The outcome of Peripartum Cardiomyopathy Patients-Single Center Experience

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Abstract

Objective: Peripartum cardiomyopathy (PPCM) diagnosis made by excluding identifiable causes of heart failure (HF) and occurs end of the pregnancy or during the postpartum period of five months. It presents a clinical HF spectrum with left ventricular systolic dysfunction. **Background:** The purpose of this study is to retrospectively evaluate the clinical characteristics, cardiac magnetic resonance (CMR) imaging features, and end-points consisting of left ventricle recovery, left ventricular assist device implantation, heart transplantation, and all-cause mortality. **Method:** Outpatient HF records between 2008 to 2021 were screened. Thirty-seven patients were defined as PPCM. Twenty-five patients had CMR evaluation at the time of diagnosis, and six patients were re-evaluated with CMR. **Results:** The mean age was 30.5±5.6 years, and the mean LVEF was 28.2±6.7%. In thirteen(35.7%) patients, LVEF recovered during the follow-up course. The median recovery time was 281(IQR [78-358]) days. LVEF on CMR was 35.3±10.5, and three patients exhibited late gadolinium enhancement(LGE) patterns. Subendocardial and mid-wall uptake pattern types were detected. 18(75%) patients met the Petersen left ventricle non-compaction cardiomyopathy(LVNC) criteria. Patients with NC/C ratio lower than 2.3 had lower LVEDVi and LVESVi (124.9±35.4,86.4±7.5, p=0.003;86.8±34.6,52.6±7.6, p=0.006), respectively. The median follow-up time was 2129 (IQR [911-2634]) days. The primary endpoint-free one-year survival was 88.9%(event rate 11.1%), and five-year survival was 75.7%(event rate 24.3%). **Conclusion:** In a retrospective cohort of PPCM patients, 35.7% of patients' LVEF recovered, and the primary end-point of free-five-year survival was 75%. Twenty-five patients were assessed with CMR; three of four met the Petersen CMR-derived LVNC at initial evaluation.

TITLE

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ABSTRACT:

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Background: The purpose of this study is to retrospectively evaluate the clinical characteristics, cardiac magnetic resonance (CMR) imaging features, and end-points consisting of left ventricle recovery, left ventricular assist device implantation, heart transplantation, and all-cause mortality.

Method: Outpatient HF records between 2008 to 2021 were screened. Thirty-seven patients were defined as PPCM. Twenty-five patients had CMR evaluation at the time of diagnosis, and six patients were re-evaluated with CMR.

Results: The mean age was 30.5±5.6 years, and the mean LVEF was 28.2±6.7%. In thirteen(35.7%) patients, LVEF recovered during the follow-up course. The median recovery time was 281(IQR [78-358]) days. LVEF on CMR was 35.3±10.5, and three patients exhibited late gadolinium enhancement(LGE) patterns. Subendocardial and mid-wall uptake pattern types were detected. 18(75%) patients met the Petersen left ventricle non-compaction cardiomyopathy(LVNC) criteria. Patients with NC/C ratio lower than 2.3 had lower LVEDVi and LVESVi (124.9±35.4,86.4±7.5, p=0.003;86.8±34.6,52.6±7.6, p=0.006), respectively. The median follow-up time was 2129 (IQR [911-2634]) days. The primary endpoint-free one-year survival was 88.9%(event rate 11.1%), and five-year survival was 75.7%(event rate 24.3%).

Conclusion: In a retrospective cohort of PPCM patients, 35.7% of patients' LVEF recovered, and the primary end-point of free-five-year survival was 75%. Twenty-five patients were assessed with CMR; three of four met the Petersen CMR-derived LVNC at initial evaluation.

KEYWORDS:

Peripartum cardiomyopathy

Non-compaction cardiomyopathy

Cardiac magnetic resonance imaging

ABBREVIATIONS-ACRONYMS:

ACE-i: Angiotensin-converting enzyme inhibitor

ARB: Angiotensin receptor blocker

CI: Confidence interval

CM: Cardiomyopathy

CMR: Cardiac magnetic resonance

DCM: Dilated cardiomyopathy

HF: Heart failure

HR: Hazard ratio

LGE: Late gadolinium enhancement

LVEDd: Left ventricular end-diastolic diameter

LVEDV: Left ventricular end-diastolic volume

LVEDV(i): Left ventricular end-diastolic volume index

LVEF: Left ventricular ejection fraction

LVESd: Left ventricular end-systolic diameter

LVESV: Left ventricular end-systolic volume

LVESV(i): Left ventricular end-systolic volume index

LVmass: Left ventricular mass

LVmass(i): Left ventricular mass index

LVNC: Left ventricular non-compaction cardiomyopathy

MACE: Major advanced cardiovascular event

PPCM: Peripartum cardiomyopathy

TTE: Transthoracic echocardiography

BACKGROUND/INTRODUCTION:

The European Society of Cardiology Working group accepted PPCM as idiopathic cardiomyopathy (CM) with unknown pathophysiology and agreed as different CM from other types of cardiomyopathies. (1) PPCM incidence varies worldwide concerning ethnic and regional differences. The reported incidence rates have increased awareness of PPCM in the recent decade. PPCM may present with cardiogenic shock, acute HF, ventricular arrhythmias, peripheric embolism, and may have complete recovery. PPCM is a qualified instantaneous emerging clinical spectrum with a high probability of recovery than other cardiomyopathies. (2)

The diagnosis is made by excluding other identifiable causes of HF. It occurs towards the end of the pregnancy or during the postpartum period of five months presenting as HF clinical spectrum with left ventricular systolic dysfunction of LVEF$<$45%. There are no specific findings of PPCM; the diagnosis is based on clinical findings. (1)

CMR enables better visualization of cardiac morphology and functions and may show the diagnostic morphological characteristics of cardiomyopathies. In this paper, we aimed to evaluate clinical characteristics, CMR features, and relationship with endpoints that consist; of left ventricle recovery, left ventricular assist device implantation, and all-cause of mortality.

METHODS:

The Ege University institutional review board approved the study, and informed consent has been taken from the subjects or first-degree relatives. Patients with HF admitted to HF outpatient clinics between January 2008-May 2021 were included in this study (Figure-1). The diagnosis of PPCM was based on European Society of Cardiology position paper recommendations. (1) The clinical, echocardiographic, and CMR data of these patients' analyses were assessed retrospectively. Clinical data were collected from the university medical records and the phone call of the patients or relatives.

Echocardiography data includes left ventricular dimensions, interventricular thickness, LVEF, systolic pulmonary artery pressure (SPAP), and valvular assessment. Qualified CMR assessed patients to visualize cardiac dimension measurements, CMR functional analysis, and fibrosis with late gadolinium enhancement (LGE).

Cardiac magnetic resonance imaging assessment:

Cardiac magnetic resonance imaging was performed with 1.5 tesla or 3.0-tesla unit scanners (Amira and Verio, Siemens Healthineers, Erlangen, Germany). Patients were scanned with the electrocardiogram (ECG), triggering a 16-channel surface phased array of body coils. Briefly, 10 to 12 consecutive short-axis images covering the entire LV and 2-, 3-, and 4-chamber long-axis images were acquired with a cine steady-state free precession sequence (SSFP) to assess myocardial function mass and quantification of non-compaction. Two-dimensional LGE images were acquired in short axis, 2, and 4 chamber views by phase-sensitive inversion recovery sequence (PSIR) ten to 15 min after 0.2 mmol/kg gadolinium contrast agent injection. Cardiac volume, function, and mass on cardiac images were analyzed with software; Medis medical imaging systems-Medis Suite 3.1 (Leiden, Netherlands) by three radiologists for disagreements on data between two readers. A consensus agreement was achieved with the third expert opinion. The non-compacted and compacted ratio calculated distal to the papillary muscle that any segment reveals the highest proportion except the left ventricular apex. LGE distribution was reviewed in long and short axis contrast-enhanced images, and LGE presence was accepted in short and long-axis imaging planes. LGE distributions are visually classified

as sub-endocardial, mid-myocardial (mid-wall), sub-epicardial, and right ventricular insertion involvement. Two radiologists determined the LGE distribution pattern; a third senior radiologist was consulted when there was disagreement.

Survival analysis and end-points:

The primary end-point of our study was a composite end-point of major cardiovascular events comprising left ventricular assisted device implantation, heart transplantation, and all-cause mortality. LV systolic function recovery is defined as improving LVEF>10% and increasing over 40%. A total of 37 patients were included in the study.

Statistical Analysis:

Statistical analysis was performed with Medcalc 19.0 (R) and SPSS version 25.0 software (IBM SPSS Statistics, IBM Corporation, Armonk, New York) statistical program. Distribution normality was tested by the Shapiro Wilk test. Continuous variables are calculated as mean, SD, or median (IQR), and categorical variables as counts and percentages. Comparisons between groups were performed with a two-sided Student$t$ -test, Wilcoxon-Mann-Whitney U test, and chi-square or Fisher exact test for categorical variables. Values of p <0.05 were accepted to be statistically significant.

The follow-up duration is determined using the index date to the first MACE date or the last follow-up of patients. Survival curves compared with the log-rank (Mantel-Cox) test for defined primary end-points.

RESULTS:

Thirty-seven patients that met the ESC PPCM criteria were included in the study. The mean age was 30.5±5.6 years. All patients first presented with HF symptoms; six patients also had left ventricular thrombus, and two had a concomitant acute pulmonary embolism.

Six patients (16.2%) had a diagnosis of hypertension, four patients had preeclampsia before the diagnosis of HF, seven (18.9%) patients had diabetes mellitus, and three (8.1%) patients had a smoking history before pregnancy. Four (10.8%) patients reported a family history of HF related to non-ischemic CM. Two (8.3%) patients' rhythm was atrial fibrillation, two patients had left bundle branch block (LBBB), one patient presented with right bundle branch block (RBBB) at baseline, and eight (21.6%) patients had implanted ICD.

Of the PPCM patients, 28 (80%) were treated with ACE-i or ARB, 33 (94.2%) patients with beta-blocker, and 25 (75.3%) patients were on mineralocorticoid receptor antagonists during the follow-up period. Three patients who presented acute HF were treated with bromocriptine (Table 1).

The mean baseline LVEF was 28.2±6.7%, the mean left ventricular end-diastolic diameter (LVEDd) was 59.6±7.4 mm, and the left ventricular end-systolic diameter (LVESd) was 50.1±8.5 mm. Twenty-two (62.9%) patients had moderate or severe functional mitral regurgitation, and 15 (42.9%) patients had moderate or severe functional tricuspid regurgitation. On the last follow-up, 24 patients' echocardiography was re-assessed, and the mean LVEF was 39.9±13.5%. During the follow-up period, the mean LVEF change was 11.7±15.7% (p=0.001) (Table 2).

In thirteen (35.7%) patients, left ventricular systolic function recovered during the follow-up course. The median recovery time was 281(IQR [78-358]) days.

Cox regression analysis did not demonstrate a significant predictor for recovery.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed on 25 patients. CMR measured mean LVEF was 35.3±10.5, mean LVEDd was 58.8±8.0 mm, and mean LVESd was 50.4 ±10.4 mm. Seven (28%) patients LVEDd was in the normal range. Despite the decreased LVEF and enlarged left ventricle, the mean volumes, cardiac output, and cardiac index were preserved.

Three patients exhibited late gadolinium enhancement (LGE) patterns. Sub-endocardial and mid-wall uptake pattern types were detected, one patient with subendocardial LGE experienced sudden cardiac death in a HF medication titration course, and the second patient experienced ventricular tachycardia with appropriate ICD shock. The third patient with mid-wall LGE pattern type needed heart transplantation surgery.

All patients demonstrated trabeculation at least in one left ventricular segment, and trabeculations were mostly detected in lateral and inferior segments. The mean non-compacted to compacted (NC/C) ratio was 2.73±0.88, and 18 (75%) patients met the Petersen non-compaction cardiomyopathy criteria. Patients were also compared regarding NC/C ratio; patients with NC/C ratio lower than 2.3 had lower LVEDV(i) and LVESV(i) (124.9±35.4, 86.4±7.5, p=0.003; 86.8±34.6, 52.6±7.6, p=0.006), respectively.

Seven patients underwent a second CMR to evaluate the left ventricle volumes and cardiac function. Four patients with NC/C ratio over 2.3 had a non-compaction cardiomyopathy phenotype at the second CMR examination. In all seven patients who underwent CMR, LVEF increased; the mean change was 13.85±12.5 (p=0.0035) (Table 3).

Survival data were available for all patients. The median follow-up time was 2129 (IQR [911-2634]) days. Ten (27%) patients experienced primary end-point; five (13.5%) patients experienced death, two (5.4%) patients underwent left ventricular assisted device implantation, and three (8.1%) patients experienced heart transplantation surgery. The primary end-point occurrence median time was 786 (IQR [167-1498]) days-(Figure 2).

The primary end-point free one-year survival was 88.9% (event rate 11.1%), and five-year survival was 75.7% (event rate 24.3%) (Figure 3).

DISCUSSION:

PPCM is a rare cause of HF, and incidence changes according to region and ethnicity. PPCM diagnosis is made by exclusion of the other causes of cardiomyopathies. The etiology of PPCM is uncertain; predisposition and acquired factors may take part. (1) This retrospective designed study evaluated clinical, echocardiographic, and cardiac magnetic resonance imaging, survival and recovery characteristics.

In the US, population incidence ranges from 1 in 100 to 1 in 4000, this rate was highest in Nigeria with 1/100 patients, and 1/400 in Haiti reports. (3) In our HF cohort, the incidence rate was 1.6/100 patients. This incidence rate was high as compared to the literature. The higher incidence rate in our institute could be the tertiary and referral center for HF patients. 57.9% of patients were referred to our center assessment for resolved acute HF. Ethnicity was impressed in the studies that African-American women were more predisposed to PPCM. IPAC registry results showed that African-American women had low initial LVEF, worse prognosis, and lower recovery rate than white women (4). In our study, all patients' ethnicity was caucasian white women; therefore, no comparison could be made regarding ethnicity.

Hypertension was present in six (16.2%) patients before pregnancy, and preeclampsia was developed in 4 (10.8%) patients before presentation with HF. Preeclampsia-developed patients did not reveal any differences regarding the primary end-points. However, in four patients, LVEF recovered during the follow-up course (p=0.016). This finding could be ascertained by abruptly increased afterload may have caused left ventricular dysfunction with a predisposition to HF and pregnancy-related hormonal or molecular imbalance that shares a similar mechanism. (1) Clinical and cardiac imaging findings did not relate significantly to primary end-points.

Haghikia et al. analyzed 115 patients in the German registry. 19 (16.5%) patients reported a positive family history of cardiomyopathy. Family history was accepted as positive when PPCM, DCM, sudden death, and arrhythmias in family first-degree relatives were present. The recovery rate was not influenced by family history. (5) In our study, four patients had a family history of non-ischemic HF; this finding did not affect the primary end-point or LVEF recovery. Genetic analyses could not be performed on these patients.

PPCM has been associated with higher LVEF recovery rates, primarily seen in the first six months. The

IPAC registry analyzed outcomes and predictors of recovery in 100 patients. The enrolled patient's diagnosis was consistent with idiopathic non-ischemic cardiomyopathy. In the early postpartum period, mean LVEF increased from 0.35 (0.09 to 0.55) in twelve months. For women enrolled later in the course of the disease, LVEF stayed the same for 12 months, but it was lower than early postpartum women. Follow-up LVEF differed by race at 6 and 12 months. (4)

ESC EORP PPCM registry 2020, 730 patients were assessed. Results showed that recovery (LVEF>%50) occurred in 46% of the women, and 23% of women's left ventricular dysfunction persisted at six months. (6)

In our cohort, left ventricular systolic function recovery was accepted as an improvement by 10% and increasing over 40%. Thirteen (35.1%) patients' left ventricle systolic function recovered during the follow-up. The median time to recovery was 281.5 (IQR [78.7-358]) days. In patients admitted to our hospital early in the course of the disease recovery rate was 46.7%, and in referred patients, the recovery rate was 27.3% (p=0.30).

In PPCM, known for reversibility of the left ventricular systolic function, mortality is less announced in the studies. In the IPAC registry, follow-up at one-year mortality ranged from 4% to 11%. Black women were more likely to face worse prognoses. (4) Karaye et al. stated outcomes in Nigeria and found that 18.7% of women died due to any cause in a median of 17 months. Maternal age below 20 years, hypotension at presentation, and tachycardia were positively related to mortality. Obesity and beta-blocker therapy was related to reduced risk of death. (7) In 2020, ESC EORP PPCM registry results showed six-months outcomes: overall mortality was 6%, and regional mortality differed. In European countries, the mortality rate decreased to 4% in six months compared to Middle Eastern countries, where the mortality rate was 10%. This ESC EORP PPCM cohort was assessed for composite end-point (all-cause mortality, LVAD implantation, and heart transplantation) in PPCM patients with extended follow-up time. The death rate was 10.8%, and one-year death-free survival was 97.1% (2.9 events per year). The survival probability without a primary end-point was 11.9% in one year. Our study's event rate in one year was lower than the EORP PPCM registry. (8) This could be explained by the higher rate of referred patients. Mortality probably is higher in the course of initial acute HF hospitalization. The availability of advanced HF therapies in our center probably affects more favorable survival.

In our study, we analyzed the CMR data of this patient population. In the literature, few studies present CMR data. Mouquet et al. analyzed 8 PPCM patients with CMR. LVEF measured by CMR correlated with echocardiography. The authors did not observe morphological aspects of LVNC or any other cardiomyopathies. CMR was re-performed in five patients. Neither baseline nor six months control CMR demonstrated an LGE pattern. (9) Marmursztejn et al. reported CMR results of two cases where one patient exhibited LGE. (10) Ersboll and colleagues analyzed a nationwide Danish cohort of 28 PPCM women with CMR: the mean LVEF was 62%, and one patient had LGE. The CMR was not performed in the early phase of PPCM(11). Liang et al. showed three CMR parameters correlated with recovery in PPCM: T1, T2, and extracellular volume (ECV). This study was performed on 21 PPCM patients and 20 age-matched patients. Although these parameters were related to LVEF recovery, ECV was the only independent parameter that surmised LVEF recovery. (12)

In the study performed by Arora et al., ten patients were retrospectively recruited, and their medical records paved the way for diagnosing PPCM. LGE was presented in 4 patients, all of whom had HF exacerbations during delivery. In addition, four patients had future pregnancies, and two women had LGE. These two women had HF decompensation during the following delivery(13).

This study reveals 25 patients' baseline CMR results and seven control CMR results. Patients who have reached the primary end-point did not show a difference compared to the patients in whom the primary endpoint did not occur. Three patients with LGE reached the primary end-point. Two had sub-epicardial late enhancement; the first patient had an arrhythmic event during a HF medication titration course. Although LV systolic function improved during the follow-up, she experienced sudden cardiac death on the 136 days. The second patient implanted with an ICD had an appropriate shock for ventricular tachycardia. The third

patient with LGE needed heart transplantation. These limited data revealed that PPCM with LGE had a poor prognosis, and sub-epicardial LGE exhibited patients may more likely have ventricular arrhythmia. This information may indicate that patients with sub-epicardial LGE are more likely to have arrhythmic death, so early ICD implantation strategies could be life-saving.

A few studies in the literature show trabeculations in LV consistent with LVNC during pregnancy. These trabeculations are best studied with CMR. In PPCM patients, a non-compaction cardiomyopathy phenotype was reported in case reports. Rehfeldt et al. shared a case report that suffered resuscitated cardiac arrest without past cardiac history. The echocardiographic assessment showed very low LVEF (5%), and she had LVAD surgery. She had prominent trabeculations compatible with LVNC phenotype after LVEF recovered at three months, and LVAD was removed. The NC/C ratio was not stated. (14)

Patel et al. reported two case reports claiming LVNC phenotype in PPCM patients. In the first patient, the NC/C ratio was 3.2 according to Jenni's criteria and regressed to 2.5. The second patient had an end-systolic NC/C ratio of 1.63; however, this ratio was inconsistent with LVNC criteria. (15) Lea et al. presented a single case report: the patient diagnosed with acute HF during pregnancy showed an enlarged left ventricle and hypertrabeculation coherent with LVNC. After delivery, the patient's clinical situation worsened, and they needed heart transplantation surgery. Explant material revealed LVNC properties. (16) and Rajagopalan et al. identified five patients who met the clinical definition of PPCM and LVNC imaging criteria. CMR was assessed in all patients. Three of the five patients had sustained left ventricular dysfunction; one had heart transplantation surgery, second had LVAD bridge to transplantation. In two patients, LVEF improved by over 40%.(17)

The development of trabeculations in the LV during pregnancy is another issue of discussion. Gati et al. evaluated 102 pregnant women and performed TTE in the first and third trimesters. 26 (25.4%) patients developed increased trabeculations; eight women revealed sufficient trabeculations to fulfill the criteria for LVNC. During the postpartum period, 19 (73%) women demonstrated complete resolution of the trabeculations, and five showed a reduction in the trabeculated layer. (18)

In our cohort, 25 women diagnosed with PPCM CMR were performed, and the NC/C ratio was measured. Eighteen patients met the LVNC Peterson criteria. Seven patients' NC/C ratio was lower than 2.3 and did not confirm other cardiomyopathies. In Nine of eighteen LVNC phenotype patients, LVEF recovered. However, three patients with this phenotype reached the primary end-point (two death and one heart transplantation). In Seven of the 18 patients, CMR was re-performed, and in four patients NC/C ratio was over 2.3, consistent with LVNC. Three of Four patients' NC/C ratio decreased, and in one patient NC/C ratio increased.

Studies in the literature and our paper raise the question of whether patients with LVNC who presented with first-time HF during pregnancy were misdiagnosed with peripartum CMP. PPCM is unknown idiopathic cardiomyopathy and has to be differentiated from other causes of HF. Thus a careful examination of patients with PPCM should be done, and CMR should be performed to exclude other forms of cardiomyopathies. Further research on the development of trabeculations during pregnancy is needed.

CONCLUSION:

This study evaluated 37 PPCM patients. 46% of the patients' left ventricle systolic function recovered. In five years, 25% of patients reached the primary end-point. Most of the patients were evaluated by CMR, and 75% met the criteria of left ventricle non-compaction cardiomyopathy. Three patients exhibited LGE, and two of them reached the study's primary end-point. Our study highlights the importance of CMR imaging in this patient population. First, it is essential to diagnose the disease: LVNC may be the underlying etiology for the development of HF. Second, LGE presence is a marker of poor prognosis.

LIMITATIONS:

A limited number of patients were included in our study because PPCM is a rare CM. This study was in retrospective case-control series design and represented the single-center experience. The study included

patients referred to a tertiary HF center, so a number of patients' data were missing. Two radiologists re-evaluated CMR images, but in twelve years, CMR imaging modalities' quality has changed. All patients' CMR morphological features were evaluated, but 20% of the functional analysis was missing.

HIGHLIGHTS:

1-The recovery rate of patients with peripartum cardiomyopathy is higher

2-Five years major cardiovascular event rate was 24.6% in peripartum cardiomiyopathy patients.

3-CMR imaging results revealed 75% of the patients met the Petersen LVNC criteria. This finding suggest the underlying cause of peripartum cardiomyopathy may be LVNC.

4- The presence of late gadolinium enhancement is a sign of poor prognosis in PPCM patients.

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FIGURE LEGENDS

Figure 1: Flow chart of study patients/consort diagram of peripartum cardiomyopathy patients.

ARVC=Arrhytmogenic right ventricular; CMR=Cardiac magnetic resonance; cardiomyopathy; C=compacted myocardium; NC= non-compacted myocardium; NC/C ratio= ratio of the non-compacted segment to compacted segment of the myocardium.

Figure 2: The peripartum cardiomyopathy patients' primary endpoint occurrence median time distribution box-whisker plot.

The primary end-point occurrence median time was 786 (IQR [167-1498]) days.

Figure 3: Kaplan Meier survival analysis of the peripartum cardiomyopathy patients.

Kaplan Meier survival analysis estimates free of major cardiovascular events in the PPCM patients.

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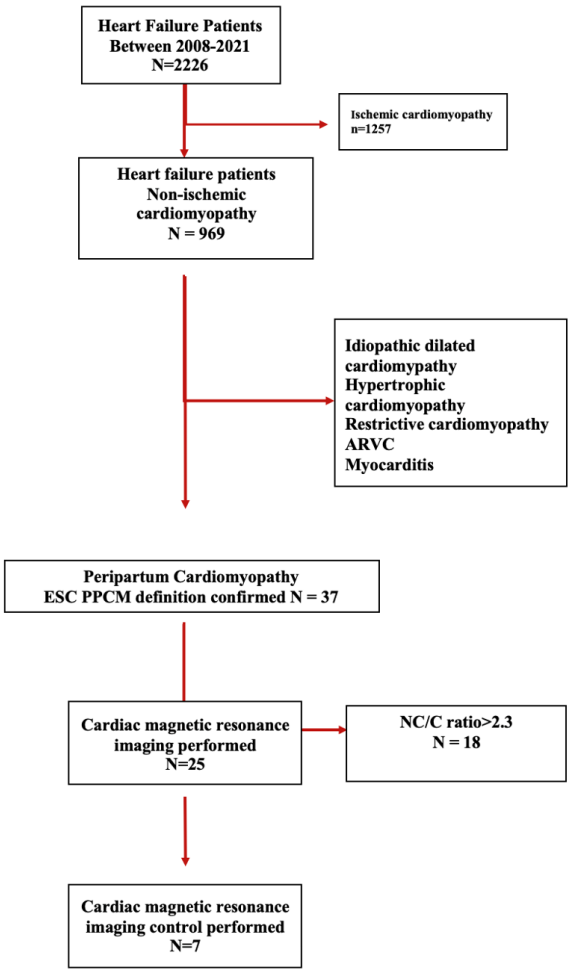

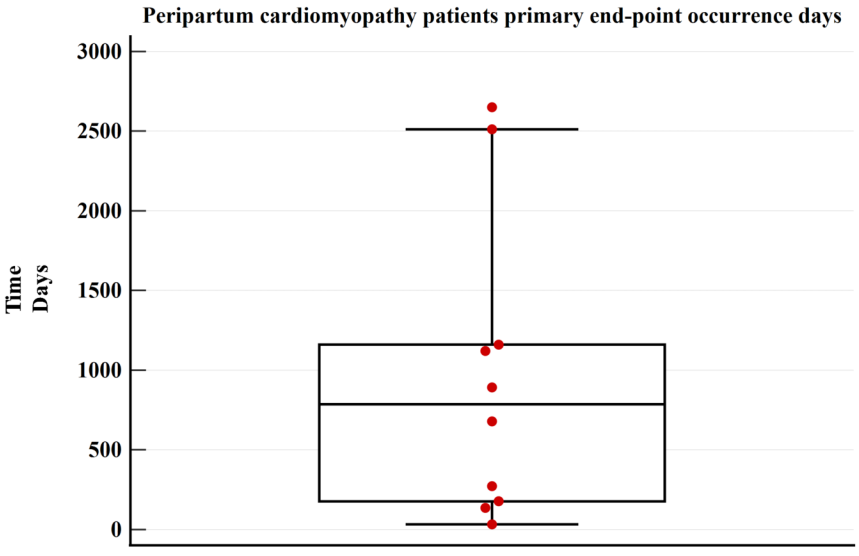

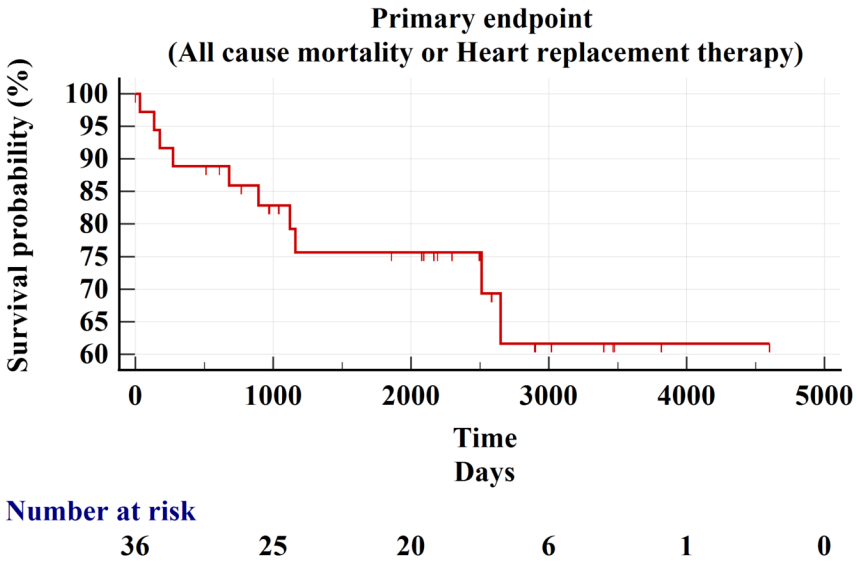

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