Effect of Advancing Age and Multiple Chronic Conditions on Mortality in Patients with End-Stage Renal Disease after Implantable Cardioverter-Defibrillator Placement

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ABSTRACT

Context: There is insufficient information on the effect that advancing age and multiple chronic conditions (MCC) have on mortality after placement of an implantable cardioverter-defibrillator in patients with end-stage renal disease (ESRD) vs non-ESRD.

Objective: To assess whether a differential effect of age and MCC exists between ESRD and non-ESRD.

Design: Population-based, retrospective cohort study using data from the national Kaiser Permanente Cardiac Device Registry of patients who underwent placement of an implantable cardioverter-defibrillator between January 1, 2007, and December 31, 2013.

Main Outcome Measures: All-cause mortality.

Results: Of 7825 patients with implantable cardioverter-defibrillator placement, ESRD-affected patients constituted 4.0% of the cohort (n = 311), were similar in age (p = 0.91), and presented with a larger comorbidity burden (3.3 ± 1.3 vs 2.4 ± 1.5, p < 0.001). The effect of advancing age (every 5 years) on mortality in the ESRD cohort (hazard ratio [HR] = 1.11, 95% confidence interval [CI] = 1.03-1.20) was less than in the non-ESRD cohort (HR = 1.28, 95% CI = 1.25-1.32). Similarly, the effect of each additional comorbidity in the ESRD cohort was less (HR = 1.04, 95% CI = 0.91-1.19) than in the non-ESRD group (HR = 1.20, 95% CI = 1.16-1.25). Lastly, ESRD was independently associated with a 3-fold greater hazard of mortality.

Conclusions: Advancing age and increasing number of MCC have a differential effect on mortality risk in patients with ESRD compared with their non-ESRD counterparts. Future studies should focus on assessment of nonlinear relationships of age, MCC, and naturally occurring clusters of MCC on mortality.

INTRODUCTION

The US Department of Health and Human Services projects that by the year 2050 there will be 80 million adults over the age of 65 years.[1] Advancing age is well known to be associated with multiple co-occurring conditions or comorbidities, henceforth called multiple chronic conditions (MCC).[2] It is projected that the prevalence of adults in the US with MCC will be 81 million by the year 2020.[3] Current guidelines have focused on single disease management with minimal or no attempt toward the management of individuals with MCC.[2,4] The importance of understanding the health and monetary costs of advancing age and MCC is crucial because patients with more than 1 chronic condition have a substantial impairment in their activities of daily living and account for 95% of Medicare expenditures.[3]

Patients with end-stage renal disease (ESRD) are known to be at high-risk of cardiovascular disease and sudden cardiac death.[5] Although advancing age and MCC[6-9] have a known unfavorable risk profile in the general population, little is known of the role these have in patients with ESRD after placement of an implantable cardioverter-defibrillator (ICD) compared with those without ESRD. The Kaiser Permanente (KP) Cardiac Device Registry,[10] with its large sample and quality control and data validation processes, supports observational studies of ICDs in a real-world situation. Using the registry, the primary aim of the current study was to improve the understanding of the role that advancing age and MCC have on mortality in patients with ESRD compared with their nondialysis counterparts after ICD placement. Our null hypothesis is that advancing age and increasing number of comorbidities have an equal effect in patients with ESRD and those without ESRD.

METHODS

We performed a retrospective cohort study from our source population of KP members from 6 geographical Regions of the US between January 1, 2007, and December 31, 2013. KP is an integrated health care delivery system that provides

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comprehensive care to more than 9.5 million members across various parts of the country, and its membership is representative of the local population.[11,12] Detailed information on quality control and data validation processes has been previously published.[10] Briefly, this registry collects patient, implant, surgeon, and hospital data for all patients undergoing ICD implantations, using internal administrative databases, including the systemwide electronic medical record. Validated electronic algorithms are applied to the data to search for postimplant complications, including infections, early clinical complications, and device replacements. Complications are verified by manual review by clinically trained registry staff.

Outcomes

Our primary predictors were advancing age and increasing MCC as a continuous variable. The primary outcome of interest was all-cause mortality obtained from Health Plan databases and Social Security Administration files. Secondary outcomes of interest were deep and superficial surgical site infections,[13] cardiac tamponade, hematoma, pneumothorax, and pulse generator replacement due to any cause. The presence of ESRD was obtained through Health Plan databases. The covariates included were patient age at implant, sex, body mass index (BMI), implant model type (single, dual, or cardiac resynchronization therapy), and baseline comorbidities (hypertension, diabetes mellitus, congestive heart failure, myocardial infarction, chronic lung disease, stroke, and ischemic heart disease) within six months before the device implantation. The baseline comorbidities mentioned, including heart failure, were based on the International Classification of Diseases, Ninth Edition codes and not on chart review. Institutional Review Board approval was obtained before the start of the study.

Statistical Analysis

The cohort characteristics and the postimplant outcomes were described using frequencies, proportions, median, interquartile range, and means and standard deviations. Categorical characteristics were compared using χ^2 tests. Age was compared using a nonparametric Wilcoxon rank sum (Mann-Whitney) test. Survival analysis for the primary outcome, all-cause mortality, was performed using a Cox proportional hazard model. Analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC) with a p value of < 0.05 used as the statistical threshold for significance.

Table 1. Comparison of baseline characteristics between patients with and without end-stage renal disease[a]

Variable	Overall (N = 7825)	ESRD (n = 311)	Non-ESRD (n = 7514)	p value
Age, years				
Mean (SD)	64.3 (13.13)	64.9 (10.95)	64.3 (13.21)	0.906
Median (IQR)	65.8 (56.5-74.2)	65.7 (57.7-72.3)	65.8 (56.5-74.3)	
Age category, years				
< 55	1680 (21.5)	50 (16.1)	1630 (21.7)	< 0.001
55-65	2083 (26.6)	100 (32.2)	1983 (26.4)	
66-75	2323 (29.7)	112 (36.0)	2211 (29.4)	
> 75	1739 (22.2)	49 (15.8)	1690 (22.5)	
Sex				
Female	2064 (26.4)	83 (26.7)	1981 (26.4)	0.900
Male	5760 (73.6)	228 (73.3)	5532 (73.6)	
BMI, kg/m^2				
< 25	2215 (28.3)	109 (35.0)	2106 (28.0)	0.018
25-30	2786 (35.6)	108 (34.7)	2678 (35.6)	
> 30	2801 (35.8)	94 (30.2)	2707 (36.0)	
ICD model type				
CRT	1776 (22.7)	44 (14.1)	1732 (23.1)	< 0.001
ICD-dual	3083 (39.4)	144 (46.3)	2939 (39.1)	
ICD-single	2966 (37.9)	123 (39.5)	2843 (37.8)	
Comorbidities				
Hypertension	4232 (54.1)	259 (83.3)	3973 (52.9)	< 0.001
Diabetes mellitus	3121 (39.9)	235 (75.6)	2886 (38.4)	< 0.001
Congestive heart failure	904 (11.6)	28 (9.0)	876 (11.7)	0.049
Myocardial infarction	2787 (35.6)	151 (48.6)	2636 (35.1)	< 0.001
Chronic lung disease	1285 (16.4)	51 (16.4)	1234 (16.4)	0.469
Stroke	442 (5.6)	23 (7.4)	419 (5.6)	0.357
Ischemic heart disease	5205 (66.5)	265 (85.2)	4940 (65.7)	< 0.001

[a] Data are number (%) except p value or if otherwise indicated. Missing data: 1 (0.01%) for Sex; 23 (0.3%) for BMI; and 400 (5.1%) for comorbidities.

BMI = body mass index; CRT = cardiac resynchronization therapy; ESRD = end-stage renal disease; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; SD = standard deviation.

RESULTS

There were 7825 patients included in the study, of which 311 (4.0%) were patients with ESRD. Baseline patient demographics and clinical characteristics are shown in Table 1. Comparing the ESRD group with the non-ESRD group, the mean age (64.9 vs 64.3 years, p = 0.91) as well as the proportion of men and women were similar (p = 0.90). Most patients in both groups had a BMI below 30 kg/m^2, with approximately one-third of the population in each group having a BMI above 30 kg/m^2. Patients with ESRD had a higher proportion of hypertension (83.3% vs 52.9%, p < 0.001), diabetes mellitus (75.6% vs 38.4%, p < 0.001), myocardial infarction (48.6% vs 35.1%, p < 0.001), and ischemic heart disease (85.2% vs 65.7%, p < 0.001). Patients with ESRD had a higher prevalence of 3 or more comorbidities compared with the non-ESRD population (76.5% vs 45.9%, p < 0.001) as well as an increase in the mean number (± standard deviation) of comorbidities (3.3 ± 1.27, 2.4 ± 1.47, p < 0.001; Table 2).

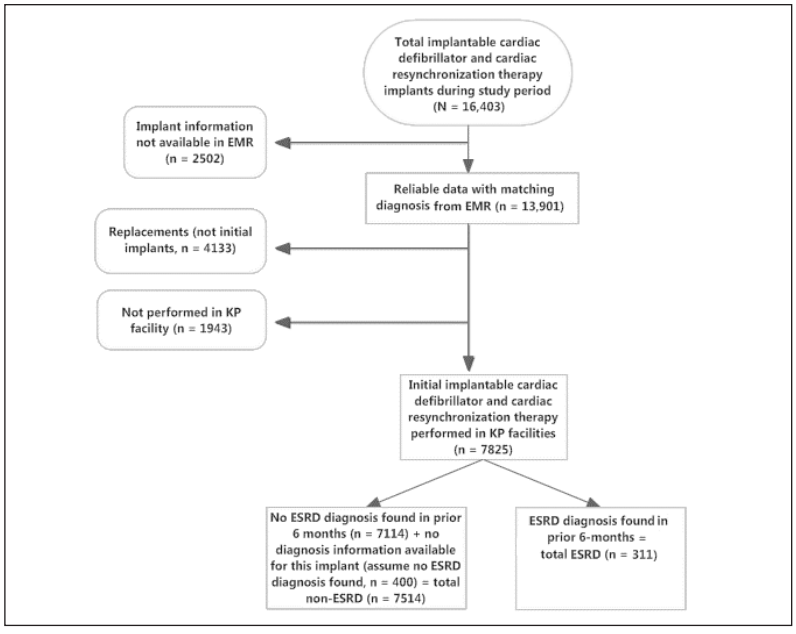

Figure 1. Patient entry into study.

EMR = electronic medical record; ESRD = end-stage renal disease; KP = Kaiser Permanente.

Table 2. Comparison of the number of comorbidities between patients with and without end-stage renal disease (ESRD)

No. of comorbidities	ESRD, n (%)	Non-ESRD, n (%)	Total, n (%)	p value
0	8 (2.57)	851 (11.33)	859 (10.98)	< 0.0001
1	26 (8.36)	1327 (17.66)	1353 (17.29)	
2	39 (12.54)	1490 (19.83)	1529 (19.54)	
3	91 (29.26)	1675 (22.29)	1766 (22.57)	
4	108 (34.73)	1287 (17.13)	1395 (17.83)	
5	32 (10.29)	423 (5.63)	455 (5.81)	
6	6 (1.93)	58 (0.77)	64 (0.82)	
7	1 (0.32)	3 (0.04)	4 (0.05)	

Table 3. Comparison of early and late complications after device placement between patients with and without end-stage renal disease (ESRD)

Outcome	Total, no. (%) 7825 (100)	ESRD, no. (%) 311 (3.97)	Non-ESRD, no. (%) 7514 (96.03)	p value[a]
Early complication (≤ 30 days)				
Death	62 (0.79)	8 (2.57)	54 (0.72)	< 0.001
Tamponade	22 (0.28)	8 (0.32)	21 (0.28)	0.591[b]
Hematoma	26 (0.33)	3 (0.96)	23 (0.31)	0.082[b]
Pneumothorax	24 (0.31)	2 (0.64)	22 (0.29)	0.247[b]
Device-related infection	14 (0.18)	0 (0)	14 (0.19)	> 0.99[b]
Device replacement	32 (0.41)	5 (1.61)	27 (0.36)	0.008[b]
Late complication (> 30 days)				
Death	1646 (21.04)	146 (46.95)	1500 (19.96)	< 0.001
Device-related infection	53 (0.68)	7 (2.25)	46 (0.61)	< 0.001
Device replacement	654 (8.36)	17 (5.47	637 (8.48)	0.060

[a] p value is derived from the χ^2 test unless otherwise indicated.
[b] p value is derived from the Fisher exact test.

Patient entry into the study is shown in Figure 1. The yearly volume of implants in the ESRD and non-ESRD cohorts is shown in Figure 2. The unadjusted outcomes are reported in Table 3, and the Kaplan-Meier survival curve, as expected, noted worse survival of patients with ESRD vs non-ESRD ($p < 0.001$; Figure 3). ESRD was independently associated with a 3-fold greater hazard of mortality compared with non-ESRD. Predictors of mortality in the entire cohort are shown in Table 4.

In a model with age, number of comorbidities, sex, and body mass index, the effect of advancing age (every 5 years) and increasing number of comorbidities demonstrated a differential effect in the ESRD vs non-ESRD cohort. We noted a decrease in the hazard of advancing age at implantation on mortality in the ESRD cohort compared with the non-ESRD cohort (HR = 1.11, 95% CI = 1.03-1.20 vs HR = 1.28, 95% CI = 1.25-1.32). Similarly, we noted a decrease in the hazard of increasing number of comorbidities in the ESRD cohort (HR = 1.04, 95% CI = 0.91-1.19) compared with the non-ESRD cohort (HR = 1.20, 95% CI = 1.16-1.25; Table 5).

DISCUSSION

The aim of this study was not to compare the effect of ESRD vs non-ESRD or ICD vs non-ICD placement, nor to determine whether mortality was cardiovascular or noncardiovascular. Numerous studies have already made headway into this area and clearly demonstrated the poorer prognosis of patients with ESRD.[14-16] However, there is a paucity of data on the possible differential effects of age and multiple chronic conditions between the 2 aforementioned groups. In the aging population with heart failure, MCC are well known to occur. In fact, more than 75% of patients in a recent study of patients with heart failure had 3 or more co-occurring conditions.[17] Current guidelines have focused primarily on single disease management and do not often incorporate older adults with multimorbidity.[2,4,18] The findings from this study clearly demonstrate that age and MCC had a differential effect in

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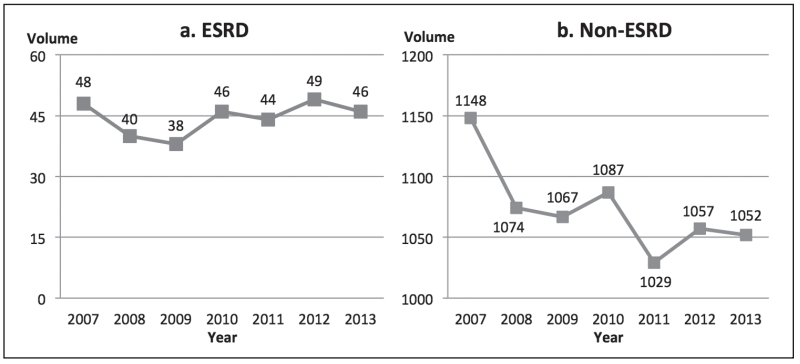

Figure 2. Volume of implantation of implantable cardioverter-defibrillators in an integrated health care delivery system in patients with end-stage renal disease (ESRD, a) and without ESRD (non-ESRD, b).

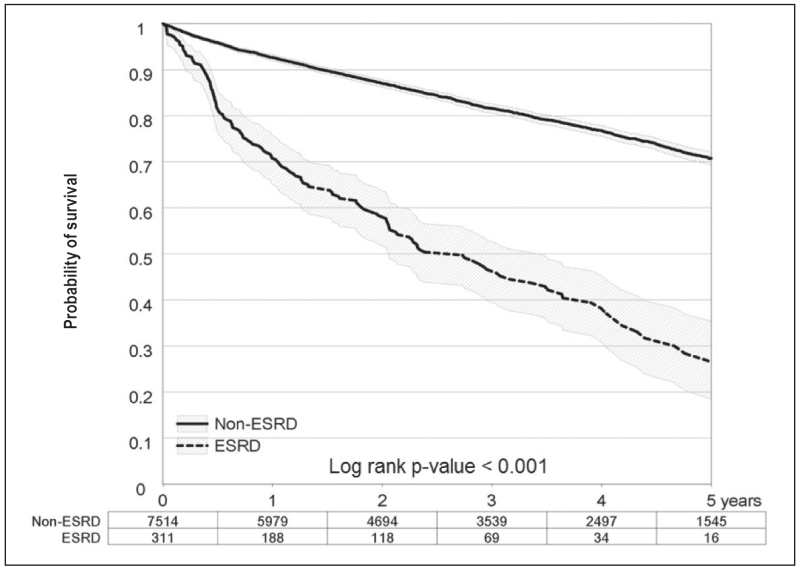

Figure 3. Kaplan-Meier survival curve with associated log-rank test stratified by presence or absence of end-stage renal disease (ESRD).

Table 4. Multivariate predictors of mortality

Risk factor	HR (95% CI)	p value[a]
ESRD	3.02 (2.53-3.62)	**< 0.001**
Age (per 5 years)	1.25 (1.22-1.29)	**< 0.001**
Male	1.08 (0.96-1.22)	0.223
BMI (per 5 kg/m^2)	0.88 (0.84-0.93)	**< 0.001**
CRT vs ICD-single	1.21 (1.05-1.38)	**0.007**
ICD-dual vs ICD-single	0.96 (0.85-1.08)	0.459
Hypertension	1.08 (0.97-1.21)	0.161
Diabetes mellitus	1.60 (1.44-1.78)	**< 0.001**
Heart failure	1.10 (0.95-1.27)	0.210
Myocardial infarction	1.01 (0.91-1.13)	0.817
Chronic lung disease	1.45 (1.29-1.63)	**< 0.001**
Stroke	1.28 (1.06-1.55)	**0.010**
Ischemic heart disease	1.26 (1.08-1.47)	**0.003**

[a] Boldface indicates statistically significant at $p < 0.05$.
BMI = body mass index; CI = confidence interval; CRT = cardiac resynchronization therapy; ESRD = end-stage renal disease; HR = hazard ratio; ICD = implantable cardioverter-defibrillator.

the ESRD cohort. This is despite the fact that the cohort of ICD recipients is already thought of as having an extremely high mortality risk. Specifically, we noted that although advancing age was associated with a significant 28% (95% CI = 25%-32%) increase in mortality in the non-ESRD group, this effect was markedly decreased in the ESRD group (11%, 95% CI = 3%-20%). Similarly, when we used the number of comorbidities as a continuous variable, each additional comorbidity was associated with a significant 20% (95% CI = 16%-25%) increase in the hazard of mortality in the non-ESRD group; this effect was markedly decreased in the ESRD group (4%, 95% CI = -9% to 19%).

Recent studies have described the effect of age and MCC in the overall group of patients referred for ICD placement.[9,19,20] Hess et al,[20] using pooled data from 5 clinical trials, very clearly demonstrated that although the benefit of ICD placement exists throughout the age spectrum, the effect decreases with increasing age. In another study restricted to a cohort of patients with chronic kidney disease, Hess et al[19] demonstrated that advancing age (every 5 years) was significantly associated with a 19% increase in mortality. Steinberg et al[9] addressed the association of MCC and outcomes after ICD placement. They showed that an increasing number of baseline comorbidities decreased the survival benefit after ICD placement. In the current study, we first demonstrated that age was indeed a powerful predictor of mortality in the overall cohort (HR = 1.27, 95% CI = 1.24-1.30). The increase in the hazard of age in our overall population may have been caused by slightly decreased comorbidity burden compared with the second study by Hess et al.[19] Because our patient population consisted only of patients after ICD placement, we could not show any differential benefits on survival after ICD placement with advancing age.

Next, we confirmed that each additional comorbidity was associated with a 19% increase in mortality for the entire cohort of ICD recipients. Our study findings were relatively similar to the study by Steinberg and associates,[9] with a slight difference in how the variable, number of comorbidities, was modeled. Future studies with larger samples sizes of ESRD-affected patients will need to be undertaken to either acknowledge or refute the findings from the current study.

Why is there a differential effect of age and MCC between ESRD and non-ESRD, and is this important? Although it is well known that patients with ESRD have an increased risk of mortality,[5] it is sobering to think that the presence of ESRD is such a powerful dominant predictor of mortality that even advancing age and total comorbidities pale in comparison. However, we and others believe that

Table 5. Effect of advancing age and number of comorbidities[a]

Risk factor	Full cohort, HR (95% CI)	ESRD, HR (95% CI)	Non-ESRD, HR (95% CI)
Advancing age (every 5 years)	1.27 (1.24-1.30)	1.11 (1.03-1.20)	1.28 (1.25-1.32)
Advancing number of comorbidities	1.19 (1.15-1.23)	1.04 (0.91-1.19)	1.20 (1.16-1.25)

[a] Model contains age, body mass index, number of comorbidities (as a continuous variable), and gender.
CI = confidence interval; ESRD = end-stage renal disease; HR = hazard ratio.

"therapeutic nihilism"[21] is not justified. As an example, temporal improvement in survival in the ESRD population after coronary revascularization[22] has been demonstrated similar to the overall temporal improvement in survival in the ESRD cohort.[23] The pressing question is not whether we should be implanting ICDs in patients with ESRD. Herzog et al[245] and others[14-16,] have shown the benefit of ICD therapy in the ESRD population after a cardiac arrest. Rather, the question should be, How do we identify the optimal patient with ESRD who should be referred for ICD placement?

Our findings suggest the possibility that referral at an earlier age may be beneficial because advancing age was still associated with mortality in a risk-adjusted model that included sex, BMI, and number of comorbidities. Although advancing number of comorbidities was not statistically significant in the current study, further work should focus on certain combinations of comorbidities that may be of higher risk compared with others. If we are to try to identify the ideal ESRD cohort that may maximally benefit, future research must improve on risk assessment,[25] incorporate variables for frailty,[26] and understand the role that autonomic dysfunction,[27] sympathetic overactivity,[28] and biomarkers[29] play, along with obtaining dialysis-specific variables (eg, duration of dialysis, type of dialysis, frequency of dialysis) and obtaining data on the mechanism of mortality (cardiovascular or noncardiovascular). Finally, of note, a much-needed randomized clinical trial being undertaken in the Netherlands may shed further light in this field.[30]

Limitations

The current study should be evaluated by a balance of the strengths and weaknesses. The strengths of our study include accurate outcome measurements using well-validated methods. Baseline comorbidities were carefully assessed using multiple KP databases. Our limitations include not having important additional covariates such as those for frailty, type and frequency of dialysis, other dialysis-specific variables, assessment of residual renal function, and novel electrophysiologic variables that may have further refined the model. However, we do not believe that those variables would have significantly changed the summary estimate of the association of age and MCC to mortality—the main focus of the current study. To improve our knowledge in this area, larger studies with a greater number of patients with ESRD will need to be conducted.

CONCLUSIONS

The current study demonstrated that age and advancing comorbidities were associated with a 15% to 20% increased risk in the non-ESRD group compared with the ESRD group. In both groups, advancing age had a 7% to 8% higher associated risk compared with increasing comorbidities. Possible implications of these findings could be that in patients with ESRD, consideration of referral for an ICD should be done at earlier ages with a clinically acceptable comorbidity burden, and in the non-ESRD patients, referral for ICD implantation could be done at later ages, taking into consideration the comorbidity burden. Future work will need to assess nonlinear relationships of age and MCC on mortality as well as the association of naturally occurring clusters of chronic conditions[3] on mortality in this cohort. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Hardness of the Kidneys

The signs of hardness of the kidneys are that the quantity of the urine is diminished, that there is heaviness of the kidneys, and of the spine with some pain: and the belly begins to swell up after a time and dropsy is produced the second day.

— Gulielmus de Salicento, 1210-1277, Italian surgeon and cleric