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The prognostic significance of the 12-lead ECG in peripartum cardiomyopathy☆,☆☆

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ABSTRACT

Background: Peripartum cardiomyopathy (PPCM) is an important cause of pregnancy-associated heart failure, which appears in previously healthy women towards the end of pregnancy or within five months following delivery. Although the ECG is widely used in clinical practice, its prognostic value has not been established in PPCM.
Methods: We analysed 12-lead ECGs of patients with PPCM, taken at index presentation and follow-up visits at 6 and 12 months. Poor outcome was determined by the composite endpoint of death, readmission, NYHA functional class III/IV or left ventricular ejection fraction (LVEF) of ≤35% at follow-up.
Results: This cohort of 66 patients had a median age of 28.59 (IQR 25.43–32.19). The median LVEF at presentation (33%, IQR 25–40) improved significantly at follow-up (LVEF 49%, IQR 38–55, $P < 0.001$ at 6 months; 52% IQR 38–57, $P = 0.001$ at 12 months). Poor outcome occurred in 27.91% at 6 months and 41.18% at 1 year. Whereas sinus tachycardia at baseline was an independent predictor of poor outcome at 12 months (OR 6.56, 95% CI 1.17–20.41, $P = 0.030$), sinus arrhythmia was associated with event free survival (log rank $P = 0.013$). T wave inversion was associated with an LVEF ≤35% at presentation ($P = 0.038$), but did not predict poor outcome. A prolonged QTc interval at presentation (found in almost half of the cohort) was an independent predictor of poor outcome at 6 months (OR 6.34, 95% CI 1.06–37.80, $P = 0.043$).
Conclusion(s): A prolonged QTc and sinus tachycardia at baseline were independent predictors of poor outcome in PPCM at 6 months and 1 year respectively.

1. Introduction

Peripartum cardiomyopathy (PPCM) is defined as heart failure secondary to left ventricular (LV) systolic dysfunction, which develops in women without previous heart disease towards the end of pregnancy or up to five months following delivery [1]. The exact etiology of PPCM remains unclear, but the effects of oxidative stress on prolactin seem to play a crucial part in the pathogenesis [2]. More recent reports also show imbalanced angiogenesis to be fundamentally involved in the disease [3]. PPCM contributes significantly to maternal morbidity and mortality worldwide, and remains the largest cause of cardiovascular maternal death in South Africa [4,5].

The recovery rate from PPCM appears to be heterogeneous. Ethnicity, as well as the degree of systolic dysfunction and left ventricular dilatation on echocardiography, have previously been reported as predictors of poor outcome in PPCM [6,7]. Although normalization of LV function is more likely than in other forms of non-ischaemic cardiomyopathy, in a cohort of 176 South African patients only 23 to 54% of patients with PPCM had full LV recovery after 6 months of therapy [8]. However, it remains difficult to predict which patients will have full LV recovery and which will continue to develop chronic heart failure with persistently reduced LV ejection fraction (LVEF).

Electrocardiography (ECG) is one of the most frequently performed diagnostic procedures in cardiovascular disease [9]. The ECG is inexpensive and widely available, even in healthcare centres with limited resources. Although ECG abnormalities appear to be commonly visible at the time of diagnosis of PPCM, it is not known whether any electrocardiographic features are specific to the condition [10]. To the best of

Abbreviations: PPCM, peripartum cardiomyopathy; LVEDD, LV end-diastolic diameter; LVESD, left ventricular end-systolic diameter; SCD, sudden cardiac death; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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our knowledge, the prognostic value of the 12-lead ECG has not yet been established in PPCM.

2. Methods

2.1. Study design and patient recruitment

This study was conducted at the Cardiac Clinic at Groote Schuur Hospital (GSH) in Cape Town, South Africa. Patients were referred from local clinics and secondary hospitals, as well as from the Department of Obstetrics at GSH. Between May 2012 and July 2017, a total number of 66 consecutive patients with confirmed diagnosis of PPCM, and who fulfilled the inclusion criteria, were prospectively enrolled into the study.

Inclusion criteria included: (1) documented clinical evidence of LV systolic dysfunction towards the end of pregnancy or during the first five months postpartum; (2) no other identifiable causes of heart failure; (3) LVEF ≤45% on presentation confirmed by transthoracic echocardiography. Exclusion criteria were: (1) patient unable to give informed consent; (2) other identifiable causes of heart failure.

2.2. Protocol

The study was formally approved by the Human Research Ethics Committee (HREC) of the University of Cape Town, South Africa (R033/2013) and complies with the Declaration of Helsinki. All participants provided written informed consent prior to study entry.

Patients were enrolled at the baseline visit, at which time socio-demographic parameters, medical and obstetric history, clinical examination findings and prescribed medication were recorded. A physician blinded to the study data evaluated the patients' New York Heart Association Functional Class (NYHA) at baseline, as well as at their scheduled 6 month and 12 month follow-up visits. Patients were monitored for death and readmission to hospital for cardiac failure or stroke during the study period.

2.3. 12-Lead electrocardiogram (ECG)

Resting 12-lead ECGs were performed by a trained ECG technologist using a MAC 5500 HD (GE Healthcare, Chicago, Illinois, USA) machine. A baseline ECG was done for all enrolled patients, as well as at their follow up visits. The ECGs were retrospectively analysed in accordance with the Minnesota criteria by two reviewers blinded to the study outcome [11].

Sinus tachycardia was defined as a heart rate of ≥100 beats per minute (bpm), whereas sinus bradycardia was set as a heart rate of ≤60 bpm. Sinus rhythm with normal rate was classified according to RR interval variability (sinus arrhythmia vs. sinus rhythm with regular RR interval). A QRS axis between −30 and +90° was considered as normal. Left ventricular hypertrophy (LVH) was assessed by Sokolow-Lyon criteria [12]. Poor R wave progression was defined as an R wave amplitude < S wave amplitude in lead V4. QRS fragmentation was taken to be present if there was evidence of an RSR′ pattern or notched S or R wave, or when a fragmented QRS complex occurred in two or more contiguous leads [13]. J waves (small deflection between the QRS complex and the ST segment) were acknowledged if present in ≥2 contiguous leads. Q waves deeper than 2 mm or wider than 40 ms were considered as pathological. Heart rate-adjusted QT intervals (QTc) were calculated using Bazett's formula [14]. A QTc interval of ≥460 ms was regarded as prolonged [15].

2.4. Echocardiography

Two-dimensional and targeted M-mode echocardiography with Doppler color flow mapping were performed using either a Philips CX50 (Philips, Amsterdam, Netherlands) or a VIVIDi (General Electric Company, Fairfield, Connecticut, USA) echocardiography machine. LVEF as well as systolic and diastolic LV diameters were measured according to the American Society of Echocardiography (ASE) Guidelines [16].

2.5. Outcome

Poor outcome was determined by the composite endpoint of death or readmission to hospital prior to follow-up, remaining in NYHA class functional III/IV or having a left ventricular ejection fraction (LVEF) of ≤35% at follow-up [8]. By accessing the National Death Registry, the mortality outcomes were known for all enrolled patients. In accordance with the current ESC Guidelines on acute and chronic heart failure, an LVEF ≥50% was regarded as a full recovery of LV function [17].

2.6. Statistical analyses

Data was collected on Research Electronic Data Capture (REDCap Version 7.5.2), a secure electronic database hosted by the University of Cape Town [18], before being exported to Stata (Version 14.2, StataCorp, College Station, TX, USA) for statistical analysis. Descriptive statistics were used to summarize data. Continuous variables were summarized as means with standard deviations (SD) for parametric data or median with interquartile range (IQR) for non-parametric data. Categorical variables were expressed as frequencies and percentages. Variables were compared between outcome measures at follow-up using either the Student's *t*-test (parametric data) or Wilcoxon rank-sum test (non-parametric data). Within group change from baseline to follow-up was analysed using the signed-rank test (continuous variables) or McNemar's test (categorical variables). Univariable and multivariable logistic regression were used to analyse factors associated with poor outcome at 6 and 12 months (composite of death, readmission, NYHA functional class III/IV or LVEF ≤ 35% at follow-up). Variables considered for regression analysis included sinus tachycardia, sinus bradycardia, sinus arrhythmia, sinus rhythm with no heart rate variability, left atrial enlargement, right atrial enlargement, wide QRS complex (>120 ms), QRS axis deviation, left ventricular hypertrophy, poor R wave progression, fragmented QRS complex, pathological Q waves, T wave inversion and prolonged QTc interval. Variables that were significantly associated with poor outcome ($P < 0.05$) in the univariable analysis were retained in the multivariable model. The fit of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test. For descriptive purposes, Kaplan-Meier curves were used to illustrate event free survival for death and readmission to hospital during the study period for QTc interval (≥460 ms vs. <460 ms), heart rate (≥100 vs. <100 bpm) and RR interval variability (sinus arrhythmia vs. sinus rhythm with regular RR interval). Log-rank tests were used to compare the survival curves. A *P* value of <0.05 was interpreted as statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Baseline socio-demographic and clinical characteristics are listed in Table 1. The median age of this cohort was 28.59 (IQR 25.43–32.19) with a median gravidity and parity of 2 (IQR 1–3) and 2 (IQR 1–3), respectively. The majority of patients were Black African (53.49%), with the remainder being either of mixed ancestry (39.53%) or Caucasian (6.98%) ethnicity. Approximately a quarter of the patients had a smoking history, with a median of 7 pack-years (IQR 5–10) amongst those who smoked. A proportion of 45.23% presented with a NYHA functional class III or IV. Prescription on discharge after the diagnosis of PPCM was made included beta-blockers in 95.35%, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 76.74% and diuretics in 88.37% of the patients. The ergot alkaloid, bromocriptine, which inhibits prolactin secretion, was prescribed in 44.19% of patients in this cohort. As shown in Table 1, patients with poor outcome at 6 months initially presented with a significantly increased heart rate and decreased systolic blood pressure. None of the socio-demographic parameters emerged as a significant predictor of outcome.

3.2. Echocardiography

Echocardiography showed a median LVEF of 33% (IQR 25–40) at presentation, with around two-thirds of patients having an LVEF of ≤35% at the first visit. As shown in Table 2, the median LVEF improved to 49% at 6 months (IQR 38–55, $P < 0.001$) and 52% (IQR 38–57, $P = 0.001$) at 12 months. Median LV end-diastolic dimension (LVEDD) at baseline was 58 mm (IQR 53–63) with >80% of the cohort showing evidence of left ventricular dilatation (LVEDD ≥ 53 mm). A persistent, severely reduced LVEF of ≤35% was seen in eight patients at 6 months and seven patients at 12 months.

3.3. Electrocardiographic characteristics of PPCM

Table 2 summarizes the electrocardiographic characteristics seen at index presentation and follow-up visits. Collectively, 59.09% of patients had a normal heart rate, of which 43.59% presented with regular RR intervals and 56.41% having sinus arrhythmia. Sinus tachycardia was found in 31.82% of women. None of the patients had atrial fibrillation. Electrocardiographic evidence of left atrial enlargement (wide, bifid P-wave in standard lead II) was found in 18.18% of the patients. The median PR interval was 142 ms (IQR 124–160) and there were no patients who presented with AV block. The median QRS width was 84 ms (IQR 78–88) and the majority of patients (87.88%) had a normal QRS axis. Although no patients presented with left or right bundle branch block (LBBB, RBBB), two patients had developed complete LBBB at follow-up. Both patients who subsequently developed LBBB had a persistently reduced LVEF of <35% at follow-up. At baseline, about a quarter of the patients met the Sokolow-Lyon criteria for LVH on the ECG, but none

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Table 1
Baseline characteristics (including demographic, clinical, therapeutic, electrocardiographic and echocardiographic characteristics) predicting good and poor outcome after 6 and 12 months.

		Outcome after 6 months				Outcome after 12 months			
		All n = 43	Good outcome n = 31	Poor outcome n = 12	*P* value	All n = 34	Good outcome n = 20	Poor outcome n = 14	*P* value
Age (years)	Median (IQR)	27.89 (24.35–31.69)	28.49 (23.36–32.47)	27.86 (25.93–29.57)	0.745	28.58 (25.57–30.20)	28.91 (24.88–30.97)	28.10 (26.30–29.91)	0.834
Ethnicity	N (%)				0.271				0.942
African		23 (53.49)	18 (58.06)	5 (41.67)		18 (52.94)	11 (55)	7 (50)	
Mixed ancestry		17 (39.53)	12 (38.71)	5 (41.67)		14 (41.18)	8 (40)	6 (42.86)	
Caucasian		3 (6.98)	1 (3.23)	2 (16.67)		2 (5.88)	1 (5)	1 (7.14)	
Obstetric history									
Gravidity	Median (IQR)	2 (1–3)	2 (1–3)	2 (1–3.5)	0.900	2 (2–3)	2.5 (2–3)	2 (2–4)	0.596
Parity	Median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	0.933	2 (2–3)	2 (2–3)	2 (2–3)	0.885
Medical history									
Hypertension prior to pregnancy	N (%)	8 (18.60)	7 (22.58)	1 (8.33)	0.407	3 (8.82)	2 (10)	1 (7.14)	1
Smoking	N (%)	9/42 (21.43)	5/30 (16.67)	4 (33.33)	0.406	8 (23.53)	2 (10)	6 (42.86)	0.042
HIV positive	N (%)	10 (23.26)	6 (19.35)	4 (33.33)	0.427	10 (29.41)	5 (25)	5 (35.71)	0.704
Clinical presentation									
Height (cm)	Median (IQR)	160 (156–163)	160 (156–163)	158.5 (156–163.5)	0.797	159 (156–163)	159 (155–162.50)	162 (156–164)	0.375
Weight (kg)	Median (IQR)	65 (56–75)	68 (56–77)	60 (55.5–66)	0.119	63.5 (56–71)	63.5 (53.5–70)	61 (57–71)	0.779
BMI (kg/m^2)	Median (IQR)	25.34 (22.15–29.69)	26.62 (22.15–30.08)	24.14 (21.54–25.78)	0.129	24.78 (22.50–27.59)	25.4 (21.95–27.78)	24.65 (23.42–26.78)	0.868
NYHA functional class	N (%)				0.445				0.343
I		8/42 (19.05)	6/30 (20.00)	2 (16.67)		6 (17.65)	3 (15)	3 (21.43)	
II		15/42 (35.71)	12/30 (40.00)	3 (25.00)		12 (35.29)	9 (45)	3 (21.43)	
III		14/42 (33.33)	10/30 (33.33)	4 (33.33)		12 (35.29)	7 (35)	5 (35.71)	
IV		5/42 (11.90)	2/30 (6.67)	3 (25.00)		4 (11.76)	1 (5)	3 (21.34)	
Haemoglobin (g/dl)	Median (IQR)	11.9 (10.7–12.4)	11.35 (10–12.4)	12.25 (11.35–12.5)	0.225	12 (11.1–12.4)	11.65 (11.1–12.4)	12.25 (11.1–12.6)	0.371
Heart rate (bpm)	Median (IQR)	88 (80–102)	84 (68–100)	98 (90.5–120)	0.017	93.5 (80–112)	88 (80–102)	102 (90–120)	0.056
Systolic blood pressure (mm Hg)	Median (IQR)	111 (100–138)	120 (110–140)	109 (100−110)	0.044	110 (101−133)	117 (101–138)	110 (105–115)	0.379
Diastolic blood pressure (mm Hg)	Median (IQR)	70 (66–80)	80 (67–84)	70 (61–74.5)	0.104	77 (67–85)	80 (69–88)	72 (62–85)	0.537
Prescribed medication on discharge									
Carvedilol	N (%)	41 (95.35)	30 (96.77)	11 (91.67)	0.485	29 (85.29)	17 (85)	12 (85.71)	1
ACE-Is/ARBs	N (%)	33 (76.74)	22 (70.97)	11 (91.67)	0.237	25 (73.53)	12 (60)	13 (92.86)	0.050
Spironolactone	N (%)	18 (41.86)	14 (45.16)	4 (33.33)	0.731	12 (35.29)	6 (30)	6 (42.86)	0.440
Diuretics	N (%)	38 (88.37)	27 (87.10)	11 (91.67)	1	27 (79.41)	15 (75)	12 (85.71)	0.672
Bromocriptine	N (%)	19 (44.19)	14 (45.16)	5 (41.67)	1	15 (44.12)	10 (50.00)	5 (35.71)	0.409
Electrocardiogram at presentation									
Heart rate (bpm)	Median (IQR)	91 (78–106)	85 (69–102)	104.5 (89–114.5)	0.014	93 (72–104)	88 (62.5–96.5)	106 (85–115)	0.022
Rhythm	N (%)								
Sinus rhythm, regular RR interval		9 (20.93)	6 (19.35)	3 (25)	0.683	6 (17.65)	4 (20)	2 (14.29)	1
Sinus arrhythmia		14 (32.56)	13 (41.94)	1 (8.33)	0.035	11 (32.35)	9 (45)	2 (14.29)	0.076
Sinus bradycardia		3 (6.98)	3 (9.68)	0	0.264	4 (11.76)	3 (15)	1 (7.14)	0.627
Sinus tachycardia		17 (39.53)	9 (29.03)	8 (66.67)	0.024	13 (38.24)	4 (20)	9 (64.29)	0.014
QRS duration (in ms)	Median (IQR)	84 (78–88)	84 (78–88)	83 (79–88)	0.903	83 (78–88)	83 (77–86)	84 (78–88)	0.494
Good R wave progression (R > S in V4)	N (%)	24 (55.81)	18 (58.06)	6 (50)	0.633	16 (47.06)	10 (50)	6 (42.86)	0.681
LVH	N (%)	17 (25.76)	10 (32.26)	2 (16.67)	0.456	7 (20.59)	6 (30)	1 (7.14)	0.198
Fragmented QRS complex	N (%)	23 (53.49)	16 (51.61)	7 (58.33)	0.692	17 (51.52)	10 (50)	7 (53.85)	0.829
J wave	N (%)	18 (41.86)	16 (51.61)	2 (16.67)	0.037	12 (36.36)	9 (45)	3 (23.08)	0.278
Pathological Q waves	N (%)	7 (16.28)	6 (19.35)	1 (8.33)	0.652	5 (15.15)	3 (15)	2 (15.38)	1
T wave inversion	N (%)	29 (67.44)	21 (67.74)	8 (66.67)	0.946	23 (79.31)	14 (77.78)	9 (81.82)	1
T wave inversion in >6 leads	N (%)	7 (16.28)	5 (16.13)	2 (16.67)	0.966	5 (14.71)	2 (10)	3 (21.43)	0.627
QTc interval (in ms)	Median (IQR)	457 (435–479)	449 (426–479)	469 (462.5–477)	0.067	454 (435–470)	449 (438–469)	467 (428–470)	0.484
Long QTc interval (≥460 ms)	N (%)	21 (48.84)	11 (35.48)	10 (83.33)	0.007	15 (44.12)	7 (35)	8 (57.14)	0.201
Echocardiogram at presentation									
LVEDD (in mm)	Median (IQR)	58 (53–64)	58 (53–64)	56 (52.5–64)	0.849	57.5 (53–65)	58.5 (52.5–64)	56.5 (53–66)	0.624
LVESD (in mm)	Median (IQR)	47 (44–52)	47 (44–51)	48 (46–58)	0.249	47 (44–54)	46.5 (41.5–51.5)	48 (45–58)	0.190
Ejection fraction (in %)	Median (IQR)	33 (25–40)	36 (25–42)	26.5 (24–31)	0.032	30.5 (24–37)	33 (24.5–38)	27 (24–35)	0.420
LVEF ≤35%	N (%)	25 (58.14)	15 (48.39)	10 (83.33)	0.046	22 (64.71)	11 (55)	11 (78.57)	0.275

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVH = left ventricular hypertrophy; NYHA = New York Heart Association; R > S = R wave taller than S wave.
Values are median and IQR unless otherwise specified.

Table 2
Electrocardiographic and echocardiographic characteristics at baseline as compared to the 6 and 12 month follow-up visits.

12-Lead ECG		All enrolled patients (N = 66)	Patients followed up over 6 months (N = 41[a])			Patients followed up over 12 months (N = 30[a])		
		Baseline visit	Baseline visit	6 month visit	*P* value	Baseline visit	12 month visit	*P* value
QRS rate	Median (IQR)	86.5 (72–103)	89 (78–103)	75 (67–89)	0.009	88 (66–101)	75 (72–85)	0.033
Rhythm	N (%)							
Sinus rhythm with regular RR interval		17 (25.76)	9 (21.95)	11 (21.95)	0.527	7 (23.33)	6 (20)	0.564
Sinus arrhythmia		22 (33.33)	14 (34.15)	22 (53.66)	0.011	11 (36.67)	19 (63.33)	0.077
Sinus bradycardia		6 (9.09)	3 (7.32)	4 (9.76)	0.705	4 (13.33)	2 (6.67)	0.625
Sinus tachycardia		21 (31.82)	15 (36.59)	4 (9.76)	0.023	8 (26.67)	1 (3.33)	0.016
P wave morphology	N (%)							
Left atrial enlargement		12 (18.18)	10 (24.39)	11 (26.83)	0.705	8 (26.67)	5 (16.67)	0.453
Right atrial enlargement		8 (12.12)	7 (17.07)	7 (17.07)	1	4 (13.33)	4 (13.33)	1
PR interval (in ms)	Median (IQR)	142 (124–160)	142 (130–160)	150 (134–162)	0.031	148 (130–164)	146 (140–160)	0.680
QRS complex width (in ms)	Median (IQR)	82 (78–88)	84 (80–88)	88 (84–96)	0.001	83 (78–86)	87 (82–94)	0.001
Normal QRS axis	N (%)	58 (87.88)	37 (90.24)	39 (95.12)	0.414	27 (90)	27 (96.43)	1
Good R wave progression (R > S in V4)	N (%)	41 (62.12)	23 (56.10)	24 (58.54)	0.763	15 (50)	19 (65.52)	0.227
LVH	N (%)	17 (25.76)	12 (29.27)	11 (26.83)	0.782	10 (33.33)	8 (27.59)	0.727
J wave	N (%)	27 (40.91)	18 (43.90)	22 (53.66)	0.157	11 (37.93)	15 (53.57)	0.063
Pathological Q waves	N (%)	12 (18.46)	7 (17.07)	5 (12.20)	0.479	6 (20)	6 (20.69)	1
T wave inversion	N (%)	46 (70.77)	27 (65.85)	23 (56.10)	0.248	20 (66.67)	14 (48.28)	0.109
T wave inversion in >6 leads	N (%)	14 (21.2)	6 (14.63)	4 (9.76)	0.414	3 (10)	3 (10)	1
QTc interval (in ms)	Median (IQR)	456 (427–473)	456 (435–479)	443 (414–472)	0.054	449.5 (435–469)	426.5 (410–451)	0.001
Long QTc interval (≥460 ms)	N (%)	29 (43.94)	19 (46.34)	14 (34.15)	0.165	12 (40)	4 (13.33)	0.022

Echocardiography		All enrolled patients (N = 66)	Patients followed up over 6 months (N = 41[a])			Patients followed up over 12 months (N = 23[a])		
		Baseline visit	Baseline visit	6 month visit	*P* value	Baseline visit	12 month visit	*P* value
LVEDD (in mm)	Median (IQR)	58 (53–63)	58 (53–63)	56 (50–60)	0.009	57 (52–64)	51 (47–60)	0.008
LVESD (in mm)	Median (IQR)	47 (44–52)	47 (44–52)	41 (35–50)	<0.001	46 (44–52)	38.5 (32–54)	0.002
Ejection fraction (in %)	Median (IQR)	33 (25–40)	33 (25–40)	49 (38–55)	<0.001	33 (25–37)	52 (38–57)	0.001
LVEF ≤35%	N (%)	41 (62.12)	23 (56.10)	8 (19.51)	<0.001	18 (62.07)	7 (25.93)	0.023
LVEF ≥50%	N (%)	0	0	21 (48.84)	<0.001	0	16 (55.17)	0.001

LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVH = left ventricular hypertrophy.
Values are median and IQR unless otherwise specified.
[a] Patients who died during the study period could not be included in this analysis as their death occurred prior to follow-up.

of these patients had LVH on echocardiography (sensitivity 0%, specificity 72.1%, PPV 0, NPV 97.8%). Pathological Q waves were seen in 17.07% of the patients with PPCM. Almost all patients had normal ST segments (as assessed at the J point), whereas T wave inversion was commonly present (70.77%) at the index consultation.

3.4. Electrocardiographic changes seen at 6 and 12 months

The median heart rate decreased from 89 bpm (IQR 78–103) to 75 bpm (IQR 67–89, $P = 0.009$) at 6 months, which remained unchanged at 1 year. Concomitantly, the number of patients with sinus tachycardia at initial presentation decreased significantly at the follow-up visits, as shown in Table 2. T wave inversion resolved in some patients at follow-up (56.10% at 6 months, 48.28% at 12 months). Though the median QTc interval at baseline steadily decreased over 12 months ($P = 0.001$), a third of patients still had a prolonged QTc at the 6-month visit.

Screening for drugs that could potentially prolong the QT interval (using CredibleMeds® [a university-based, federally funded Center for Education and Research on Therapeutics (CERT)], accessed at crediblemeds.org), it was found that five HIV positive patients were on an antiretroviral regimen containing efavirenz at index presentation and follow-up visit. However, for both these visits, there was no significant difference in the QTc interval between patients who received efavirenz or not. The two patients who received antibiotics with known risk of QT prolongation had normal QTc intervals at index and follow-up visits.

3.5. Electrocardiography as a predictor of poor outcome

Four women died during the 12-month study period, two of which died prior to the 6-month follow-up. Eleven patients were readmitted to hospital after the baseline visit (ten with heart failure, one with stroke). Of these admissions, nine occurred within the first 6 months after diagnosis.

Overall twelve patients (27.91%) had a poor outcome at 6 months. These patients had a significantly higher heart rate at presentation as compared to women with a good outcome. Sinus tachycardia (66.67%, $P = 0.024$) and a prolonged QTc interval (83.33%, $P = 0.007$) at presentation were frequently encountered amongst patients with poor outcome at the 6-month follow-up visit. On the contrary, sinus arrhythmia (41.94%, $P = 0.035$) or J waves (51.61%, $P = 0.037$) at baseline was associated with a favorable outcome at 6 months (Table 1).

More than 80% of the patients who presented with an LVEF ≤35% had a poor outcome after 6 months. Amongst these patients with severely reduced LVEF, 69.57% had T wave inversion at the initial presentation. Although T wave inversion in any lead was associated with LVEF ≤35% at presentation ($P = 0.038$), it was not associated with poor outcome at follow-up.

As shown in Table 3, univariable logistic regression analysis revealed that sinus tachycardia and a prolonged QTc interval at the initial presentation predicted poor outcome at 6 and 12 months respectively. Poor R wave progression, fragmented QRS complexes, pathological Q waves and T wave inversion in any lead did not predict a poor outcome after 6 months or 12 months. On multivariable regression analysis, a prolonged QTc interval at baseline remained an independent predictor of poor outcome at 6 months (OR 6.34, 95% CI 1.06–37.80, $P = 0.043$), whereas sinus tachycardia at first presentation was an independent predictor of poor outcome at 12 months (OR 6.56, 95% CI 1.24–34.47, $P = 0.026$).

As illustrated in Fig. 1, event free survival (i.e. absence of death or readmission) in the first 12 months differed significantly between patients who initially presented with sinus tachycardia versus a normal

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Table 3
Univariable and multivariable logistic regression analysis of predictors of poor outcome and recovery after 6 and 12 months.

	Univariable regression analysis			Multivariable regression analysis		
	Unadjusted OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
ECG feature predicting poor outcome at 6 months[a]						
Sinus tachycardia	4.89	1.17–20.41	0.030	2.57	0.53–12.52	0.244
Poor R wave progression	1.38	0.36–5.28	0.633	–	–	–
Fragmented QRS complex	1.31	0.34–5.05	0.692	–	–	–
Pathological Q waves	0.38	0.04–3.53	0.394	–	–	–
T wave inversion	0.95	0.24–3.93	0.946	–	–	–
Long QTc interval (≥460 ms)	9.09	1.68–49.12	0.010	6.34	1.06–37.80	0.043
ECG feature predicting poor outcome at 12 months[a]						
Sinus tachycardia	9.23	2.14–39.88	0.003	6.56	1.24–34.47	0.026
Poor R wave progression	1.96	0.53–7.20	0.309	–	–	–
Fragmented QRS complex	1.55	0.40–6.10	0.528	–	–	–
Pathological Q waves	0.47	0.05–4.14	0.501	–	–	–
T wave inversion	1.02	0.23–4.32	0.983	–	–	–
Long QTc interval (≥460 ms)	4.36	1.05–18.22	0.043	1.27	0.25–6.60	0.771

OR = odds ratio; CI = confidence interval.
[a] The ECG features that were considered for the regression analysis included sinus tachycardia, sinus bradycardia, sinus arrhythmia, sinus rhythm with no heart rate variability, left atrial enlargement, right atrial enlargement, wide QRS complex (>120 ms), QRS axis deviation, left ventricular hypertrophy, poor R wave progression, fragmented QRS complex, pathological Q waves, T wave inversion and prolonged QTc interval. Variables that were significantly associated with poor outcome ($P < 0.05$) in the univariable analysis were retained in the multivariable model.

heart rate (log rank $P < 0.001$), and those who had a prolonged versus a normal QTc interval (log rank $P = 0.029$). Event free survival in the first 12 months was more likely in patients who presented with sinus arrhythmia than those who initially had sinus rhythm with fixed RR interval (log rank $P = 0.013$).

4. Discussion

Our study found that amongst the frequently encountered electrocardiographic abnormalities in patients with PPCM, a prolonged QTc interval at baseline appeared to be an independent predictor of poor outcome at 6 months, whereas an initial sinus tachycardia was associated with poor outcome after 12 months. Patients who presented with sinus tachycardia or prolonged QTc were at increased risk of readmission to hospital or death within the first year after diagnosis, whereas sinus arrhythmia at the time of diagnosis predicted event free survival.

Similar to previous studies, ECG abnormalities were commonly found at baseline [19,20].

In this cohort, all patients had at least one major ECG abnormality, which included: sinus tachycardia, pathological Q waves, right or left axis deviation, poor R wave progression, ST segment elevation or depression, T wave inversion, and prolonged QTc interval.

Cumulatively, 36.59% of the cohort presented with sinus tachycardia, which decreased substantially at the 6 month and 1-year follow-up visits. Sinus tachycardia was previously described as predictor of poor outcome after 6 months [21]. We found that initial sinus tachycardia was an independent predictor of poor outcome after 12 months (Table 3), with increased risk of death or readmission to hospital in the first year after diagnosis (Fig. 1). These findings correspond with the results of a recent German study, which suggested a potential clinical benefit by reducing the heart rate with ivabradine, in addition to standard heart failure medication in acute PPCM [22].

Sinus arrhythmia was associated with a better outcome than sinus rhythm with a lack of heart rate variability. This is in line with previous studies which found that a lack of heart rate variability correlates with severity of heart failure [23,24]. In patients with heart failure, impaired heart rate variability suggests autonomic dysfunction and has been shown to be associated with adverse outcomes [25].

In contrast to studies on dilated cardiomyopathy (DCM) [26,27], we did not encounter any ventricular tachycardia (VT), atrial fibrillation (AF) or atrioventricular block (AV block). Left and right bundle branch blocks (RBBB, LBBB) were infrequent in our cohort. However, the two patients who developed LBBB at follow-up had severely impaired systolic function on echocardiography. The QRS complex was mostly narrow and the axis was predominantly normal.

QRS fragmentation (fQRS) is an electrocardiographic marker for myocardial fibrosis and represents interventricular conduction delay [28]. Previous studies on patients with cardiomyopathy showed that fQRS is associated with sudden cardiac death [13]. We did not find fQRS to be a predictor of poor outcome in our cohort. This could potentially be explained by the large number of patients with PPCM who recover their LV function.

It should be noted that although about a quarter of the cohort fulfilled ECG criteria for LVH, none of these patients showed echocardiographic evidence of LVH. The ECG criteria for LVH by Sokolow and Lyon are not validated for patients under the age of 40 and are therefore not applicable in a relatively young population such as the PPCM cohort [12].

We observed J waves to be more common in patients who had a favorable outcome. Although J waves have previously been reported to be associated with poor outcome, it is considered to be a normal ECG variant and is common amongst healthy individuals [29].

Almost half of the patients in our study presented with a prolonged QTc interval, and about a third of the cohort still had a long QTc at the 6 month follow-up visit. We found no evidence of drug-induced QT prolongation in this cohort [30,31]. Although pregnancy has previously been shown to prolong the QT interval, these measurements remained within the normal range throughout gestation [32]. Estrogen is thought to be the potential mechanism for QT prolongation, as it has previously been reported that unopposed estrogen treatment mildly prolonged myocardial repolarization in menopausal women [33]. To the best of our knowledge, there is no evidence to suggest that healthy postpartal women develop QT prolongation. Therefore, in the absence of any other causes, we postulate that the prolonged QTc interval forms part of the pathogenesis of PPCM.

In our study, we highlight that a prolonged QTc at baseline is an important independent predictor of a poor outcome in the first 6 months after diagnosis. These findings correspond with a recent publication reporting that a prolonged QTc interval was a predictor of adverse prognosis in patients with inflammatory dilated cardiomyopathy (DCMi) [34]. However, further studies are needed to evaluate whether a persistently prolonged QTc interval at follow-up impacts on the long-term prognosis of patients with PPCM.

Diao et al. [35] performed Holter analysis in a small cohort of 19 patients with PPCM, but only detected one patient who showed four episodes of non-sustained VT. A retrospective study from the United

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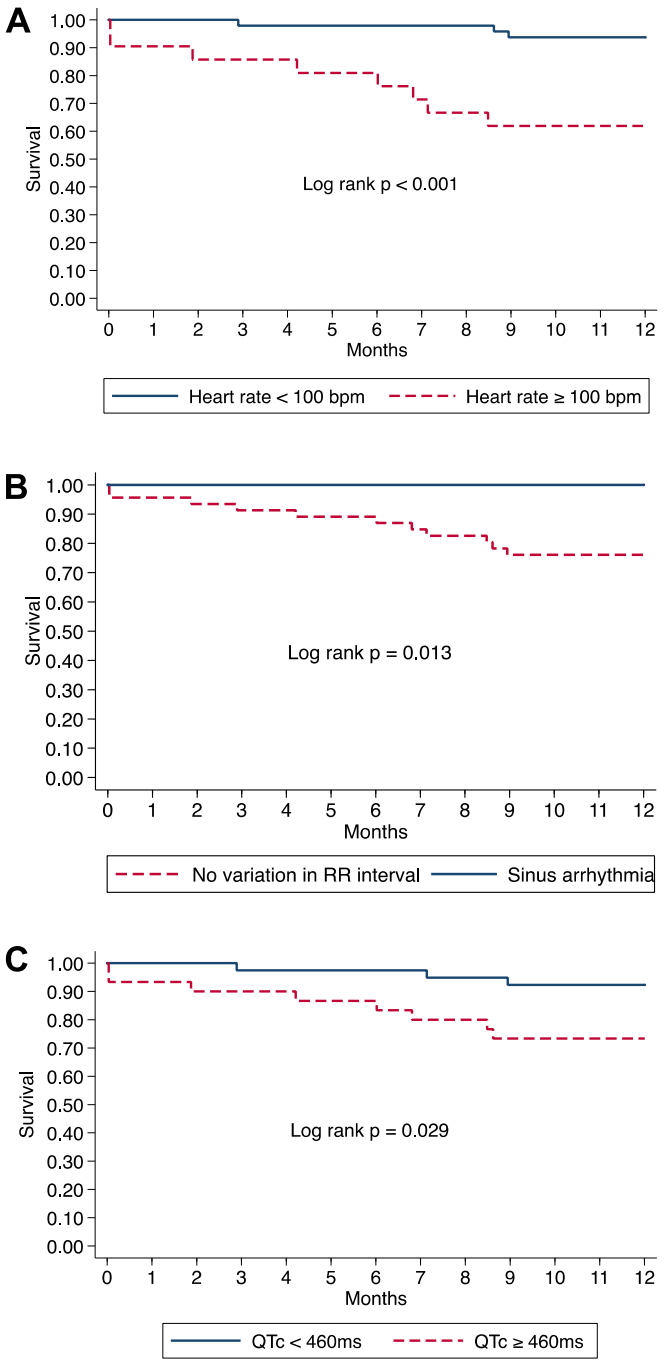

Fig. 1. Kaplan-Meier curves showing total death and readmission in the first 12 months after PPCM diagnosis, according to whether the initial ECG demonstrated sinus tachycardia (A), sinus arrhythmia (B) prolonged QTc interval (C). (A) Blue line: Heart rate < 100 bpm, red line: Heart rate ≥ 100 bpm, (B) red line: sinus rhythm with no variation in RR interval, blue line: sinus arrhythmia (C), blue line: QTc interval < 460 ms, red line: QTc interval ≥ 460 ms. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

States found an arrhythmia to be present in 18.7% of a hospitalized PPCM cohort, with ventricular arrhythmia being the most commonly noted form (4.2%), followed by bundle branch block and atrial fibrillation [36]. Sudden cardiac death (SCD) due to a ventricular arrhythmia was speculated to be a leading cause of death in PPCM [37,38]. Recent studies from Germany showed that patients with PPCM presenting with severely reduced LVEF (≤35%) had an elevated risk for ventricular tachyarrhythmias three to six months after diagnosis and benefited from a wearable cardioverter/defibrillator (WCD) [39,40]. A prolonged QTc interval is a well-established risk factor for ventricular arrhythmias [41,42] and might be accountable for some of the observed deaths in our cohort, as all patients who died in this study initially presented with a prolonged QTc interval and subsequently suffered from sudden cardiac death.

In our cohort, 48.84% of the patients had a full functional LV recovery after 6 months, and 55.17% at 1 year, which is an improvement when compared to previous reports from South Africa [8]. Comparable recovery rates are shown in cohorts from Turkey [43], China [20] and the Philippines [44]. In contrast, higher rates of recovery are reported from Germany and the United States [7,45]. The marked regional differences seen for LV recovery might also be partly attributed to better access to health care in these countries, as well as their ethnic demographies. Black African ethnicity has previously been described as a risk factor for poor outcome [7,46] and the majority of our cohort were of African descent.

Using the combined endpoint of death or readmission to hospital prior to follow-up, NYHA functional class III/IV or LVEF ≤35% at follow-up [8], we found that 27.91% of the patients had an adverse outcome at 6 months and 41.18% at 12 months. Readmissions to hospital occurred more frequently in the first 6 months after diagnosis.

4.1. Limitations

Considering that PPCM is a relatively rare disease, the patient cohort enrolled in this study is small, which limited analysis and interpretation. The precision of estimates in the logistic regression analysis in particular could be affected by sparse data. Furthermore, in the South African public sector, patients are referred back to the original referral centres once they are stabilized. We therefore do not have sufficient data on long-term follow-up. The observations in our study would need to be confirmed by studies with longer follow-up. At our hospital, heart failure therapy was initiated considering the clinical status and stability of the patient, as well as their ability to tolerate heart failure therapy (median systolic blood pressure 111 mm Hg, IQR 100–138). For this reason, some patients did not receive an ACE-I at first consultation. However, we did not find any significant differences in ECG features amongst patients who received these therapies or not. Finally, we did not find any arrhythmias on the 12-lead ECGs. This might be an underestimation of the true incidence of arrhythmias, as none of the patients had 24-hour Holter monitoring or implanted loop recorders.

5. Conclusions

We observed a high rate of electrocardiographic abnormalities at the time of presentation and could show that the ECG has a predictive value in PPCM. To the best of our knowledge, this is the first study to demonstrate the prognostic value of the 12-lead ECG in PPCM. A prolonged QTc and sinus tachycardia at baseline were independent predictors of poor outcome in PPCM at 6 months and 12 months respectively. Similarly, sinus tachycardia and prolonged QTc were associated with increased risk of death or readmission to hospital. Based on our findings, we recommend that patients with PPCM who present with sinus tachycardia or a prolonged QTc interval should be followed-up more closely. Care should also be taken to avoid drugs that prolong the QT interval in these patients. Larger, multi-centred trials are needed, however, to better evaluate the potential vulnerability to arrhythmias in patients with PPCM. At present, there is an ongoing study with an implantable Reveal device for the early identification of patients at risk for arrhythmic events. If it is confirmed that a prolonged QTc is associated with arrhythmic events in PPCM, clinical guidelines may be directed towards a more frequent use of 24-hour Holter monitoring and wearable cardioverter defibrillator (WCD)/implantable ICDs to prevent SCD in high-risk patients with PPCM.

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Contributions

JH, CV, KS, and JB designed the study. JH, CV and KM analysed the data. JH and CV drafted the manuscript, which was critically revised by KM, LH, MN, JB and KS.

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Conflict of interest

All authors take the responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. The authors report no relationships that could be construed as a conflict of interest.

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