Predictors of long-term mortality after transvenous lead extraction of an infected cardiac device: a risk prediction model for sustainable care delivery.

Roberto Scacciavillani[1], Maria Lucia Narducci[1], Eleonora Ruscio[1], Mario Cesare Nurchis[1], Pascucci Domenico[1], Gianluigi Bencardino[1], Francesco Perna[1], Gemma Pelargonio[1], Massimo Massetti[1], Gianfranco Damiani[1], and Filippo Crea[2]

[1]Fondazione Policlinico Universitario Agostino Gemelli IRCCS
[2]Universita Cattolica del Sacro Cuore - Campus di Roma

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Abstract

Background and aims: Transvenous lead extraction (TLE) has become a pivotal part of a comprehensive lead management strategy, dealing with a continuously increasing demand. Nonetheless, literature about the long-term impact of TLE on survivals still lacking. Given these knowledge gaps, the aim of our study was to analyse very long-term mortality in patients undergoing TLE in public health perspective. **Methods**: This prospective, single-centre, observational study enrolled consecutive patients with cardiac implantable electronic device (CIED) who underwent TLE, from January 2005 to January 2021. The main goal was to establish the independent predictors of very long-term mortality after TLE. We also aimed at assessing procedural and hospitalization related costs. **Results**: We enrolled 435 patients (mean age 70 $\pm$ 12 years, with mean lead dwelling time 6.8 $\pm$ 16.7 years), with prevalent infective indication to TLE (92%). Initial success of TLE was achieved in 98% of population. After a median follow-up of 4.5 years (range 1 month- 15.5 years),150 of the 435enrolled patients (34%) died. At multivariate analysis, death was predicted by: age ([?] 77 years, OR: 2.55, CI: 1.8-3.6, $p<0.001$), chronic kidney disease (CKD)defined as severe reduction of estimated glomerular filtration rate (eGFR <30 mL/min/1.73m2, OR:1.75, CI: 1.24-2.4, p=0.001), systolic dysfunction assessed before TLE defined as left ventricular ejection fraction (LVEF) <40%, OR:1.78, CI 1.26-2.5, p=0.001). Mean extraction and reimplantation-related costs were \euro5989 per procedure. **Conclusions**: Our study identified three predictors of long-term mortality in a high-risk cohort of patients with a cardiac device infection, undergoing successful TLE. The future development of a mortality risk score before might impact on public health strategy.

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Maria Lucia Narducci[1]*, Eleonora Ruscio[1]*, Nurchis Mario Cesare[2,3], Pascucci Domenico[2,4], Roberto Scacciavillani[1], Gianluigi Bencardino[1], Francesco Perna[1], Gemma Pelargonio[1,5], Massimo Massetti[1,5], Gianfranco Damiani[2,4], Filippo Crea[5]

1 Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli

IRCCS, Rome, Italy

2 Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, 00168 Rome, Italy

3 School of Economics, Università Cattolica del Sacro Cuore, 00168 Rome, Italy

4 Department of Health Sciences and Public Health, Section of Hygiene, Università Cattolica del Sacro Cuore, 00168 Rome, Italy

5 Institute of Cardiology, Catholic University of Sacred Heart, Rome, Italy

***equal contribution**

Corresponding Author: Maria Lucia Narducci MD PhD,*marialucia.narducci@policlinicogemelli.it*

Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

Largo Agostino Gemelli, 8

Rome 00168, Italy

Tel: +39 06 3015 4187; fax: +39 06 3055535

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ABSTRACT

Background and aims : Transvenous lead extraction (TLE) has become a pivotal part of a comprehensive lead management strategy, dealing with a continuously increasing demand. Nonetheless, literature about the long-term impact of TLE on survivals still lacking. Given these knowledge gaps, the aim of our study was to analyse very long-term mortality in patients undergoing TLE in public health perspective.

Methods : This prospective, single-centre, observational study enrolled consecutive patients with cardiac implantable electronic device (CIED) who underwent TLE, from January 2005 to January 2021. The main goal was to establish the independent predictors of very long-term mortality after TLE. We also aimed at assessing procedural and hospitalization related costs.

Results : We enrolled 435 patients (mean age 70 ± 12 years, with mean lead dwelling time 6.8 ± 16.7 years), with prevalent infective indication to TLE (92%). Initial success of TLE was achieved in 98% of population. After a median follow-up of 4.5 years (range 1 month- 15.5 years),150 of the 435enrolled patients (34%) died. At multivariate analysis, death was predicted by: age ([?] 77 years, OR: 2.55, CI: 1.8-3.6, p<0.001), chronic kidney disease (CKD)defined as severe reduction of estimated glomerular filtration rate (eGFR <30 mL/min/1.73m2, OR:1.75, CI: 1.24-2.4, p=0.001), systolic dysfunction assessed before TLE defined as left ventricular ejection fraction (LVEF) <40%, OR:1.78, CI 1.26-2.5, p=0.001). Mean extraction and reimplantation-related costs were \euro5989 per procedure.

Conclusions : Our study identified three predictors of long-term mortality in a high-risk cohort of patients with a cardiac device infection, undergoing successful TLE. The future development of a mortality risk score before might impact on public health strategy.

KEYWORDS

personalized medicine; transvenous lead extraction; long-term outcomes; mortality risk; elderly; chronic renal disease; systolic dysfunction; public health; sustainability

Background

As a result of growing life expectancy and broadening indication, there has been a significant increase in the proportion of cardiac implantable electronic device (CIED) with consequent increase of infection rate, prevalence of comorbid and frail recipients, lead dysfunction, system revisions and upgrade (1–3). Thus, transvenous lead extraction (TLE) has become a pivotal part of a comprehensive lead management strategy (4), dealing with a continuously increasing demand (5). Nonetheless, literature about the long-term follow-up of patients undergoing TLE is still lacking. In particular, short-term safety and efficacy of TLE have been extensively investigated (2,6,7), while reports on very long-term outcomes after TLE are still limited and particularly focused on infection-related predictors of mortality (8–15). Moreover, there is evidence in the scientific literature of substantial costs associated with extraction and reimplantion procedures (16). Given these knowledge gaps, the aim of our study was to provide a careful analysis of very long-term mortality from a single high-volume tertiary referral center for TLE, in a public health perspective, with regard to the sustainability of TLE procedure and clinical follow-up. In addition to that, we evaluated and reported the costs of CIED extraction and reimplantation in a long term follow-up perspective.

Methods and materials

Study design and patient population

This prospective, single-centre, observational study consecutively enrolled 451 patients with indication for TLE, according with 2018 EHRA expert consensus statement (5). Patients were admitted from spoke centres to our TLE hub centre, from January 2005 to January 2021. Exclusion criteria were: age $<$ 18 years, pregnancy, life expectancy $<$6 months.

The enrolment started at the time of TLE. All the population was followed-up for early (before discharge) and long-term (after discharge) mortality. Institutional Ethics Committee approval (prot. 202/18, study ID 1846) was taken and a written informed consent was obtained from each participant.

Data collection and data management

Thorough information about the patients' history, clinical and echocardiographic data, intracardiac device data, extraction indication, comorbidites, procedural success, hospitalization length, early (before discharge) and long-term follow-up (after discharge) mortality data were collected on case-report forms. Particularly, chronic kidney disease was defined according with NICE UK-KDIGO US guideline (17); reduced LVEF is defined as [?] 40%, as recently reported on the Universal Definition and Classification of Heart failure (18). The consistency and accuracy of the data have been audited by health data management. Costs associated with the procedure and the hospitalization were derived from the Diagnosis Related Group (DRG) reimbursements our Institution received from Regione Lazio in Italy.

Transvenous lead extraction

All patients with indication for TLE of CIED were treated in the hybrid room or electrophysiology laboratory, according to current guidelines (2,5,19). Definitions for TLE procedures and outcomes were derived from EHRA expert consensus statement (5).

Pacemaker-dependent patients received a percutaneous active fixation lead, which was placed in the right ventricle and connected to an external pacemaker. After extraction, all patients received 24-hourintensive care unit (ICU) monitoring for occurring complications and were secondarily transferred to Arrhythmology Unit, until the discharge. Patients come from spoke centres were back transferred to the source centre after achieving clinical stabilization. Early mortality and related causes were evaluated before discharge.

Follow-up and outcome

All patients were followed at regular intervals (every 12 months) for complete clinical evaluation, reassessment of reimplantation indication, device interrogation. Mortality data were collected using the "Regione Lazio SISMED portal" and Death Records by hub and spoke centres, in order to determine the cause of death.

Statistical analysis

Continuous variables were expressed as mean +- SD. Categorical data were expressed as frequencies and percentages. Two-sided p-values $<$ 0.05 were considered statistically significant.

To assess long-term predictors of mortality after TLE, the Cox proportional hazards regression model was used. The statistical models were adjusted for typical risk factors and potential baseline confounders including sex, age, type of the extracted device, indication for the extraction, major complications, procedural failure, cardiovascular risk factors.

Statistical analysis was performed using SPSS Version 23.0.0 (Statistical Package for Social Sciences Inc.) and STATA 17.0 software (Stata Corporation, College Station, TX, USA).

Results

General population findings

We enrolled 451 patients, with 16 patients (3%) lost to follow-up and consequent a total population of 435 patients. Table I showed the main baseline characteristics of our cohort (435 patients, mean age was 70+-12, male prevalence 77%), with evidence of systolic dysfunction (mean left ventricular ejection fraction LVEF: 44 +- 13%) and high rates of comorbidities (14% of patients affected by coexisting hypertension, diabetes mellitus and severe chronic renal disease, 86% of patients affected by two of these risk factors).The source hospital in 269 patients (62% of population) was our hub centre, whereas 38% of patients were referred from spoke centres to our hub in order perform TLE. Noteworthy, on a total of 929 extracted leads, the mean lead dwelling time was 6.8 +- 16.7 years. The majority of extracted devices were bicameral (51%). Three hundred ninety-six patients (92%) presented with an infective indication to TLE, whereas the remaining 39 patients (8%) underwent TLE due to a malfunctioning cause. In particular, the most frequent indications to TLE were pocket infection (68%) and definite CIED endocarditis (46%). Complete procedural success rate was reached in 98% of patients. Furthermore, 313 patients (72%) were reimplanted before discharge (Table I).

Follow-up: mortality outcomes, long-term predictors

The median follow-up time was 54 months (4.5 years). We found that 182 out of the 435 total enrolled patients died, with a global mortality rate of 41%. In particular, early mortality (first 30 post-operative days) rate accounted for 32 patients (7%) and long-term mortality rate for 150 patients (34%) of the total population. With regard to early mortality causes, the most frequent was sepsis (accounting for 16 patients, 50% of deaths), followed by cardiovascular non-arrhythmic causes (10 patients, 31% of deaths, including ischemia, pulmonary embolism and heart failure), intra-procedural complications (2 patient 6%), non-cardiovascular events (3 patients 9%) and arrhythmic cause (1 patient, 3%). The most frequent cause of long-term mortality was represented by multiple chronic diseases (94 patients out of 150 deaths, 62%); secondly, non-arrhythmic cardiovascular causes accounted for 36 patients (24% of deaths), sepsis for 6 patients (4%) (Figure 1).

At univariate analysis, as showed in Table II, long-term mortality predictors were: chronic kidney disease defined as severe reduction of eGFR ($<$30ml/min/1.73m^2), elderly, referral from spoke centres, diabetes, left ventricular (LV) systolic dysfunction defined as LVEF [?]40%, infective indication to TLE, sepsis at admission, number of extracted leads, intravenous antibiotic therapy and diuretics. At multivariate analysis, long-term mortality independent predictors were represented by advanced age, severe chronic kidney disease and reduced LVEF (Table III, Figure 2).

Kaplan-Meier curves summarized the different survival on the basis of three independent predictors of long-term mortality (Figures 3a-c). At 54 months of follow-up, elderly patients with severe chronic kidney disease and patients with LV systolic dysfunction had a higher mortality rate compared to younger, patients with normal or mild chronic kidney disease and patients with LVEF $>$40% (Figure 3a-c). Particularly, Kaplan–Meier analysis demonstrated a cumulative mortality rate of 83% in patients with age [?]77 years, 68% in patients with severe chronic kidney disease, and 73% in those with LV systolic dysfunction at 90 days from discharge.

TLE procedure cost description

In relation to the costs associated with the clinical activities, the mean costs were \euro5989 +- \euro7751 per TLE procedure. Patients undergoing reimplantation showed, obviously, notably higher costs (\euro6336 +-

\euro8108) with respect to those who did not receive another implantable device (\euro5011 +- \euro6535). Total costs amounted to \euro2,606,215, over the period of the study, of which patients without reimplantation.

Discussion

This observational single-centre prospective cohort study with 435 patients undergoing TLE showed a high long-term mortality, also after a complete resolution of CIED infection. With a very long-mortality rate of 34%, this first analysis on the cause of death-data after TLE, supported the notion that the survival continues to be burdened by multiple chronic diseases progression, beyond the clinical resolution of infection.

In the last two decades, numerous reports of single and multi-centres experiences outlined mainly positive short-term results, paving the way for guidelines definition (7). The largest "real-word" prospective registry confirmed both "acute" safety and efficacy of TLE, with a complete clinical success of 96.7% and all cause in-hospital deaths of 1.2% in high volume centres (2). Nonetheless, evidences on long-term mortality after TLE are still scarce, as described by recent studies focused on "CIED infection"-related predictors of long-term outcomes after TLE (8–15).

Our results showed how patients undergoing a successful TLE, especially for an infective cause, remain at high-risk of death at median follow-up of 54 months due to progression of underlying multiple chronic diseases. Conversely, the infective cause is the leading cause of death before discharge. However, it should be noted that, after the initial phase of short- and medium-term follow-up in which mortality may be due to septic relapses or complications such as valvular insufficiencies or heart failure, the mortality of the population could be similar to that of an equivalent group of patients.

Moreover, we observed a relatively short-time interval to death after discharge in elderly subjects, in patients with severe CKD and systolic LV dysfunction.

More in detail, our population is high-risk population with high rates of comorbidities and 92% of patients with evidence of infection as TLE indication: as formerly stated, infective indication itself represents a mortality risk enhancer as showed By Mehta et al. (11). Nonetheless, clear evidence regarding mortality rates for untreated patients supports the indication TLE in case of CIED-related infections (20).

With particular regard to long-term predictors, the postprocedural risk conveyed by age confirms previous findings (12) as also the risk conferred by chronic kidney disease strongly supported by the literature, mainly with regard to short-term follow-up (10,12,15,21).

Conversely, long-term data on systolic LV dysfunction after TLE remained unclear. According to Metha et al (11), our results showed LV systolic dysfunction as an independent long–term predictor of death at multivariate analysis in patients undergoing TLE with CIED infection as indication. Recently, Nishii et al demonstrated that the survival rate after TLE was not significantly different between patients with LVEF [?] 35% and those with LVEF $>$ 35% at 30 days and 1 year after TLE. Nevertheless, patients with systolic LV dysfunction were more likely to require additional hemodynamic support and temporary cardiac resynchronization therapy pacing after TLE and brain natriuretic peptide levels as marker of heart failure represented a significant predictor for 1-year mortality (22).

With regard to lead related data, number of extracted leads or dwelling time were not significant predictors of mortality in our cohort, but the impact of leads on long term mortality was more noticeable in the non-infection group of patients undergoing TLE than in CIED infection group (11).

As important limitation of our study focused on tertiary care center dataset, referral bias could have affected the clinical data, thereby limiting the generalization of our results to other populations.

Our findings suggest the urgent need for a risk score including age at explant, CKD and reduced LVEF, in larger populations undergoing TLE to better define not only the risk/benefit analysis of lead extraction and related follow-up by the multidisciplinary team but also the cost-effectiveness of this entire clinical pathway (Figure 4). In particular, risk stratification allows a coherent segmentation that divides patients into groups with relative service needs is a relevant foundation for effective, equitable and sustainable care delivery consistent with a public health perspective. This main clinical implication is strongly reinforced by the analysis of the costs related to the TLE procedure which showed a significant economic impact for the national health service with particular regard for reimplanted patients. A "risk prediction model" should help optimizing clinical management since hospital admission, moving toward personalized, patient-centred medicine. Given the goal of improving outcomes, these assumptions also imply value-based care considerations in a global health perspective and economic sustainability.

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Table I. Baseline characteristics of patients included in the study

	All population (n=435)
Clinical characteristics	*Clinical characteristics*
Age, years, mean ± SD	70 ± 12
Male, n (%)	337 (77)
Lead dwelling time, months, mean ± SD	81.7 ± 201.2
Total leads extracted, n	929
Source hospital (FPG*), n (%)	269 (62)
TLE room (EP^{+} room/hybrid room)	282/153 (65/35)
TLEindication (infection/malfunctioning), n (%)	396/39 (92/8)
LVEF°, %, mean ± SD	44 ± 13
Chronic kidney disease§, n (%)	166 (38)
Diabetes mellitus, n (%)	136 (31)
Hypertension	328 (78)
Type of infection	*Type of infection*
Definite endocarditis, n (%)	201 (46)
Sepsis/bactaeremia only, n (%)	174 (40)
Endocarditis + sepsis/bacteraemia, n (%)	81 (19)
Pocket infection only, n (%)	295 (68)
Pocket infection + sepsis/bacteraemia, n (%)	100 (23)
Device extracted	*Device extracted*

	All population (n=435)
PM, n (%) 211 (49)	PM, n (%) 211 (49)
ICD, n (%) 224 (51)	ICD, n (%) 224 (51)
Type of device	*Type of device*
Bicameral, n (%)	222 (51)
Biventricular, n (%)	122 (28)
Monocameral, n (%)	91 (21)
Reimplanted patients, n (%)	313 (72)
Therapy	
ACEi[ç]/sartans, n (%)	261 (60)
Beta-blockers, n (%)	300 (69)
ASA, n (%)	177 (41)
Statin, n (%)	197 (45)
AADs[£], n (%)	82 (19)
Diuretics, n (%)	238 (55)
Antibiotics iv[$]	338 (78)
Extraction costs analysis	
Extraction hospitalization length, days, mean ± SD	27 ± 21
Cost (euros) per patient	5989 ± 7751
Without reimplantation (n= 122, 28%) With reimplantation (n= 313, 72%)	5011 ± 6535 6336 ± 8108

*FPG: Foundation Policlinico Gemelli. [+]EP room: Electrophisiology room. °LVEF: left ventricular ejection fraction. §Chronic kidney disease defined as eGFR < 30 mL/min.[$]Empirical intravenous (IV) antibiotics administration before TLE. [Ç] ACEi: Angiotensin-Converting Enzyme inhibitors. [£]AADs: antiarrhythmic drugs. DRG: diagnosis related group.

Table II. Univariate analysis of long-term mortality predictors.

Univariate analysis			
	OR	IC 95%	p-value
Chronic kidney disease[§]	2.67	1.77-4.02	<0.001
Age (> 77 years)	2.56	1.70-3.86	<0.001
Diabetes mellitus	1.55	1.02-2.36	0.040
LVEF (%)°	0.98	0.96-0.99	0.006
Major Bleeding	3.25	1.32-8.03	0.011
Infective indication	4.72	1.64-13.62	0.004
Number of extracted leads (>3)	1.46	1.12-1.90	0.005
Antibiotics iv[$]	2.38	1.39-4.07	0.002
Diuretics iv[ç]	1.67	1.11-2.51	0.013

°LVEF: left ventricular ejection fraction. § Chronic kidney disease defined as eGFR < 30 mL/min. [$]Empirical intravenous (IV) antibiotics administration before TLE.[Ç] Intravenous diuretics as surrogate index of heart failure.

Table III. Multivariate analysis of long-term mortality predictors.

Multivariate analysis			
	OR	IC 95%	p-value
Chronic kidney disease[§]	1.75	1.24-2.4	0.001

Multivariate analysis			
Age (> 77 years)	2.55	1.8-3.6	<0.001
LVEF (%)°	1.78	1.26-2.5	0.001
Major Bleeding	0.91	0.5-1.64	ns
Diabetes mellitus	1.15	0.70-1.87	ns
Infective indication to TLE	2.66	0.69-10.15	ns
Number of extracted leads (>3)	1.11	0.81-1.52	ns
Antibiotics iv[$]	1.53	0.81-2.89	ns
Diuretics iv[ç]	1.47	1.03-2.09	<0.005

°LVEF: left ventricular ejection fraction. §Chronic kidney disease defined as eGFR < 30 mL/min. [$]Empirical intravenous (IV) antibiotics administration before transvenous lead extraction (TLE).[Ç]Intravenous diuretics as surrogate index of heart failure.ns: not significative

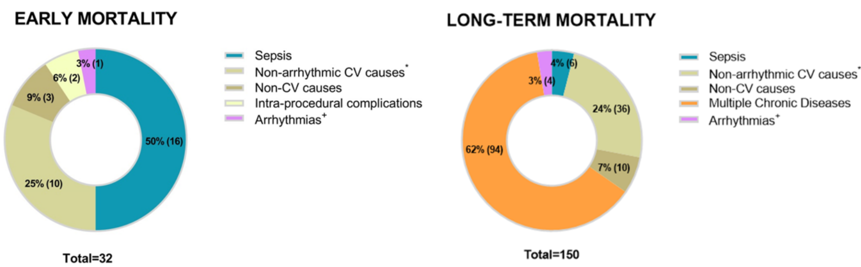

Figure 1.Early and long-term mortality pie charts (n=435 patients). *Non arrhythmic cardiovascular (CV) causes:ischaemia, pulmonary embolism, heart failure. +Arrhythmias: ventricular tachycardia, ventricular fibrillation, pulseless electrical activity.

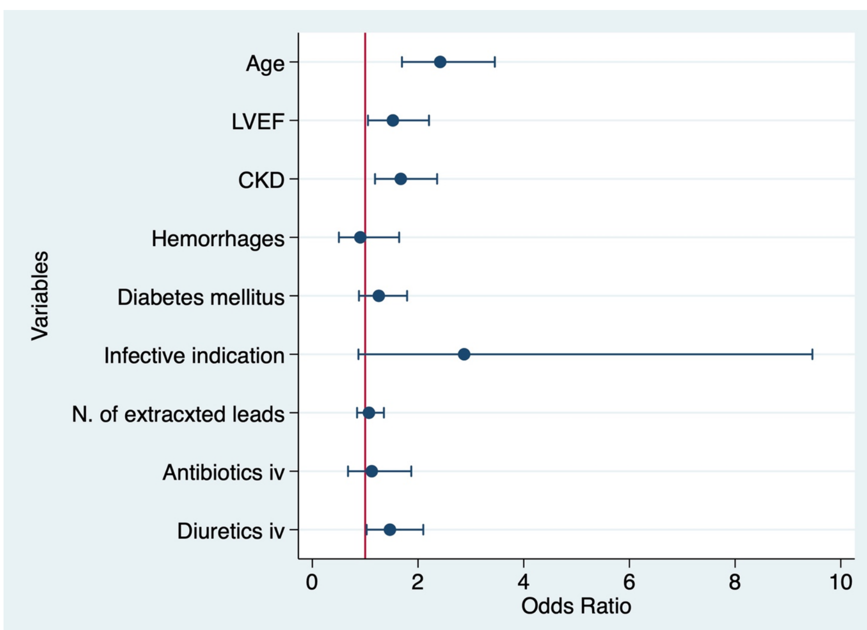

Figure 2. Forest plot of predictors at multivariate analysis.

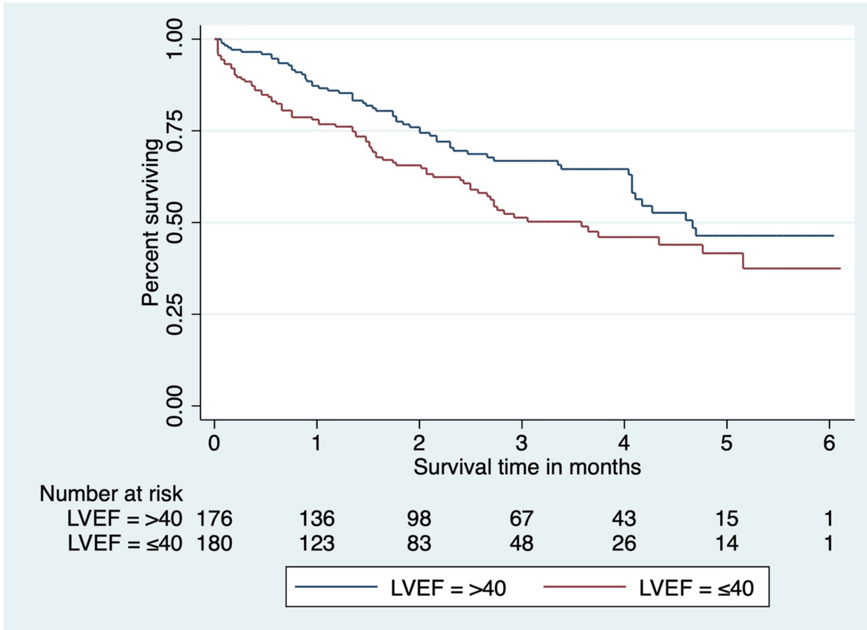

Figure 3a. Survival curve for independent predictors significant at multivariate analysis: Left Ventricular Ejection Fraction (LVEF [?] or > than 40%).

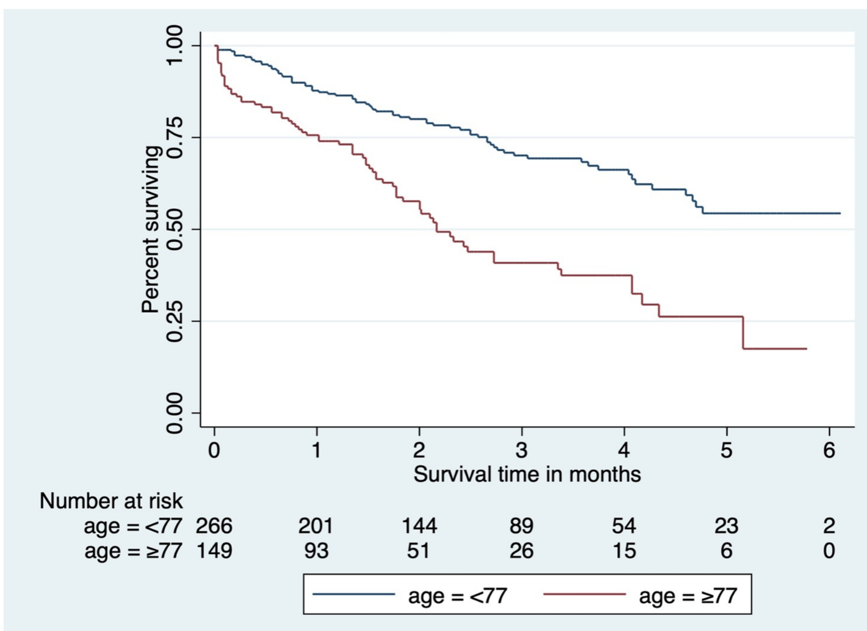

Figure 3b. Survival curve for independent predictors significant at multivariate analysis: Age (< or [?] than 77 years).

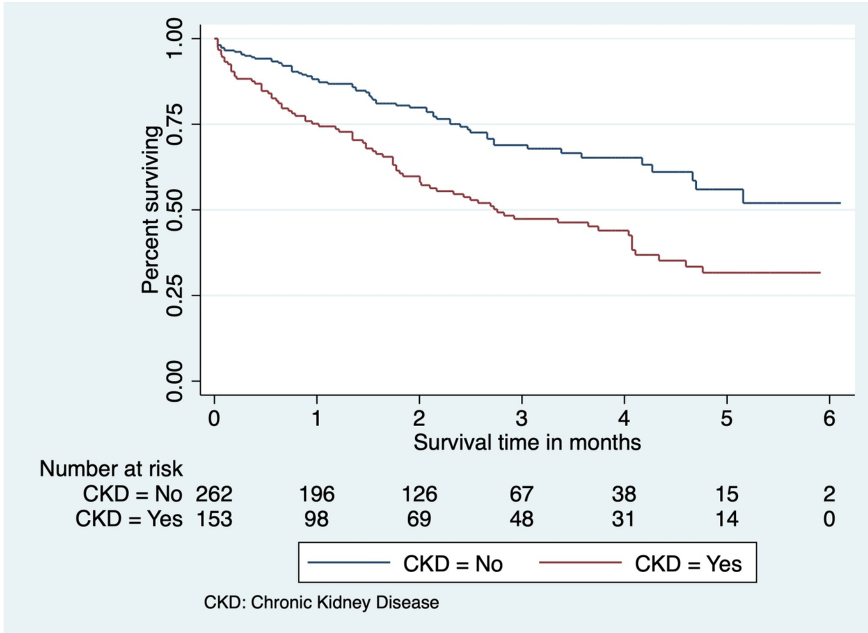

Figure3c. Survival curve for independent predictors significant at multivariate analysis: chronic kidney disease (defined as eGFR <30 mL/min/1.73m2).

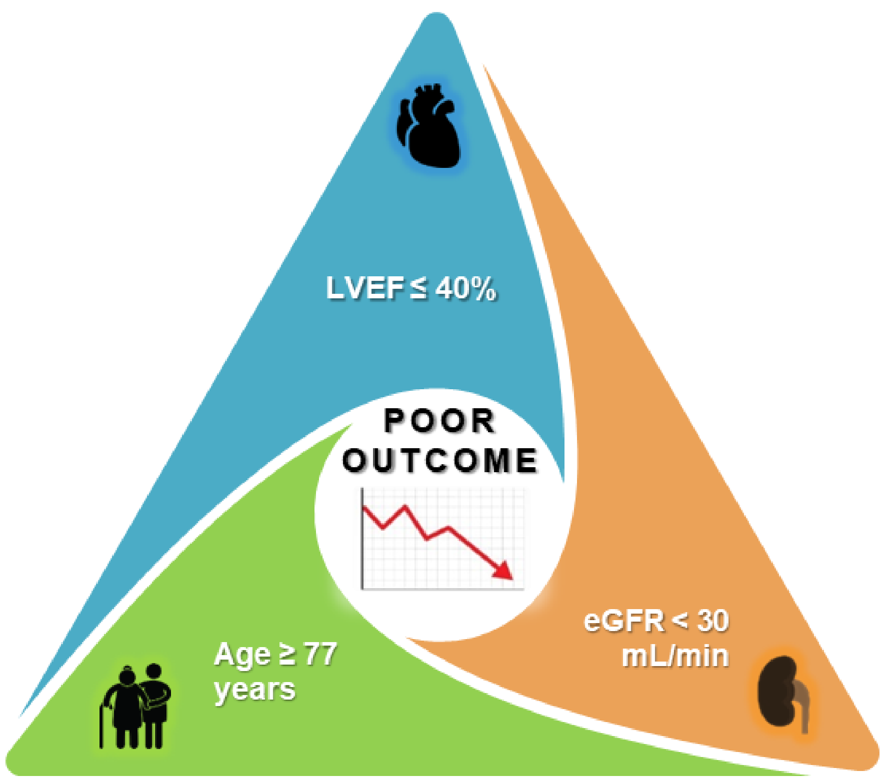

Figure 4. Independent baseline predictors of long-term mortality risk after TLE.