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Original Article

Impact of Moderate to Severe Chronic Kidney Disease for Long Term Survival of Implantable Cardioverter Defibrillator Patients in Taiwan

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SUMMARY

Background: The influence of renal impairment on long-term mortality in Taiwanese patients with an ICD was uncertain. The aim of our study was to examine the impact of moderate to severe CKD on outcome in patients with ICD implantation for secondary prevention in Taiwan.

Methods: From 2005 to 2013, patients who underwent ICD implantation who were survivors of sudden cardiac arrest or unstable hemodynamics due to ventricular arrhythmia at a single medical center were included in this registry. We divided the patients into two groups, group 1 with estimated glomerular filtration rates (eGFRs) of ≥60 mL/(min·1.73 cm^2) and group 2 with eGFRs of <60 mL/(min·1.73 cm^2). The clinical end point was defined as the occurrence of all-cause mortality during the follow-up.

Results: 84 consecutive patients were enrolled in this registry. The mean age of the patients was 62.7 ± 13.2 years, and 54.8% were male. The patients of group 2 were older (mean age: 66.4 vs. 56.2 years) and had worse renal function (42 ± 12.3 vs. 89.0 ± 18.5 mL/(min·1.73 cm^2)). They more often had hypertension (56.5% vs. 31.6%), diabetes mellitus (52.2% vs. 15.8%), and previous hospitalization for congestive heart failure as comorbidity (71.7% vs. 28.9%). During the mean follow-up duration of 952 days, 19 patients (22.6%) died. After adjustment for the parameters, eGFRs <60 mL/(min·1.73 cm^2) was an independent predictor of all-cause mortality (AHR:6.21, 95%CI:1.28–30.06, P = 0.02).

Conclusion: Moderate to severe CKD is independently associated with increased mortality in Taiwanese patients who underwent ICD implantation for secondary prevention.

1. Introduction

Chronic kidney disease (CKD) is a current global public health issue that has received increasing attention owing to its increasing number of patients, high-risk progression to end-stage renal disease (ESRD), and increased morbidity and mortality[1,2]. In Taiwan, the prevalence of CKD was 9.8–11.9%; the range is owing to the variations in sampling method and estimated glomerular filtration rate (eGFR) calculation system in the data source, different study subjects, and disuniform definition of CKD[3].

Most deaths in patients with CKD occurred due to cardiovascular disease (43%) and sudden cardiac death (SCD; nearly 60%)[4]. For the prevention of SCD, the previous large randomized clinical trials of the implantable cardioverter defibrillator (ICD) demonstrated a survival benefit over medical therapy in patients with a history of SCD or sustained ventricular arrhythmia, and in primary and secondary prevention[5–7].

Regarding ICD for secondary prevention, the recent study demonstrated old age, low left ventricular ejection fraction (LVEF), and history of diabetes mellitus (DM) as significant predictors of mortality in Taiwanese patients[8]. However, the impact of renal impairment on long-term mortality in Taiwanese patients with ICD for secondary prevention was not available in the aforementioned study. Thus, the aim of our study was to examine the impact of moderate to severe CKD on the outcomes in the Taiwanese population with ICD implantation for secondary prevention.

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2. Materials and methods

2.1. Study population

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Mackay Memorial Hospital. The patient records and information were hided and de-identified prior to analysis. We included 99 consecutive patients in this registry who were survivors of sudden cardiac arrest and unstable hemodynamics due to ventricular arrhythmia without any reversible cause and underwent ICD implantation for secondary prevention at a single medical center "Taipei Mackay Memorial Hospital" between 2005 and 2013. Patients were excluded from the study if they met the following exclusion criteria: 1) <20 or >90 years of age, 2) missing biochemistry information needed for calculating eGFR at the time of device implantation, 3) unavailability of follow-up data, 4) died during their hospital stay, 5) receiving dialysis for ESRD, 6) had neoplasms. Malignancy was excluded due to limited life expectancy.

2.2. Data collection and definition

Demographic data, medical disease history (e.g., hypertension [HTN], coronary artery disease, type 2 diabetes mellitus [DM], or congestive heart failure), and prescribed medications were obtained from the healthcare records in the hospital. We calculated eGFR by using the simplified Modification of Diet in Renal Disease (MDRD) equation[9]. Patients were stratified into 2 groups, the normal renal function to mild CKD group and the moderate CKD to severe CKD group. Based on the National Kidney Foundation classification, the patients with stage 1 and 2 CKD constituted group 1 (eGFR $\geq$ 60 mL/[min$\cdot$1.73 m^2]) and those with stage 3–5 CKD composed group 2 (eGFR < 60 mL/[min$\cdot$1.73 m^2])[10]. The LVEF was determined by using transthoracic echocardiography, gated radionuclide angiography, or contrast left ventriculography. Follow-up data were obtained at 3- to 6-month intervals in the pacemaker outpatient clinic with device interrogation. If any therapy was recorded, each episode was stored in a disc and printed out for further analysis. Patients were reminded to contact the clinic regarding any problem with the devices, such as being shocked, recurrent syncope, or other cardiovascular conditions.

2.3. Clinical outcome

The end point defined in our analysis was the duration from the date of ICD implantation to the occurrence of all-cause mortality.

2.4. Statistical analysis

Results are expressed as mean ± SD or percentages. The Student *t*-test was used to compare differences between the groups for continuous variables, and the chi-square test was used for categorical data. Then, we used a Cox proportional hazards model to calculate hazard ratios (HRs) and to determine the factors contributing to all-cause death. The HRs (95% confidence intervals [CIs]) were adjusted for sex, age, HTN, DM, previous admission for congestive heart failure, and eGFR (<60 versus $\geq$60 mL/[min$\cdot$1.73 m^2]). Kaplan-Meier survival curves were constructed and compared by using the log-rank test. A P value of <0.05 was considered significant. All statistical analyses were performed by using the SPSS version 19 software (IBM SPSS Statistics, New York).

3. Results

3.1. Patient characteristics

Ninety-nine patients were initially recruited for this study. However, 8 patients were excluded because they were undergoing dialysis for ESRD, 3 because of neoplasm, 2 died during their hospital stay, and another 2 were lost to follow-up. Overall, 84 consecutive patients were included in our study for analysis. The mean age of the patients was 62.7 ± 13.2 years (range, 31–88 years), and 54.8% of the patients were male. Table 1 shows the baseline characteristics of the patients stratified according to eGFR. The patients who had moderate to severe CKD (eGFR < 60 mL/[min$\cdot$1.73 m^2]) were older (mean age: 66.4 vs. 56.2 years, P = 0.02) and had more prevalent underlying diseases such as HTN (56.5% vs. 31.6%, P = 0.02), DM (52.2% vs. 15.8%, P < 0.001) and previous hospitalization for congestive heart failure as comorbidity (71.7% vs. 28.9%, P < 0.001). The medications used, which included beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, and LVEF were similar between the 2 groups.

Table 1
Clinical and angiographic characteristics of patients with normal renal function to mild CKD and moderate to severe to CKD.

	eGFR≧60 mL/min/1.73 m^2(N = 38)	eGFR <60 mL/min/1.73 m^2(N = 46)	P value
	Normal renal function to mild CKD	Moderate to severe to CKD	
Age (years)	56.2 ± 17.3	66.4 ± 10.4	0.02
Gender (men,%)	28(73.7%)	31 (67.4%)	0.53
Hypertension (n,%)	12 (31.6%)	26 (56.5%)	0.02
Diabetes mellitus (n,%)	6 (15.8%)	24 (52.2%)	<0.001
Coronary artery disease (n,%)	16 (42.1%)	22 (47.8%)	0.6
Previous hospitalization for congestive heart failure(n,%)	11 (28.9%)	33 (71.7%)	<0.001
Biventricular pacing(n,%)	11 (7.7%)	14 (8.9%)	0.71
Blood urea nitrogen(mg/dL)	13.8 ± 5.2	26.2 ± 13.9	<0.001
Creatinine(mg/dL)	0.9 ± 0.2	1.7 ± 0.9	<0.001
Estimated glomerular filtration rate(mL/min/1.73 m^2)	89.0 ± 18.5	42 ± 12.3	<0.001
Medication			
Beta blocker(n,%)	16 (42.1%)	26 (56.5%)	0.19
Angiotensin converting enzyme(n,%)	7 (18.4%)	9 (19.6%)	0.28
Angiotensin receptor blocker(n,%)	13 (34.2%)	20 (43.5%)	0.6
Echocardiography			
Left ventricular ejection fraction(%)	45.7 ± 15.4	40.4 ± 15.2	0.13
Left ventricular end-diastolic dimension(mm)	54.5 ± 11.8	55.4 ± 10.6	0.71
Left ventricular end-systolic dimension(mm)	42.3 ± 12.9	44.3 ± 12.1	0.47
Left atrial dimension(mm)	33.9 ± 7.2	38.9 ± 7.3	0.3

Table 2
Cox regression analysis for mortality.

	All course mortality	P value
	Hazard ratio (95% CI)	
Age	1.02 (0.97–1.08)	0.42
Hypertension	0.55 (0.19–1.61)	0.27
Diabetes mellitus	0.24 (0.64–5.96)	0.81
Previous hospitalization for congestive heart failure	2.65 (0.73–9.68)	0.14
eGFR <60 mL/min/1.73 m^2	6.21 (1.28–30.06)	**0.02**

Abbreviation as Table 1; CI: confidence interval
Bold indicates P value <0.05. eGFR of <60 in comparison with eGFR of ≥60 mL/(min 1.73 m^2) was an independent predictor of all-cause mortality.

3.2. Clinical outcomes

All the patients received clinical follow-up with a median duration of 952 days. Of the total cohort, 19 persons (22.6%) had all-cause death. The Cox proportional hazards regression model was used for the multivariate analysis of all-cause mortality. Clinical covariates included age, sex, HTN, DM, previous hospitalization for congestive heart failure, and eGFR <60 mL/(min·1.73 m^2) that were significant between two groups were entered into final models. Other variables such as coronary artery disease and others are non-significant between two groups and were not included in models.

The predictors of all-cause mortality are shown in Table 2. After adjustment for the above-mentioned parameters, eGFR of ≥60 in comparison with eGFR of <60 mL/(min·1.73 m^2) (adjusted HR [AHR]: 6.21, 95% CI: 1.28–30.06, P = 0.02) was an independent predictor of all-cause mortality. As we found that moderate to severe CKD was a strong predictor of all-cause mortality, a Kaplan-Meier analysis was performed to examine the univariate association between eGFR (≥60 vs. <60 mL/[min/1.73 m^2]) and the outcome of the cohort (Fig. 1). The patients with moderate to severe CKD exhibited a significantly lower free rate of all-cause mortality (0.19 vs. 0.92; P < 0.001).

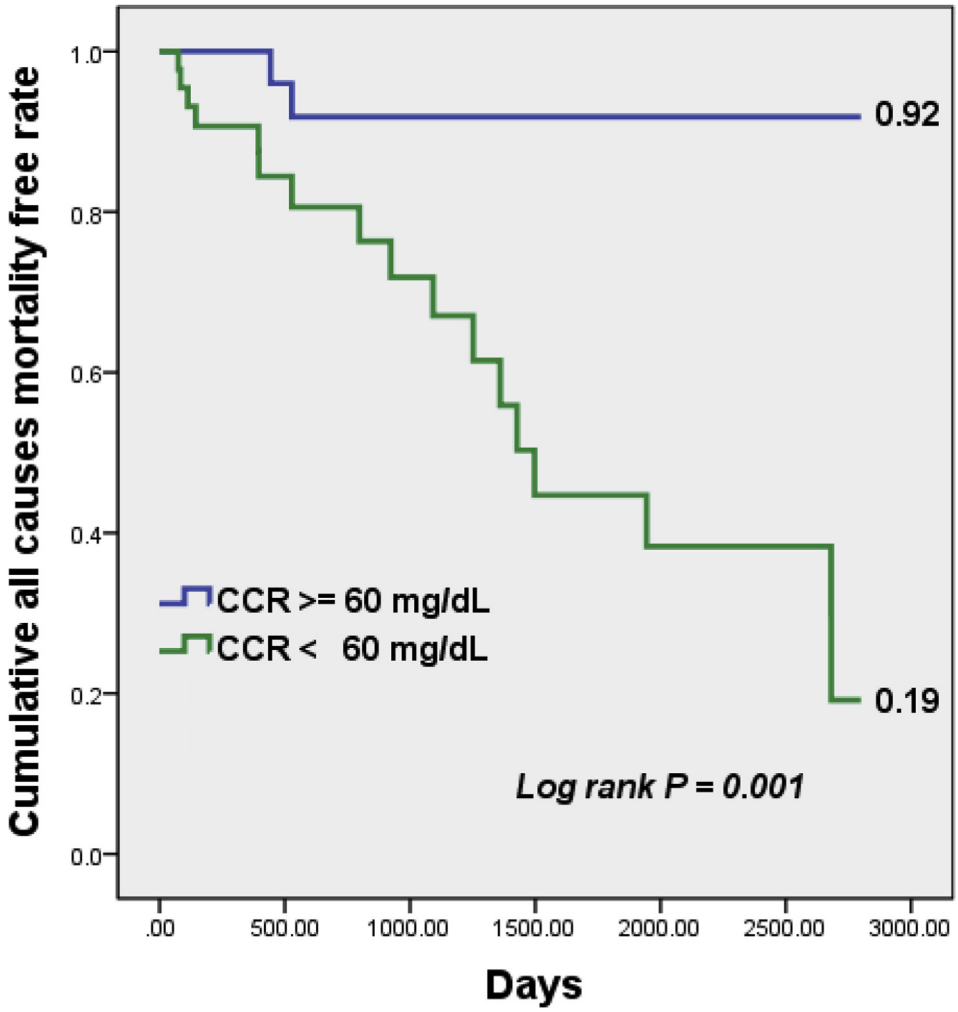

Fig. 1. Kaplan–Meier analysis of all-cause mortality subdivided according to eGFR (≥60 vs. <60). The patients with moderate to severe CKD exhibited a significantly lower free rate of all-cause mortality (0.19 vs. 0.92; log rank P < 0.001).

4. Discussion

CKD provokes exaggerated inflammatory response to the myocardium, alters myocardial structure, and causes electrolyte and autonomic imbalance, rendering a proarrhythmic state[11]. Moderate reductions in kidney function that adversely impact cardiovascular outcome in patients with CKD has been a growing issue[12]. Kramer et al. found that peripheral arterial disease, age of ≥70 years, creatinine level of ≥2.0 mg/dL, and ejection fraction of ≤20% were recognized as significant predictors of 1-year ICD mortality in a US cohort study[13]. A representative analysis showed a strong and stepwise association between mortality and renal dysfunction, even with a milder level of renal impairment[14]. To date, ≥5 meta-analyses have been performed to evaluate the use of ICD therapy in the CKD population. The data on the benefit of ICD in patients with CKD has been derived primarily from meta-analyses, where the conclusions are divergent. A large number of patient-based analysis of Multicenter Automatic Defibrillator Implantation Trials I and II, and the Sudden Death in Heart Failure Trial showed no survival benefit in the ICD primary prevention for CKD patients, 36.3% of whom had an eGFR of <60 mL/(min·1.73 m^2)[15]. Conversely, in a meta-analysis of 3 retrospective observational studies that compared survival in end-stage patients with CKD with and without ICD therapy regardless of primary or secondary prevention, the 2-year survival was significantly better in the patients treated with an ICD[16]. Until recently, 2 separate meta-analyses to evaluate (1) the effect of ICD on mortality in patients with CKD and (2) the effect of CKD on mortality in patients with an ICD implanted for either primary or secondary prevention had been published. One analysis showed a reduction in overall mortality in the CKD patients treated with an ICD when compared with those who were not treated with an ICD. Another meta-analysis of patients treated with an ICD in 15 studies showed no significant increase in mortality in the ICD group with CKD when compared with the ICD group without CKD[17].

However, those studies were not suitable for Taiwanese ICD cohorts because almost all the patients received ICD implantation for secondary prevention according to the rules of the National Health Insurance system in Taiwan. Regarding ICD for secondary prevention, only a few studies elucidated the impact of moderate to severe CKD excluding patients undergoing dialysis. Hage et al.[18] studied 115 of 287 patients with moderate to severe CKD (40%) treated with an ICD, and reported 1- and 5-year all-cause mortality rates of 10% and 37% for patients with CKD and 8% and 23% for patients without CKD, respectively ($p = 0.003$). However, after adjusting for age and multiple risk factors, CKD was not predictive of all-cause mortality in the secondary prevention group (HR 1.27 [0.81−2.00], $p = 0.3$). On the contrary, our study demonstrated that moderate to severe CKD was a strong predictor of all-cause mortality. The cause of this discrepancy may be the difference in baseline characteristics between the two populations.

According to a previous study, the clinical factors that independently predicted increased mortality in Taiwanese patients who underwent ICD implantation included old age, low LVEF, and history of DM[8,19,20]. However, the impact of renal function in a previous cohort of patients was not elucidated. This is the first study that compared the effect of CKD on clinical outcome in Taiwanese patients who received ICD implantation for secondary prevention.

Our observation is that the Taiwanese patients who had moderate to severe CKD were older and often had HTN and DM. The main finding of our study was that moderate to severe CKD is an independent predictor of all-cause mortality and is associated with a six-fold increase in all-cause mortality in patients with ICD compared to patients without ICD.(adjusted HR [AHR]: 6.21, 95% CI: 1.28−30.06, $P = 0.02$).

Several limitations of the present study should be mentioned. The main limitation is that our study was a retrospective observational study from a single center and not a randomized prospective study. Unfortunately, we did not have data on the cause of death and therefore could not determine the proportion of deaths that were cardiac or arrhythmic in nature. As we excluded patients who were undergoing dialysis in this study, the impact of ESRD in ICD patients remained uncertain. Owing to the limited sample size and this study being conducted in a single hospital, the patients included might not be representative of the entire population of patients who undergo ICD for secondary prevention. To confirm our findings, a study with a larger sample of patients is required. However, the results of our analysis should be considered a hypothesis-generating research. Further prospective interventional research should be performed to confirm the present data.

5. Conclusion

Our study demonstrated that the patients with moderate to severe CKD were older and more frequently had HTN, DM, and previous hospitalization for congestive heart failure as comorbidity. Moderate to severe CKD was an independent predictor of all-cause mortality.

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