Title: Assessing long term survival and hospitalisation following transvenous lead extraction in patients with cardiac resynchronisation therapy devices: A propensity score matched analysis

Short Title: Survival following TLE in CRT patients

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Abstract

Background:

Longer term outcomes of patients post transvenous lead extraction (TLE) is poorly understood in patients with cardiac resynchronisation therapy (CRT) devices.

Objectives:

A propensity score (PS) matched analysis evaluating outcomes post-TLE in CRT and non-CRT populations was performed.

Methods:

Data from consecutive patients undergoing TLE between 2000 to 2019 were prospectively collected. Patients surviving to discharge and re-implanted with the same device were included. The cohort was split depending on presence of CRT device. Associations with all-cause mortality and hospitalisation was assessed by Kaplan-Meier estimates. An exploratory endpoint was evaluated whether early (<7 days) or late (>7 days) reimplantation was associated with poorer outcomes.

Results:

Of 1005 patients included, 285 (25%) had a CRT device. Median follow-up was 57.00 [27.00-93.00] months, age at explant was 67.7±12.1 years, 83.3% were male and 54.4% had an infective indication for TLE. PS were calculated using 43 baseline characteristics. After matching, 192 CRT patients were compared with 192 non-CRT patients. In the matched cohort, there was no significant difference with respect to mortality (hazard ratio [HR]=1.01, 95% confidence interval [CI] [0.74-1.39], p=0.093) or hospitalisation risk (HR=1.2[0.87-1.66], p=0.265) was observed. In the matched CRT group, late reimplantation was associated with increased mortality (HR=1.64[1.04-2.57], p=0.032) and hospitalisation risk (HR=1.57[1.00-2.46], p=0.049].

Conclusion:

Outcomes of CRT patients post-TLE is similarly poor to non-CRT patients in matched populations. Reimplantation within 7 days was associated with better outcomes in a CRT population but was not observed in a non-CRT population, suggesting prolonged periods without biventricular pacing should be avoided.

Key Findings:

- This is the largest matched analysis of mortality and clinical outcomes of patients with and without cardiac resynchronisation therapy (CRT) devices following transvenous lead extraction (TLE).
- In an unmatched analysis, patients with CRT devices post TLE were more likely to die and be readmitted to hospital for any cardiovascular cause
- In a matched analysis, patients with and without CRT devices post TLE had similar outcomes with respect to mortality and hospitalisation.
- Delayed reimplantation following TLE in the CRT group was associated with greater risk of mortality and hospitalisation. This was not observed in the non-CRT group. This suggests minimising time without biventricular pacing following TLE in a CRT population is desirable.

Introduction

The rise in the use of intracardiac implantable electronic devices (CIEDs) has been paralleled by an increase in the number of procedures required for the removal of such devices and their associated leads[1]. Transvenous lead extraction (TLE) forms the basis of the management of infected CIEDs, malfunctioning and redundant leads[2]. High procedural success rates with low rates of major in-hospital complications as achieved in the European Lead Extraction ConTRolled Registry (ELECTRa), demonstrate a complete clinical success at 96.7% and an in-hospital major complication rate at 1.7%[3]. Overall hospital mortality was low at 1.4% with a procedural related mortality of 0.5%. The outcomes for the subgroup of patients who have TLE procedures with cardiac resynchronization therapy (CRT) devices is less well understood. CRT is an effective therapy to improve symptoms and reduce mortality in patients with dyssynchronous heart failure, however these patients have a higher morbidity and mortality rate related to poorer left ventricular ejection fraction (LVEF) and co-morbidity burden. Similarly, the number of CRT devices implanted with left ventricular (LV) leads has been paralleled by an increased requirement for CRT system extraction[4]. Current evidence suggests that there is no significant difference in acute complications, or 30-day mortality associated with CRT system extraction[5]. Less is understood regarding long term outcomes regarding mortality and morbidity following TLE in this group. In addition, the impact of delayed reimplantation of a CRT device following TLE is poorly understood, despite the theoretical risk of negative reverse remodelling [6] or acute haemodynamic compromise[7] caused by the absence of biventricular pacing. We hypothesised that patients had poorer outcomes who had a CRT device vs non-CRT device, however it was unclear if matching the baseline characteristics would maintain this effect. In addition, we hypothesised that delayed reimplantation post TLE in a CRT population would result in poorer outcomes compared to non-CRT populations. We studied data from a single, high-volume tertiary referral centre for TLE, regarding long-term outcomes in a CRT and non-CRT population.

Methods

Data Collection

All consecutive patients undergoing TLE in a high-volume centre in the UK were prospectively recorded onto a computer database between October 2000 and November 2019. Multiple parameters were recorded, including demographics, extraction indication, device and lead type, comorbidities, biochemistry and pathology results, procedural success, major complications, and technical extraction information. Patients reimplanted with the same device and surviving to discharge following TLE were included. Only the most recent entry for patients with multiple TLEs during the study period were included. Mortality was recorded retrospectively by linking unique patient registration numbers (National Health Service (NHS) numbers) and the Office for National Statistics (ONS) mortality data updated as of February 2020[8]. Hospital readmission information was obtained from the source data feeding directly to the Hospital Episodes Statistics (HES) national database, which records all NHS hospital-based activity in England and has been validated as an accurate way of recording medical activity and is used for allocating resources based on needs in the NHS[9]. Any cardiovascular cause of inpatient admission was identified as the primary outcome measure of hospitalisation, as defined by the World Health Organisation International Classification of Diseases (ICD-10-CM) coding system (ICD-10-CM codes: Diseases of the circulatory system: ICD I00-199; Heart failure: I50; Complications of cardiac and vascular prosthetic devices: ICD T82)[10]. The database collection and analysis were approved by the Institutional Review Board of Guy's and St Thomas' Hospital.

Definitions

TLE was defined as per the EHRA and HRS guidelines[11]. The 2018 EHRA guidelines defined the extraction indication, procedural success and complication rate[12]. The extraction procedure undertaken at this centre has been described in detail elsewhere[13]. If there was more than one indication for lead extraction or original implantation indication, this was counted independently. Number of previous device interventions was defined as the number of CIED procedures undertaken on the patient prior to the recorded lead extraction. Lead dwell time was calculated as the oldest

targeted lead in situ at time of extraction. Follow-up time and age were calculated from date of TLE. Major cardiovascular co-morbidities were recorded. Glomerular filtration rate (GFR) was estimated by the MDRD 4-variable equation[14].

Statistical Analysis

Missing data for variables of interest were handled by multiple imputation with chained equations and the multiple imputed data frames were merged into a single data frame by computing the mean or selecting the most likely imputed value (R-packages mice and sjmisc; 10 imputed datasets)[15]. The propensity score (PS) for the CRT group was calculated by a logistic regression model using 43 clinically relevant covariates. CRT patients were matched 1:1 to non-CRT patients by their PSs, using the nearest neighbour method with a calliper of 0.10 and no replacements. Variables included in either the multiple imputation models or considered for PS calculation are shown in table 1. The ability of the matching to balance baseline characteristics in CRT versus non-CRT group was assessed by absolute standard differences, with a value of <10% considered as not significant[16].

Baseline variables of the matched cohort were compared by calculating standardised mean differences and the chi-squared test, student's t-test or Mann Whitney U-test when appropriate. Primary outcomes in this analysis were overall survival and time to first cardiovascular hospitalisation at follow-up. Kaplan-Meier method was used to estimate survivor functions in the CRT vs non-CRT group, with a secondary outcome analysis dependent on whether patients were reimplanted within or after 7 days of initial TLE. A sub-analysis of the matched CRT and non-CRT groups was undertaken with the same outcomes assessed as above. Univariable cox (proportional hazard) regression was performed, and the results are presented as (Hazard Ratio (HR) [95% Confidence Interval (CI)], p-value).

Results

Study Cohort

Between October 2000 and November 2019, 1171 consecutive patients underwent TLE at the reference centre. After applying the inclusion criteria, 1005 patients were eligible. Of these, 285 (28.4%) patients had a CRT device. After PS matching, the analysis was restricted to 384 patients, 192 in both the CRT and non-CRT groups.

Baseline Characteristics (Table 1)

In the overall cohort, mean age was 65.1±14.7 years, 72.7% were male and 51.9% had a TLE for an infective indication. Median lead dwell time was 5.40 [1.80-9.80] years, 28.5% had an ICD, 43.2% had a permanent pacemaker and the remainder had a CRT-D/P device at time of TLE. Most of the baseline characteristics were differently distributed in the CRT versus non-CRT group. CRT patients were older (68±10.7 vs 64±15.6 years, $p<0.001$), had higher mean number of co-morbidities (3.18 vs 1.49, $p<0.001$), poorer renal function (108.00 [86.00-136.00] vs 89.00 [75.00-110.00] mg/dL, $p<0.001$), and lower LVEF (35.5±12.4 vs 47.4±12.1, $p<0.001$). The CRT group also had shorter lead dwell time (4.70 [1.80-8.10] vs 5.90 [1.80-10.50] years, $p=0.01$), were less likely to have their device reimplanted within 7 days of TLE procedure (n=159, 55.8% vs n=470, 65.3%, $p=0.006$), longer time to reimplantation ($p=0.029$) and have had a previous device intervention ($p=0.038$). After PS matching, baseline characteristics considered for PS calculation were equally distributed between the 2 study groups, with well-matched PS in both groups (supplement figure 1).

Outcome analysis

All-Cause Mortality (Figure 1)

In the overall cohort, during long-term follow-up with a median of 57.00 [27.00-93.00] months, 345 (34.3%) patients died. Kaplan-Meier survival analysis demonstrated a survival probability of 93.4% at 1 year, 88.4% at 2 years, 73.1% at 5 years and 50.4% at 10 years. At follow-up a higher proportion of patients died in the CRT vs non-CRT group (43.9% vs 30.6%, $P<0.001$) with survival probability of

88.9% vs 97.1% at 1 year; 80.7% vs 91.4% at 2 years; 59.3% vs 78.3% at 5 years, and 27.6% vs 56.7% at 10 years. Overall unadjusted hazard ratio (HRs) for mortality and 95% CIs in the CRT group were [HR = 2.16, 95% CI (1.72-2.70), p<0.001].

In the matched cohort, during long-term follow-up with a median of 46.00 [25.00-76.25] months, 159 (41.4%) patients died. At follow-up a similar proportion of patients died in the matched CRT vs non-CRT group (40.1% vs 42.7%, P=0.68) with survival probability of 91.4% vs 91.5% at 1 year; 83.9% vs 86.9% at 2 years; 65.0% vs 63.6% at 5 years, and 33.5% vs 34.9% at 10 years. Similar unadjusted HR were observed for the matched CRT group [HR = 1.02, 95% CI (0.74-1.39), p=0.933].

Cardiovascular Hospitalisation (Figure 2)

In the overall cohort during long-term follow-up, 371 (36.9%) patients were hospitalised. Kaplan-Meier survival analysis demonstrated a freedom from hospitalisation probability of 76.7% at 1 year, 71.0% at 2 years, 62.2% at 5 years and 50.1% at 10 years. At follow-up a higher proportion of patients were hospitalised in the CRT vs non-CRT group (58.9% vs 44.9%, P<0.001) with survival probability of 71.6% vs 78.7% at 1 year; 62.8% vs 74.0% at 2 years; 51.6% vs 65.9% at 5 years, and 42.8% vs 53.1% at 10 years. Overall unadjusted hazard ratio (HR) and 95% CIs for hospitalisation in the CRT group were greater than in the non-CRT group [HR = 1.46, 95% CI (1.17-1.83), p<0.001].

In the matched cohort during long-term follow-up, 147 (38.3%) patients died. At follow-up a similar proportion of patients were hospitalised in the matched CRT vs non-CRT group (41.1% vs 35.4%, P=0.294), with hospitalisation probability of 72.2% vs 76.3% at 1 year; 63.3% vs 70.6% at 2 years; 54.0% vs 60.4% at 5 years, and 43.7% vs 46.5% at 10 years. Similar unadjusted HR were observed for the matched CRT group for risk of hospitalisation [HR = 1.20, 95% CI (0.87-1.66), p=0.265].

Sub-group analysis

Re-implantation timing

In the sub-group analysis within the matched cohorts, an analysis of survival probability with respect to mortality and hospitalisation following TLE was performed. There were similar baseline characteristics between the late reimplantation groups in the matched CRT and non-CRT groups, with similar infective indications for TLE (local: 64.1% vs 64.9%; systemic: 26.9% vs 27.0%; any infection: 91.0 vs 91.9%), eGFR (61.6 vs 61.9 ml/min/m^2), LVEF (38.4 vs 40.1%) and age at explant (69.2 vs 70.0 years) (supplement table 1).

Within the matched non-CRT group, there was no significant difference with regards to risk if reimplantation occurred late (i.e. 7 days after TLE procedure) with an unadjusted HR for death of [HR = 1.33, 95% CI (0.86-2.05), p=0.208] and for hospitalisation [HR = 1.14, 95% CI (0.69-1.89), p=0.601]. Within the matched CRT group, there was a significant difference with regards to risk associated with late reimplantation with an unadjusted HR for death of [HR = 1.64, 95% CI (1.04-2.57), p=0.032] and for hospitalisation [HR = 1.57, 95% CI (1.00-2.46), p=0.0.49]. There was no evidence of differences in risk of mortality (p=0.576) or hospitalisation (p=0.911) between the early reimplantation groups in the CRT and non-CRT groups. There was increased risk of hospitalisation in the late reimplantation group in the CRT group vs non-CRT group [HR=1.71 95% CI (1.01-2.9), p=0.048] (figures 3 and 4).

Risk depending on cause of hospitalisation

There was a greater risk of hospitalisation associated with TLE in the CRT group compared to the non-CRT group with regards to any cardiovascular cause (ICD-10 I00-I99 codes) for hospitalisation [Relative Risk (RR) 3.79, 95% CI (2.04-7.02), p<0.001], or heart failure decompensation (ICD I50-I59 codes) [RR 1.45, 95% CI (1.14-1.86), p=0.004]. No significant difference was identified with respect to risk of device related complications requiring hospitalisation [RR 1.13, 95% CI (0.79-1.64), p=0.515] (figure 5).

Discussion

An understanding of mortality and morbidity at follow-up post TLE in the CRT population is important to evaluate the longer-term implications of the procedure. To our knowledge, this analysis is the largest registry analysis to date evaluating mortality and morbidity outcomes following TLE in patients who survive to discharge and are reimplanted with the same device.

The main findings are that:

1. The baseline characteristics of patients undergoing TLE in the CRT group are significantly different to the non-CRT group, and this is reflected in a higher risk of mortality and cardiovascular hospitalisation following TLE.
2. In a matched cohort, CRT and non-CRT patients had similar outcomes with respect to mortality and hospitalisation risk post TLE.
3. Following TLE, CRT patients had a higher risk of hospitalisation for any cardiovascular cause or heart failure, however no increased risk of hospitalisation due to a device related complication.
4. Reimplantation within 7 days was associated with better outcomes in a matched population in patients with a CRT device compared to a non-CRT population.

Few studies have compared long term outcomes of patients following TLE specifically evaluating patients with CRT and non-CRT devices. Larger registry analyses have not evaluated outcomes beyond early complications and mortality in both CRT and non-CRT cohorts, including the ELECTRa study[17] and the Cleveland Clinic series of 5000 TLEs[18]. Data from the same reference centre by Gould et al utilising a smaller cohort of patients, has demonstrated no significant difference in 30-day mortality rates between CRT (3.0%, n=7) and non-CRT patients (2.0%, n=14) (p=0.443)[5]. This study also evaluated outcomes using case-control matching, which also demonstrated no significant difference in 30-day outcomes, however only 185 patients were included in each group,

and were matched only for 4 variables (lead dwell time, age, renal impairment, and systemic infection), whereas the current analysis matched for 43 variables (table 1). Zuchelli et al, demonstrated a 1-year mortality of 5.5% in a CRT population post TLE[19], whereas our study demonstrated higher incidence of mortality of 11.1%. In a more recent study, Nishii et al compared the prognosis of patients who had severe LV systolic dysfunction (SLVD) compared to those who did not. Whilst not looking specifically at patients with CRT devices, they demonstrated that those with SLVD were not more likely to die at 30 days (97.2% vs 99.4%, p=0.215) or 1 year (80.6% vs 91.5%, p=0.053) post TLE[7]. They also identified that patients with SLVD were more likely to require additional hemodynamic support, such as temporary cardiac resynchronization therapy pacing (27.8% vs 1.2%; p<0.001), which may attest to the findings in our study identifying poorer outcomes for those who had delayed reimplantation. Of note, this study only included 36 patients with SVLD, out of a total cohort of 200 patients, whereas our study utilises data from 1005 patients. Few studies have evaluated cardiovascular hospitalisation as an endpoint in CRT patients post TLE. Regoli et al identifying 37.0% requiring hospitalisation, and 23.9% dying at a median follow-up of 21 months post TLE[20], which compared similarly to our study at the same follow-up time (hospitalisation: 34.9%; mortality: 16.5%).

Most published data involving PS matching in patients with cardiac resynchronisation therapy has been to compare outcomes of CRT cohorts with and without defibrillator devices [21,22], with only one study utilising PS matching in patients following TLE [23]. This study is the first to match CRT and non-CRT patients post TLE. Matching resulted in an increase in mean age at explant (64.0 to 67.8 years), total number of comorbidities (1.49 to 2.78 comorbidities), and reduction in LVEF (47.4 to 37.7%) and eGFR (70.5 to 63.9 ml/min/1.73m^2) of the non-CRT group. In the unmatched cohort, CRT patients were at significantly increased risk of any cardiovascular hospitalisation and mortality, with an increased relative risk of heart failure hospitalisation, compared to a non-CRT population. Matching resulted in similarly poor outcomes in the CRT and non-CRT group, which suggests that all patients with a greater co-morbidity burden regardless of whether they have a CRT may benefit from

closer evaluation following TLE. This could confer significant cost savings for healthcare services, which can tailor services to reduce risk of hospitalisation in these at-risk patients[24].

Notably, the exploratory endpoint demonstrated poorer outcomes in those who had delayed implantation following CRT explant. It is possible that those with CRT devices explanted for an infective indication may have a greater burden of infective material due to the presence of an LV lead, which may contribute to the poorer outcomes associated with delayed reimplantation. It may also be argued that an infective indication, whether this be systemic or local may be an unidentified confounder. However, within each matched cohort there was not a survival difference depending on whether there was an infective indication for TLE, and whether this was a systemic or local infection (Supplement Figure 1). This suggests that the presence of infection was unlikely to be a confounder influencing this observation within the matched cohorts. Additionally all patients had interrupted biventricular pacing from time of TLE procedure to time of reimplantation. Most published work evaluates the acute implications of interrupting continuous biventricular (BiV) pacing. These studies have demonstrated that even brief interruptions in BiV pacing can result in worsening dyssynchrony and mitral regurgitation (MR)[25], left atrium and left ventricular dimensions[26], and contractile reserve[27]. Changes in cardiac biomarkers have also been associated with 48 hours of BiV interruption of CRT responders, with Rubaj et al identifying a significant increase in proinflammatory cytokines and BNP concentrations[28]. These findings may be a reason for the observed negative outcomes observed in this study associated with delayed reimplantation seen in the matched CRT cohort, but not observed in the matched non-CRT cohort.

Limitations

Although the database collects many variables and allowed us to perform adjustments by PS matching, residual and unmeasured confounding within the matched and unmatched cohorts cannot be ruled out. Although our PS models were fitted based on several variables to foster adequate adjustments, we did not consider potential interactions among the covariates. The findings of our

study are limited by the inherent issues identified with observational studies. Associations with mortality and hospitalisation for the groups were discussed, however the cause-and-effect relationship remain associative. Causes of death in these patients is unknown. We opted to only include patients who survived to discharge, which may have introduced survival and treatment bias. As our institution is a tertiary care centre, referral bias could have affected the clinical data, thereby limiting generalisation of these findings to other patient populations. The analysis on the impact of delayed reimplantation was performed within the matched cohorts as the baseline characteristics of the CRT and non-CRT groups were similar after matching was performed. Within these constrains, a PS match analysis was considered an appropriate method of evaluating this hypothesis and potentially form the basis of further investigation in the form of a randomised trial which could more effectively reduce the potential number of unidentified confounders which are often unavoidable as part of observational studies. As the baseline characteristics of the matched groups were very balanced, particularly with respect to the proportion of systemic and local infective indications for TLE, we believe there was justification for this comparison.

Conclusions

The prognosis of patients with CRT who undergo TLE demonstrates similar mortality and hospitalisation risk to non-CRT patients in a matched population. In an unmatched population, CRT patients had notably poorer outcomes and merit close follow-up post TLE procedures. There was increased risk of adverse outcomes associated with delayed reimplantation of CRT devices compared to other devices. This may be due to prolonged periods without continuous BiV pacing following TLE in patients with CRT devices, and this should be avoided where possible.

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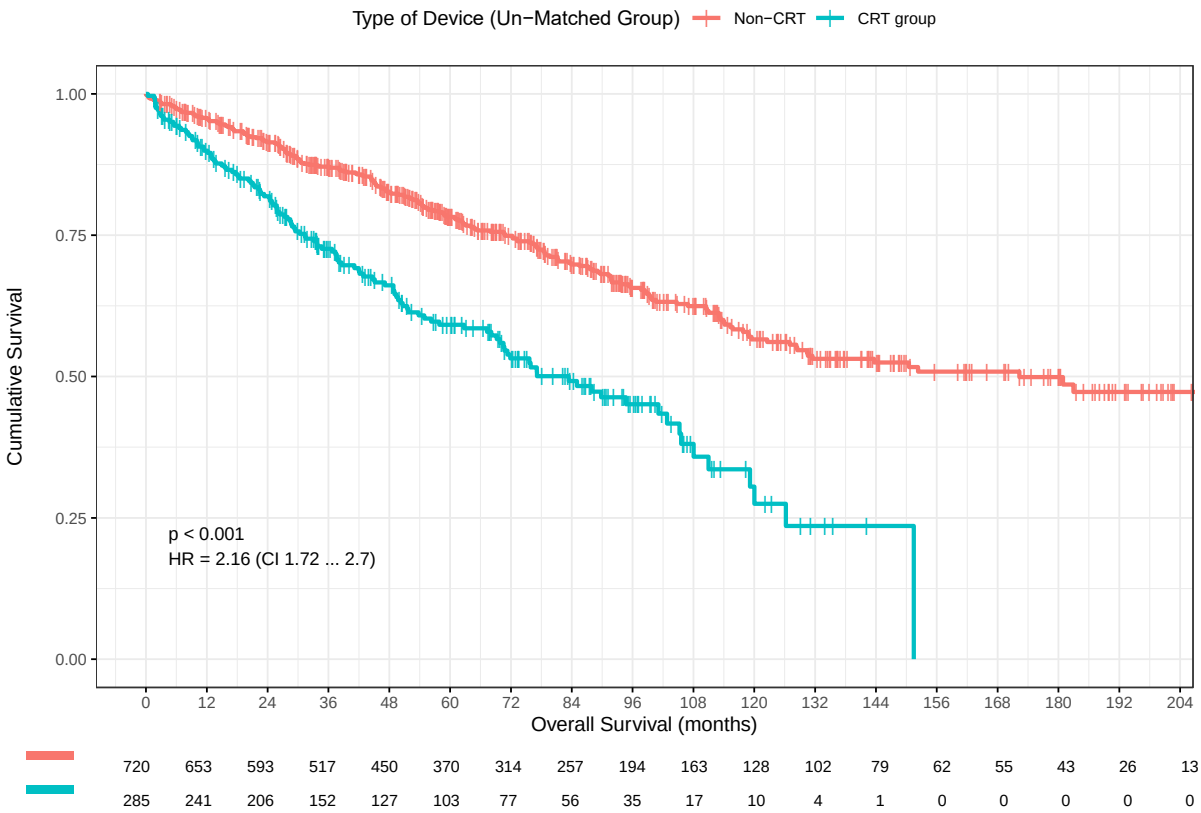
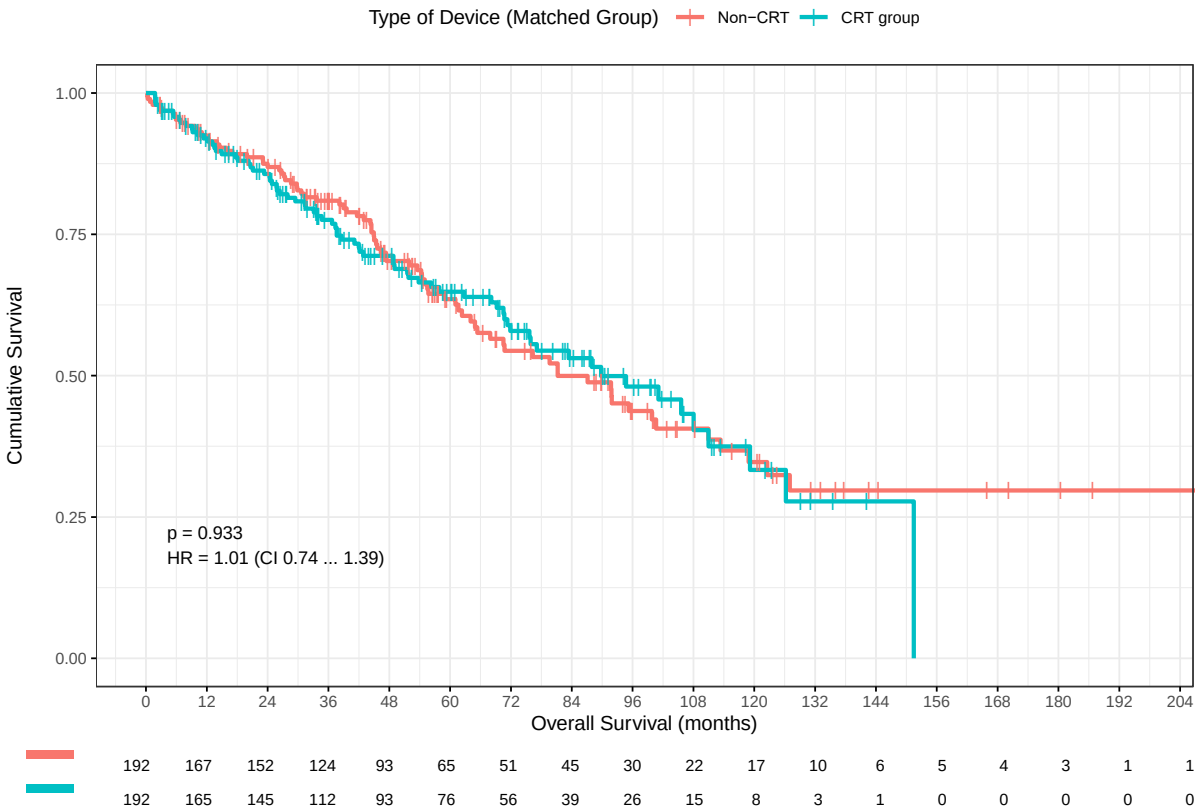
Figures

Figure 1

Kaplan-Meier survival probability for mortality in patients depending on type of device explanted. Figure 1A – unmatched cohort. Figure 1B – Matched group. CRT - Cardiac Resynchronisation Therapy




Type of Device (Matched Group)
Non−CRT
CRT group
Cumulative Survival
1.00
0.75
0.50
0.25
0.00
p = 0.933
HR = 1.01 (CI 0.74 ... 1.39)
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204
Overall Survival (months)
192 167 152 124 93 65 51 45 30 22 17 10 6 5 4 3 1 1
192 165 145 112 93 76 56 39 26 15 8 3 1 0 0 0 0 0

476

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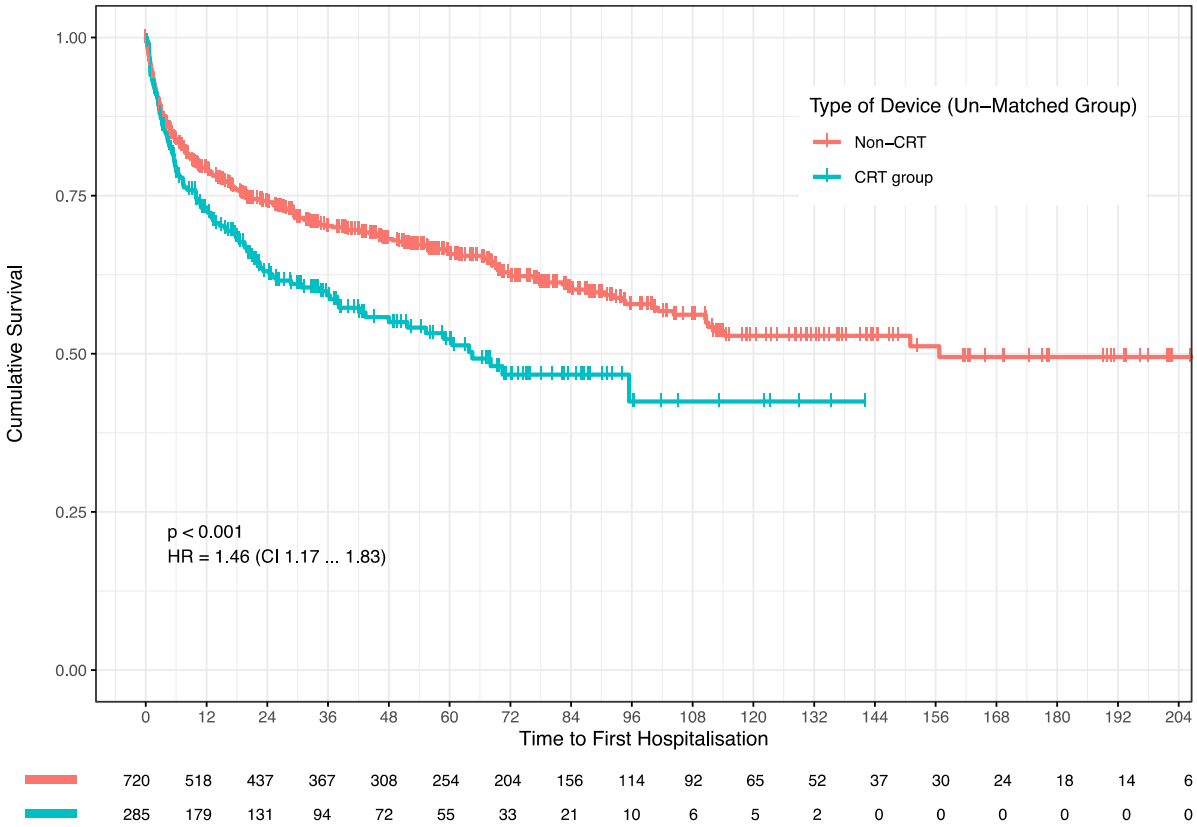
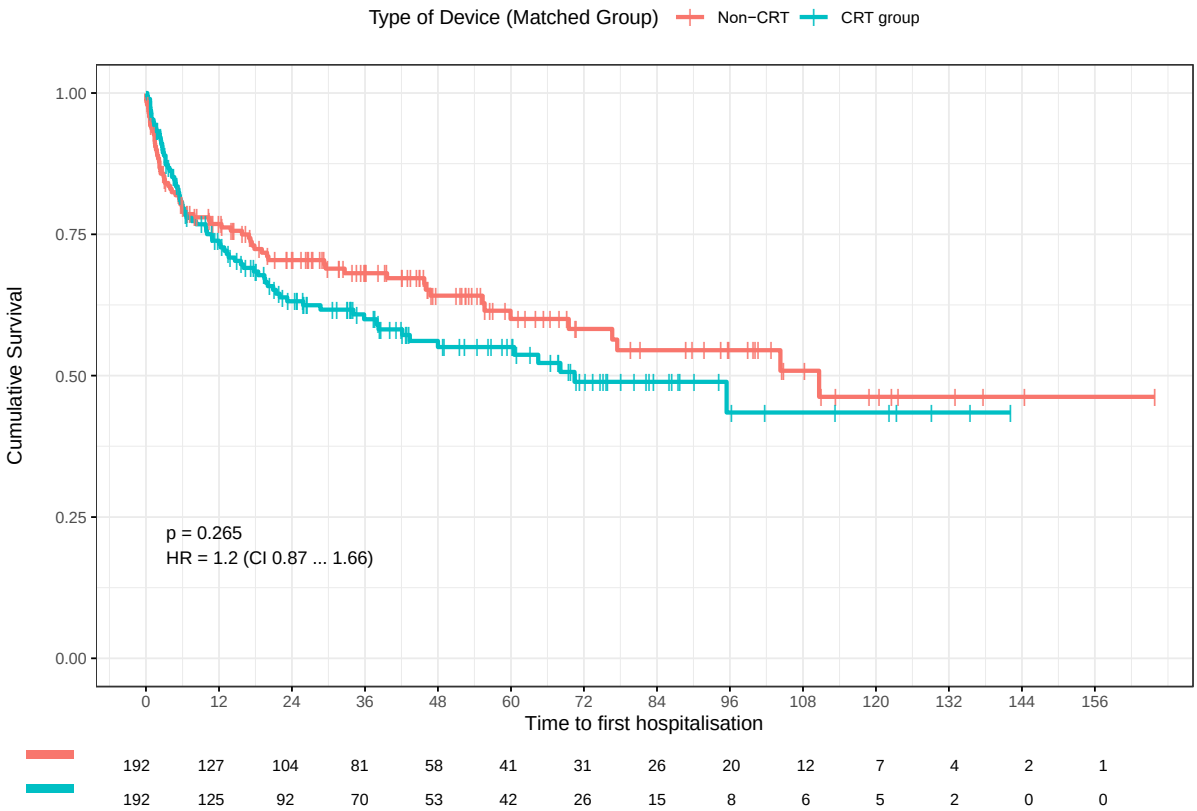
478

Figure 2

Kaplan-Meier survival probability for hospitalisation in patients depending on type of device explanted. Figure 2A – unmatched cohort. Figure 2B – Matched group.




Type of Device (Matched Group)
Non−CRT
CRT group
Cumulative Survival
1.00
0.75
0.50
0.25
0.00
p = 0.265
HR = 1.2 (CI 0.87 ... 1.66)
0
12
24
36
48
60
72
84
96
108
120
132
144
156
Time to first hospitalisation
192 127 104 81 58 41 31 26 20 12 7 4 2 1
192 125 92 70 53 42 26 15 8 6 5 2 0 0

484

485

486

Figure 3

Kaplan-Meier survival probability for mortality in patients depending on timing for reimplantation post TLE in subgroup analysis of matched groups.

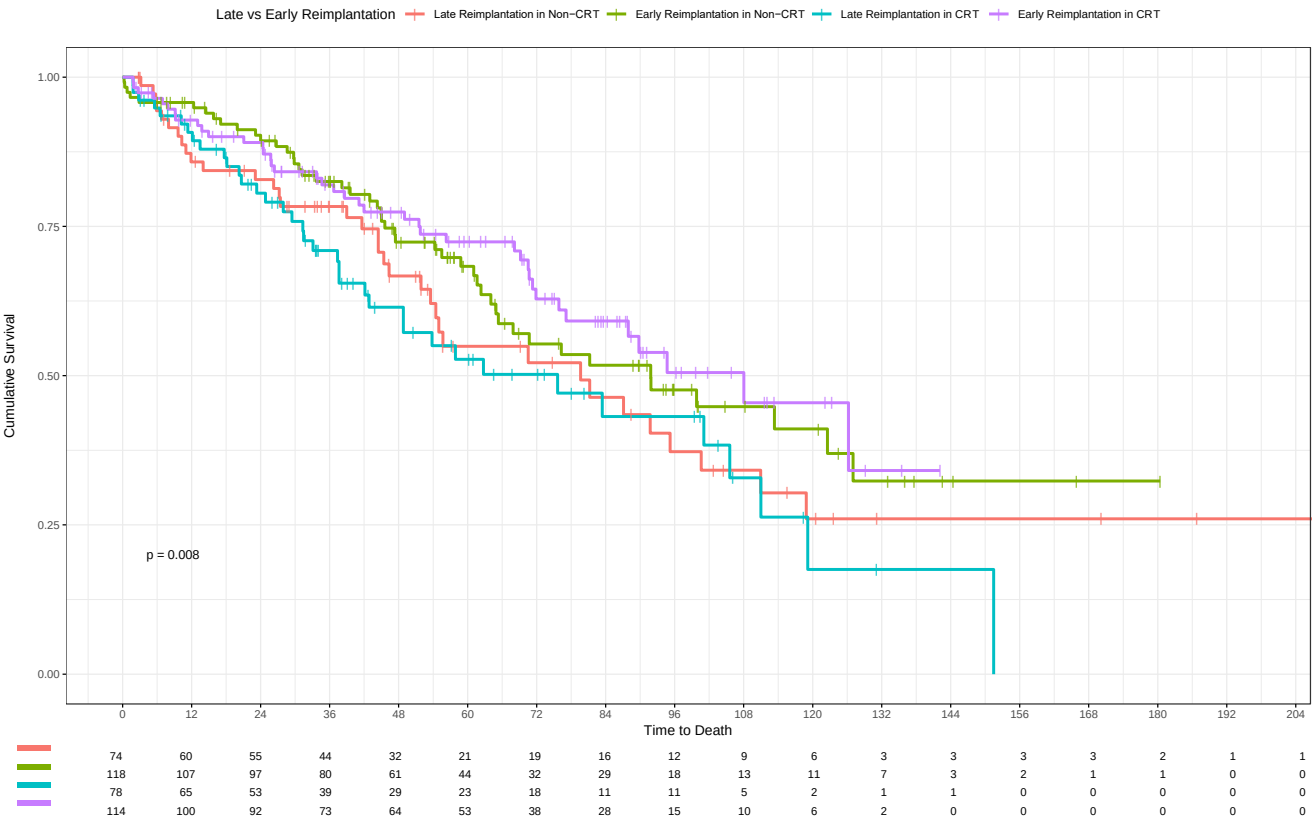


Figure 4

Kaplan-Meier survival probability for hospitalisation in patients depending on timing for reimplantation post TLE in subgroup analysis of matched group.

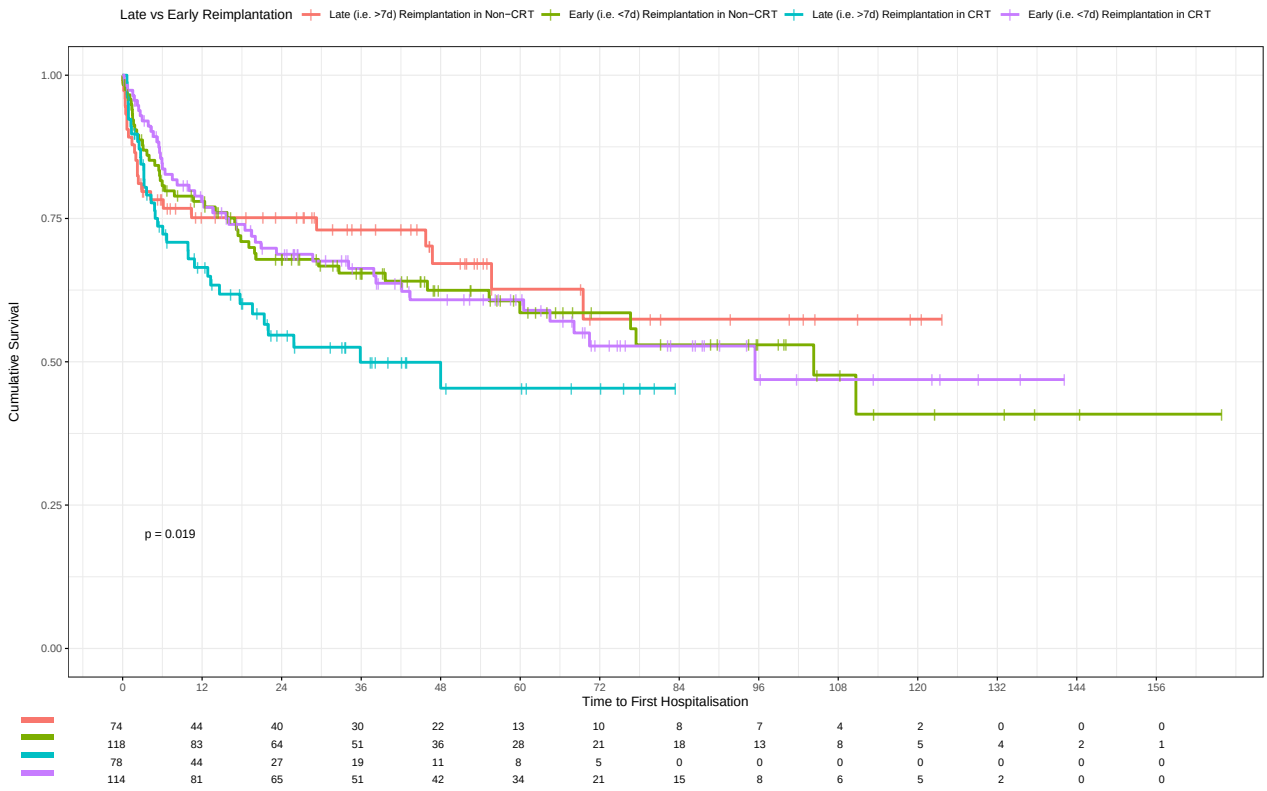
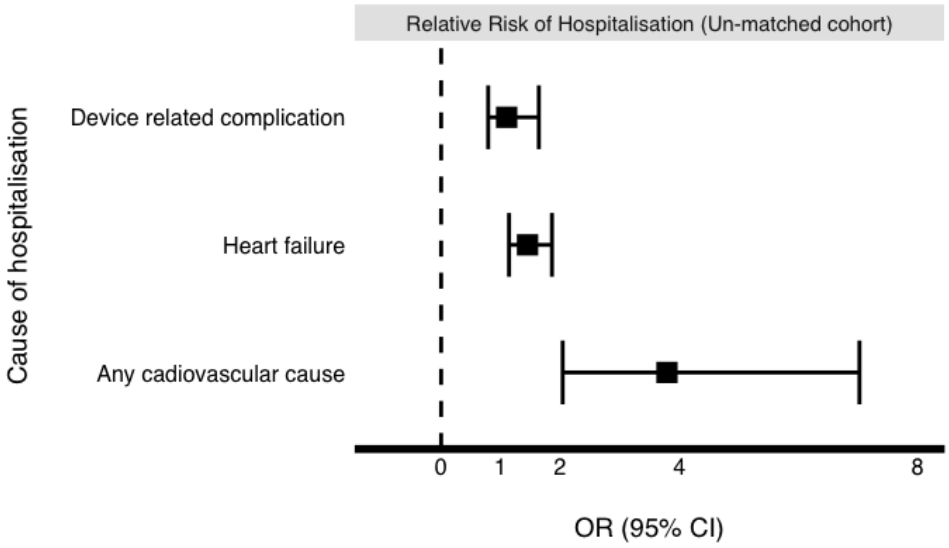


Figure 5

Cause of hospitalisation analysis.



Forest plot assessing relative risk of hospitalisation for a specified cause following TLE in patients with cardiac resynchronisation therapy (CRT) devices compared to non-CRT devices in the un-matched cohorts.