(6.7%) had non-sustained VT runs, 2(4.4%) had premature ventricular complexes (PVCs) (Table 3). 6 (13.6%) patients had complete heart block, 7 (15.9 %) had high-grade AV block. An Electrophysiological (EP) study was done in 10 patients, out of which 5 (11.1%) had an inducible VT, 1 of them underwent VT ablation, while 2 had atrial flutter ablation, and others had normal EP study (Table 3).

Table 3

Baseline clinical parameters at presentation		
Heart Rate (bpm)		
	Mean (SD)	72.6 (28.7)
	Range	33.0 - 200.0
SBP (mm Hg)		
	Mean (SD)	121.6 (19.3)
	Range	90.0 - 163.0
DBP (mm Hg)		
	Mean (SD)	74.6 (12.0)
	Range	52.0 - 108.0
Baseline ECG findings		
PR interval (ms)		
	Mean (SD)	187.7 (49.4)
	Range	120.0 - 310.0
QRSd (ms)		
	Mean (SD)	122.1 (34.4)
	Range	80.0 - 200.0
Conduction delay	LBBB	7 (15.6%)
	RBBB	8 (17.8%)
	IVCD	4 (8.9%)
VT /PVC	Sustained VT	19 (42.2%)
	Non-Sustained VT	3 (6.7%)
	PVC	2 (4.4%)

EP study	Counts	% of Total
Inducible VT	5	11.1 %

1- Scar VT ablation

1 LA flutter ablation, 1 attempted RA FI abation

Echocardiography findings at presentation showed a mean LV ejection fraction (EF) of 44.5±16.9 % (minimum 20 % & maximum 78 %), with a mean LV diastolic dimension of 53.9±9.6 mm & LV systolic dimension of 41.6±11.5 mm. The mean RV TAPSE was 18.4±4.3 mm. Regional wall motion anomaly or dyskinesia was noted in 15 (33.3%) (Table 4).

Table 4. Echocardiographic findings at presentation

LVDD (mm)		
	Mean (SD)	53.9 (9.6)
	Range	33.0 - 73.0
LVSD (mm)		
	Mean (SD)	41.6 (11.5)
	Range	24.0 - 63.0
LVEF (%)		
	Mean (SD)	44.5 (16.9)
	Range	20.0 - 78.0
RV TAPSE (mm)		
	Mean (SD)	18.4 (4.3)
	Range	8.0 - 26.0
RWMA/Dyskinesia		
	Absent	30 (66.7%)
	Present	15 (33.3%)

Extra-cardiac involvement was seen in 22 (48.9%) patients with 14 having mediastinal lymphadenopathy (2 biopsy proven), 7 with lung involvement, 3 having neurological involvement, 1 each with liver and renal involvement. 6 (13.3%) had elevated Angiotensin Converting enzyme(ACE) level. The mean NT-pro BNP level was 2880 pg/ml (n=22), mean ESR 20.7 mm (n=38), mean serum Calcium level was 8.65 mEq/L(n=24), among those who had been investigated. (Table 5)

Table 5

EXTRA-CARDIAC INVOLVEMENT

EXTRA-CARDIAC INVOLVEMENT	Counts	% of Total
Absent	23	51.1 %
Present	22	48.9 %

1- Facial Nerve, 1- Radial/ Ulnar neuropathy, 1- Neuro-sarcoidosis
1- Liver biopsy
1- Renal
14- Lymphadenopathy (2 Biopsy proven)
7- Lungs

	N	Mean	Median	SD	Minimum	Maximum
NT pro-BNP (pg/ml)	22	2880.59	1811.50	2879.992	70	9320
ESR (mm)	38	20.74	14.50	19.921	0	90
Ca (meq/l)	24	8.65	8.80	0.693	6.30	9.60

ACE level	Counts	% of Total
Elevated	6	13.3 %

Coronary angiogram was done in 28 patients, among which 22(48.9 %) had normal coronaries, while 6 (13.3%) had minor coronary artery disease. Among the different imaging modalities, cardiac MRI was done in 32 patients at some point of time during evaluation- 16 (43.2%) had multifocal sub-epicardial LGE pattern, 9 (24.3%) focal subepicardial LGE, 7 (18.9%) had mixed pattern, while 4 (10.8 %) had atypical/ different pattern (subendocardial). 1 patient had a normal MRI (done after resolution phase (Fig 6). 21 patients underwent PET CT- majority (15, 68.2%) were in the progressive phase of disease (increased FDG uptake with reduced perfusion), 4 (18.2

%) were in resolution/normalised phase, 2 (9.1%) were in early phase (only perfusion defect), while 1(4.5%) was in fibrosis phase (Table 6, Fig 7). 5 (23%) underwent repeat PET CT during follow-up out of which 2 showed complete resolution, 3 had improvement.

Table 6. Imaging characteristics

CAG		
	Not done	17 (37.8%)
	Normal	22 (48.9%)
	Minor CAD	6 (13.3%)
MRI pattern		
	Multifocal LV subepicardial	16 (43.2%)
	Focal subepicardial	9 (24.3%)
	Mixed (subendo + subepi)	7 (18.9%)
	Others	4 (10.8%)
	Normal	1 (2.7%)
PET Stage		
	Early	2 (9.1%)
	Progressive	15 (68.2%)
	Fibrosis	1 (4.5%)
	Normal	4 (18.2%)

Fig. 7

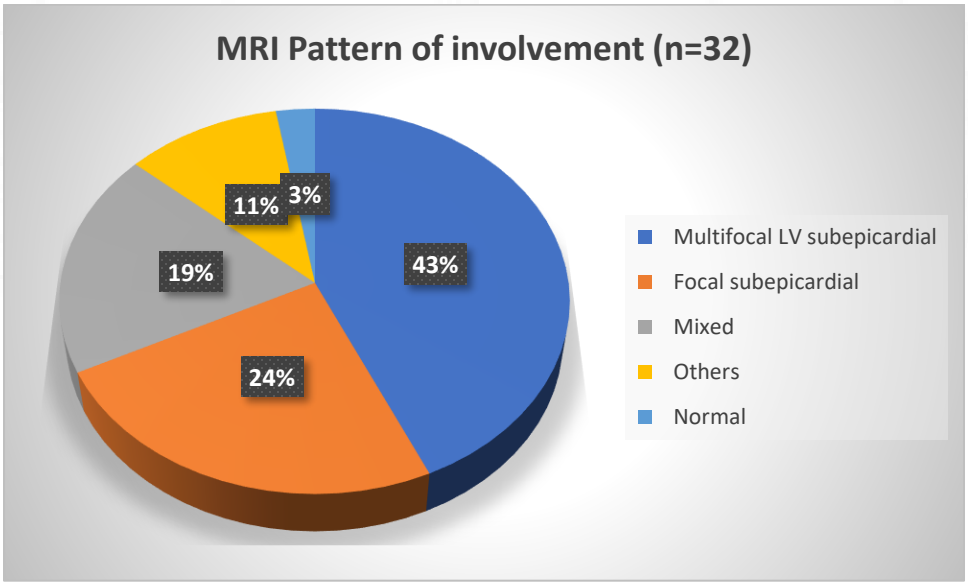
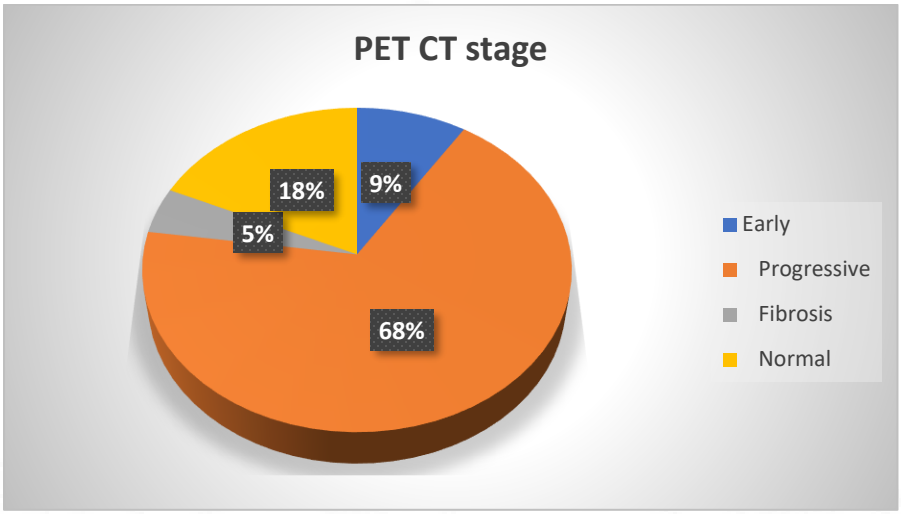


Fig. 8



Device-Related Variables:

Device types varied, with single-chamber AICDs (33.3%) and dual-chamber AICDs (8.9%) being common. CRT devices (CRT-P: 13.3%, CRT-D: 17.8%) were also implanted in significant subgroups, LOT-CRT-D was implanted in 1 (2.2%) patient, while single and dual-chamber PPI devices accounted for 6.7% and 11.1%, respectively with 3 (6.7%) with left bundle area pacing (Table 7, Fig 8). Among device manufacturers, Medtronic was the most commonly used (40%), followed by SJM/Abbott (24.4%), Boston Scientific (22.2%), and Biotronik (13.3%) (Table 7). The mean age at device implantation was 50.5 years (SD = 12.9), with a range of 19 to 73 years. The mean duration after implantation at last follow-up was 1695.8 days (approximately 4.6 years), ranging from 115 to 5148 days.

Table 7. Device Details

DEVICE		
	Single chamber PPI	3 (6.7%)
	Dual Chamber PPI	5 (11.1%)
	Single chamber AICD	15 (33.3%)
	Dual Chamber AICD	4 (8.9%)

	CRT-P	6 (13.3%)
	CRT-D	8 (17.8%)
	LBBB pacing	3 (6.7%)
	LOT CRT-D	1 (2.2%)
COMPANY		
	Medtronic	18 (40.0%)
	Biotronik	6 (13.3%)
	SJM/Abott	11 (24.4%)
	Boston Sc	10 (22.2%)

Fig. 9

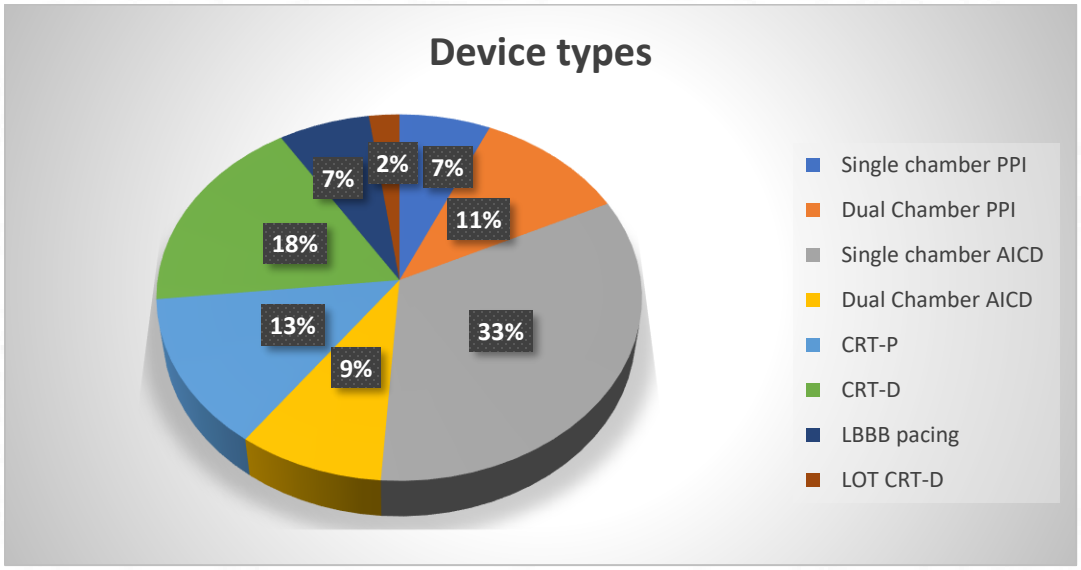


Table 8. Indication for CIED implantation

INDICATION	
CHB	6 (13.6%)
HIGH-GRADE AV BLOCK	7 (15.9%)
NSVT	4 (9.1%)
VT (Sustained)	15 (34.1%)
Scar/Imaging	1 (2.3%)
LV Dysfunction	11 (25.0%)

Among the various indications for device implantation- sustained VT (either spontaneous or induced) was the most common (15, 34.1 %), followed by CHB/high-grade AV block (13, 29.5%), LV dysfunction (11, 25 %), NSVT (4, 9.1 %) and imaging-based (significant scar- 1, 2.3 %) (Table 8). 43 (95.6 %) had acute success during implantation with all desirable parameters achieved. 1 patient had poor CRT-D response with CS lead displacement and required lead repositioning on follow-up, 1 patient with LBB pacing had non-selective left bundle capture with wide QRS on ECG. 1 patient with single chamber VVI pacemaker had chronically elevated lead impedance, 1 patient had minor wound gaping post-implantation, which resolved with conservative management. 1 patient had dual chamber PPI upgradation from single chamber PPI, 1 had dual chamber AICD upgradation from single chamber PPI, 1 had CRT-P upgradation from single chamber PPI. Patient with LOT-CRT-D implantation had initial left bundle area acing attempted but, had suboptimal response due to scarred basal septum, so changed to LOT CRT. Among those with AICD/CRT-D/ LOT CRT-D implantation, the indication was secondary prophylaxis in 20 (71.4 %) patients, while primary prophylaxis in 8 (28.5 %)(Table 9).

Table 9. Prophylaxis & Complications

PRIMARY/SECONDARY PROPHYLAXIS		
	Primary	8 (17.8%)
	Secondary	20 (44.4%)
COMPLICATIONS		
	1	Poor CRT-D response with CS lead displacement requiring lead repositioning
	1	Non-selective left bundle capture with wide QRS on ECG
	1	VVI with chronically elevated lead impedance
	1	Minor wound gaping

Medications: The patients were prescribed a variety of cardiovascular medications/ antiarrhythmics as well as immunosuppressants. Beta-blockers were commonly used (38,84.4 %) – most commonly metoprolol succinate (62.2%). ARNI was used in 15 (33.3%), ACEI in 4 (8.1%), ARBs in 3 (6.6 %), MRA in 12 (26.7 %), SGLTI in 24 (53.3 %). Among other antiarrhythmics, amiodarone was most commonly used (46.7%), followed by Mexiletine (8.9 %), Sotalol (6.7 %). Diuretics were administered in 24 (53.3%) patients (Table 10).

Table 10: Cardiac Medications

BETA BLOCKER (38, 84.4%)		
	METOPROLOL	28 (62.2%)
	PROPRANOLOL	1 (2.2%)
	CARVEDILOL	8 (17.8%)
	BISOPROLOL	1 (2.2%)
ACEI (4, 8.1%)		
	ENALAPRIL	2 (4.4%)
	RAMIPRIL	1 (2.2%)
	PERINDOPRIL	1 (2.2%)
ARNI	SACUBITRIL/VALSARTAN	15 (33.3%)
ARB (3, 6.6%)		
	LOSARTAN	2 (4.4%)
	TELMISARTAN	1 (2.2%)
MRA	SPIRONOLACTONE	12 (26.7%)
SGLTI (24, 53.3%)		
	DAPAGLIFLOZIN	23 (51.1%)
	EMPAGLIFLOZIN	1 (2.2%)
CCB (2, 4.4%)		
	VERAPAMIL	1 (2.2%)
	AMLODIPINE/ CILNIDIPINE	1 (2.2%)
AMIODARONE		21 (46.7%)
SOTALOL		3 (6.7%)
		4 (8.9%)

MEXILETINE	
DIURETICS	24 (53.3%)

18 patients were on some form of immunosuppressant medication at any time during the course of their follow-up- 15 (33.3 %) were on steroids (oral Prednisolone/ IV Methylprednisolone/ Deflazacort), 8 (17.8 %) were on oral Methotrexate, 1 (2.2%) on Cyclophosphamide and 1 (2.2 %) on Mycophenolate mofetil (Table 11).

Table 11. Immunosuppressant medications

Immunosuppressant / DMARDS		
	STEROIDS	15 (33.3%)
	METHOTREXATE	8 (2.2%)
	MMF	1 (2.2%)
	CYCLOPHOSPHAMIDE	1 (2.2 %)

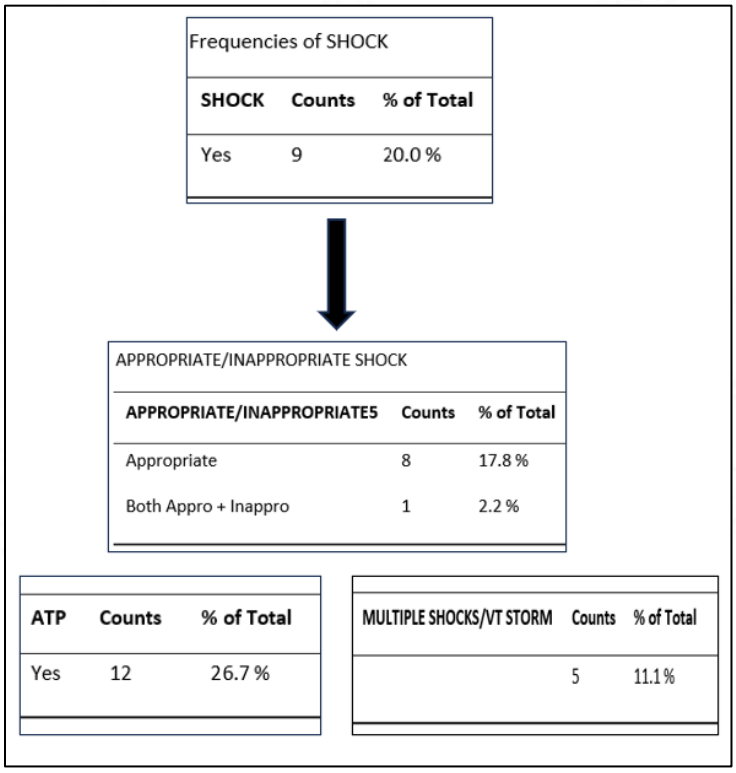
Device follow-up details: Data collected from device clinic follow-up showed the following observations (Table 12 & Fig 9)). Among device-detected arrhythmias on follow-up - 14 (31.1%) patients had a sustained VT detected, 1 (2.2%) patient had non-sustained VT detected, 8 (17.8%) patients had supra-ventricular tachycardia detected, 1 (2.2%) patient had isolated PVC detected. 14 (31.1%) had received device therapy- 9 (20 %) received shock, 12 (16.7 %) had received ATP. 8 of the patients among those who received ICD shock- appropriately received so, while 1 patient had received both appropriate and inappropriate shock (AF with high ventricular rate detected as VT). 31 (68.9 %) patients did not experience any device therapy. 5 (11.1%) had experienced

multiple shocks or had VT storm- out of which 2 did not terminate with ICD therapy and had to be externally cardioverted along with anti-arrhythmic infusion. One of them required VT ablation.

Table 12. Device therapy on follow-up

DETECTED ARRHYTHMIA			
	Sustained VT		14 (31.1%)
	NSVT		1 (2.2%)
	SVT		8 (17.8%)
	Others (PVCs)		1 (2.2%)
THERAPY			
	Received		14 (31.1%)
ATP			
	Received		12 (26.7%)
SHOCK			
	Yes		9 (20.0%)
APPROPRIATE SHOCK			
	Yes	8 (17.8%)	
	Both (appro/inappro)	1 (2.2%)	
MULTIPLE SHOCKS/VT STORM			
	Yes		5 (11.1%)

Fig 10. Device Therapy details



Outcome: The primary outcome, which is a composite of clinically important arrhythmias (sustained ventricular arrhythmia/ appropriate ICD therapy), hospitalisation due to arrhythmia, heart failure & death - was noted in 44.4% (20) patients (Table 13). 13 (28.9%) had clinically important arrhythmias requiring device therapy or hospitalisation, 7 (15.6 %) required heart failure hospitalisation, while 1(2.2 %) patient had death due to decompensated heart failure. The mean time to first event was 980 days or 32.6 months (minimum 4 days, maximum 4136 days or 138 months)(Table 14 & Fig 10, 11).

Table 13

PRIMARY OUTCOME	**20 (44.4%)**
CLINICALLY IMPORTANT ARRHYTHMIAS	13 (28.9%)
HF HOSPITALISATIONS	7 (15.6%)
ALL-CAUSE MORTALITY	1 (2.2%)
ARRHYTHMIA THERAPY/ HOSPITALISATION	13 (28.9%)

Table 14: Time to first event

	N	Mean	Median	SD	Min	Max
Time to first event (days)	20	980	370	1277	4	4136

Fig 11: Distribution of patients with primary outcome over time

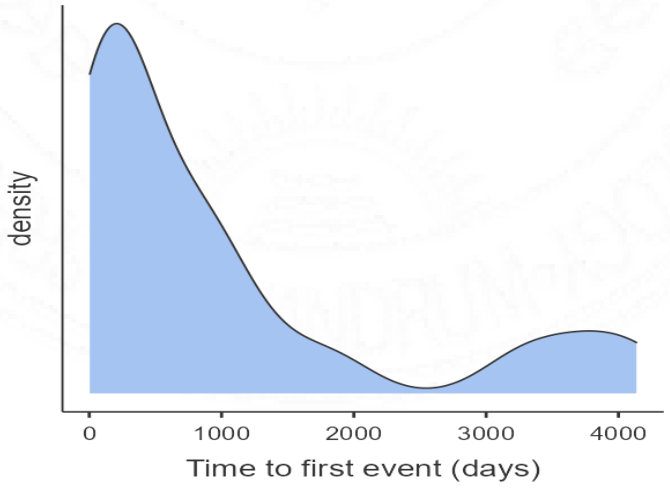


Fig. 12 Kaplan Meier curve for the primary composite outcome

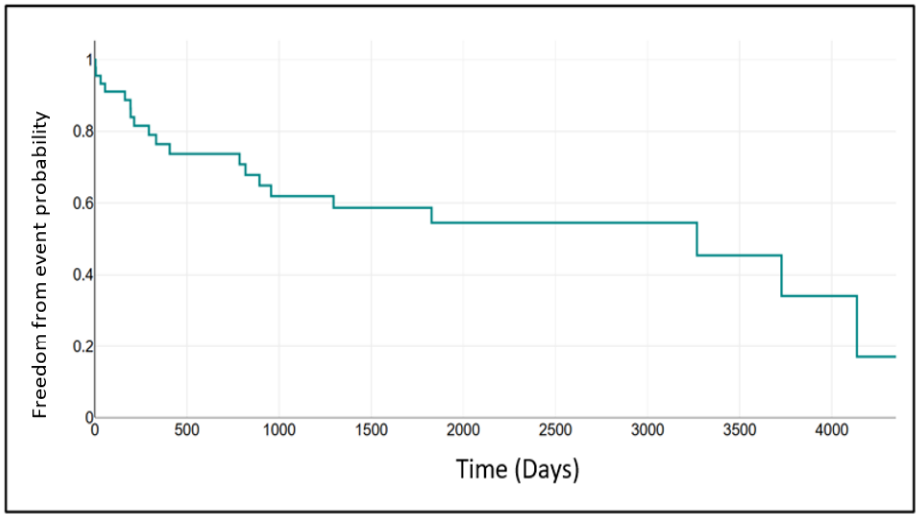
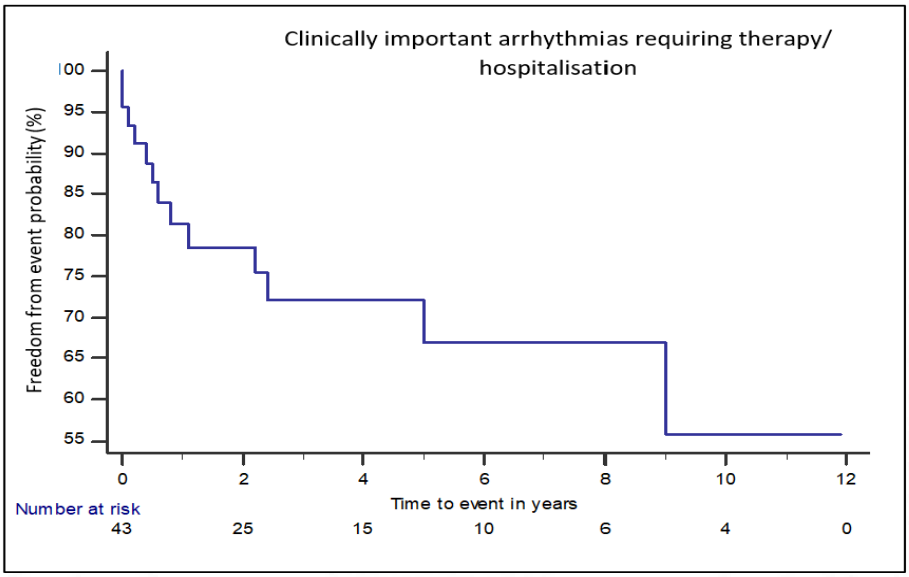


Fig. 13 Kaplan Meier curve for clinically important arrhythmias

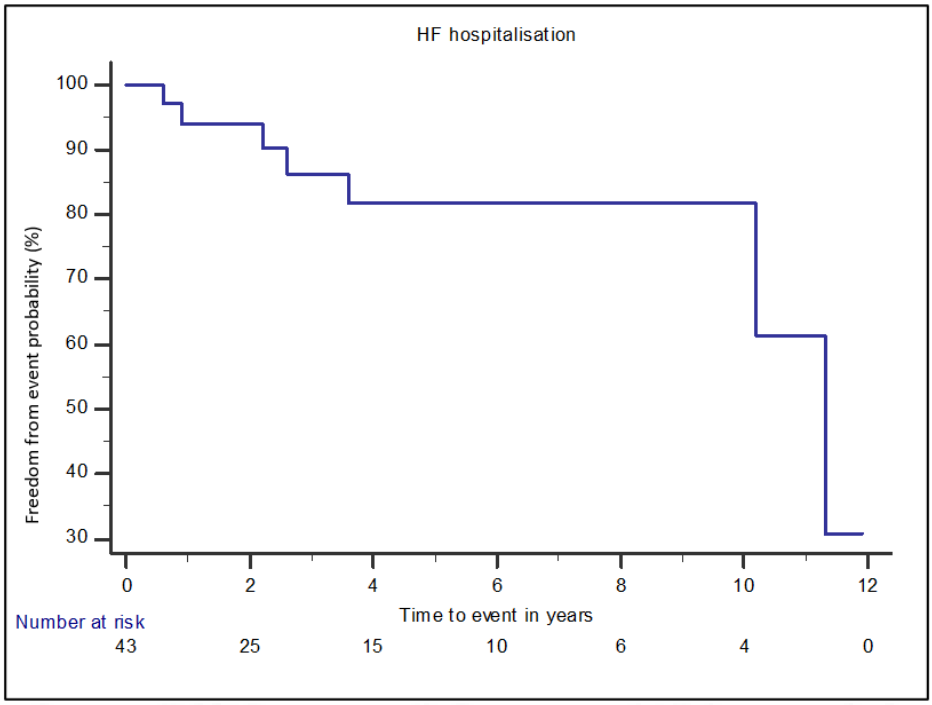


Mean and median time in years

Event	Mean	SE	95% CI for the mean
CLINICALLY IMPORTANT ARRHYTHMIAS	8.1	0.9	6.5 to 9.8

Event	Number of events		Number censored		Total sample size
	N	%	N	%	
CLINICALLY IMPORTANT ARRHYTHMIAS	13	28.89	32	71.11	45

Fig. 14 Kaplan Meier curve for heart failure hospitalisation



Mean and median survival time in years

Event	Mean	SE	95% CI for the mean	Median	95% CI for the median
HF hospitalisation	9.6	0.7	8.1 to 11.0	11.3	10.2 to 11.3

Event	Number of events		Number censored		Total sample size
	N	%	N	%	
HF hospitalisation	7	15.56	38	84.44	45

Baseline demographics and clinical characteristics (Table 15)

The mean age was similar across both groups, with no significant difference (p = 0.988). Males constituted a higher proportion in both groups, but the difference was not statistically significant (p = 0.239). The mean heart rate at presentation was higher in the outcome group (81.7 bpm, SD = 35.1) compared to the no-outcome group (65.2 bpm, SD = 20.2), approaching significance **(p =**

0.055). The wider range in the positive event group (45.0–200.0 bpm) as compared to the non-event group might suggest variability in heart rate affecting the outcome. Systolic and Diastolic Blood Pressure (SBP and DBP)**:** Both groups had similar SBP (mean = 121.6 mmHg) and DBP (mean = 74.6 mmHg) values, with no significant differences (p = 0.957 and p = 0.535, respectively). Symptoms at presentation, including underlying cardiac pathology (p = 0.380), were distributed similarly across both groups, with no significant differences. The distribution across NYHA classes showed no significant difference (p = 0.418). The mean heart rate at final follow-up was higher in the outcome group (76.4 bpm, SD = 16.6) compared to the no-outcome group (69.0 bpm, SD = 9.9), with a p-value of 0.075, suggesting a trend toward significance. SBP and DBP at final follow-up were comparable between groups, with no significant differences (p = 0.817 and p = 0.370, respectively). Significant differences were observed in NYHA functional class at final follow-up (p = 0.012), with a trend towards poorer functional status in the outcome group.

ECG Characteristics

Among ECG findings, in those with sinus rhythm, the mean PR interval was longer in the outcome group (205.0 ms, SD = 55.9) compared to the no-outcome group (173.5 ms, SD = 39.7), with a p-value of 0.077, indicating a trend toward significance. The mean QRS duration was similar between groups (p = 0.545). Other ECG characteristics including intraventricular conduction delays (e.g., LBBB, RBBB, IVCD etc) and ventricular arrhythmias (e.g., sustained VT, NSVT etc) were distributed similarly, with no significant group differences. Though sustained VT was more prevalent in the outcome group (66.7%) compared to the no-outcome group (33.3%), but this difference was not statistically significant (p = 0.077).

Echocardiographic characteristics

Both left ventricular diastolic dimension (LVDD) and systolic dimension (LVSD) showed no significant differences between groups ($p = 0.356$ and $p = 0.682$, respectively). The mean LVEF was almost identical between groups, averaging 44.5% ($p = 0.961$). RV TAPSE was lower in the outcome group (mean = 17.1 mm, SD = 5.0) compared to the no-outcome group (mean = 19.4 mm, SD = 3.4), showing a trend toward significance ($p = 0.084$)- which might be suggestive of worsening RV function as a predictor of poor outcome (Table 15).

Biochemical parameters

Both groups had comparable mean NT-proBNP levels (~2880 pg/mL), with no significant difference ($p = 0.957$). The outcome group had a lower mean ESR (18.1 mm/hr, SD = 17.6) compared to the no-outcome group (22.7 mm/hr, SD = 21.7), but the difference was not statistically significant ($p = 0.488$). Mean serum calcium levels were similar across groups ($p = 0.648$).

Imaging : MRI pattern of involvement and PET CT stage of disease showed was no significant differences between the outcome groups (p=0.26 & 0.20).

Medications

The majority of medication use including heart failure medications and immunosuppressants was not significantly different across both groups ($p > 0.05$). However, **Amiodarone and Sotalol use** was significantly higher in the group with the primary event (**p= 0.012 & 0.045** respectively) (Table 15), indicating the higher complexity of management and requirement of additional antiarrhythmics required for these patients.

Device Related parameters:

The mean age at implantation was similar in both groups (p = 0.810). There was a statistically significant difference in the need for therapy between groups (p < 0.0012) with ATP therapy (p = 0.002), shocks (p = 0.024), multiple shocks/ VT storm (p=0.008) being significantly more common in the group with the primary outcome (table 15), suggestive of the fact that clinically important arrhythmias requiring device therapy contributed mostly towards adverse event. Deaths were rare, with only one case in the outcome group (5%), showing no statistical significance (p = 0.258).

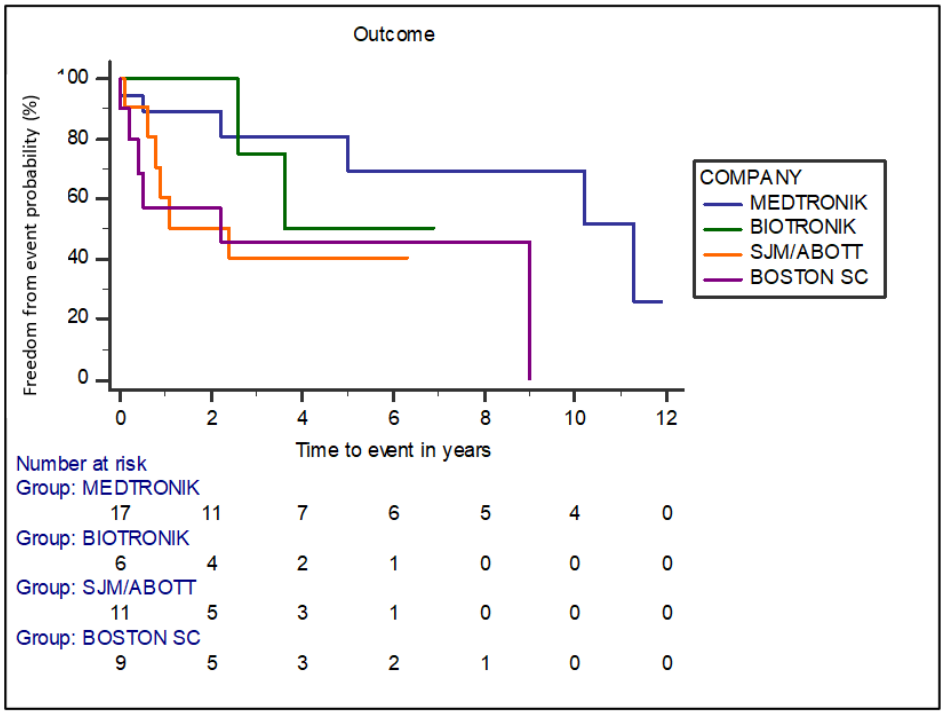
Table 15: Variables associated with Primary Outcome

		Primary Outcome		p- value
		No	Yes	
HR at presentation (bpm)				0.055
	Mean (SD)	65.2 (20.2)	81.7 (35.1)	
	Range	33.0 - 120.0	45.0 - 200.0	
PR (ms)				0.077
	Mean (SD)	173.5 (39.7)	205.0 (55.9)	
	Range	120.0 - 300.0	140.0 - 310.0	
RVTAPSE				0.084
	Mean (SD)	19.4 (3.4)	17.1 (5.0)	
	Range	13.0 - 26.0	8.0 - 24.0	
HR at last follow-up (bpm)				0.075
	Mean (SD)	69.0 (9.9)	76.4 (16.6)	
	Range	58.0 - 94.0	50.0 - 118.0	
AMIODARONE				
	No	19 (76.0%)	5 (25.0%)	< 0.0012
	Yes	6 (24.0%)	15 (75.0%)	
SOTALOL				
	No	25 (100.0%)	17 (85.0%)	0.045
	Yes	0 (0.0%)	3 (15.0%)	
DETECTED ARRHYTHMIA				
	Sustained VT	2 (33.3%)	12 (66.7%)	0.077
	NSVT	1 (16.7%)	0 (0.0%)	
	SVT	2 (33.3%)	6 (33.3%)	
	Others	1 (16.7%)	0 (0.0%)	

ICD THERAPY				
	No	23 (92.0%)	8 (40.0%)	< 0.0012
	Yes	2 (8.0%)	12 (60.0%)	
ATP				
	No	23 (92.0%)	10 (50.0%)	0.002
	Yes	2 (8.0%)	10 (50.0%)	
ICD SHOCK				
	No	23 (92.0%)	13 (65.0%)	0.024
	Yes	2 (8.0%)	7 (35.0%)	
MULTIPLE SHOCKS/ VTSTORM				
	No	25 (100.0%)	15 (75.0%)	0.008
	Yes	0 (0.0%)	5 (25.0%)	
NYHA FC at last follow-up				
	1	14 (56.0%)	3 (15.8%)	0.012
	2	11 (44.0%)	14 (73.7%)	
	3	0 (0.0%)	2 (10.5%)	

There were no significant differences in the various companies of devices implanted with log rank test comparing event rate curves indicating no statistically significant difference in probabilities across the groups (Fig 14).

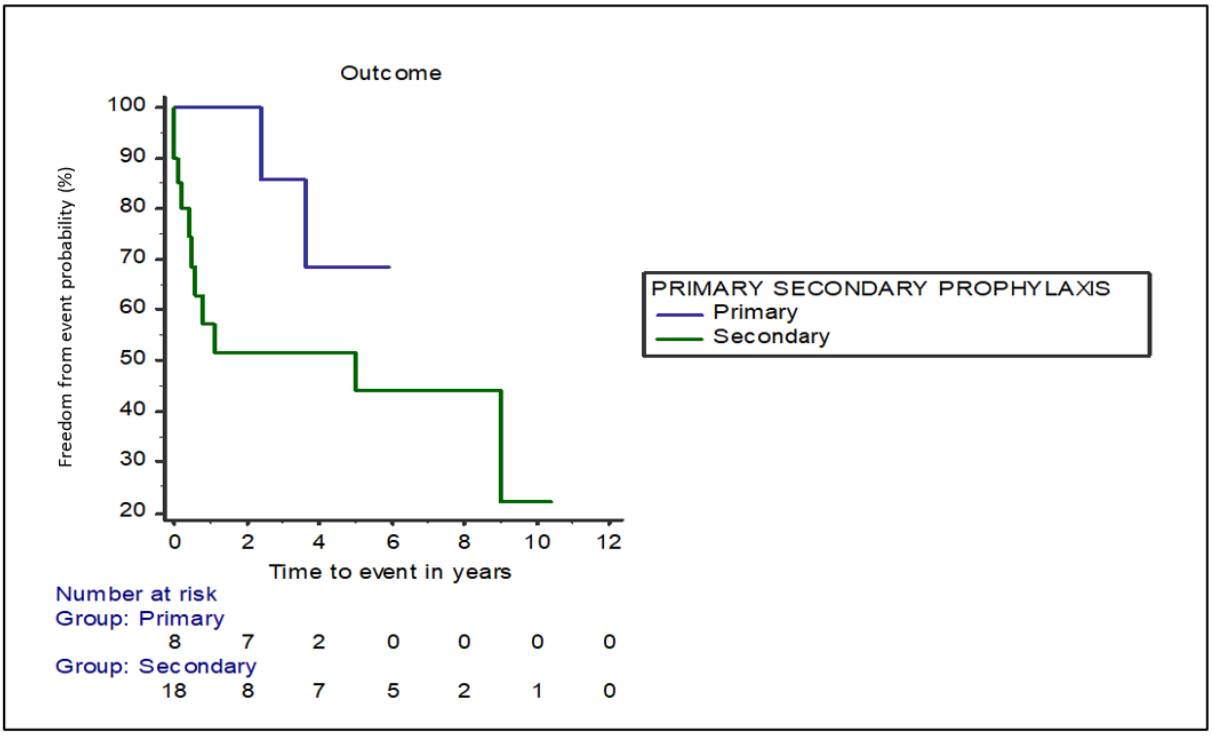
Fig. 15. Log-rank test comparing different companies



Chi-squared	5.937
DF	3
Significance	P = 0.115

Log rank test comparing survival curves between the primary and secondary prophylaxis group yielded a Chi-squared value of 1.680 with 1 degree of freedom and a p-value of 0.195 indicating no statistically significant difference in survival probabilities between participants receiving primary and secondary prophylaxis. Using the primary prophylaxis group as the reference, the Hazard Ration for the secondary prophylaxis group was 2.52 (95% CI: 0.78 to 8.14). While this suggests a higher risk of events for the secondary prophylaxis group compared to the primary group, the wide confidence interval and lack of statistical significance indicate that this finding should be interpreted with caution.

Fig. 16. Log-rank test comparing event rate curves between those with primary & secondary prophylaxis



Chi-squared	1.680
DF	1
Significance	P = 0.195

Hazard ratio with 95% Confidence Interval

Factor	HR
Primary vs Secondary	2.52
95% CI	0.78 to 8.14

DISCUSSION

This single-centre retrospective cohort study included 45 participants with CS and CIED implantation with a mean follow-up of 56 months. The patients were found to be at high risk for the primary adverse event (44.4 %) on follow-up- either clinically important ventricular arrhythmias (VA), requiring device therapy or hospitalisation (28.9 %) or HF hospitalisation (15.6 %) or mortality (2.2%). Primary outcome was primarily driven by clinically significant VA followed by HF hospitalisations. Only one mortality was noted.

The patient cohort had a varied presentation with majority (43.2 %) presenting with arrhythmia, 31.8 % presenting with conduction system disease and 25 % presenting with heart failure or LV dysfunction. However, the primary outcome did not vary significantly among the cohorts with different presenting symptoms, suggestive of the fact that disease progression and prognosis is not related to the initial clinical presentation. Although incidence of CS is reported to be equally distributed among men and women in autopsy and imaging series, many large studies in patients with CS and device implantation (12,14) have showed a male predominance; our study also reflects similar male predominance (71.1%) comparable to previous studies.

31.1% patients in our study had received some form of device therapy - 20 % had received appropriate shocks and 26.7 % had received ATP. 1 patient had received both appropriate and inappropriate shock. Unlike the previous large multicentric study by Kron et al, which showed a high incidence of inappropriate shock (24%) (12), our study showed a relatively lower incidence of inappropriate therapy, thus reaffirming the beneficial role ICDs over their complications. While previous studies had individually looked at follow-up among AICD or pacemakers in CS, our study provides a holistic view of outcomes in all CIEDs- including CRTs as well. The implantation

rates of CRT devices were also high in our study cohort in subgroups with LV dysfunction and significant ventricular dyssynchrony - 15 patients (33.3%) underwent same (8 among them CRT-D, 1 with LOT-CRT-D, 6 with CRT-P). One of these patients had upgradation from previous pacemaker to CRT-P. One of the patients with CRT-P also had a clinically significant VA detected on follow-up, which required hospitalisation and external cardioversion. Very few studies have been done in CS patients with CRT. A recent meta-analysis by Ahmed et al (15) showed that after a mean follow-up of 60.1 months, the incidence of hospitalizations related to heart failure was 23.2% and the incidence of all-cause mortality was 7.6% in CS patients with CRT implantation. Our study showed much lower HF hospitalisation among CRT subgroup with 2 out of 15 (13.3 %) having HF hospitalisation and no mortality, suggestive of significant clinical benefit. One of the patients had lead related complication, leading to suboptimal response.

Although majority of the cohort with defibrillators were implanted for secondary prophylaxis (44.4 %), the percentage of primary prophylaxis recipients was also high (17.7 %). However there was no statistically significant difference in primary outcome and event free survival curve among them, though event rates were higher in secondary prophylaxis group. This suggests ICD/CRT-D implantation in CS patients with significant LV dysfunction without previous sustained VT or cardiac arrest should be strongly considered with a lower threshold for implantation. This finding is also substantiated by the study by Nordenswan et al which showed that at five years of follow-up, the combined incidence of life-threatening VAs and emerging ICD indications exceeded 50% and a risk of SCD of nearly 5% was present in CS patients even without Class I indication for ICD implantation as per HRS 2014 expert consensus criteria or ACC/AHA/HRS 2017 consortium guidelines(13).

The comparison of clinical, ECG and echocardiographic parameters between patients with and without primary outcomes revealed several notable trends, though most differences were not statistically significant. Higher heart rates at presentation, longer PR intervals, and lower RV TAPSE values, which may reflect underlying subclinical physiological cardiac stress, showed increased trend toward the adverse outcome group. Although biochemical parameters like NT-Pro BNP & serum ACE levels did not show any significant association, partly limited by the fact that these investigations were done only in limited patients. This also suggest underutilisation of these investigations in our setting. Our study also showed no significant association among the MRI pattern of involvement and PET CT stage of disease and the primary outcome with no significant differences between the groups, suggesting that although the imaging investigations may have a definite role in the diagnosis and follow-up of the patients with CS, including response to immunosuppressive therapy, they failed to predict adverse outcome or prognosis. However, Kouranos et al (3) have demonstrated a clear role of cardiac MRI- which was found to be the most specific and sensitive test in diagnosing CS, even in those with clinically silent disease and normal echocardiographic findings. The study also demonstrated LGE as an independent predictor of adverse outcomes in CS patients. A large subset of patients in our study underwent cardiac MRI (71.1%) which had a clear role in CS diagnosis, as per our institutional multi-disciplinary team analysis. Except one patient among them, who had a normal MRI (done later on during follow-up) after the resolution of active phase, all others had demonstrated LGE with different distribution patterns. So the critical role of cardiac MRI can never be discounted for. Only 5 patients in our study cohort had a follow-up PET done, suggestive of the inadequate use of the modality to monitor response to therapy and follow-up activity of the disease. The cohort of patients in our study also had a significant. The significantly increased use amiodarone and sotalol in the adverse

outcome group indicates the higher requirement of antiarrhythmics in the management required for these patients. Limited data exist to guide the use of immunosuppressive therapy in the treatment of VA in CS patients; it has been noted that, in patients with positive FDG, the burden of PVCs and non-sustained VT frequently increases (16). There is heterogeneity of data in prior studies regarding this, a few studies support the prompt use of immunosuppressive therapy to prevent MACE events(17), however others suggest a greater role in resolution of AV blocks and LV dysfunction with a limited role in preventing VAs(18). Our study however showed that use of immunosuppressants however, had no association with adverse outcome, necessitating the fact that although they are an essential component in the management of active disease, the occurrence of clinically significant VAs or HF may not be preventable despite their use. All these observations underscore the importance of individualized monitoring and intervention strategies in managing patients at higher risk for adverse outcomes.

LIMITATIONS

Firstly, the study is a single-centre retrospective one, hence data collected was dependent on the accuracy of EMR charts. Secondly, a convenient sampling method was used, in which consecutive patients with CS implanted with CIED were enrolled. The diagnosis was based on institutional criteria based on clinical, imaging and other supportive findings rather than established HRS/ACC expert consensus criteria, as most patients did not have a biopsy-proven sarcoidosis. Finally, this study is not powered for detecting associations with the various individual factors, as the sample size is limited owing to the rarity of the disease and hence the results might not apply to the entire population of CS as a whole.

SUMMARY

Patients with CS are at increased risk for cardiovascular events necessitating the use of CIEDs in many patients. In this single-centre retrospective cohort Indian population of 45 patients over a mean follow-up of 4.2 years, we found that patients with CS implanted with CIEDs were at high risk for adverse cardiovascular events (44.4%) primarily driven by clinically significant VAs requiring device therapy (28.9%), followed by HF hospitalisations (15.6%). There were no significant factors except heart rate at presentation and higher use of antiarrhythmics, which could predict adverse events in this cohort. Our study also shows a lower use of imaging modalities like PET scans for monitoring therapy response. This underscores the importance of personalised strategies and monitoring as each patient may have a variable course. Further long-term prospective studies are needed to guide the judicious use of CIEDs in the management of CS patients.

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ANNEXURES

Proforma

Curriculum Vitae

Appendices

ETHICS COMMITTEE APPROVAL

PLAGIARISM CHECK REPORT

PROFORMA

TOPIC: Outcomes after cardiovascular implantable electronic devices in patients with cardiac sarcoidosis at a tertiary-care centre in South India

1. Patient Details:

Study ID: Date of review: Sex: M/F

Date of Birth

Present Age Years Months

2. Initial Medical History:

First Visit date:

Underlying Symptoms-

NYHA FC:

Heart Rate: /min
BP: /mm Hg
SpO2:

General Examination:

CVS Examination :

Underlying Rhythm:

Medications:

Investigations :

Investigation	Date	Result
Echo		LV dimensions EF RWMA

ECG		
Imaging: • Cardiac MRI • PET CT • Others:		
Extra cardiac findings/ Biopsy		
Blood Investigations CRP/ESR ACE levels Serum Calcium		

3. Device Implantation Details:

Date: Age at implantation: Interval from first review:

Type of Device: AICD- Single/ Dual chamber/ CRT-D/ PPI- Single Chamber/ Dual Chamber/ILR

Company:

Indication:

Primary/ Secondary Prophylaxis:

VT/VF/ CHB/ Others:

Acute Success:

Post Implantation complications:

4. Follow-up in Device clinic:

Date:		
Interval from implantation:		
Device parameters: Life/ lead details		
Detected Arrhythmia: Y/N VA/ SVT/ others		
Therapy received: ATP/ Shock Appropriate/ Inappropriate:		
Details of therapy:		
Late Device complications:		

5. Clinical Details at Last Review:

Symptoms:

NYHA FC:

Heart Rate: /min
BP: /mm Hg
SpO2:

General Examination:

CVS Examination :

Re Investigations (if any):

CARDIAC MEDICATIONS	
Beta Blocker	
Ace Inhibitor/ARB/ARNI	
Calcium Channel Blocker (Verapamil/Diltiazem)	
SGLT2I	
Statin	
Digoxin	
Amiodarone	
Class (Ia/Ib/Ic) Antiarrhythmic	
Sotalol	
Diuretics	
Heart Failure Admissions After ICD Implantation	
Other Hospitalizations	

6. **Primary Outcome**: Composite of sustained VA, appropriate ICD therapy, hospitalisation due to arrhythmia & cardiac death: Y/N

7. **Secondary Outcome:** All-cause mortality, clinically important arrhythmias HF hospitalisation, time to first event.

CV of the Investigators

IEC/Ver3/09

CV of the Investigators

ADHIKARI	USNISH	
Last Name	First Name	Middle Name
Date of Birth (dd/mm/yy) **23/12/1991**		Sex **MALE**
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator): PI		
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Senior Resident, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011		Senior Resident, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695011
Telephone (Office): **9475819303**		Mobile Number: **9779249303**
Telephone (Residence): **9779249303**		Email: **adhikari.usnish1991@gmail.com**

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
MD (PEDIATRICS)	**2018**	**PGIMER, Chandigarh, India**
MBBS	**2015**	**Medical College, Kolkata, India**
DM (CARDIOLOGY)	**2023**	**SCTIMST, Trivandrum**

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc includingRegistration Number and Year of Registration
WEST BENGAL MEDICAL COUNCIL: **WBMC 72447 (YEAR-2015)**
THE TRAVANCORE COCHIN COUNCIL OF MODERN MEDICINE: **79613 (YEAR- 2021)**

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
01/2024- till date	PDF, Cardiac Electrophysiology	SCTIMST, Trivandrum
01/2021 – 12/2023	Senior Resident (DM Cardiology)	SCTIMST, Trivandrum
07/2015-06/2018	Junior Resident (MD Pediatrics)	PGIMER, Chandigarh, India

Brief summary of relevant research experience: [Publications:]

i. Aortopathy in Tetralogy of Fallot Follow-Up in a Tertiary Care Centre in India (Indian Heart Journal Dec 2023, DOI:10.1016/j.ihj.2023.11.038)
ii. Severe Thrombocytopenia after PCI: Think GP IIb/IIIa Receptor Antagonist Induced rather than Heparin-induced Thrombocytopenia (Nov 2023; Indian Journal of Clinical Cardiology 4(30), DOI:10.1177/26324636231213452)
iii. Refractory Anemia and Pigment Nephropathy in a Case with Mitral Prosthesis (April 2024, Indian Journal of Clinical Cardiology; DOI: 10.1177/26324636241239163)
iv. Child with Progressive Hemiparesis: Think beyond Neoplastic Disorders. (The Indian Journal of Pediatrics, May 2018: 12098-018-2700-6)
v. Recurrent Cerebrospinal Fluid Pleocytosis (Indian Journal of Pediatrics 2019 Mar;86(3):308-309)

Current project/s at hand: Nil

Signature: Usnish Adhikari | Date: 27/06/2024 | Place: TRIVANDRUM

CV : Narayanan Namboodiri

Last Name **Namboodiri**	First Name **Narayanan**	Middle Name KK
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Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
Fellowship (Cardiac Electrophysiology)	2009	RAH, Adelaide
Fellowship (Cardiac Electrophysiology)	2004	SCTIMST, Trivandrum
DM (Cardiology)	2003	PGIMER
MD (Medicine): Best outgoing student	2000	PGIMER
MBBS	1997	MCH, Calicut, Kerala

Details of professional registration : TMC/25506 Year of registration 1998

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
Since June 2015	Professor (Cardiology)	SCTIMST, Trivandrum

Brief summary of relevant research experience: In-Charge Cardiac Electrophysiology Programme, SCTIMST for 14 years; initiated many novel clinical areas like regular 3D mapping, pediatric ablation, conduction system pacing, cryoablation etc. in the institute and pioneered its development in the country by various academic activities, Multiple intramural, extramural funding projects in the last 10 years; Supervisor for many DM/PDF resident thesis in SCTIMST, in the last 15 years; 220 Plus international publications at international index journals; More than 50 international invited lectures in the last 14 years; A member of scientific subcommittee (Writing committee) by APHRS for 7 years; Was a part of 3 international writing committee groups for guidelines by Heart rhythm Society / European heart rhythm association. Editorial board member of PACE, and IPEJ. Trained more than 21 prospective cardiac electrophysiology postdoctoral fellows in the last 18 years; Outstanding achievement award for clinical and academical work by SCTIMST (2022), CSI Kerala (2023) and Indian Heart Rhythm Society (2017); Rated by an independent US agency expertscape as the 9th best expert in the field globally in 2011-2021 period. Was the editor-in-chief of IPEJ, indexed journal under Elsevier during 2014-20

Current project/s at hand: (Truncated to 5)

1) Genotype-phenotype correlation in cardiac channelopathies: ICMR task force funded project 2) Left bundle branch pacing : Role of anodal parameters: Funded by Medtronic India 3) Cryo ablation in AF : National project funded by Medtronics India 4) Bipolar stimulation model using bovine heart template : Funded by Indian Heart rhythm society. 5) EP device registry: PI at institute level

Signature: (Narayanan Namboodiri)	Date: 2/07/2024 Place: Trivandrum

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Last Name S P	First Name Abhilash	Middle Name
Date of Birth (dd/mm/yy) 12/05/1979		Sex: Male
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Academic Qualifications (Most recent qualification first):

Degree/Certificate	Year	Institution, Country
Fellowship (Cardiac Electrophysiology)	2020	Canberra, Australia
DM Cardiology	2010	MCH, Trivandrum, University of Kerala
DNB (Medicine)	2010	National Board, India
MD (Medicine): Gold medal	2006	Madras Medical College, Chennai
MBBS (Best outgoing student)	2002	MCH, Alappuzha, University of Kerala

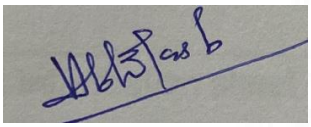
Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration:

TMC/30951 Year of registration 2002

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
Since June 2017	Professor (Cardiology)	SCTIMST, Trivandrum

Brief summary of relevant research experience: Part of cardiac electrophysiology program and interventional cardiology at SCTIMST for last 10 years; Co guide for many DM/PDF resident thesis in SCTIMST, in the last 10 years. Did 3 funded trials.

Current project/s at hand: 1)DM student projects 1 2) Co PI of Meres 1 3) PI of Merethon Trial	
Signature: 	Date:25/06/2024 Place: Trivandrum

Last Name: **Vijay MS**	First Name **Jyothi**	Middle Name
Date of Birth (dd/mm/yy):11/12/1988		Sex: Male
Study Site Affiliation : Co-PI		

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Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
Postdoctoral fellowship cardiac electrophysiology	2022	SCTIMST, Thiruvananthapuram
DNB cardiology	2021	NBEMS new Delhi
DM Cardiology	2020	PGIMER, Chandīgarh

Details of professional registration : (Travancore Cochin Medical Council, including Registration Number and Year of Registration)

Reg no TCMC 49150 ,Year of registration -2012

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
July 2023	Assistant professor,Cardiology	SCTIMST, Thiruvananthapuram
January-july 2023	Assistant professor(adhoc),Cardiology	SCTIMST, Thiruvananthapuram
Jan -December 2021	Assistant professor(adhoc),Cardiology	SCTIMST, Thiruvananthapuram

Brief summary of relevant research experience:

Multiple publications in various indexed journals and textbook chapters. GCP(Good clinical trial practices) training from NABH-QCI	
Current project/s at hand: Site co principal investigator for multicenter funded studies like RISE-HF Trial, Understanding HF in Indians, PURI-HF trial, Device registry, Cryoglobal registry. Site co principal investigator for the study SBRT in VT	
Signature: 	Date:25-06-24 Place: Trivandrum

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Institutional Ethics Committee

CDSCO Registration No: ECR/189/Inst/KL/2013/RR-24
DHR Registration No: EC/NEW/INST/2022/2775

SCT/IEC/2281/NOVEMBER-2024 16.12.2024

Dr. Usnish Adhikari
Post Doctoral Fellow
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Usnish Adhikari,

The Institutional Ethics Committee held on 2nd November, 2024, reviewed and discussed your application to conduct the study titled "**OUTCOMES AFTER CARDIOVASCULAR IMPLANTABLE *ELECTRONIC DEVICES* IN PATIENTS WITH CARDIAC SARCOIDOSIS AT A TERTIARY-CARE CENTRE IN *SOUTH INDIA (IEC /2281)***".

Principal Investigator	Dr.Usnish Adhikari, PDF – Cardiac Electrophysiology, Department of Cardiology, SCTIMST
Co-Principal Investigator(s)	Dr. Narayanan Namboodiri KK, Professor, Department of Cardiology, SCTIMST Dr. Abhilash SP, Professor, Department of Cardiology, SCTIMST Dr. Jyothi Vijay MS, Assistant Professor, Department of Cardiology, SCTIMST
Duration of the study	1 month

The following members of the Ethics Committee were present at the meeting held on 2nd November, 2024

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Annapurna Y	MD	Female	Basic Medical Scientist	No
2.	Dr. Manoj Murhekar	MD (Preventive & Social Medicine)	Male	Social Scientist	No
3.	Dr. Indu PV	MBBS, DPM, MPhil, PhD	Female	Clinician	No
4.	Adv. N Anand	BAL, L LB	Male	Legal Expert	No
5.	Smt. Rekha Radhakrishnan	M A (Eng.); B Ed	Female	Lay person	No
6.	Dr. Manikandan S	MBBS,MD,PDCC	Male	Clinician	Yes
7.	Dr. Syam K	MBBS, MD, DM	Male	Clinician	Yes
8.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
9.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

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The following documents were reviewed:

Original submission

1. Covering letter addressed to the Chairman, IEC, SCTIMST
2. IEC Application Form
3. Informed Consent Form in English and Malayalam
4. Patient Information Sheet in English and Malayalam
5. Declaration form
6. CV of PI and Co-PIs
7. Study Proposal

Revised submission

1. Covering letter addressed to the Chairman, IEC, SCTIMST
2. IEC Application Form
3. Study Proposal
4. Proforma
5. CV of PI and Co-PIs
6. Declaration form
7. Checklist Form

IEC Decision
The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

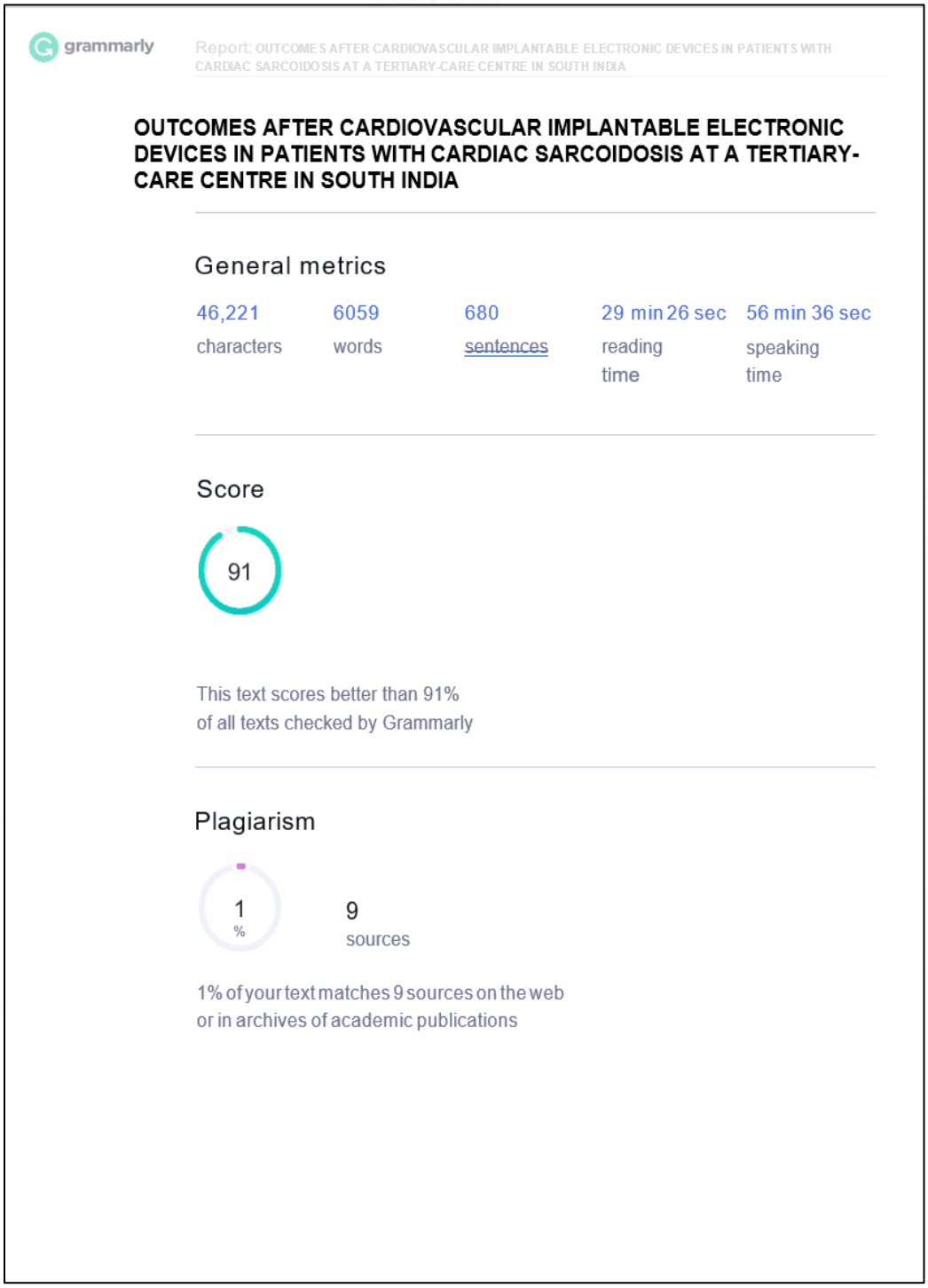
Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

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Report: OUTCOMES AFTER CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES IN PATIENTS WITH CARDIAC SARCOIDOSIS AT A TERTIARY-CARE CENTRE IN SOUTH INDIA

OUTCOMES AFTER CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES IN PATIENTS WITH CARDIAC SARCOIDOSIS AT A TERTIARY-CARE CENTRE IN SOUTH INDIA

General metrics

46,221	6059	680	29 min 26 sec	56 min 36 sec
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