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Original clinical research study

Prognostic value of Charlson Comorbidity Index in the elderly with a cardioverter defibrillator implantation

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Key Words: Implantable cardioverter-defibrillator; Geriatrics; Sudden death; Heart failure; Ventricular tachycardia; Prevention;

STRUCTURED ABSTRACT (WC=248)

Background: Elderly patients are often underrepresented in implantable cardioverter defibrillator (ICD) trials, and ICD implantation in patients ≥ 75 years consequently remains controversial. We aimed to evaluate mortality, appropriate ICD therapy rates and survival gain in an elderly population after risk stratification according to the Charlson Comorbidity Index (CCI).

Methods: This monocentric retrospective study included elderly ICD patients ≥ 75 years. They were subdivided according to their CCI score into 3 categories (0-1, 2-3 or ≥ 4 points). Elderly patients were matched 1:2 with younger control ICD patients on gender, type of prevention (primary or secondary) and type of device (associated cardiac resynchronization therapy or not).

Results: Between January 2009 and July 2017, 121 elderly patients (mean age 78 ± 3 ; 83% male) matched with 242 controls (mean age 66 ± 5) were included. At 5 year follow-up after ICD implantation, overall survival was 78%, 57%, and 29% ($P=0.002$) in the elderly according to their CCI category respectively, and 72% in controls. There was no significant difference regarding ICD appropriate therapy between the 3 subgroups despite a trend towards lower rates of therapy in $CCI \geq 4$ points patients (34.2%, 39.7% and 22.8% respectively; $P=0.45$). Median potential survival gain after an appropriate therapy was >5 , 4.7 and 1.4 years, respectively ($P=0.01$).

Conclusion: Elderly patients with CCI score ≥ 4 had the lowest survival after ICD implantation and little survival gain in case of appropriate defibrillator therapy. More than age alone, the burden of comorbidities assessed by the CCI could be helpful to better select elderly patients for ICD implantation.

KEY WORDS: Implantable cardioverter-defibrillator; Geriatrics; Sudden death; Heart failure; Ventricular tachycardia; Prevention;

1. INTRODUCTION

Even though by now, the benefits of implantable cardioverter defibrillator (ICD) have been clearly established in many indications, potential overuse of this therapy has been pointed out by different studies and its cost-effectiveness is also being debated [1].

In elderly patients, comorbidities have a meaningful impact on life expectancy, which may increase competing risk with arrhythmic death and therefore reduce overall effectiveness of ICD therapy [2]. Moreover, there is a lack of evidence-based data regarding the benefit of ICD therapy in elderly patients, since most individuals enrolled in large randomized trials have been < 70 years old [3,4]. This selected population contrasts with real-life older comorbid patients, who may theoretically be eligible for an ICD implantation [5].

Several studies have identified variables of interest to stratify non-sudden cardiac death and while different scores have been published, they are not used in clinical practice, due to their complexity or lack of external validity [3, 6-8]. The Charlson Comorbidity Index (CCI) is a simple standardized score used to predict mortality with respect to the weight of comorbidities in diverse pathologies [9,10].

This study aimed to assess whether the CCI, a simple standardized score, could be valuable to stratify ICD therapy usefulness regarding survival, occurrence of appropriate shock and potential survival gain in elderly patients ≥ 75 years old.

2. METHODS

2.1. Study design

This retrospective single-center registry included consecutive elderly patients who were referred to our institution for ICD implantation between January 2009 and July 2017.

Inclusion criteria were: i) Patient ≥ 75 years at the time of implantation; ii) *De novo* primary

or secondary prevention ICD implantation (including up-grading from pacemaker to defibrillator therapy).

To obtain a point of comparison, these elderly patients were matched with control adult patients, aged < 75 years at the time of their ICD implantation, who were implanted over the same period. Matching was performed with a 1:2 fashion (elderly/control patients) according to gender, indication (primary or secondary prevention) and device type (associated cardiac resynchronization therapy (CRT) or not). The study was conducted according to the ethical principles of the Declaration of Helsinki and the current guidelines for good clinical practice. The local ethics committee approved the study. Every patient admitted at the University Hospital Center of Poitiers is informed that their data could be anonymously used for research in our center unless they express their refusal. Specific information about this study was delivered and oral consent was obtained from all patients who were still alive at the time of data collection. Data files were declared to the French data protection committee (Commission Nationale Informatique et Liberté, CNIL, N° CHU86-R2018-12-04).

2.2. Patient characteristics

Medical history and baseline characteristics at the time of ICD implantation were extracted from the Poitiers University Hospital Center electronic medical database, gathering together hospitalization and consultation reports. If necessary, general practitioners and referring cardiologists were contacted to provide missing information.

Underlying cardiomyopathy was categorized as ischemic or non-ischemic cardiomyopathy. History of atrial fibrillation, New-York Heart Association functional class and left ventricular ejection fraction assessed with echocardiography performed during the month before the implantation were collected. PR interval and QRS duration were measured on a 12-lead electrocardiogram recorded less than 24 hours before the time of the procedure.

Three biological parameters, assayed the day before implantation, were considered: hemoglobin (g/dL), serum creatinine ($\mu\text{mol/L}$), and N-terminal pro B-type Natriuretic Peptide (ng/L). Cardiovascular medications such as beta-blocker, amiodarone, calcium inhibitor, anticoagulant or anti-platelet therapy were collected.

2.3. Charlson Comorbidity Index (CCI)

We used the CCI to assess elderly patients' comorbidities before ICD implantation [10]. All the variables of the CCI are detailed in Supplementary Table A and were completed on the day before the procedure, with a score ranging from 0 to 10 points. Elderly patients were stratified according to their CCI into 3 categories 0-1 point, 2-3 points and ≥ 4 points. The cut-off values were chosen to allow the best homogeneous proportion between classes (n=46 for CCI 0-1, n=49 for CCI 2-3, n=26 for CCI ≥ 4).

2.4. Follow-up

Follow-up was conducted through 6 month-interval face-to-face clinical visits, of which the variables were prospectively entered in the hospital database. If needed, phone contact with the referring cardiologists or general practitioners was performed. Patients were considered lost to follow-up if they did not complete 2 consecutive follow-up visits, and if their vital status was unknown after contacting cardiologist, or general practitioner. Follow-up was complete in 363 patients (100%). Median follow-up was 4.6 [2.8-6.6] years, and maximum follow-up reached 9.0 years.

2.5. Endpoints

The events taken into account during follow-up were death from any cause and occurrence of appropriate ICD therapy (anti-tachycardia-pacing and/or shock). In case of multiple shocks or

spacing over time, follow-up was censored at first event. Date of the first appropriate therapy was obtained through device interrogation reports and/or by screening the clinical reports. Vital status was obtained from the hospital database and was systematically corroborated through the French National Institute for Statistics and Economic Research, which is a nationwide database on medical causes of death.

The primary endpoint was all-cause mortality. The secondary endpoints were occurrence of the first appropriate therapy and potential survival gain [11]. Potential survival gain is the life prolongation after a successful ICD intervention on the first potentially lethal ventricular arrhythmia. It is median survival estimated and calculated only for patients having experienced at least one appropriate therapy.

2.6. Statistical Analysis

Continuous variables were expressed as mean and standard deviation or median and interquartile range as appropriate, and categorical variables were presented as numbers and percentages. Comparisons between groups were performed using Student t-tests or Mann-Whitney tests for continuous variables as appropriate, and Chi2 test for categorical variables. For overall mortality, survival curves were composed using Kaplan-Meier estimates and subgroups were compared using the Log-rank test. One-year and five-years death rates were expressed as percentage and standard error. For probability of an ICD appropriate therapy occurrence, cumulative incidence curves were built and compared using the Fine and Gray competing risk model. One-year and five-year probabilities for occurrence of an appropriate therapy were expressed as percentage and standard error. Proportional hazards regression was used to identify predictors of all-cause mortality, while analysis on appropriate shocks was performed using the Fine–Gray model to obtain subdistribution hazard ratios, thereby taking the competing risk of death into consideration. The variables associated with the prognosis

with $P < 0.20$ on the univariate analysis, were entered in a multivariate model and selected using a backward elimination procedure. Basic serum creatinin levels were dichotomized at $177 \mu\text{mol/L}$ (2 mg/dl) for these analyses, as previously published [6]. Analyses were performed using SPSS 22 (SPSS, Inc., Chicago, IL, USA) and SAS 9.3 (SAS Institute, Inc., Cary, NC, USA) statistical software.

3. RESULTS

3.1. Population characteristics

A total of 121 patients (mean age 78.0 ± 2.6 years; 83% males) ≥ 75 years-old at the time of ICD implantation were enrolled in this study. Of them, 89 (74%) were implanted for primary prevention of sudden cardiac death and 62 (51%) had cardiac resynchronization therapy. Baseline characteristics of elderly patients are detailed in Table 1. Age, sex, body mass index and NYHA class were not statistically different between the 3 subgroups. As expected, numerous differences were found, with many more comorbidities in patients with the highest CCI score.

Elderly patients were compared to 242 controls (mean age 66.1 ± 5.2 years, 83% males). There was no significant difference between the two groups regarding history of hypertension, diabetes, atrial fibrillation and type of cardiomyopathy. Ischemic cardiomyopathy was the most represented underlying heart disease in both groups. Compared to controls, elderly patients exhibited higher rates of cancer history (16.5% vs 9.1%, $P=0.04$), mild cognitive impairment (4.1% vs 0%, $P=0.004$), higher N-terminal pro B-type Natriuretic Peptide blood level ($4\ 638 \pm 6\ 351 \text{ ng/L}$ vs $2\ 607 \pm 3\ 405 \text{ ng/L}$, $P=0.004$) and longer PR interval ($210 \pm 44 \text{ ms}$ vs $196 \pm 38 \text{ ms}$, $P=0.009$). Supplementary Table B shows baseline characteristic comparison between elderly and controls.

3.2. Follow-up and survival analysis

Median follow-up after implantation of the device was 4.3 [2.3- 6.5] years for elderly patients and 4.8 [3.0- 6.6] years for controls (P=0.11).

Death occurred in 47 (38.8%) patients in the elderly group (Supplementary Table D). Among them, 13 (26.5%) had CCI 0-1, 16 (34.8%) had CCI 2-3 and 18 (38.8%) had CCI \geq 4. The most frequent cause of death was heart failure (n=24, 51.0%) distributed as follows: 6 (46.2%) in CCI 0-1 group, 8 (50.0%) in CCI 2-3 group and 10 (55.6%) in CCI \geq 4 group. Neoplasia and sepsis both accounted for 5 (10.6%) deaths. Sepsis was the cause of death in 1 (7.7%) patient in CCI 0-1 group, 2 (12.5%) patients in CCI 2-3 group and 2 (12.5%) patients in CCI \geq 4 group. Neoplasia was the cause of the death in 0 patients for CCI 0-1 group, 2 (12.5%) patients for CCI 2-3 group and 3 (16.7%) patients in CCI \geq 4 group.

Median survival was superior to 6 years for controls and for elderly with a CCI score \leq 1 point, 5.7 years for elderly with CCI 2-3 points and 2.7 years for elderly group with CCI score \geq 4 points. Figure 1 displays Kaplan Meier estimates of survival in the elderly group stratified by CCI score. Survival was significantly different between the 3 subgroups (P<0.001). One-year and five-year death rates were 4.4 \pm 3.0 % and 21.9 \pm 8.0 % for elderly with CCI score 0-1 point, 12.3 \pm 4.7 % and 43.5 \pm 8.9% for CCI score 2-3 points, 23.1 \pm 8.3 % and 71.0 \pm 9.8% in case of CCI score \geq 4. Mortality among patients with CCI 2-3 was not significantly higher than among patients with CCI 0-1 (HR = 1.45; 95% CI 0.69 – 3.04; P=0.33). Mortality was significantly higher among patients with CCI \geq 4 compared to both patients with CCI 0-1 (HR = 3.45; 95% CI 1.65 – 7.21; P=0.001) and patients with CCI 2-3 (HR = 2.43; 95% CI 1.25 – 4.72; P=0.009). In controls, one-year and five-year death rates were 9.1 \pm 1.9 % and 27.8 \pm 3.3 % respectively. Mortality among patients with CCI 0-1 was

not significantly different than among controls (HR = 1.04; 95% CI: 0.56 – 1.92; P=0.91). In multivariate analysis (Table 2), only a CCI score ≥ 4 (HR = 2.91; 95% CI 1.37 – 6.20; P=0.006) and a creatinin level ≥ 177 $\mu\text{mol/L}$ (HR = 2.75; 95% CI: 1.20 – 6.32; P=0.02) were independently associated with all-cause mortality after ICD implantation.

Cumulative incidence of first appropriate therapy was not significantly different between the 3 elderly subgroups according to their CCI category (P=0.45) (Figure 2). One-year and five-year probabilities for occurrence of an appropriate therapy after implantation were 11.6 ± 3.1 % and 34.2 ± 6.7 % for CCI 0-1 category, 13.8 ± 4.0 % and 39.7 ± 9.0 % for CCI 2-3 group, and 7.3 ± 3.1 % and 22.8 ± 8.6 % for CCI ≥ 4 group. In the control group, one-year and five-year probabilities for occurrence of an appropriate therapy after implantation were 7.5 ± 1.4 % and 23.4 ± 2.9 % respectively. CCI category was not significantly associated with appropriate therapy in multivariate analysis (Supplementary Table C). Only secondary prevention ICD indication was associated with a higher rate of appropriate therapy: HR = 3.13; 95% CI 1.41 – 6.95; P=0.005.

Finally, median potential survival gain, defined as the life prolongation after a successful appropriate ICD intervention, was >5.0 [1.9; -], 4.7 [1.2; -], and 1.4 [0.4; 2.5] years in CCI 0-1, CCI 2-3 and CCI ≥ 4 groups respectively (P=0.01). In terms of comparison, the median potential survival gain was 5.7 [2.49; -] years in the control group.

4. DISCUSSION

The current study assessed the triage value of CCI regarding mortality, appropriate therapy rates and survival gain after therapy in ICD recipients ≥ 75 years. The main findings can be summarized as follows: i) Prognosis after ICD implantation in the elderly population is heterogeneous ii) For elderly with few comorbidities (CCI 0-1 point), survival after ICD

implantation was not significantly different than in the control group, of which the mean age was 66 ± 5 years) iii) a high comorbidity burden, defined as a CCI score ≥ 4 , was associated with a 3-fold increased risk of 5-year all-cause mortality compared to CCI 0-1, as well as the lowest cumulative incidence of first appropriate therapy and potential gain of survival

4.1. Lack of scientific evidence for defibrillator therapy in the elderly population

Current guidelines do not specify an age limit for ICD implantation and the number of elderly patients with a theoretical indication of ICD is increasing due to population ageing [12,13]. However, the results of ICD implantation in the elderly are controversial, both for primary and secondary prevention. Huang et al. analyzed 204 elderly patients from the MADIT II trial and did not find a significant mortality reduction in ICD patients >75 years as compared to medical therapy alone [14]. Consistently, a meta-analysis of three randomized trials failed to show a significant decrease in mortality for ICD patients ≥ 75 years, as compared to medical therapy alone, in secondary prevention of sudden cardiac death [15]. A recent article showed that age ≥ 70 years was associated with a 1.8-fold higher risk of dying ≤ 1 year after ICD implantation [16]. Finally, survival was not improved in elderly when defibrillation was added to CRT in a retrospective study [17, 18]. Clearly, a large randomized trial specifically designed to assess the usefulness of ICD implantation in the elderly population is needed.

Moreover, elderly patients require careful evaluation since they often exhibit numerous comorbidities. While a decision of ICD implantation in the elderly should involve a multidisciplinary team, including cardiologists and geriatricians, but no simple tool has been validated to standardize clinical practice and to help practitioners to identify patients in whom implantation may be futile [5,19]. This study showed that the CCI may represent a useful and simple tool to better select elderly patients who would benefit the most from an ICD implantation, and to avoid potential futile implantations.

4.2. Charlson comorbidity index, a simple and standardized score

We found that 5-year mortality was more than 3 times higher in elderly patients with CCI class ≥ 4 group compared to CCI ≤ 1 group whereas 5-year probability of appropriate therapy was lower. Competing risk between arrhythmic death and other causes of death is difficult to assess despite different statistical approaches [20]. CCI score is a simple score, which has already demonstrated its usefulness in patients with different heart diseases as a means of predicting overall mortality [21]. In the present study, we have shown for the first time its interest among elderly patients implanted with an ICD. In multivariate analysis, a CCI score ≥ 4 was indeed significantly and independently associated with lower long-term survival in this particular population. Several studies developed scores to determine mortality in ICD recipients. Barsheshet et al. used age, heart failure functional class, blood urea nitrogen, QRS duration, and atrial fibrillation in their score to explore the 8-year survival benefit of ICD among 1,119 patients. The 5-year survival was 85% in patients with low risk (0 risk factor), 62% in patients with intermediate risk (1 or 2 risk factors), and 36% in patients at high risk (≥ 2 risk factors) [22]. This study used a much larger cohort than ours, but appropriate therapy and potential survival gain were not assessed. Levy et al published the Seattle Heart Failure Model, which comprised NYHA class, ischemic etiology, diuretic dose, ejection fraction, systolic blood pressure, sodium, hemoglobin, percent lymphocytes, uric acid, and cholesterol [23]. Even if this score might be more robust because it was created with a larger cohort, it uses more sophisticated items and is, as a result, less convenient. Moreover, it has been developed in cohorts older than 15 years. Since then, medical therapy has evolved considerably. Finally, Kraaier et al developed a simple clinical risk score to predict <1-year mortality after ICD implantation based on 4 variables: age ≥ 75 years, LVEF $\leq 20\%$, history of atrial fibrillation, and estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73 m².

Patients with ≥ 3 risk factors had 1-year survival of 61.1% in the prediction cohort and 53.7% in the validation cohort [7]. These 3 works assessed the global mortality in ICD recipients regardless of age and did not focus on the usefulness of ICD in the elderly.

4.3. Beyond mortality: Potential Survival gain

Some data advocate for ICD usefulness in the elderly. For example, Zakine et al found that 19.4% of ICD recipients ≥ 80 years received at least one appropriate therapy before dying [25]. Nevertheless, this does not assume the benefit of therapy on life expectancy. Potential survival gain is an estimation of the life prolongation after occurrence of a first appropriate therapy [6,26]. This notion may be of peculiar interest in elderly patients, with a more limited life expectancy than younger patients, and is a cornerstone for discussion regarding ICD usefulness. In the present study, 50% of the elderly with CCI score ≥ 4 were dead 1.4 year after their first appropriate therapy: a high co-morbid burden is not only associated with low life expectancy after ICD implantation, but is also associated with a poor life prolongation despite appropriate ICD intervention.

4.5. Study limitations

This is a monocentric and retrospective study with a limited sample size. Larger prospective trials are needed to confirm these preliminary results. However, the monocentric nature of this study allowed for homogeneous treatment and follow-up of the population. Due to the retrospective nature of the present study, only the efficacy or usefulness of ICD were considered, not quality-of-life parameters. Moreover, ACE inhibitors and eplerenone therapy were not collected and this may have impacted the results. Finally, presumably not all patients ≥ 75 years with ICD indication were implanted, which may constitute a bias.

5. CONCLUSION

In this community-based of elderly patients, comorbidities were found to have a major impact on prognosis after defibrillator implantation. A CCI score ≥ 4 was significantly associated with higher mortality rates and limited survival gain despite appropriate therapy. In order to better detect elderly subjects who may derive less benefit of ICD implantation, a comorbid burden assessment using the CCI appears simple and relevant.

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CONFLICT OF INTEREST

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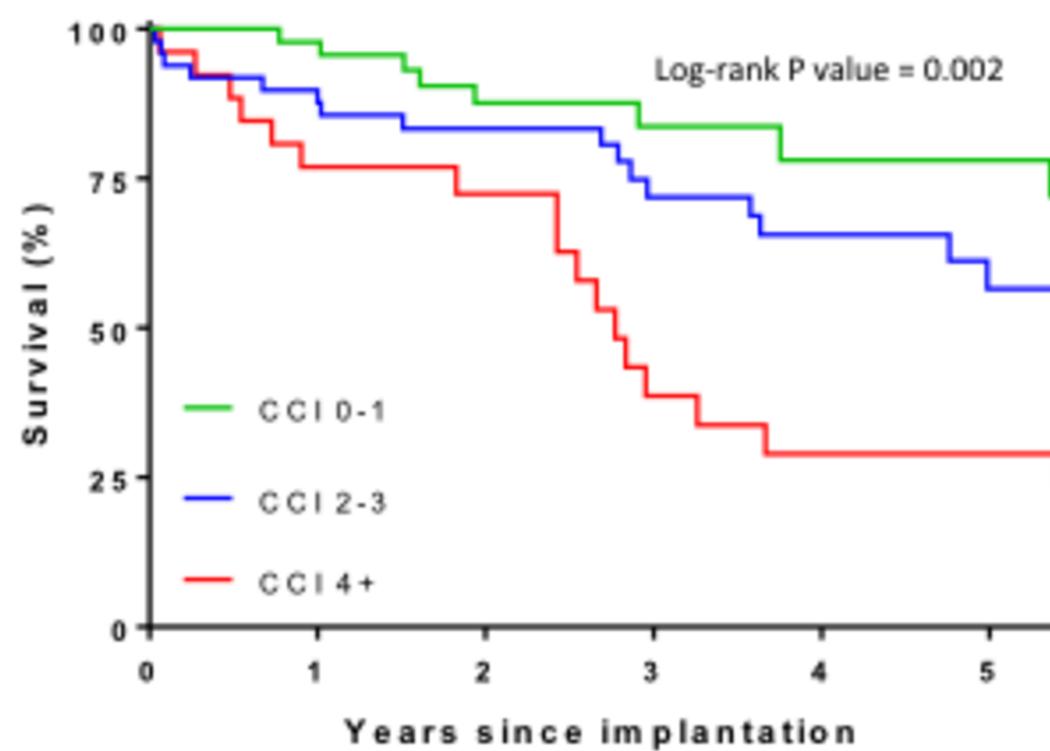
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FIGURE CAPTIONS

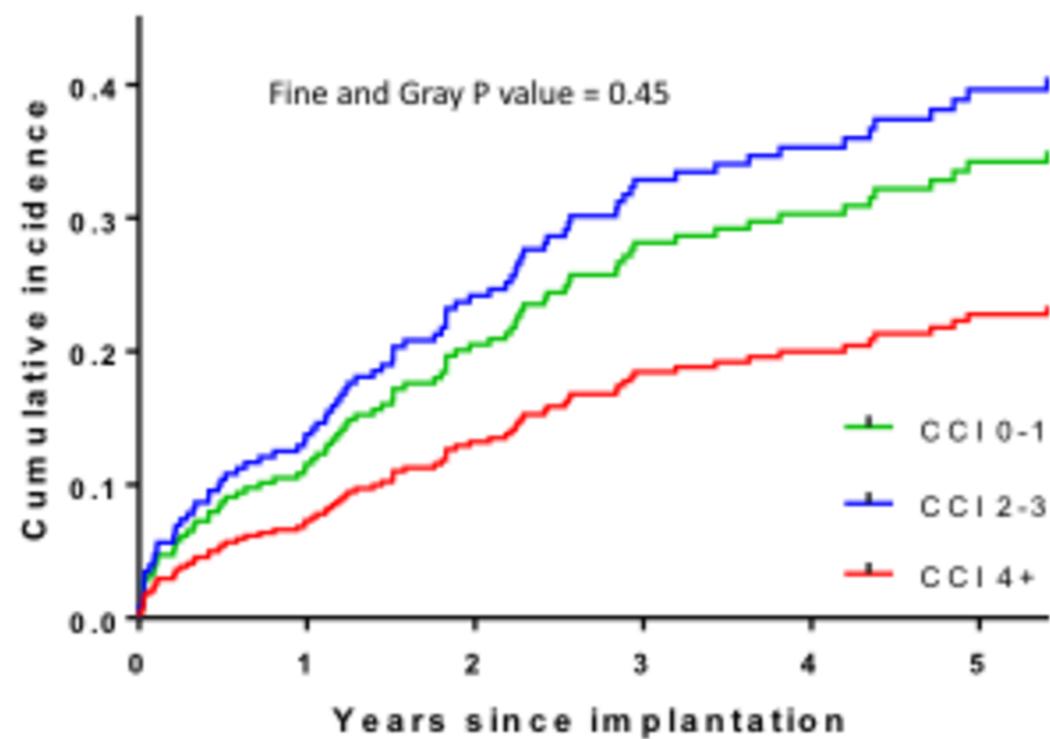
Figure 1. Kaplan Meier curves of overall mortality after ICD implantation in elderly patients according to 3 subgroups: CCI score ≤ 1 , CCI score 2-3 and CCI score ≥ 4 .

Figure 2. Cumulative incidence of first appropriate therapy in elderly patients according to 3 subgroups: CCI score ≤ 1 , CCI score 2-3 and CCI score ≥ 4 .



NAR:

CCI 0-1	46	45	30	20	14	14
CCI 2-3	49	42	33	24	17	12
CCI ≥4	26	20	16	8	6	3



NAR:

CCI 0-1	46	45	30	20	14	14
CCI 2-3	49	42	33	24	17	12
CCI ≥4	26	20	16	8	6	3

Triage value of the Charlson Comorbidity Index (CCI) in patient with an ICD indication after 75 years

Patients were categorized according to 3 groups: CCI ≤ 1 , CCI 2-3 or CCI ≥ 4 points

5-year Mortality

- 22% in CCI ≤ 1
- 43% in CCI 2-3
- 81% in CCI ≥ 4

Appropriate therapy

- No significant difference between groups

Median survival gain

- ≥ 5 years in CCI ≤ 1
- 4.7 years in CCI 2-3
- 1.4 years in CCI ≥ 4

Patients with CCI ≥ 4 points had the lowest survival and little survival gain in case of appropriate therapy

Table 1 Baseline characteristics among elderly patients according to CCI score

	Elderly patients Total (n=121)	Elderly patients CCI 0-1 (n=46)	Elderly patients CCI 2-3 (n=49)	Elderly patients CCI≥4 (n=26)	P value
Age, years	78.0 ± 2.6	78.2 ± 2.7	77.9 ± 2.6	77.7 ± 2.2	0.88
Male gender	100 (82.6)	35 (76.9)	42 (85.7)	23 (88.5)	0.31
Body Mass Index Kg/cm²	26 ± 4	30.0 ± 2.8	26.2 ± 4.6	26.1 ± 5.3	0.78
NYHA class					
I-II	32 (46.4)	12 (46.2)	11 (42.3)	9 (52.9)	0.79
III-IV	37 (53.6)	14 (53.9)	15 (57.7)	8 (47.1)	
Comorbidities					
Hypertension	77 (63.6)	26 (56.5)	32 (65.3)	19 (73.1)	0.36
Diabetes	35 (28.9)	1 (2.2)	20 (40.8)	14 (53.4)	<0.0001
Active smoking	3 (2.5)	2 (4.4)	1 (2.0)	0 (0)	0.18
Cancer	20 (16.5)	0 (0)	5 (10.2)	15 (57.7)	<0.0001
Cerebrovascular disease	8 (6.6)	0 (0)	4 (8.2)	4 (15.4)	<0.01
Mild Cognitive impairment	5 (4.1)	1 (2.2)	2 (4.1)	2 (7.7)	0.44
Ischemic cardiomyopathy	77 (63.6)	20 (43.5)	26 (73.5)	21 (80.8)	0.001
Atrial fibrillation history	50 (41.3)	18 (39.1)	21 (42.9)	11 (42.3)	0.93
Medication					
Beta-Blockers	92 (76.7)	37 (80.4)	39 (79.6)	17 (65.4)	0.29
Amiodarone	33 (27.5)	12 (26.1)	15 (30.6)	6 (23.1)	0.76
Calcium channel inhibitors	15 (12.4)	6 (13.0)	4 (8.2)	5 (19.2)	0.38
Anticoagulant	60 (49.6)	20 (43.5)	25 (51.0)	15 (57.7)	0.49
Antiplatelet therapy	90 (74.3)	28 (60.9)	39 (79.6)	23 (88.5)	0.02
Electrocardiogram					
PR interval, <i>ms</i>	210 ± 44	201 ± 40	215 ± 52	218 ± 32	0.42
QRS duration, <i>ms</i>	137 ± 34	138 ± 38	135 ± 32	142 ± 32	0.61
LVEF, %	33 ± 13	36 ± 15	32 ± 12	30 ± 11	0.12
Hemoglobin, g/dL	13.2 ± 1.9	13.3 ± 1.6	13.1 ± 1.9	12.3 ± 2.0	0.01
Creatinin, umol/L	118 ± 58	106 ± 32	123 ± 78	131 ± 45	0.03
NT-proBNP, ng/L	4 638 ± 6 351	3 303 ± 5 351	4 068 ± 3 974	7 652 ± 9 442	0.01

Results are expressed as mean ± SD or number (%). Abbreviations: LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro B-type Natriuretic Peptide NYHA: New-York Heart Association

Table 2. Proportional hazard regression to identify pre-implant variables significantly associated with all-cause mortality

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	1.03	0.91 – 1.16	0.67			
Male gender	1.15	0.51 – 2.58	0.73			
Body Mass Index	0.97	0.89 – 1.04	0.41			
NYHA class						
I-II: reference						
III-IV	3.83	1.62 – 9.09	<0.01			
Comorbidities						
Hypertension	1.17	0.65 – 2.14	0.59			
Diabetes	2.08	1.15 – 3.78	0.02			
Active smoking	1.54	0.90 – 2.61	0.11			
Cancer	1.60	0.79 – 3.22	0.19			
Stroke	0.54	0.13 – 2.22	0.54			
Mild Cognitive impairment	0.91	0.12 – 6.62	0.93			
Ischemic cardiomyopathy	1.59	0.82 – 3.05	0.17			
Atrial fibrillation history	1.10	0.61 – 1.98	0.76			
Medication						
Beta-Blockers	0.66	0.35 – 1.26	0.21			
Amiodarone	0.99	0.52 – 1.89	0.99			
Calcium channel inhibitors	0.74	0.33 – 1.67	0.47			
Anticoagulant	0.96	0.55 – 1.71	0.91			
Antiplatelet therapy	1.72	0.81 – 3.70	0.16			
Electrocardiogram						
PR interval	1.01	0.99 – 1.01	0.15			
QRS duration	0.99	0.98 – 1.01	0.51			
LVEF	0.98	0.95 – 1.01	0.12			
Hemoglobin	0.83	0.70 – 0.99	0.03			
Creatinine $\geq 177 \mu\text{mol/L}$	3.75	1.74 – 8.10	<0.001	2.75	1.20 – 6.32	0.02
NT-pro BNP (/1000 units increase)	1.05	1.02 – 1.10	<0.01			
CCI score						
CCI score 0-1: reference						
CCI score 2-3	1.40	0.67 – 2.94	0.37			
CCI score ≥ 4	3.41	1.64 – 7.11	0.001	2.91	1.37 – 6.20	0.006

Abbreviations: CCI: Charlson Comorbidity Index; HR: Hazard Ratio; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro B-type Natriuretic Peptide; NYHA: New-York Heart Association; 95% CI: 95% confidence interval