Long-term survival following transvenous lead extraction: unpicking differences according to sex.

Short Title: Sex dependent survival following TLE

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Conflict of interest

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Structured Abstract

Background: Female sex is a recognized risk factor for procedural related major complications including in hospital mortality following transvenous lead extraction (TLE). Long term outcomes following TLE stratified by sex is unclear.

Aim: The purpose of this study was to evaluate factors influencing long-term survival in patients undergoing TLE according to sex.

Methods: Clinical data from consecutive patients undergoing TLE in the reference centre between 2000 and 2019 were prospectively collected. The total cohort was divided into groups based on sex. We evaluated the association of demographic, clinical, device-related and procedure-related factors on long-term mortality.

Results: 1151 patients were included, with mean 66-month follow-up and mortality of 34.2% (n=392). The majority of patients were male (n=834, 72.4%) and 312 (37.4%) died. Males were more likely to die on follow up (HR = 1.58 (1.23-2.02), $p<0.001$). Males had a higher mean age at explant (66.2±13.9 vs 61.3±16.3 years, $p<0.001$), greater mean comorbidity burden (2.14 vs 1.27, $p<0.001$) and lower mean LVEF (43.4±14.0 vs 50.8±12.7, p=0.001). For the female cohort, age>75 years (HR = 3.45 (1.99-5.96), $p<0.001$), eGFR<60 (HR = 1.80 (1.03-3.11), p=0.037), increasing comorbidities (HR = 1.29 (1.06-1.56), p=0.011) and LVEF per percentage increase (HR = 0.97 (0.95-0.99), p=0.005) were all significant factors predicting mortality. The same factors influenced mortality in the male cohort, however the HRs were lower.

Conclusion: Female patients undergoing TLE have more favourable long-term outcomes than males with lower long-term mortality. Similar factors influenced mortality in both groups.

Keywords

Transvenous lead extraction; TLE; Infection; Mortality; Prognosis; Sex

What's new

This is the largest registry analysis of long-term mortality following lead extraction stratified by sex. The main findings from this study are:

- Females have a significantly better survival probability following TLE.
- Males are at higher risk of mortality with an infective indication for TLE.
- Both cohorts had the same risk factors for death, however the hazard ratios were noticeably lower in the male group. This suggests sex plays a disproportionately larger role in influencing survival.

Introduction

The rise in the implantation of cardiac implantable electronic devices (CIEDs) has been mirrored by an increase in the number of procedures required for re-intervention and removal of these devices and associated leads[1]. Transvenous lead extraction (TLE) forms the basis of the removal of infected, redundant, and malfunctioning leads[2]. The European Lead Extraction ConTRolled Registry (ELECTRa) demonstrated a high complete clinical success at 96.7% and an in-hospital major complication rate at 1.7% [3]. Whilst complication rates are low in general, there is a reported increased risk of major complication and difficulty obtaining procedural success following TLE in female patients [4,5]. In the ELECTRA study, female sex was associated with increased procedural related complications and in hospital mortality and clinical failure.[3] Long term mortality following lead extraction in a mixed population has been explored in registry analyses[6] with high rates of mortality on long term follow up in a mixed cohort of patients, with an increased risk of death reported for patients with aged>75 years (HR=2.98), eGFR<60ml/min/1.73m2 (HR=1.67), higher cumulative co-morbidity (HR=1.17) and reduced risk per percentage increase in left ventricular ejection fraction (LVEF) (HR=0.98)[7]. A better understanding of the long-term outcomes following TLE based on sex, has not been extensively explored. Longer term outcomes are important as they can inform decision and consent when deciding to perform TLE. We set out to assess long-term mortality following TLE and predictors of mortality. We studied data from a single, high-volume tertiary referral centre for TLE and potential correlates based on sex subgroups.

Methods

All consecutive patients who survived to discharge 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. 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]. The database collection and analysis were approved by the Institutional Review Board of Guy's and St Thomas' Hospital. The current analysis was split according to sex: i) Female cohort, ii) Male cohort. This study complies with the Declaration of Helsinki.

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Definitions

TLE was defined as per the EHRA and HRS guidelines[9]. The 2017 HRS guidelines defined the extraction indication, procedural success and complication rate [10]. For procedural success definitions see supplement table 1. If any remnants remained in the intravascular space post TLE this was defined as a "radiological success" if <4cm remained in the intravascular space, and a "radiological failure" if >4cm remained. The extraction procedure undertaken at this centre has been described in detail elsewhere[11]. 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[12].

Statistical Analysis

Categorical variables were compared with a chi-squared test or Fisher's exact test. Continuous variables were assessed for normality using an appropriate test. Normally distributed data was analysed using independent samples t-test. Non-normally distributed continuous data was analysed using the Kruskal-Wallis one-way analysis of variance test. The results are presented as mean±standard deviation for normally distributed variables and median [interquartile range (IQR)] for non-normally distributed variables. Categorical variables are presented as number of patients (% of group). Univariable and multivariable cox (proportional hazard) regression was performed to determine predictors of mortality. The results are presented as (Hazard Ratio (HR) [95% Confidence Interval (CI)], p-value). Only factors that met the proportional hazards and linear relations assumption as appropriate were included in the final multivariable analysis. Relevant variables found to be statistically significant at univariable analysis alongside covariates considered clinically important were used in the multivariable analysis. Kaplan-Meier survival curves were formulated to estimate unadjusted survival distributions from death and tested with the log-rank test. Across all statistical tests, a P-value (two-tailed) of ≤0.05 was considered statistically significant. Analyses were performed using R version 2022.12.0+353.

Results

Demographics (Table 1)

A total of 1151 consecutive patients were included. Baseline demographics of the combined male and female cohorts has been described in detail previously[7]. For reference, the baseline demographics of the total cohort is in supplement table 2. Overall, the majority of patients undergoing TLE were male (n=834, 72.4%). Males had a higher mean age at explant (66.2±13.9 vs 61.3±16.3 years, p<0.001), greater mean comorbidity burden (2.14 vs 1.27, p<0.001), lower mean LVEF (43.4±14.0 vs 50.8±12.7), higher mean leads extracted per procedure (2.14 vs 1.86, p=0.001) and more had extraction for local infection (n=329, 39.5% vs n=94, 29.7%, p=0.003). Lead dwell time was similar between males and females (5.30 (1.80-9.50) vs 5.80 (1.78-11.3) years, p=0.422). The most common indication for original device implantation was primarily pacing (males: n=373, 44.7%; females: n=187, 59.0%, p<0.001). Amongst males, the most common comorbidities were ischaemic heart disease (IHD) (n=365, 45.3%), heart failure (HF) (n=354, 43.9%) and hypertension (HTN) (n=332, 41.8%). Amongst females, the most common comorbidities were HTN (n=102, 33.2%), HF (n=64, 20.9%), and IHD (n=60, 19.6%).

Success rate and in hospital complications

Clinical success was achieved in 99.1% of females and was similar to males at 98.9%. Similarly, radiological success was similar between the groups at 96.6% for females and 96.4% for males. The incidence of major complications was not significantly higher in females (male: n=14, 1.7%; female: n=8, 2.5%, p=0.487), however minor complications were significantly higher in the female group (n=38, 12% vs n=61, 7.3%, p=0.016).

Mortality at follow-up

Within the male cohort, patients were more likely to die on follow up (HR = 1.58 (1.23-2.02), p<0.001). Mean follow up for the male group was 4.96±4.02 years, and 312 (37.4%) died. Kaplan-Meier survival analysis demonstrated a survival probability of 95.4% at 6 months, 92.4% at 1 year, 87% at 2 years, 70.9% at 5 years and 46.5% at 10 years (Figure 1). Male patients who died were more likely to be older (72.2±10.7 vs 62.6±14.3 years, p<0.001), have shorter lead dwell time (57.65 [16.5-98.0] vs 66.40 [23.0-120.5] months, p<0.001), more LV leads extracted (p=0.003), lower mean LVEF (38.7±13.8 vs 46.2±13.4, p<0.001), higher mean co-morbidity burden (2.75 vs 1.78, p<0.001), and an infective indication for extraction (n=287, 55.0% vs n=200, 64.1%, p=0.012).

Within the female cohort, patients were less likely to die on follow up (HR = 0.63 (0.5-0.81), p<0.001) despite a higher rate of in-hospital complications. Mean follow up for the female group was longer (5.39±4.66 years), and fewer died (n=80, 25.3%). Kaplan-Meier survival analysis demonstrated a better survival probability of 96.5% at 6 months, 94.5% at 1 year, 90.3% at 2 years, 80.4% at 5 years and 65.1% at 10 years (Figure 1). Females who died were more likely to be older (57.3±15.3 vs 73.1±12.8 years, p<0.001), have shorter lead dwell times (p=0.009), lower LVEF (46.3±15.0 vs 52.3±11.5, p=0.001) and a higher mean co-morbidity burden (1.80 vs 1.09, p<0.001).

When comparing all patients who died at follow up, males were more likely to have a higher mean comorbidity burden (p=0.001), HF indication for their device (p=0.003), lower LVEF (p<0.001), a dual coil defibrillator lead extracted (p=0.025), and worse baseline creatinine level (109.00 [90.00, 141.00] vs 90.00 [73.00, 123.25] µmol/L, p<0.001) than females. Male and female patients who died had a similar mean age (72.18±10.74 vs 73.15±12.83 years, p=0.491), suggesting age at explant was not a significant factor determining death.

Univariable analysis of long-term survival

On univariable cox regression analysis, older age at explant, eGFR<60, increasing LV leads extracted, burden of comorbidities, lower LVEF, shorter lead dwell time and any heart failure indication for device implantation all correlated with mortality in the female cohort (table 2).

The impact of increasing age (HR = 3.4 (2.7-4.2), p<0.001, renal function (HR = 2.9 (2.3-3.6), p<0.001) was less pronounced in the male cohort. Infection was a significant mortality risk in the male cohort (HR = 1.3 (1.1-1.7), p=0.016) (figure 2). The impact of lead burden was significant in the male cohort (total leads extracted: HR = 1.3 (1.1-1.4), p<0.001; LV leads extracted: HR = 1.8 (1.4-2.2), p<0.001). The burden of comorbidities was associated with significantly higher risk of death in the female vs male group (1 vs 0 CM, HR = 2.9 vs 1.61, p<0.001; 4-7 CMs, HR = 6.29 vs 5.96, p<0.001) (figure 3).

Multivariable analysis of long-term survival (figure 4)

Factors considered clinically important and those close to and reaching statistical significance (Table 2) were included in the multivariable cox regression model to predict mortality after TLE. For the female cohort, age>75 years (HR = 3.45 (1.99-5.96), p<0.001), eGFR<60 (HR = 1.80 (1.03-3.11), p=0.037), increasing comorbidities (HR = 1.29 (1.06-1.56), p=0.011) and LVEF per percentage increase (HR = 0.97 (0.95-0.99), p=0.005) were all significant factors predicating mortality. In the male cohort, age>75 years (HR = 2.83 (2.18-3.66), p<0.001), eGFR<60 (HR = 1.68 (1.28-2.20), p<0.001), increasing comorbidities (HR = 1.16 (1.07-1.25), p<0.001), and LVEF (HR = 0.98 (0.97-0.99), p<0.001) were significant predictors for mortality.

Discussion

This is the largest registry analysis of long-term mortality following lead extraction stratified by sex. The main findings from this study are:

1. Females have a significantly better survival probability following TLE.
2. Males are at higher risk of mortality with an infective indication for TLE.
3. Both cohorts had the same risk factors for death, however the hazard ratios were noticeably lower in the male group. This suggests sex plays a disproportionately larger role in influencing survival.

Comparison with previous studies

Most published studies relate to the short term and procedural risks based on sex following TLE. The largest such study was a post-hoc analysis of the ELECTRa registry of 3555 patients. The baseline demographics based on sex of the data presented in this study, is very similar to the multicentre ELECTRa dataset. Compared to our dataset, the ELECTRa population had similar mean ages at explant (females: 63.3 vs 61.3, males: 65.5 vs 66.2 years), LVEF (females: 51.0 vs 50.8, males: 43.4 vs 43.4 per cent), and rates of infection (females: 42.6 vs 45.7, males: 57.4 vs 58.4%). The ELECTRa analysis observed a higher rate of major complications (1.96 vs 0.71%, p=0.0025) and lower procedural success (98.14 vs 99.21%, p=0.0098) amongst women [5]. Another analysis of the registry demonstrated that females were at greater risk of major cardiac and vascular complications following TLE[13]. Similarly, a nationwide database study by Deshmukh et al, identified increased risk of early adverse outcomes associated with female sex (HR = 1.19 (1.12-1.26), p<0.001)[14]. The EROS risk score based on the ELECTRa registry suggested female patients were more likely to be in the lower risk category of for complications[15,] and further analysis shows no difference between sex whether the procedure is performed in a high or low volume centre[16]. 30-day all-cause mortality was assessed by Brunner et al of approximately 3000 TLE procedures, and no significant sex differences were noted[17]. Prior studies specifically evaluating long term mortality by Deharo (n=197, HR = 0.78 (0.41-1.47), p=0.439)[18] and Habib et al (n=415, HR = 1.06 (0.74-1.50), p=0.76) [19] showed no difference in long term mortality based on sex however these were relatively small studies in relation to the current study. A larger retrospective study of >1000 procedures by Maytin showed no significant adjusted risk based on male sex (HR = 0.94 (0.64-1.39), p=0.77)[6]. It is important to note that previous studies evaluated survival in a mixed cohort (i.e., males and females combined), and the current study is the first to determine the different factors influencing survival in each group.

Differences in factors influencing mortality

In general, the male cohort represented an older and more comorbid demographic. The same factors significantly influenced mortality in both groups on multivariable analysis. Notably, all the shared factors were less hazardous in the male group. For example, age>75 years old represented a 3.45 increased risk in females compared with males which was 2.83. A similar observation was observed in eGFR<60 (HR =

1.80 vs 1.68), per additional comorbidity (HR = 1.29 vs 1.16) and per percentage in LVEF (HR = 0.97 vs 0.98).

In addition, males were at significantly increased risk of death if there was an infective indication for the TLE on univariable analysis (HR = 1.3 (1.1-1.7), p=0.016). This was reflected by a higher incidence of positive microbiology (n=333, 68.4% vs n=78, 53.8%, p=0.002), and lead cultures following TLE (n=221, 45.4% vs n=51, 35.2%, p=0.037). This is likely due to the higher incidence of comorbidities, particularly CKD (n=167, 20.6% vs n=41, 13.2%, p=0.005) in males.

Procedure related factors

It is established that female patients have lower rates of clinical success, which may reflect difference in the size of the vascular system and differing lead management strategies including an inclination to abandon leads[20]. The current analysis does not clearly link any procedural factors as influencing survival in the longer term. As this study follows up a large number of patients for a long period of time coupled with the low rates of major complication and procedure related death, over the long term, factors related to their CIED and leads may be less relevant to their overall survival. This suggests that comorbidities and patient demographics are more influential to survival.

Study Limitations

The findings of our study are limited by the inherent issues identified with observational studies, namely the possibility of unidentified confounders. Predictors of long-term mortality for the group were discussed, however the cause-and-effect relationship remain associative. We opted to only include patients who survived to discharge, which may have introduced survival bias, however only 20 patients (1.7%) did not survive to discharge. To mitigate this, a model taking into account the competing risk of death was also performed, with no significant difference in the results (see supplementary figure 1). Whilst our cohort was large, there was limited power to detect small differences in mortality, and the female cohort was smaller than the male cohort resulting in marginally larger confidence intervals. Therefore, there is greater doubt with respect to the true hazard ratios. 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, however the demographics of the study subjects is reflective of other major multicentre studies. Causes of death in these patients is unknown and data specifically related to the hospitalisation period, in particular duration of inpatient stay was not available as part of the current analysis.

Conclusion

This study is the largest study to evaluate long term outcomes following lead extraction stratified by sex. The literature demonstrates increased procedure related risk and in hospital mortality for females. The current study suggests that long term outcomes for females following TLE are better in comparison to their male counterparts. This is likely accounted for by lower age, comorbidity burden and lower incidence of infection in females, however our analysis suggests that male sex may independently predict worse outcomes following TLE.

Figure 1

Kaplan-Meier survival probability in patients stratified by sex.

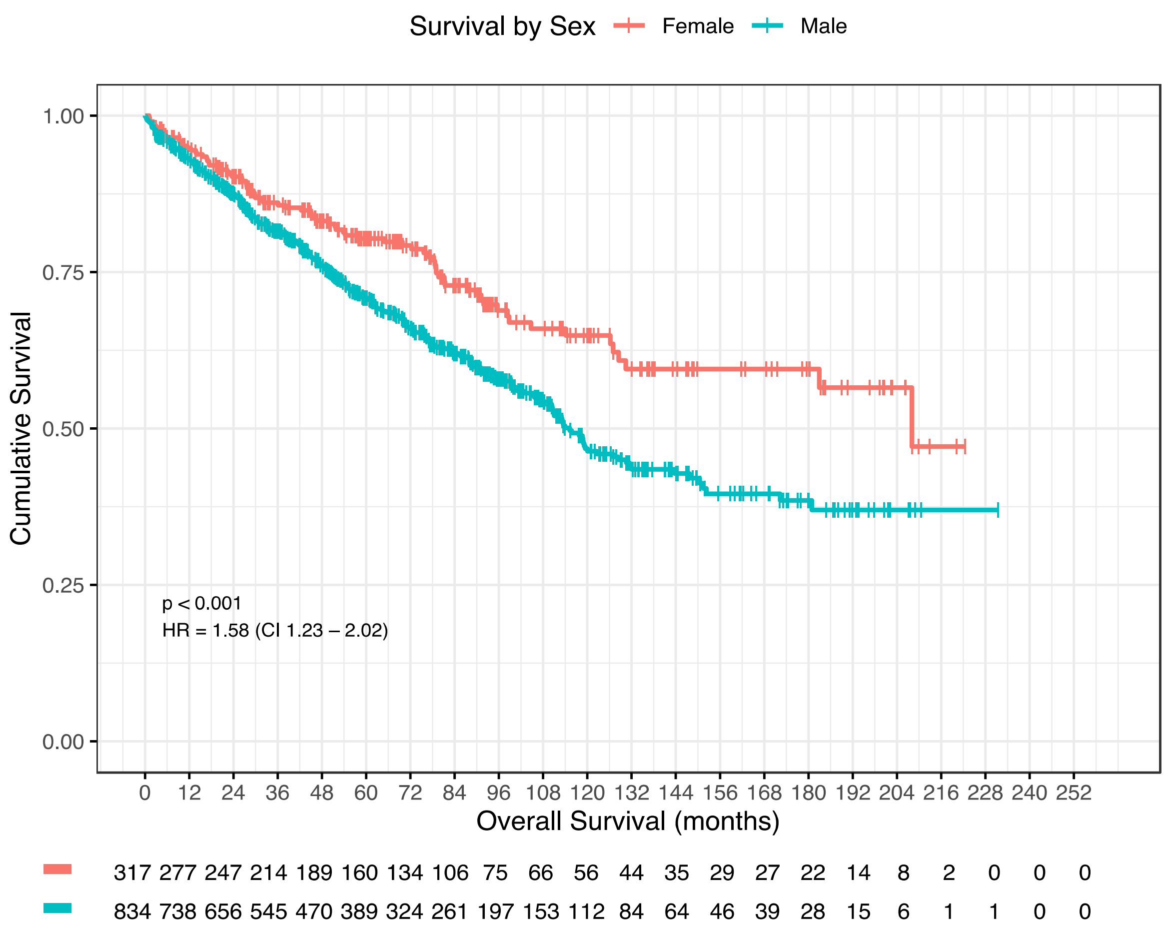


Figure 2

Kaplan-Meier survival probability in patients stratified by indication for TLE. Female cohort (A) and male cohort (B).

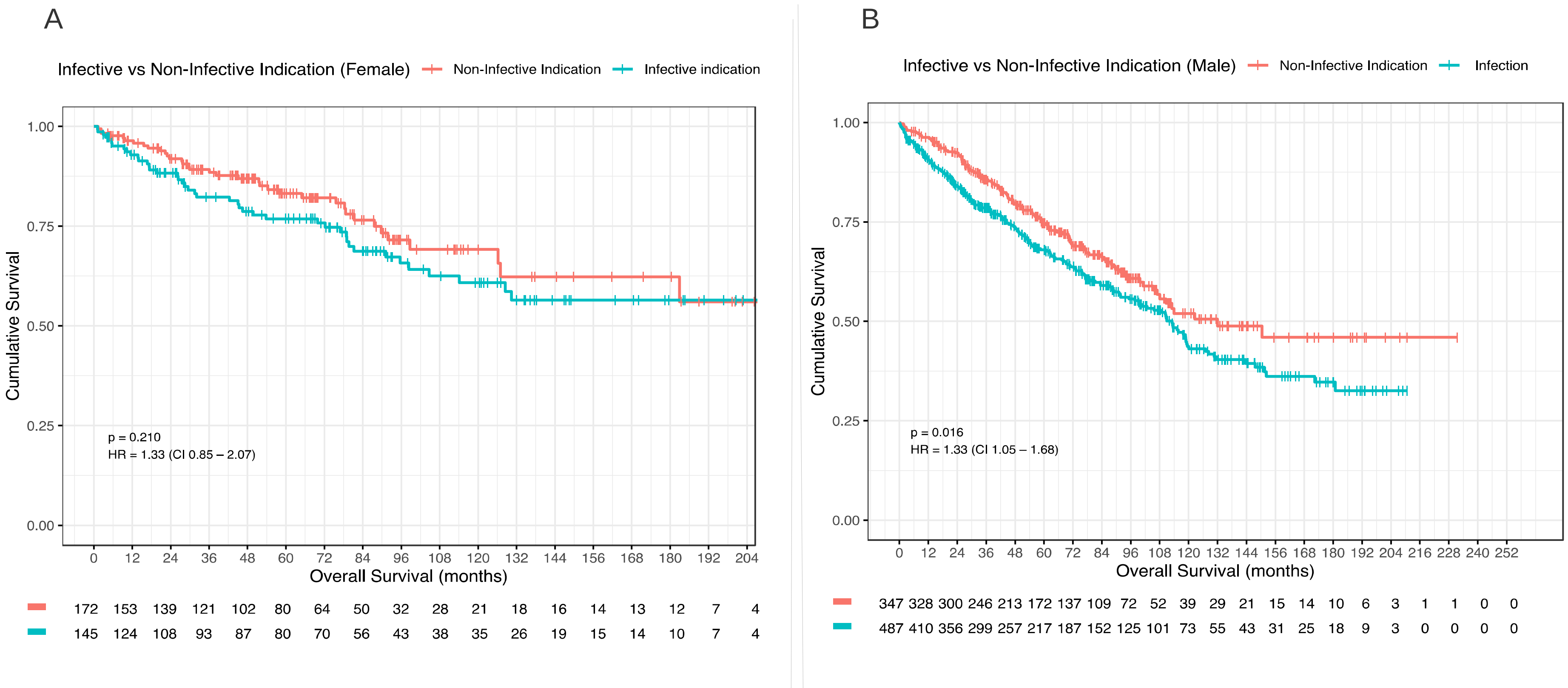


Figure 3

Kaplan-Meier survival probability in patients stratified by comorbidities. Female cohort (A) and male cohort (B).

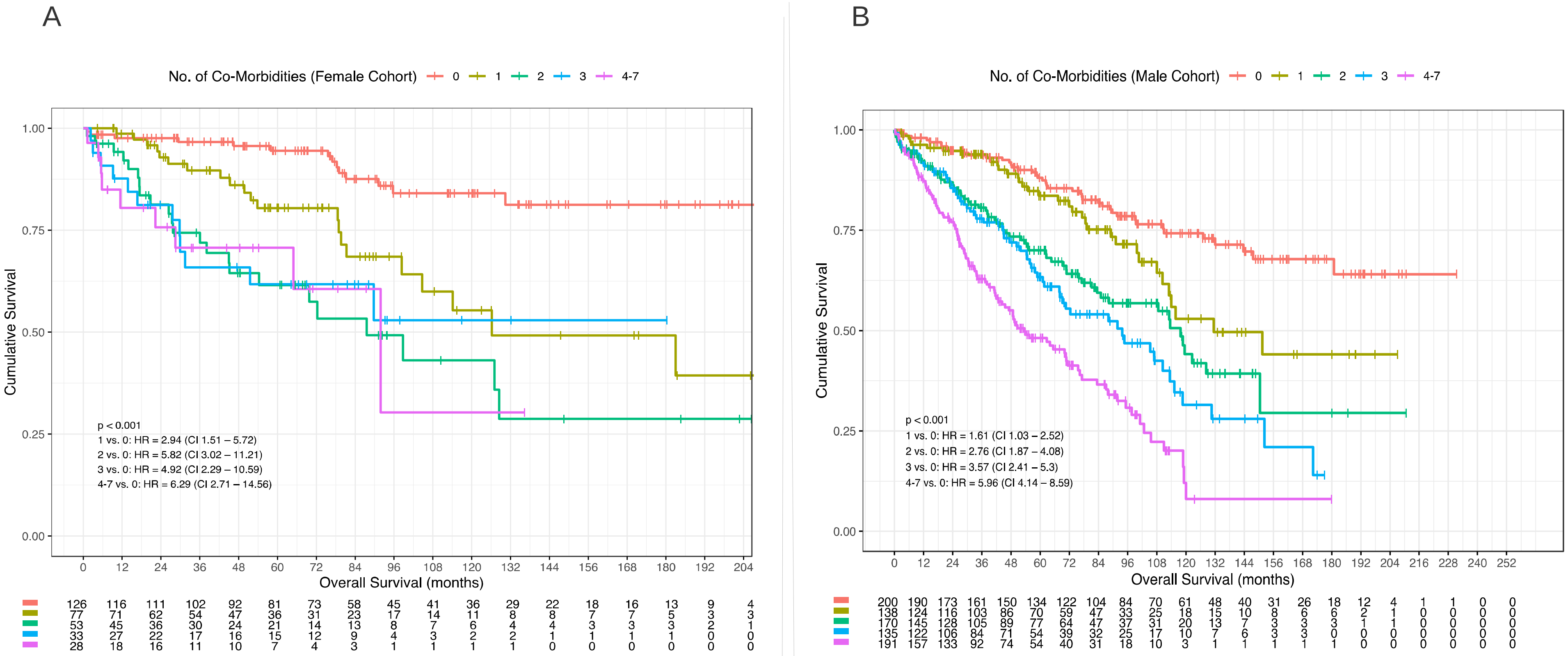


Figure 4

Multivariable cox proportional hazards regression models (p<0.001) to predict mortality after TLE in the female (A) and male (B) cohorts.

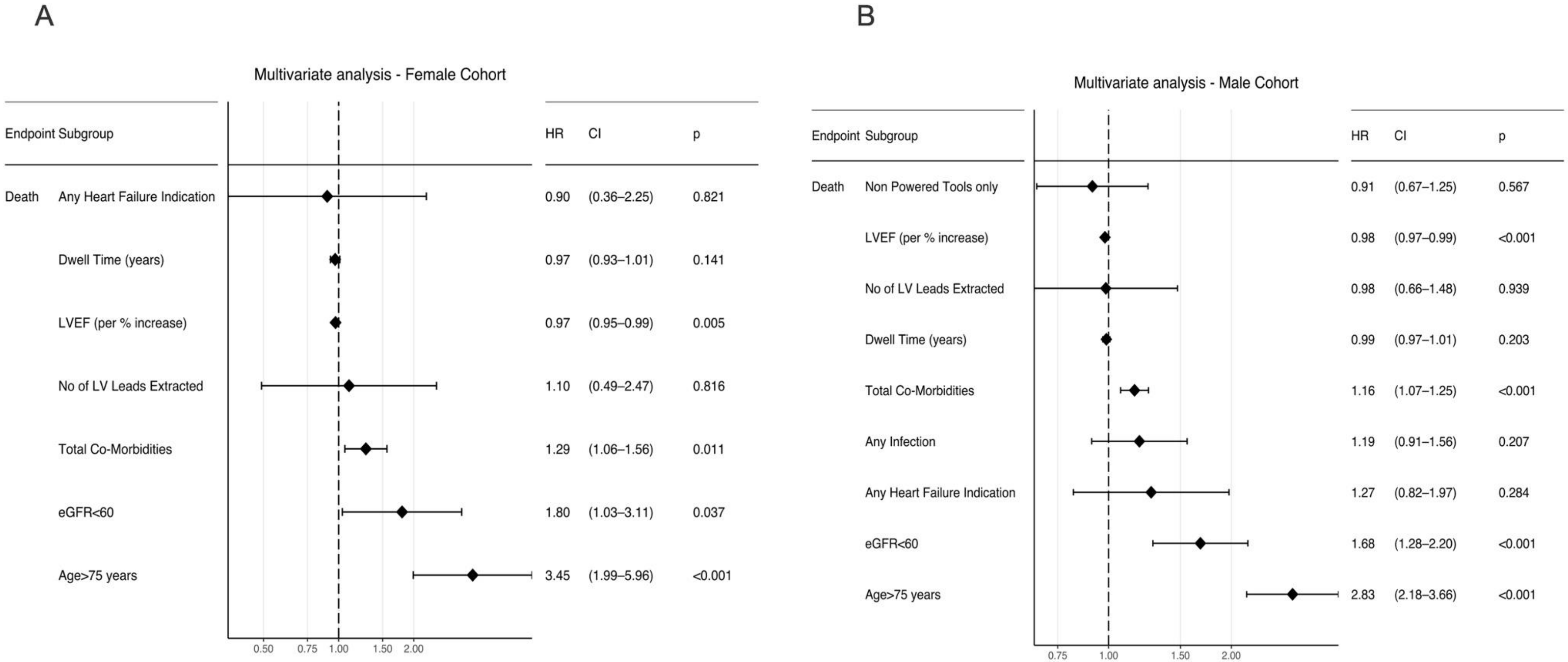


Table 1

Baseline characteristics.

	Male				**Female**					
	Total	**Alive**	**Dead**	**p-value***	**Total**	**Alive**	**Dead**	**p-value†**	**p-value‡**	**p-value§**
Total Number of Patients	834	522	312		317	237	80			
Follow up time in years (mean (SD))	4.96 (4.02)	5.77 (4.24)	3.61 (3.18)	<0.001	5.39 (4.52)	5.99 (4.66)	3.62 (3.57)	<0.001	0.969	0.12
Follow up time in months (median [IQR])	56.00 [27.00, 94.00]	67.50 [33.00, 102.00]	41.00 [17.00, 72.00]	<0.001	60.00 [27.00, 94.00]	68.00 [33.00, 103.00]	34.00 [15.75, 78.25]	<0.001	0.834	0.316
Age										
Explant Age in Years (mean (SD))	66.18 (13.88)	62.59 (14.30)	72.18 (10.74)	<0.001	61.30 (16.25)	57.30 (15.33)	73.15 (12.83)	<0.001	0.491	<0.001
>75 years old	253 (30.3)	102 (19.5)	151 (48.4)	<0.001	75 (23.7)	34 (14.3)	41 (51.2)	<0.001	0.741	0.03
Dwell Time										

Dwell Time in Months (median [IQR])	62.40 [20.85, 113.05]	66.40 [23.00, 120.50]	57.65 [16.45, 97.97]	0.009	65.60 [16.02, 135.52]	76.20 [21.80, 144.60]	38.30 [12.50, 95.10]	0.009	0.204	0.514
Dwell Time in Years (median [IQR])	5.30 [1.80, 9.50]	5.70 [2.00, 10.07]	3.61 (3.18)	0.008	5.80 [1.78, 11.33]	6.60 [2.08, 12.22]	3.62 (3.57)	0.008	0.969	0.422
Type of infection										
Any Infection	487 (58.4)	287 (55.0)	200 (64.1)	0.012	145 (45.7)	101 (42.6)	44 (55.0)	0.07	0.171	<0.001
Local Infection	329 (39.5)	194 (37.2)	135 (43.3)	0.099	94 (29.7)	62 (26.3)	32 (40.0)	0.029	0.689	0.003
Systemic Infection	158 (19.0)	93 (17.9)	65 (20.8)	0.331	51 (16.1)	39 (16.5)	12 (15.0)	0.896	0.311	0.296
Non-Infective Indication										
Lead Dysfunction (%)	236 (28.3)	158 (30.3)	78 (25.0)	0.12	113 (35.6)	86 (36.3)	27 (33.8)	0.784	0.151	0.019
Functional Lead (%)	23 (2.8)	16 (3.1)	7 (2.3)	0.625	8 (2.5)	8 (3.4)	0 (0.0)	0.208	0.378	0.991
Lead Complication (%)	62 (7.4)	37 (7.1)	25 (8.0)	0.722	16 (5.0)	13 (5.5)	3 (3.8)	0.751	0.281	0.191
Lead Access (%)	33 (4.0)	23 (4.4)	10 (3.2)	0.487	16 (5.1)	11 (4.7)	5 (6.2)	0.797	0.35	0.514
Lead Pain (%)	7 (0.8)	6 (1.2)	1 (0.3)	0.377	8 (2.5)	8 (3.4)	0 (0.0)	0.208	1	0.05
Other indication (%)	71 (8.5)	43 (8.2)	28 (9.0)	0.81	34 (10.7)	29 (12.2)	5 (6.2)	0.198	0.577	0.294
Lead Type and number										

Single Coil Defibrillator Leads (%)				0.069				0.191	0.048	0.232
1	171 (20.5)	98 (18.8)	73 (23.4)		57 (18.0)	47 (19.8)	10 (12.5)			
2	5 (0.6)	5 (1.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)			
Dual Coil Defibrillator Leads (%)				0.216				0.182	0.025	0.002
1	187 (22.4)	111 (21.3)	76 (24.4)		43 (13.6)	34 (14.3)	9 (11.2)			
2	8 (1.0)	7 (1.3)	1 (0.3)		1 (0.3)	0 (0.0)	1 (1.2)			
No. of LV leads (%)				0.003				0.129	0.032	<0.001
1	194 (23.3)	100 (19.2)	94 (30.1)		31 (9.8)	18 (7.6)	13 (16.2)			
2	8 (1.0)	6 (1.1)	2 (0.6)		1 (0.3)	1 (0.4)	0 (0.0)			
3	1 (0.1)	1 (0.2)	0 (0.0)		1 (0.3)	1 (0.4)	0 (0.0)			
Total Leads Extracted (%)*	1785	*1108*	*706*	0.103	*590*	*438*		0.695	0.187	0.001
1	190 (22.8)	145 (27.8)	74 (23.7)		100 (31.5)	74 (31.2)	3 (3.8)			
2	355 (42.6)	228 (43.7)	127 (40.7)		150 (47.3)	117 (49.4)	26 (32.5)			
3	180 (21.6)	105 (20.1)	75 (24.0)		42 (13.2)	29 (12.2)	33 (41.2)			
4	62 (7.4)	34 (6.5)	28 (9.0)		11 (3.5)	7 (3.0)	13 (16.2)			

5	13 (1.6)	6 (1.1)	7 (2.2)		4 (1.3)	3 (1.3)	4 (5.0)			
6	3 (0.4)	2 (0.4)	1 (0.3)		0 (0.0)	0 (0.0)	1 (1.2)			
7	2 (0.2)	2 (0.4)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)			
Indication for CIED										
Primary Prevention	82 (9.8)	58 (11.1)	24 (7.7)	0.138	31 (9.8)	26 (11.0)	5 (6.2)	0.312	0.841	1
Secondary Prevention	171 (20.5)	119 (22.8)	52 (16.7)	0.042	62 (19.6)	49 (20.7)	13 (16.2)	0.484	1	0.784
Any Pacing Indication	373 (44.7)	244 (46.7)	129 (41.3)	0.148	187 (59.0)	139 (58.6)	48 (60.0)	0.633	0.004	<0.001
Any HF indication	234 (28.1)	122 (23.4)	112 (35.9)	<0.001	34 (10.7)	20 (8.4)	14 (17.5)	0.04	0.003	<0.001
Echocardiographic Findings										
LVEF (mean (SD))	43.39 (13.99)	46.21 (13.37)	38.70 (13.75)	<0.001	50.76 (12.66)	52.23 (11.47)	46.34 (14.96)	0.001	<0.001	<0.001
Presence of Vegetation	63 (7.6)	42 (8.0)	21 (6.7)	0.575	26 (8.2)	23 (9.7)	3 (3.8)	0.149	0.465	0.807
Vegetation >10mm	26 (3.1)	20 (3.8)	6 (1.9)	0.184	11 (3.5)	11 (4.6)	0 (0.0)	0.108	0.46	0.908
Pacing Lead Vegetation	50 (6.0)	35 (6.7)	15 (4.8)	0.334	18 (5.7)	16 (6.8)	2 (2.5)	0.254	0.551	0.949
Co-Morbidities										
Ischaemic Heart Disease	365 (45.3)	186 (36.9)	179 (59.5)	<0.001	60 (19.6)	37 (16.0)	23 (30.7)	<0.001	<0.001	<0.001

CABG	132 (16.5)	57 (11.3)	75 (25.1)	<0.001	11 (3.6)	8 (3.4)	3 (4.0)	<0.001	<0.001	<0.001
Valve Disease	77 (9.6)	35 (7.0)	42 (14.0)	0.002	34 (11.1)	23 (10.0)	11 (14.7)	0.002	1	0.52
Heart Failure	354 (43.9)	187 (37.0)	167 (55.5)	<0.001	64 (20.9)	39 (16.9)	25 (33.3)	<0.001	0.001	<0.001
Diabetes Mellitus	134 (16.8)	73 (14.5)	61 (20.7)	0.031	40 (13.0)	32 (13.8)	8 (10.7)	0.031	0.067	0.144
Hypertension	332 (41.8)	194 (38.6)	138 (47.1)	0.024	102 (33.2)	65 (28.0)	37 (49.3)	0.024	0.829	0.011
Peripheral Vascular Disease	40 (5.0)	17 (3.4)	23 (7.8)	0.009	3 (1.0)	2 (0.9)	1 (1.3)	0.009	0.076	0.003
Stroke	74 (9.3)	40 (8.0)	34 (11.5)	0.12	13 (4.2)	9 (3.9)	4 (5.3)	0.12	0.172	0.008
Chronic Respiratory Disease	112 (14.1)	66 (13.2)	46 (15.6)	0.399	35 (11.4)	23 (9.9)	12 (16.0)	0.399	1	0.284
Chronic Kidney Disease	167 (20.6)	73 (14.4)	94 (31.2)	<0.001	41 (13.2)	21 (9.0)	20 (25.6)	<0.001	0.412	0.005
Total Number of co-morbidities (%)*				<0.001				<0.001	0.001	<0.001
0	200 (24.0)	157 (30.1)	43 (13.8)		126 (39.7)	111 (46.8)	15 (18.8)			
1	138 (16.5)	103 (19.7)	35 (11.2)		77 (24.3)	56 (23.6)	21 (26.2)			
2	170 (20.4)	106 (20.3)	64 (20.5)		53 (16.7)	30 (12.7)	23 (28.7)			
3	135 (16.2)	73 (14.0)	62 (19.9)		33 (10.4)	21 (8.9)	12 (15.0)			
4	101 (12.1)	44 (8.4)	57 (18.3)		20 (6.3)	15 (6.3)	5 (6.2)			
5	47 (5.6)	20 (3.8)	27 (8.7)		7 (2.2)	4 (1.7)	3 (3.8)			

6	36 (4.3)	15 (2.9)	21 (6.7)		1 (0.3)	0 (0.0)	1 (1.2)			
7	7 (0.8)	4 (0.8)	3 (1.0)		0 (0.0)	0 (0.0)	0 (0.0)			
Pre extraction biochemistry										
Creatinine Level (median [IQR])	98.00 [83.00, 123.00]	92.00 [80.00, 112.00]	109.00 [90.00, 141.00]	<0.001	75.00 [65.00, 91.50]	71.00 [63.00, 83.50]	90.00 [73.00, 123.25]	<0.001	<0.001	<0.001
eGFR (mean (SD))	66.91 (21.30)	72.07 (18.87)	58.29 (22.34)	<0.001	68.42 (21.15)	73.16 (18.34)	54.38 (22.74)	<0.001	0.164	0.285
eGFR<60	264 (31.7)	121 (23.2)	143 (45.8)	<0.001	88 (27.8)	47 (19.8)	41 (51.2)	<0.001	0.459	0.227
Peak CRP (median [IQR])	6.00 [2.00, 18.00]	5.00 [1.00, 14.00]	8.00 [4.00, 25.00]	0.001	6.00 [2.50, 14.50]	6.00 [2.00, 14.75]	7.00 [5.00, 14.00]	0.353	0.597	0.731
Microbiology Results (for infective group only)										
Positive Microbiology	333 (68.4)	217 (75.6)	116 (58.0)	<0.001	78 (53.8)	56 (55.4)	22 (50.0)	0.672	0.423	0.002
Positive Blood Cultures	108 (22.2)	80 (27.9)	28 (14.0)	<0.001	28 (19.3)	20 (19.8)	8 (18.2)	1	0.636	0.534
Positive Swab Cultures	129 (26.5)	71 (24.7)	58 (29.0)	0.345	29 (20.0)	19 (18.8)	10 (22.7)	0.752	0.513	0.14

Positive Lead Cultures	221 (45.4)	135 (47.0)	86 (43.0)	0.431	51 (35.2)	35 (34.7)	16 (36.4)	0.993	0.523	0.037
Previous Device Procedures										
History of Previous Extraction	96 (11.5)	62 (11.9)	34 (10.9)	0.751	32 (10.1)	25 (10.5)	7 (8.8)	0.805	0.722	0.563
No. of Previous Device Interventions				0.538				0.924	0.84	0.755
0	737 (88.5)	459 (88.1)	278 (89.1)		285 (89.9)	212 (89.5)	73 (91.2)			
1	58 (7.0)	40 (7.7)	18 (5.8)		18 (5.7)	14 (5.9)	4 (5.0)			
2	37 (4.4)	21 (4.0)	16 (5.1)		13 (4.1)	10 (4.2)	3 (3.8)			
3 or more	1 (0.1)	1 (0.2)	0 (0.0)		1 (0.3)	1 (0.4)	0 (0.0)			
Extraction Tools*										
Manual Traction Only (%)	156 (18.7)	104 (19.9)	52 (16.7)	0.282	63 (19.9)	42 (17.7)	21 (26.2)	0.136	0.071	0.713
Non-powered only (%)	151 (18.1)	76 (14.6)	75 (24.0)	0.001	55 (17.4)	40 (16.9)	15 (18.8)	0.832	0.393	0.832
Powered Only (%)	99 (11.9)	59 (11.3)	40 (12.8)	0.586	20 (6.3)	16 (6.8)	4 (5.0)	0.771	0.075	0.008
Powered and Non-Powered (%)	368 (44.1)	242 (46.4)	126 (40.4)	0.107	139 (43.8)	108 (45.6)	31 (38.8)	0.351	0.89	0.986

Extraction Approach										
Inferior Approach (%)	86 (10.3)	67 (12.9)	19 (6.1)	0.003	31 (9.8)	25 (10.6)	6 (7.5)	0.558	0.838	0.873
Primary Femoral Approach (%)	9 (1.1)	6 (1.2)	3 (1.0)	1	5 (1.6)	4 (1.7)	1 (1.2)	1	1	0.699
Secondary Femoral Approach (%)	80 (9.6)	64 (12.3)	16 (5.1)	0.001	29 (9.2)	24 (10.2)	5 (6.2)	0.409	0.905	0.905
Pacing during extraction										
Temporary Pacing Wire (%)	201 (24.1)	122 (23.4)	79 (25.3)	0.58	67 (21.1)	54 (22.8)	13 (16.2)	0.28	0.119	0.325
Procedural Success										
Clinical Success	825 (98.9)	516 (98.9)	309 (99.0)	1	314 (99.1)	234 (98.7)	80 (100.0)	0.731	0.972	1
Clinical Failure	9 (1.1)	6 (1.1)	3 (1.0)	1	3 (0.9)	3 (1.3)	0 (0.0)	0.731	0.872	1
Radiological success*										
Radiological success (<4cm remain)	804 (96.4)	503 (96.4)	301 (96.5)	1	305 (96.2)	229 (96.6)	76 (95.0)	0.749	0.774	1
Radiological failure (>4cm remain)	30 (3.6)	19 (3.6)	11 (3.5)	1	12 (3.8)	8 (3.4)	4 (5.0)	0.749	0.774	1

Complications										
All Minor Complications	61 (7.3)	39 (7.5)	22 (7.1)	0.93	38 (12.0)	31 (13.1)	7 (8.8)	0.405	0.781	0.016
Total Major Complications	14 (1.7)	10 (1.9)	4 (1.3)	0.681	8 (2.5)	8 (3.4)	0 (0.0)	0.21	0.693	0.487

†**- the p value is when comparing the alive and dead groups of each cohort**

‡ **- the p value is when comparing the dead groups of the male and female cohorts**

§ **- the p value is when comparing the total (i.e., dead and alive) male and female cohorts**

*** - these categories are mutually exclusive (i.e. the totals of these sub-categories represent 100% of the total in each subgroup)**

Table 2

Univariate Cox regression model to predict long term mortality after TLE in male and female cohorts. Reference group is "yes vs no" unless stated otherwise, e.g., if the variable is categorical, the hazard ratio relates to the change in hazard when the variable is present.

	Male		**Female**	
	HR (CI)	**p-value**	**HR (CI)**	**p-value**
Explant Age in Years (per year)	1.1 (1-1.1)	<0.001	1.1 (1.1-1.1)	<0.001
Explant Age>70 years (yes vs no)	3.4 (2.7-4.2)	<0.001	4.6 (3-7.2)	<0.001
Dwell Time in Years (per additional year)	0.98 (0.96-1)	0.018	0.96 (0.92-0.99)	0.022
Lead Type				
Dual Coil Defibrillator Leads (vs Single Coil)	1.1 (0.87-1.4)	0.4	1 (0.54-1.9)	0.96
No. of LV leads (per additional LV lead)	1.8 (1.4-2.2)	<0.001	1.7 (1.1-2.8)	0.018
Total Leads Extracted (per additional lead)	1.3 (1.1-1.4)	<0.001	1.1 (0.86-1.4)	0.41
Indication for CIED				
Primary Prevention (vs Secondary Prevention)	0.92 (0.61-1.4)	0.71	0.67 (0.27-1.7)	0.39
Any Pacing Indication (yes vs no)	0.72 (0.53-0.97)	0.031	0.83 (0.46-1.5)	0.54
Any HF indication (yes vs no)	2.1 (1.7-2.7)	<0.001	2.4 (1.3-4.2)	0.0038
Echocardiographic Findings				
LVEF (per % increase)	0.97 (0.96-0.98)	<0.001	0.97 (0.96-0.99)	0.0013
Pacing Lead Vegetation (yes vs no)	0.91 (0.54-1.5)	0.72	0.5 (0.12-2)	0.33
Microbiology Results (only if infective indication)				
Positive Microbiology (yes vs no)	0.75 (0.57-0.99)	0.045	1.1 (0.58-1.9)	0.86
Positive Blood Cultures (yes vs no)	1 (0.69-1.6)	0.84	2.5 (1.1-5.5)	0.026
Positive Swab Cultures (yes vs no)	1.1 (0.8-1.5)	0.58	1.4 (0.71-2.9)	0.31

Peak CRP pre-extraction (per increase in mg/dL)	1 (1-1)	<0.001	1 (1-1)	0.31
Indication for Extraction				
Any Infective Indication (yes vs no)	1.3 (1.1-1.7)	0.016	1.3 (0.85-2.1)	0.21
Local Infection (yes vs no)	1.2 (0.97-1.5)	0.091	1.4 (0.92-2.3)	0.11
Systemic Infection (yes vs no)	1.1 (0.86-1.5)	0.36	0.9 (0.49-1.7)	0.73
Non-Infective Indication (yes vs no)	0.75 (0.6-0.95)	0.016	0.75 (0.48-1.2)	0.21
Lead Dysfunction (yes vs no)	0.84 (0.65-1.1)	0.19	0.95 (0.6-1.5)	0.83
Functional Lead (yes vs no)	0.62 (0.29-1.3)	0.21	3.9e-08 (0-Inf)	1
Lead Complication (yes vs no)	0.97 (0.64-1.5)	0.87	0.79 (0.25-2.5)	0.69
Lead Access (yes vs no)	0.91 (0.48-1.7)	0.76	1.6 (0.66-4.1)	0.29
Lead Pain (yes vs no)	0.69 (0.096-4.9)	0.71	1.1e-07 (0-Inf)	0.99
Other indication (yes vs no)	0.97 (0.65-1.4)	0.86	0.71 (0.29-1.8)	0.47
Co-Morbidities				
Ischaemic Heart Disease (yes vs no)	2.1 (1.7-2.6)	<0.001	1.9 (1.2-3.2)	0.008
CABG (yes vs no)	1.8 (1.4-2.4)	<0.001	0.93 (0.29-3)	0.9
Valve Disease (yes vs no)	2 (1.4-2.7)	<0.001	1.7 (0.87-3.2)	0.12
Heart Failure (yes vs no)	2.4 (1.9-3.1)	<0.001	3 (1.8-4.9)	<0.001
Diabetes Mellitus (yes vs no)	1.8 (1.4-2.4)	<0.001	1 (0.49-2.1)	0.95
Hypertension (yes vs no)	1.6 (1.3-2)	<0.001	2.7 (1.7-4.3)	<0.001
Peripheral Vascular Disease (yes vs no)	2.2 (1.4-3.4)	<0.001	1.7 (0.24-12)	0.59
Stroke (yes vs no)	1.8 (1.2-2.5)	<0.001	2.1 (0.77-5.8)	0.14
Chronic Respiratory Disease (yes vs no)	1.5 (1.1-2)	0.015	2.4 (1.3-4.5)	0.0064
Chronic Kidney Disease (yes vs no)	2.8 (2.2-3.6)	<0.001	4.5 (2.7-7.6)	<0.001
Total Number of co-morbidities (yes vs no)	1.4 (1.3-1.5)	<0.001	1.6 (1.3-1.8)	<0.001
Pre extraction biochemistry				
Creatinine Level (per 10mg/dL increase)	1.1 (1.1-1.1)	<0.001	1.2 (1.1-1.3)	<0.001

eGFR<60 ml/min/1.73m2	2.9 (2.3-3.6)	<0.001	4 (2.6-6.3)	<0.001
eGFR (per increase in ml/min/1.73m2)	0.98 (0.97-0.98)	<0.001	0.97 (0.97-0.98)	<0.001
Extraction Technique				
Manual Traction Only (yes vs no)	0.87 (0.64-1.2)	0.35	1.6 (1-2.7)	0.052
Non-powered only (vs powered)	1.3 (1-1.7)	0.037	1 (0.58-1.8)	0.94
Powered and Non-Powered (vs manual traction only)	0.93 (0.74-1.2)	0.53	0.81 (0.52-1.3)	0.37
Inferior Approach (vs superior approach)	0.91 (0.29-2.8)	0.87	1.1 (0.15-7.7)	0.95
Secondary Femoral Approach (vs primary femoral approach)	0.84 (0.51-1.4)	0.5	1.1 (0.46-2.9)	0.77
Surgical Extraction (yes vs no)	0.73 (0.3-1.8)	0.49	3.9e-08 (0-Inf)	1
Pacing during extraction				
Temporary Pacing Wire (yes vs no)	1.2 (0.95-1.6)	0.11	0.73 (0.4-1.3)	0.3
External Pacing (yes vs no)	1.4 (0.99-1.9)	0.056	1.6 (0.63-3.9)	0.33
Procedural Success				
Complete procedural success	1.2 (0.84-1.7)	0.32	0.68 (0.39-1.2)	0.18
Clinical Success	0.57 (0.18-1.8)	0.34	1.1e-07 (0-Inf)	1
Radiological success*				
Radiological success (<4cm remain)	1.2 (0.63-2.1)	0.63	0.89 (0.33-2.5)	0.83
Radiological failure (>4cm remain)	0.86 (0.47-1.6)	0.63	1.1 (0.41-3.1)	0.83
Complications				
All Minor Complications (vs no complications)	1.3 (0.83-2)	0.26	1.1 (0.49-2.4)	0.84
Total Major Complications (vs no complications)	0.99 (0.37-2.6)	0.98	1.1e-07 (0-Inf)	0.99
Previous Device interventions				
No. of Previous Device Interventions (per additional intervention)	0.99 (0.9-1.1)	0.85	0.9 (0.75-1.1)	0.23

History of Previous TLE (yes vs no)	0.91 (0.64-1.3)	0.59	0.5 (0.2-1.2)	0.13
Number of Previous TLEs (per additional TLE procedure)	0.99 (0.79-1.3)	0.95	0.79 (0.47-1.3)	0.37

LV – Left Ventricular, LVEF – Left Ventricular Ejection Fraction, CABG – Coronary Artery Bypass Grafting, TLE – Transvenous Lead Extraction, eGFR – estimated Glomerular Filtration Rate, CRP – C-Reactive Protein, HR – Hazard Ratio, CI – Confidence Interval

Appendices

Supplementary table 1

Definitions for extraction procedures	
Complete procedural success	Lead extraction procedure with removal of all targeted leads and all lead material from the vascular space, with the absence of any permanently disabling complication or procedure-related death.
Clinical success	Lead extraction procedures with removal of all targeted leads and lead material from the vascular space or retention of a small portion of the lead (<4 cm) that does not negatively impact the outcome goals of the procedure.
Failure	Lead extraction procedures in which complete procedural or clinical success cannot be achieved, or the development of any permanently disabling complication, or procedure-related death.

Supplementary table 2

Baseline characteristics of the total cohort. Reference group is "yes vs no" unless stated otherwise.

	Combined Cohort			
	Total	**Alive**	**Dead**	**p-value**
Total Number of Patients	1151	759	392	
Follow up time in months (median [IQR])	62.90 [20.20-118.80]	70.75 [22.92-127.67]	53.60 [15.50-97.40]	<0.001
Sex				
Male (%)	834 (72.5)	522 (68.8)	312 (79.6)	<0.001
Explant Age in Years (mean (SD))	64.83 (14.72)	60.94 (14.82)	72.38 (11.19)	<0.001
>75 years old	328 (28.5)	136 (17.9)	192 (49.0)	<0.001
Lead Dwell Time				
Months (median [IQR])	62.90 [20.20-118.80]	70.75 [22.92-127.67]	53.60 [15.50-97.40]	<0.001
Indication for Extraction				
Any Infective Indication	632 (54.9)	388 (51.1)	244 (62.2)	<0.001
Local Infection	423 (36.8)	256 (33.8)	167 (42.6)	0.004
Systemic Infection	209 (18.2)	132 (17.4)	77 (19.6)	0.396
Non-Infective Indication				
Lead Dysfunction (%)	349 (30.3)	244 (32.1)	105 (26.8)	0.071
Functional Lead (%)	31 (2.7)	24 (3.2)	7 (1.8)	0.236
Lead Complication (%)	78 (6.8)	50 (6.6)	28 (7.1)	0.817
Lead Access (%)	49 (4.3)	34 (4.5)	15 (3.8)	0.698
Lead Pain (%)	15 (1.3)	14 (1.9)	1 (0.3)	0.047
Other indication (%)	105 (9.1)	72 (9.5)	33 (8.4)	0.625
Lead Type and number				
Single Coil Defibrillator Leads (%)				0.201

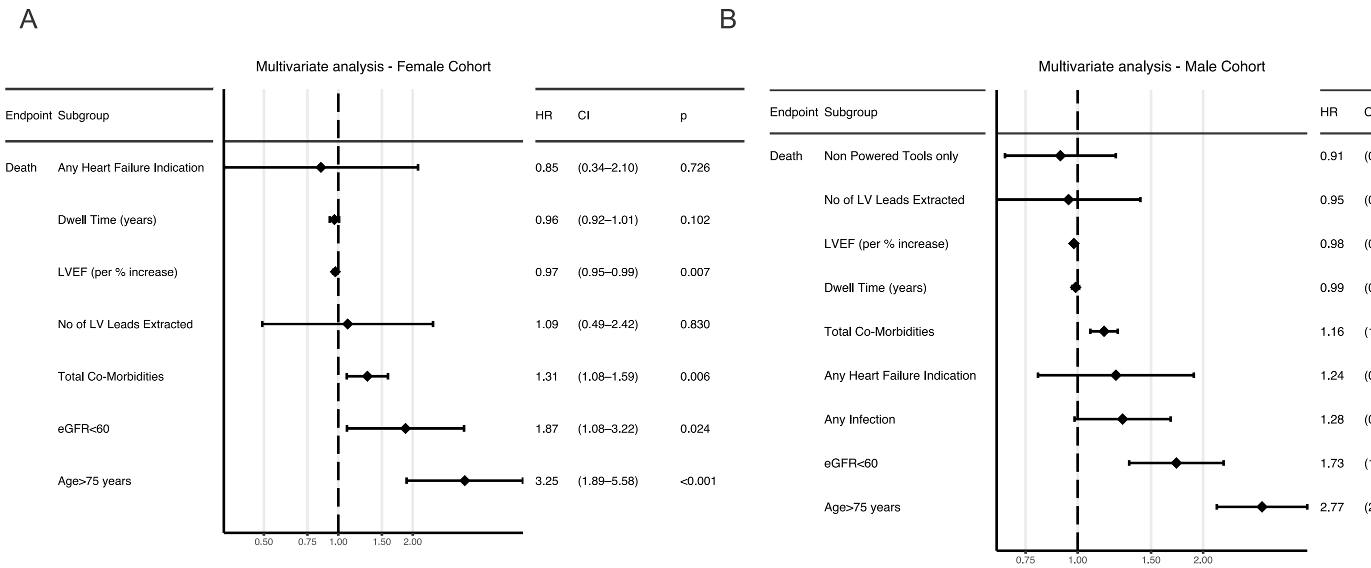
1	228 (19.8)	145 (19.1)	83 (21.2)	
2	5 (0.4)	5 (0.7)	0 (0.0)	
Dual Coil Defibrillator Leads (%)				0.455
1	230 (20.0)	145 (19.1)	85 (21.7)	
2	9 (0.8)	7 (0.9)	2 (0.5)	
No. of LV leads (%)				<0.001
1	225 (19.5)	118 (15.5)	107 (27.3)	
2-3	11 (9.5)	9 (1.2)	2 (0.5)	
Total Leads Extracted (%)†				0.092
1	329 (28.6)	226 (29.8)	103 (26.3)	
2	505 (43.9)	345 (45.5)	160 (40.8)	
3	222 (19.3)	134 (17.7)	88 (22.4)	
4-7	95 (8.3)	54 (7.2)	41 (10.5)	
Indication for CIED				
Primary Prevention	113 (9.8)	84 (11.1)	29 (7.4)	0.06
Secondary Prevention	233 (20.2)	168 (22.1)	65 (16.6)	0.032
Any Pacing Indication	560 (48.7)	355 (46.8)	171 (43.6)	0.34
Any HF indication	268 (23.3)	142 (18.7)	126 (32.1)	<0.001
Echocardiographic Findings				
LVEF (mean (SD))	45.37 (14.02)	48.06 (13.11)	40.20 (14.30)	<0.001
Co-Morbidities				
Ischaemic Heart Disease	425 (38.3)	223 (30.3)	202 (53.7)	<0.001
CABG	143 (12.9)	65 (8.8)	78 (20.9)	<0.001
Valve Disease	111 (10.0)	58 (7.9)	53 (14.1)	0.002
Heart Failure	418 (37.6)	226 (30.7)	192 (51.1)	<0.001
Diabetes Mellitus	174 (15.8)	105 (14.3)	69 (18.7)	0.072
Hypertension	434 (39.4)	259 (35.3)	175 (47.6)	<0.001

Peripheral Vascular Disease	43 (3.9)	19 (2.6)	24 (6.5)	0.003
Stroke	87 (7.9)	49 (6.7)	38 (10.3)	0.048
Chronic Respiratory Disease	147 (13.3)	89 (12.1)	58 (15.7)	0.124
Chronic Kidney Disease	208 (18.6)	94 (12.7)	114 (30.1)	<0.001
Total Number of co-morbidities (%)†				<0.001
0	326 (28.3)	268 (35.3)	58 (14.8)	
1	215 (18.7)	159 (20.9)	56 (14.3)	
2	223 (19.4)	136 (17.9)	87 (22.2)	
3	168 (14.6)	94 (12.4)	74 (18.9)	
4-7	219 (19.0)	102 (13.5)	117 (29.8)	
Pre extraction biochemistry				
Creatinine Level (median [IQR])	92.00 [76.00-117.00]	86.00 [72.00-104.00]	105.00 [86.00-138.25]	<0.001
eGFR (mean (SD))	67.33 (21.26)	72.41 (18.70)	57.49 (22.45)	<0.001
Peak CRP (median [IQR])	6.00 [2.00-17.00]	5.00 [1.00-14.00]	8.00 [4.25-20.75]	0.001
No. of Previous Device Interventions				0.083
0	474 (41.2)	290 (38.3)	184 (46.9)	
1	352 (30.6)	236 (31.1)	116 (29.6)	
2	170 (14.8)	112 (14.8)	58 (14.8)	
>2	154 (13.4)	121 (15.9)	34 (8.7)	
History of Previous Extraction	128 (11.1)	87 (11.5)	41 (10.5)	0.679
Extraction Tools†				
Manual Traction Only (%)	319 (27.7)	218 (28.7)	101 (25.8)	0.321
Non-powered only (%)	206 (17.9)	116 (15.3)	90 (23.0)	0.002

Powered Only (%)	119 (10.3)	75 (9.9)	44 (11.2)	0.544
Powered and Non-Powered (%)	507 (44.0)	350 (46.1)	157 (40.1)	0.057
Extraction Approach				
Inferior Approach (%)	117 (10.2)	92 (12.2)	25 (6.4)	0.003
Primary Femoral Approach (%)	14 (1.2)	10 (1.3)	4 (1.0)	0.872
Secondary Femoral Approach (%)	109 (9.5)	88 (11.7)	21 (5.4)	0.001
Pacing during extraction				
Temporary Pacing Wire (%)	268 (23.3)	176 (23.2)	92 (23.5)	0.973
Procedural Success†				
Complete Remove	1024 (89.0)	677 (89.2)	347 (88.5)	0.804
Partial Removal	115 (10.0)	73 (9.6)	42 (10.7)	0.628
Clinical Failure	12 (1.0)	9 (1.2)	3 (0.8)	0.719
Complications				
All Minor Complications	99 (8.6)	70 (9.2)	29 (7.4)	0.35
Total Major Complications	22 (1.9)	18 (2.4)	4 (1.0)	0.174

† These categories are mutually exclusive

Supplementary Figure 1



Supplementary Figure 1 (above): Multivariable cox proportional hazards regression models (p<0.001) to predict mortality after TLE in the female (A) and male (B) cohorts including patients who died during inpatient stay.

Figure Legends

Figure 1

Kaplan-Meier survival probability in patients stratified by sex.

Figure 2

Kaplan-Meier survival probability in patients stratified by indication for TLE. Female cohort (A) and male cohort (B).

Figure 3

Kaplan-Meier survival probability in patients stratified by comorbidities. Female cohort (A) and male cohort (B).

Figure 4

Multivariable cox proportional hazards regression models ($p<0.001$) to predict mortality after TLE in the female (A) and male (B) cohorts.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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