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Predictors of death without prior appropriate therapy in ICD recipients: the comorbidities, frailty and functional status (COMFFORT study)

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ABSTRACT

Objective Most patients who have an implantable cardioverter-defibrillator (ICD) implant do not receive life-prolonging therapy from it. Little research has been undertaken to determine which patients benefit the least from ICD therapy. As patients age and accumulate comorbidities, the risk of death increases and the benefit of ICDs diminishes. We sought to evaluate the impact of comorbidity, frailty, functional status on death with no prior appropriate ICD therapy.

Methods A prospective, multicentre, observational study involving 12 English hospitals was undertaken. Patients were eligible for inclusion for the study if they were scheduled to have a de novo, upgrade to or replacement of a transvenous or subcutaneous ICD or cardiac resynchronisation therapy device and defibrillator (CRT-D). Baseline characteristics were collected. Participants were asked to complete a frailty assessment (Fried score) and a functional status questionnaire (EuroQol 5-Dimension 5-Level (EQ-5D-5L)). The Charlson Comorbidity Index was calculated. Patients were prospectively followed up for 2.5 years. The primary outcome was death with no prior appropriate therapy.

Results In total, 675 patients were enrolled, mean age 65.7 (IQR 65–75) years. A total of 63 patients (9.5%) died during follow-up, 58 without receiving appropriate ICD therapy. Frailty was present in 86/675 (12.7%) and severe comorbidity in 69/675 (10.2%). Multivariate predictors of death with no appropriate therapy were identified and a risk score comprising frailty, comorbidity, increasing age, estimated glomerular filtration rate and EQ-5D-5L was developed.

Conclusion Comorbidities, frailty and the EQ-5D-5L score are powerful, independent predictors of death with no prior appropriate therapy in ICD/CRT-D recipients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There are several predictors of non-arrhythmic death in implantable cardioverter-defibrillator (ICD) recipients including advanced age, poor renal function, very low ejection fraction, advanced heart failure symptoms and atrial arrhythmias.

WHAT THIS STUDY ADDS

⇒ We have demonstrated that baseline frailty status, number of comorbidities as well as self-rated health using the EuroQol 5-Dimension 5-Level score identifies patients at higher risk of death without prior appropriate therapy in ICD recipients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further research may be necessary to develop and validate an ICD risk score to predict death with no prior ICD therapy that includes frailty, non-cardiac comorbidity as well as self-rated health status in an ICD population. ICD practice guidelines could then reflect the importance of assessing these factors in the routine risk assessment of patients being considered for ICD implantation. Finally, further research is required to determine whether modifying an individual's frailty status will increase their chances of benefiting from ICD therapy.

INTRODUCTION

Implantable cardioverter-defibrillators (ICDs) have been shown to reduce death from ventricular arrhythmias in patients have either survived a cardiac arrest or in those at risk of future cardiac arrest. Careful selection of appropriate patients for ICD therapy is important. Randomised controlled trials have shown that ICDs reduce all-cause mortality when the proportion of deaths prevented from lethal ventricular arrhythmias is sufficiently high to outweigh the number of deaths from non-sudden cardiovascular[1 2] or non-cardiovascular[3] causes.

In real-world clinical practice, the selection of patients for an ICD is challenging. For example, consider two scenarios: (a) a 76-year-old widower with a history of remote myocardial infarction, persistent left ventricular (LV) systolic impairment despite optimal medical therapy with the most recent left ventricular ejection fraction (LVEF) estimated at 28%, chronic kidney disease stage

IIIb with proteinuria, diabetes with moderate glycaemic control, carcinoma of the prostate on hormonal therapy and previous stroke with mild residual unilateral weakness necessitating the useful of a walking stick for balance; (b) a 79-year-old married man with a remote history of myocardial infarction, persistent LV systolic impairment on optimal medical management with the most recent LVEF estimated at 28% with a history of well-controlled hypertension and hypercholesterolaemia but good functional status. Which of these two patients is most likely to derive mortality benefit from ICD implantation?

The European Society of Cardiology Guidelines recommend a patient-centred approach to communicating the risks and benefits of ICD therapy.[4] Implantation of an ICD is only recommended in patients who have an expectation of good quality survival of over 1 year.[4] However, the metrics that determine 'good quality survival' are obscure. Clinical risk scores can be employed to facilitate joint decision-making with patients but these tools should not be relied on to make decisions about ICD implantation.

As patients age and accumulate comorbidities, the risk of non-cardiac death from competitive causes increases. Such 'competing risks of death' reduce the potential benefit of ICD therapy on overall mortality.[4] Patients dying from non-cardiac comorbidities, who have not received any appropriate ICD therapy, gain no benefit from ICD implantation, and this patient group is not well characterised.

This study evaluates real world ICD clinical practice, reporting the assessment of comorbidities, frailty and self-reported health status as competitors to sudden cardiac death (SCD) for mortality in ICD recipients who never receive appropriate ICD therapy.

METHODS

A prospective, multicentre, cohort observational study involving 12 English hospitals was undertaken of real-world ICD implantation clinical practice. Two of these hospitals were tertiary referral centres: Southampton General Hospital, St Bartholomew Hospitals London. The remaining nine participating centres are district general hospitals, Airedale General Hospital, Barnet Hospital, Salisbury General Hospital, Calderdale Royal Hospital and Huddersfield Royal Infirmary (as one Trust), Dorset County Hospital, The Shrewsbury and Telford Hospital NHS Trust, Russells Hall Hospital, Dudley, Ashford and St. Peter's Hospitals NHS Foundation Trust, Watford General Hospital and Portsmouth General Hospital. Patients were eligible for inclusion in the study if they were scheduled to have a de novo, replacement or upgrade to a transvenous or subcutaneous ICD or cardiac resynchronisation therapy device and defibrillator (CRT-D). Exclusion criteria were inability to provide informed consent due to the presence of dementia or other psychological illness, or having been previously enrolled in the study. Baseline characteristics collected were age, gender, device type, LV function, medication, baseline blood assays (if available) and recruits were asked to complete the Fried score frailty assessment and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) self-reporting health status questionnaire. Precise ejection fraction (EF) figures were not available for all patients and so LV systolic function was graded in the following way if EFs had been quoted: normal LV systolic impairment, EF >55%; mild LV systolic impairment, EF=45%–54%, moderate LV systolic impairment, EF=36%–44%, severe LV systolic impairment, EF ≤35%.

The Fried score is an easy to use, validated tool, to diagnose frailty. The following parameters are measured: weight loss, exhaustion, low physical activity, slowness and weakness. Patients are classified frail (score 3–5), pre-frail (score 1–2) and not frail (score 0–1).[5] The EQ-5D-5L is a brief, health status measure comprises five questions and is a descriptive system of five dimensions of health (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), each with five levels of severity (no problems, slight problems, moderate problems, severe problems, and unable to perform or extreme problems).[6]

The Charlson Comorbidity Index score was calculated. The Charlson Comorbidity Index is a widely used tool to classify comorbidities and may influence mortality. 19 co-comorbidities are assessed, each with different weighting and score. Comorbidity is then classified as mild, with comorbidity scores of 1–2; moderate, with comorbidity scores of 3–4; and severe, with comorbidity scores ≥5.

Follow-up was at 2.5 years. Researchers at the lead site contacted other sites at follow-up to determine survival and presence or absence of ICD discharge.

Statistical analysis

Continuous variables are reported as mean±SD or median (IQR), with p values calculated by paired Student's t-test. Categorical variables are summarised with patient count and percentage, with paired change from baseline p values calculated by Wilcoxon signed-rank test. All statistical analyses were performed in R (V.4.2.0). Kaplan-Meier survival plots were generated using the R survival package (V.3.4.0). The EQ-5D-5L index score calculation was calculated in the shiny web interface.[7]

All multivariate logistic regression models were implemented, using the R caret package[8] following data pre-processing and multicollinearity checks between variables. Multicollinearity was detected between urea and creatinine, CRT-D and dual and single chamber ICDs and between pre-frail and not-frail. Subsequently the creatinine, CRT-D and not-frail variables were removed from further analysis. Medications were removed from the further analysis to reduce the risk of oversampling. The minority class imbalance (of death with no appropriate therapy as an outcome) with the majority class (of survival with no previous appropriate therapy and received appropriate therapy as an outcome) was addressed by synthetic minority oversampling technique

with k nearest neighbours sampling set to 5 and dup_size (the number of times to duplicate the minority class) to 10.

RESULTS

In total, 675 patients were enrolled, mean age 65.7 years (IQR 65–75) and 77.3% were male. Recruitment commenced on 11 March 2015 and ended on 29 March 2018. Follow-up commenced on 25 September 2017 and ended on 23 February 2021. Median follow-up was 2.6 years and the longest follow-up was 4.7 years. The baseline characteristics for the population are presented in table 1. A total of 63 patients (9.5%) died across this period with overall survival probability estimated to be 95% at 1 year and 90.2% at 2.5 years. In total, 54 patients (8.1%) received appropriate therapy (anti-tachycardia pacing and shocks) during follow-up.

Death with no prior appropriate therapy

58 (8.6%) patients died without receiving appropriate therapy (non-arrhythmic death). Patients with non-arrhythmic death were older (71.4±11.3 years vs 65.1±13.5 years; p<0.001), had worse renal function (estimated glomerular filtration rate (eGFR) 56.5±23.3 mL/min/1.73m^2 vs 72.9±43.3 mL/min/1.73m^2; p=0.037), a lower haemoglobin level (129±18.1 g/L vs 137±16.2 g/L; p=0.001), were more likely to have a history of congestive cardiac failure (35/58 (60.%) vs 252/617 (40.8%); p=0.004), peripheral vascular disease (8/58 (13.8%) vs 24/617 (3.9%); p=0.004) and cerebrovascular disease (12/58 (20.7%) vs 64/617 (10.4%); p=0.018). They also had higher rates of severe LV systolic dysfunction, more comorbidities as measured by the Charlson Comorbidity Index, more frailty and scored lower on the EQ-5D-5L.

Statin use (OR 0.48, p=0.02, 95% CI 0.26 to 0.88), ACE inhibitor use (OR 0.5, p=0.01, 95% CI 0.26 to 0.96) and mineralocorticoid receptor antagonist use (OR 0.49, p=0.04, 95% CI 0.25 to 0.95) were associated with a lower risk of death with no prior appropriate therapy. A non-significant association was seen with angiotensin II receptor antagonist and aspirin use (OR 0.56, p=0.06, 95% CI 0.26 to 0.96).

The use of loop diuretics (OR 2.34, p=0.01, 95% CI 1.19 to 4.68) and anticoagulants (OR 2.31, p=0.01, 95% CI 1.28 to 4.24) were associated with higher risk of death with no prior appropriate therapy.

Multivariate predictors of death with no appropriate therapy were identified and a risk score comprising age, the components of the Fried score, Charlson Comorbidity Index, eGFR, EQ-5D-5L was developed (table 2). The model performance was sensitivity=0.684; specificity=0.80; accuracy=0.694, negative predictive value (precision)=0.198; and area under receiver operator curve=0.742. Further information on model performance, referring hospitals and overall survial of the cohort can be found in the online supplemental file.

Comorbidities

Comorbidities as measured by the Charlson Comorbidity Index were present in 315/675 (52.9%) of the study population. Patients with severe comorbidity had a reduced survival compared with others (figure 1). Overall, 69 (10.2%) were classified as having severe comorbidity (Charlson Comorbidity Index score of ≥5). The estimated survival probability at 2.5 years was estimated to be 74% in patients with severe comorbidity versus approximately 87% in patients with moderate and 92% with mild comorbidly and 98% with no comorbidity. A patient with severe comorbidity was more likely to experience a non-arrhythmic death compared with a patient with either no-, mild- or moderate comorbidity, OR=4.5 (95% CI 2.3 to 8.5).

Frailty

Frailty, as measured by the Fried score was present in 83/675 (12.7%) of the study population. Frail patients had a reduced survival compared with non-frail and pre-frail patients (figure 2). The estimated survival probability estimated to be 68% in frail patients versus 90.2% in non-frail patients at 2.5 years. A frail patient was more likely to experience a non-arrhythmic death compared with a non-frail patient OR=8.1 (95% CI 4.5 to 14.7).

Frailty and comorbidity

The presence of frailty and comorbidity were distinct entities. Of patients with severe comorbidity, 18 (26%) were frail, 28 (40.6%) were pre-frail and 23 (33.3%) were not frail. Similarly, of frail patients, 18 (21.7%) had severe comorbidity, 22 (26.5%) had moderate comorbidity, 36 (43.3%) had mild comorbidity, 7 (8.4%) had no-comorbidities.

DISCUSSION

We have found that the presence of comorbidities, in particular severe comorbidity, and the presence of frailty, were strong predictors for death with no prior appropriate therapy in patients with ICDs. Patients with higher health-related quality of life scores, as measured by the EQ-5D-5L instrument at the time of enrolment in this study, were significantly less likely to die from non-arrhythmic death. Other variables identified as being predictive of death with no prior appropriate therapy were LV systolic (any severity), lower eGFR levels, lower haemoglobin levels. Age, as a continuous variable, was not a predictor of non-arrhythmic death in a logistic regression model, however, when dichotomised into those aged more than or less than 70 years, it was.

There is considerable evidence to support which patient populations derive benefit from ICD therapy.[4] However, most patients who receive an ICD do not go on to receive appropriate therapy. Clinical practice guidelines suggests that ‘it is of paramount importance to consider the patient’s life expectancy, quality of life, and comorbidities’ and ‘in general, the SCD risk needs

Table 1 Baseline characteristics of study population with patients who had a non-arrhythmic death compared with those who did not have a non-arrhythmic death

	All	Non-arrhythmic death	Combined group (no appropriate therapy and group with appropriate therapy)	P value
	675	58	617	
Age (years)	65.7±13.43	71.4±11.3	65.1±13.5	<0.001*
Males	522	51 (87.93%)	471 (76.34%)	0.0484
Cardiac implantable electronic device type	665	57	608	0.0534
CRT-D	303	33 (57.89%)	270 (44.41%)	
Transvenous ICD	329	24 (42.11%)	305 (50.16%)	
Subcutaneous ICD	33	0 (0%)	33 (5.43%)	
Implant type	673	57	616	0.247
De novo	380	33 (57.89%)	347 (56.33%)	
Replacement	224	15 (26.32%)	209 (33.93%)	
Upgrade	69	9 (15.79%)	60 (9.74%)	
LV systolic function	613	53	560	0.0223
Normal	40	3 (5.66%)	37 (6.61%)	
Mildly impaired	97	11 (20.75%)	86 (15.36%)	
Moderately impaired	119	2 (3.77%)	117 (20.89%)	
Severely impaired	357	37 (69.81%)	320 (57.14%)	
ICD indication	671	57	614	0.394
Primary prevention	412	32 (56.14%)	380 (61.89%)	
Secondary prevention	259	25 (43.86%)	234 (38.11%)	
Body mass index (kg/m²)	29.3±6.57	29.1±6.04	29.3±6.62	0.971*
Blood results at baseline				
Sodium (mmol/L)	138±3.3	138±4.23	139±3.19	0.102*
Potassium (mmol/L)	4.49±0.42	4.55±0.46	4.48±0.41	0.268*
Urea (mmol/L)	7.94±3.53	10.2±4.61	7.72±3.34	<0.001*
Creatinine (µmol/L)	103±42.8	130±70.41	101±38.36	0.005*
eGFR (mL/min/1.73 m²)	71.5±42.22	56.5±23.34	72.9±43.33	<0.001*
Haemoglobin (g/L)	136±16.52	129±18.09	137±16.2	0.003*
White cell count ($\times 10^9$/L)	7.93±4.29	8.13±2.12	7.91±4.44	0.549*
Platelet count ($\times 10^9$/L)	230±68.05	247±90.68	228±65.43	0.152*
Medication				
Aspirin	209	13 (22.41%)	196 (31.77%)	0.141
Clopidogrel	78	10 (17.24%)	68 (11.02%)	0.157
ß-blockers	482	46 (79.31%)	436 (70.66%)	0.164
ACE inhibitor	297	19 (32.76%)	278 (45.06%)	0.0712
Angiotensin receptor blocker	147	15 (25.86%)	132 (21.39%)	0.431
MRA	281	28 (48.28%)	253 (41%)	0.283
Loop diuretic	281	35 (60.34%)	246 (39.87%)	0.00249
Statin	348	27 (46.55%)	321 (52.03%)	0.425*
Amiodarone	68	8 (13.79%)	60 (9.72%)	0.358
Anticoagulant	245	28 (48.28%)	217 (35.17%)	0.0472*
Immunosuppressants	40	3 (5.17%)	37 (6%)	1*
Comorbidities				
Myocardial infarction	278	27 (46.55%)	251 (40.68%)	0.385

Continued

Table 1 Continued

	All	Non-arrhythmic death	Combined group (no appropriate therapy and group with appropriate therapy)	P value
Congestive cardiac failure	287	35 (60.34%)	252 (40.84%)	0.004*
Peripheral vascular disease	32	8 (13.79%)	24 (3.89%)	0.004
Cerebrovascular disease	76	12 (20.69%)	64 (10.37%)	0.018*
Chronic liver disease	9	0 (0%)	9 (1.46%)	1
Diabetes mellitus	171	20 (34.48%)	151 (24.47%)	0.09
Chronic lung disease	123	13 (22.41%)	110 (17.83%)	0.39*
Connective tissue disease	24	2 (3.45%)	22 (3.57%)	1*
Dementia	4	0 (0%)	4 (0.65%)	1*
CKD III	62	9 (16.7%)	53 (8.6%)	0.080*
Tumour without metastases	3	3 (0.5%)	0 (0%)	1.0*
Tumour with metastases	3	0 (0%)	3 (5.6%)	1.0*
Charlson Comorbidity Index	675	58	617	<0.001
None	318	25 (43.1%)	293 (47.49%)	
Mild	131	14 (24.14%)	117 (18.96%)	
Moderate	157	3 (5.17%)	154 (24.96%)	
Severe	69	16 (27.59%)	53 (8.59%)	
Fried score	675	58	617	<0.001
Frail	86	26 (44.83%)	60 (9.72%)	
Pre-frail	335	14 (24.14%)	321 (52.03%)	
Not frail	254	18 (31.03%)	236 (38.25%)	
EQ-5D-5L index score	0.738±0.22	0.613±0.23	0.75±0.21	<0.001*

Transvenous ICD includes single or dual chamber.
Normal left ventricular systolic function, left ventricular ejection fraction (LVEF) >55%; mild left ventricular systolic function, LVEF=45%–54%; moderate left ventricular systolic function, LVEF=36%–44%; severe left ventricular systolic function, LVEF ≤35%.
*P value calculated using t-test; all others used χ test.
CKD, chronic kidney disease; CRT-D, cardiac resynchronisation therapy and defibrillator; eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol 5-Dimension 5-Level; ICD, implantable cardioverter defibrillator; LV, left ventricular; MRA, mineralocorticoid receptor antagonist.

to be weighed against the individual's competing risk of a non-arrhythmic death'.[4] However, there is little to guide the clinician on how to do this apart from suggesting the use of clinical risk scores such as the MADIT-ICD benefit score. This study helps correct this imbalance.

Table 2 Logistic regression model OR table for dichotomous variables

Feature	OR estimate	SE	Z-statistic	P value	CI lower limit	CI higher limit
Severe comorbidity	11.34	0.43	5.68	<0.001	5.01	26.93
Moderate comorbidity	3.95	0.37	3.70	<0.001	1.94	8.36
Mild comorbidity	3.63	0.34	3.75	<0.001	1.89	7.32
Frail	2.46	0.30	3.00	0.003	1.38	4.49
Age (years)	1.02	0.01	2.33	0.020	1.00	1.05
eGFR	0.99	0.00	−2.00	0.046	0.98	1.00
Pre-frail	0.42	0.24	−3.62	<0.001	0.26	0.67
EQ-5D-5L index score	0.07	0.61	−4.39	<0.001	0.02	0.22
(Intercept)	0.72	1.00	−0.33	0.741	0.10	5.09

Features are organised via decreasing OR value. The Z-statistic is the coefficient estimate divided by the SE which represents the confidence in the estimate. Both lower (5%) and upper (95%) CI limits are provided.
eGFR, estimated glomerular filtration rate; EQ-5D-5L, EuroQol 5-Dimension 5-Level.

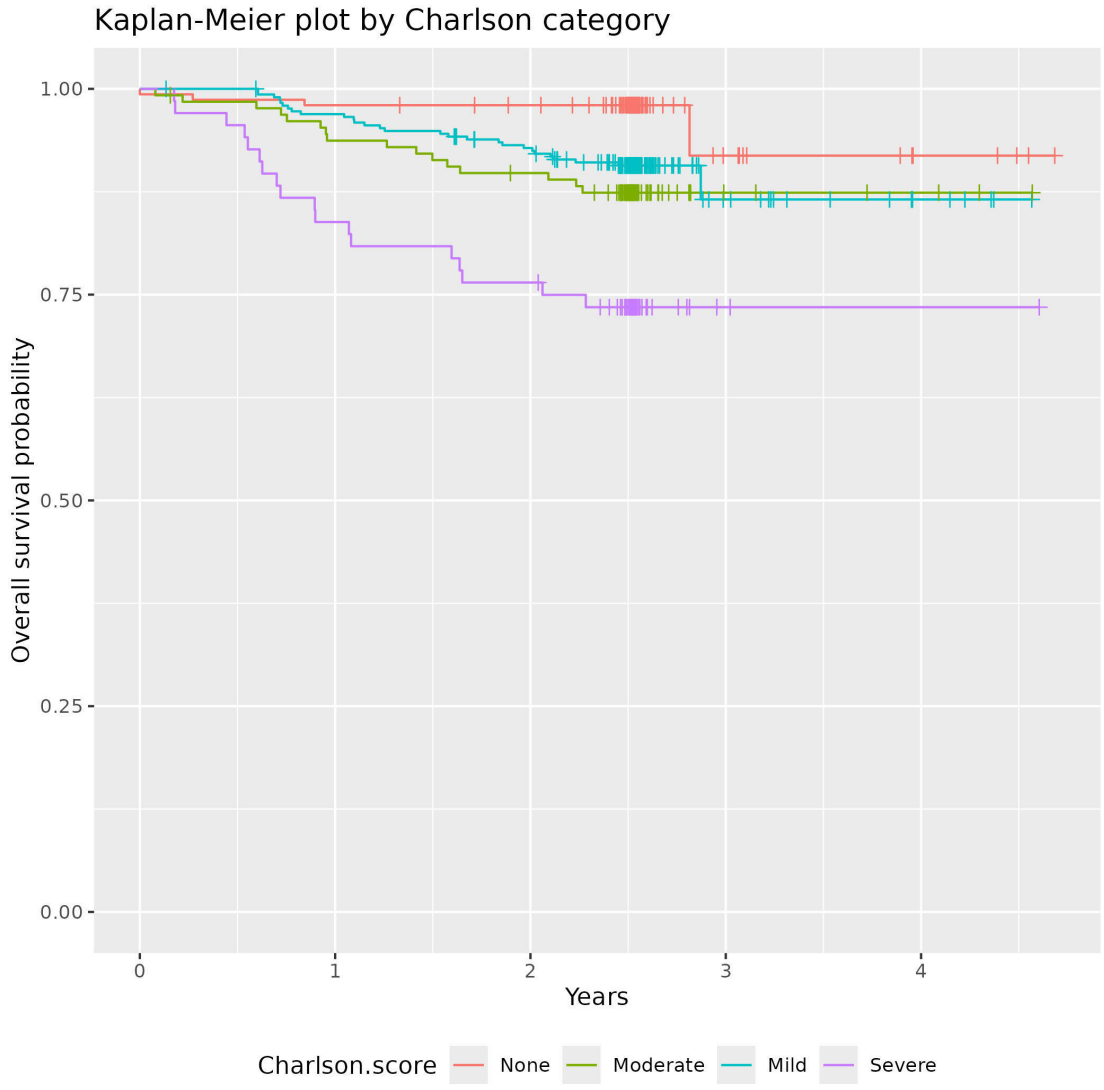

Figure 1 Multi-curve Kaplan-Meier survival plots based on comorbidity as measure by the Charlson Comorbidity Index.

Evidence of predictors of mortality in patients with ICDs

Several attempts have been made to identify patients with ICDs who have an elevated risk of mortality from clinical trial datasets. Most of these studies have used clinical characteristics that are also known to increase rates of appropriate therapy rather than other variables (such as frailty and comorbidities) which may be better at predicting non-arrhythmic death.

The older MADIT II score[9] had used five clinical characteristics—New York Heart Association (NYHA) functional class >2, age >70 years, blood urea nitrogen >26 mg/dL (9.3 mmol/L), QRS duration >120 ms and presence of atrial fibrillation. A U-shaped distribution of benefit from ICD therapy was observed; patients with either very low or very high risk derived less benefit than those with intermediate risk factors.

A risk score of mortality developed from a national registry of primary prevention ICD programme identified similar predictors of mortality to the MADIT II risk score (NYHA functional class >2, age >70 years, QRS duration, atrial fibrillation, eGFR <60 mL/min). Higher scores were associated with higher rates of non-arrhythmic death, with no differences in rates of appropriate therapy across categories.[10]

The MADIT-ICD risk score[11] combines eight predictors of VT/VF (male, age<75 years, prior non-sustained VT, heart rate>75 beats per minute, systolic blood pressure<140 mm Hg, ejection fraction≤25%, myocardial infarction and atrial arrhythmia) and seven predictors of non-arrhythmic mortality (age≥75 years, diabetes mellitus, body mass index<23 kg/m^2, ejection fraction≤25%, NYHA ≥II, ICD vs cardiac resynchronisation therapy with defibrillator and atrial arrhythmia). The two scores were combined to create three MADIT-ICD benefit groups. This score can identify patients win three groups: those with a high arrhythmia risk versus non-arrhythmic mortality (ICD net benefit), those with an attenuated arrhythmic risk versus mortality rate and those with an equivalent arrhythmic risk of ventricular arrhythmia and non-arrhythmic mortality (limited ICD benefit). The C-index for predicting non-arrhythmic death in the MADIT-ICD benefit score was 0.67 which is slightly lower

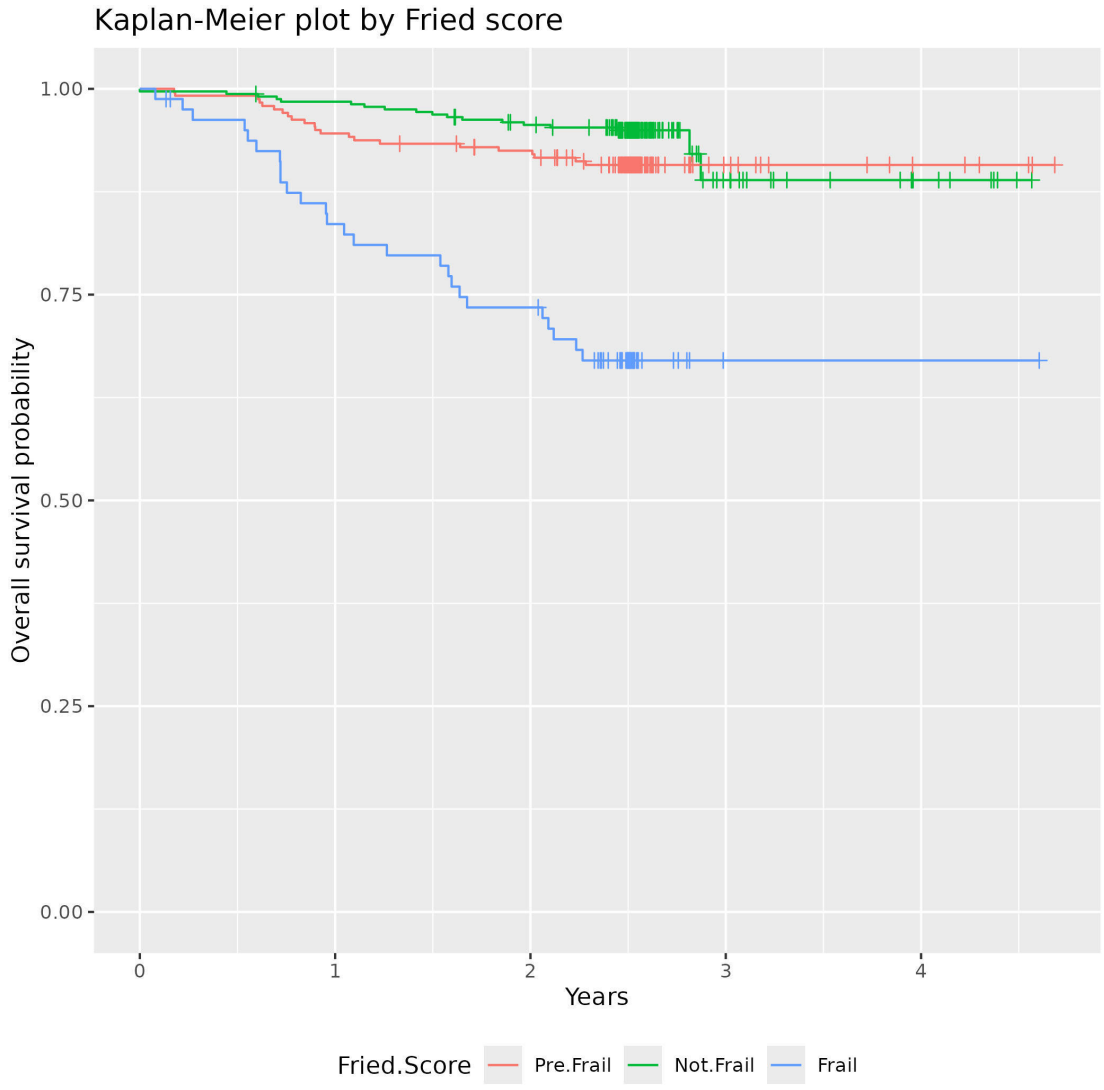

Figure 2 Multi-curve Kaplan-Meier survival plots based on frailty status (Fried score total).

than the area under the curve in our model at 0.74. This suggests that future risk models for non-arrhythmic death may be improved by using metrics such as frailty and severe comorbidity in the risk assessment.

In a secondary analysis from DINAMIT and SCD-HeFT trials as well as a meta-analysis of 36 clinical studies involving over 47 000 patients, factors that predicted arrhythmic death also predicted non-arrhythmic death.[12 13]

Use of comorbidity to assess competing risks for non-SCD death in ICD recipients

In the landmark studies that provided the evidence base that defines ICD implantation indication, patients who might have been considered by investigators for ICD therapy but were declined because physician investigators defined comorbidities in potential ICD recipients, out with of study-defined exclusion criteria were not included in registries to evaluate their outcomes. There have been several attempts since to define the impact of comorbidities that identify higher risk of mortality in ICD populations though none of these have combined these variables with an assessment of frailty.

The MAGGIC risk score is used to assess mortality risk in a heart failure population.[14] 13 clinical parameters are considered including age, renal function, smoking status, comorbidities (diabetes, chronic obstructive pulmonary disease) and use of heart failure prognostic medication. When applied to the OBSERVO-ICD registry, it proved moderately accurate (0.6, 95% CI 0.56 to 0.64) in predicting the competing risks of non-arrhythmic death in HFrEF ICD recipients.[15]

Patients enrolled in the MADIT-CRT trial who had moderate renal dysfunction had a higher risk of death without experiencing VT/VF was 3.5-fold higher in the low GFR group <52 (95% CI 2.38 to 5.12, p value <0.001).[16]

A 3359 patient-level combined analysis was conducted from four primary prevention ICD trials (MADIT I, MADIT II, DEFINITE and SCD-HeFT) and found that ICDs in diabetic patients did not reduce the risk of all-cause mortality over a follow-up of 2.6 years.[17]

Studies that have analysed a single or a combination of several comorbidities have reliably identified an ICD population with a higher risk of death with no appropriate therapy.[18 19]

In a single centre retrospective study from France, elderly patients with Charlson Comorbidity Index score ≥4 had the lowest survival after ICD implantation and little survival gain in case of appropriate defibrillator therapy.[20]

Our study has reproduced these studies' results; increased comorbidity increases the risk of death with no prior appropriate therapy. However, we have shown that the use of measures of frailty and of patient well-being in addition to measures of comorbidity measures is a more accurate predictor of death with no prior arrhythmic therapy in ICD recipients.

ICDs in the elderly

We found that patients with non-arrhythmic death were older than those who either survived with no appropriate therapy or those that had appropriate therapy. The evidence of benefit of ICD therapy in older adults is mixed. An analysis of secondary prevention trials over patients aged over 75 years found limited benefit in ICD therapy in this group due to higher rates of non-arrhythmic death.[21] There is a paucity data available from primary prevention ICD trials to support or refute the benefit of ICD therapy in the very elderly, as this population was excluded from trials. Thus, the evidence we have is based on registry, single- or multi-centre data analyses.

In a prospective Canadian registry of over 5000 ICD recipients, rates of death were higher in the older group but there were similar rates of appropriate therapy in both groups. Comparable results were reported from multi-centre studies of elderly ICD recipients.[22 23]

Frailty and ICDs

Few studies have formally assessed frailty in the context of ICD outcomes. Two randomised controlled trials have published post-hoc analyses of outcomes ICD stratified by physical activity as a surrogate marker of frailty and found that low physical activity, either by self-report or measured was associated with increased risk of mortality.

In the MADIT-II trial, low baseline physical function prior to ICD placement and low physical and mental component scores were both associated with increased death and heart failure hospitalisation. Participants with a baseline physical component score below the median 35 were nearly twice as likely to die (HR 1.89, 95% CI 1.34 to 2.65) as those with a score above the median.[24]

In the SCD-HEFT trial, the risk of mortality among those with ICD versus placebo was assessed by tertile of 6-minute walk test (6MWT) at baseline. Patients in the lowest tertile did not benefit from ICD therapy and had the highest rates of all-cause mortality compared with those in the highest and middle tertiles of 6MWT distances.[25]

A single centre study assessing the use of the NORTON pressure ulcer score,[26] a pressure ulcer scale that can also be used to assess frailty, to determine death with no appropriate therapy in ICD therapy was undertaken in 695 ICD recipients.[27] The cumulative probability of all-cause mortality within 1 year of ICD implantation in patients with low NORTON scale (worse outcome) was 30%, compared with 20% and 7% among patients with intermediate- and high-NORTON score results.

In an observational study from the USA involving 1703 ICD patients, poor functional status, low mean arterial pressure, diabetes, low body mass index and AF were strongly associated with death within a year.[28] These are all clinical parameters that are observed in the individuals with frailty, although in this study, the investigators did not specifically test for frailty.

Implications of current study

Several decades have passed since the original landmark studies that provide the core evidence base for ICD implantation. There is new interest in studies to define ICD implantation indications in the changed paradigm of modern heart failure treatments and an ageing population (PROVID EHRA Trial ClinicalTrials.gov ID NCT05665608 and the BRITISH trial, ClinicalTrials.gov ID NCT05568069). We believe this is the first study to combine use of comorbidity using the Charlson Comorbidity Index and frailty assessment, using a validated frailty tool, to determine the ICD outcomes and to help define patients who should not be considered for ICD therapy despite having risk markers for SCD. We have demonstrated powerful prognostic effect particularly on death with no prior appropriate therapy, a clinically important outcome in ICD therapy and offers the potential to aid clinical decision making in ICD implantation. This study addresses the 'knowledge gap' identified in the recently published EHRA expert consensus document on the management of arrhythmias in frailty syndrome.[29] As this study was a real world, pragmatically designed study involving 12 English hospitals (two tertiary referral centre and nine district general hospitals), we believe that the results are generalisable to a British ICD-recipient population.

The use of a frailty score provides additional value beyond age and comorbidities in predicting clinical outcomes in this study as patients with few comorbidities and lower age can still be classified as being frail and vice versa. We have also demonstrated a high rate of frailty in this ICD population with one in eight individuals in our study meeting the Fried diagnostic criteria for frailty.

Limitations

There are several limitations to this study. The effect estimates in our model are based on observational data and are therefore subject to potential bias. Selection bias may have occurred if investigators (consciously or unconsciously) enrolled patients who may have had either more or less frailty or comorbidity than they would in their usual

practice. We consider this to be unlikely as our inclusion and exclusion criteria had the fewest possible restrictions to eligibility in the study and the incidence of frailty in this cohort is identical to the incidence described by Kramer *et al* (12.6% vs 12.8%).[30]

While follow-up for mortality and for rates of appropriate therapy was high, 3.7% of data were missing, mostly reported among blood tests. Exhaustive attempts were made to contact sites where there were missing data but in many cases no baseline blood results were available as often patients had been referred to that site for the procedure from another hospital and blood tests had not been recorded. Missing eGFR scores were calculated using the Cockcroft-Gault formula, if the variables required to calculate this were available (1), and the remaining values missing across the dataset were imputed using the imputeFAMD() from the missMDA package (V.1.18).

While we have developed a risk score for the predictor of death prior to appropriate therapy this was not the primary objective of the study. This risk score is not suitable for clinical use and it has not been externally validated. Further work is required to validate such a score in another ICD population. Any future score should consider adding measures of severity of comorbidity, frailty and well-being as well as other parameters which we and others have found to be predictive of non-arrhythmic death. At present, using estimates of event rates from this study we suggest that a minimum sample size required for new model development=2350, with 118 events (assuming an outcome prevalence=0.05) and an estimated predictor parameter=11.75 (https://riskcalc.org/samplesize/) expected value of the (Cox-Snell) R^2 of the new model=0.5, number of candidate predictor parameters for potential inclusion in the new model=9, level of shrinkage desired at internal validation after developing the new model=0.9, event rate at 12 months 5% C-statistic=0.74). The score would then need to be incorporated with an arrhythmic risk score or be used alongside an existing arrhythmic risk score.

CONCLUSION

Severe comorbidity, frailty and self-reported health status are independent predictors of non-arrhythmic death in ICD/CRT-D recipients. Further research is warranted to validate these findings to help refine risk stratification of ICD recipients and prioritise ICD implantation in patients who are likely to have a good medium to long-term prognosis. Such measures may prove useful in joint decision-making discussions regarding ICD therapy.

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Contributors DW conceived the idea, wrote and submitted the ethical approval, designed the data collection template, coordinated the data assimilation, oversaw the data analysis, drafted the manuscript and submitted the manuscript. DW is the guarantor. AS-O provided oversight and guidance for the data and statistical analysis. JS and DFP performed the data and statistical analyses and image generation. JML provided oversight of data analysis. PR provided oversight of the running of the clinical study from the lead site, hosted the research grant and oversight of the clinical study. JMM refined the study idea with DW and provided overarching oversight and guidance for the whole clinical study.

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Patient and public involvement statement Patients and public were not involved in the design of this study.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and has been approved by Yorkshire and The Humber - Bradford Leeds Research Ethics Committee (14/YH/1315/AM01). Participants gave informed consent to participate in the study before taking part.

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