Original Article

Effects of β-blockers therapy on the 28-day and 3-year survival rates of end-stage renal disease patients with cardiovascular disease: a retrospective cohort study

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Background: β-blockers have been used in the treatment of end-stage renal disease (ESRD) patients and cardiovascular disease (CVD) patients, separately. However, the effects of β-blockers on ESRD patients with CVD have not been fully investigated. This study sought to investigate the effects of β-blockers therapy on the 28-day and 3-year survival rates of ESRD patients with pre-existing CVD who were admitted to the intensive care unit (ICU).

Methods: After excluding patients without CVD, receiving a kidney transplant, not admitted to the ICU, and with missing baseline data, this cohort study included 1081 ESRD participants with CVD from the Medical Information Mark for Intensive Care III database. Baseline characteristics, including demographic data and clinical data, were collected. The outcomes were 28-day and 3-year survival rates of the patients. At the 28-day of ICU hospitalization, patients had a mean inpatient hospital stay of 24.7 days. At 3-year, the patients had a median survival time of 489.2 days. Univariate and multivariate Cox regression analyses were used to evaluate the effects of β-blockers therapy on the 28-day and 3-year survival outcomes of ESRD patients with CVD.

Results: The 28-day and 3-year survival rates were 82.8% and 37.9%, respectively. The mean age of the all patients was 68 years, and 642 were male. After adjusting for age, race, hyperlipidemia, dialysis, simplified acute physiological score (SAPS) II, sequential organ failure assessment (SOFA) score, glucocorticoid, hemoglobin, diabetes, hypertension, the 28-day survival rate of the ESRD patients with CVD requiring intensive care who received β-blockers therapy was higher than that of the patients who did not receive the treatment. Similarly, after adjusting for age, race, hyperlipidemia, dialysis, SAPS II, SOFA score, glucocorticoid, hemoglobin, diabetes, hypertension, creatinine, the long-term survival rate of the patients who received β-blockers therapy was also higher than that of those who did not.

Conclusions: β-blockers therapy was associated with increased 28-day and 3-year survival rates in ESRD patients with CVD requiring intensive care. Our findings may provide a theoretical basis for the prognostic impact of β-blockers therapy among patients with ESRD and CVD who were admitted to the ICU.

Keywords: End-stage renal disease (ESRD); cardiovascular disease (CVD); β-blocker; 28-day survival; 3-year survival

Submitted Aug 31, 2022. Accepted for publication Nov 09, 2022.
doi: 10.21037/atm-22-5317
View this article at: https://dx.doi.org/10.21037/atm-22-5317

Introduction

End-stage renal disease (ESRD) refers to a permanent decline in kidney function (1). Cardiovascular diseases (CVDs) are often prevalent in ESRD patients due to the use of dialysis and the shared pathological mechanism and risk factors (2). Approximately 40% of ESRD patients die due to arrhythmias or sudden cardiac death (3). It is estimated that ESRD patients with CVDs experience a high morbidity rate of up to 50% (4), and the relative risk of death is approximately 20 times higher than that of the general population (5). Thus, it is vital to examine therapeutic options for patients with ESRD complicated with CVD.

To date, β-blockers have been recommended in the treatment of ESRD patients (6). In the study of Lin *et al.*, they pointed out that β-blockers have a protective effect on atrial fibrillation in ESRD patients (6). Not only that, β-blockers have also been widely used to treat CVD patients for more than 50 years, due to their role in reducing mortality and morbidity, hypertension (7), sudden cardiac death (8), and heart failure (9,10), and for the secondary prevention of coronary heart disease (11,12). Kotecha *et al.* conducted a meta-analysis of kidney disease patients with CVDs and found that β-blockers reduced the mortality of moderate stage chronic kidney disease patients with heart failure with preserved ejection fraction (HFrEF) (13). Compared to placebos, β-blockers have been proven to significantly reduce all-cause mortality by 15% and cardiovascular death/heart failure hospitalization by 13% in ESRD patients with HFrEF (13). However, due to the exclusion of ESRD patients with CVDs from many clinical trials, the effects of β-blockers on ESRD patients with CVDs have not been fully investigated. Additionally, β-blockers have been reported to have a potential protective effect for patients during critical illness requiring intensive care (14,15). This may be related to the fact that β-blockers have many beneficial immunomodulatory effects and might improve the prognosis of intensive care unit (ICU) patients (14,15).

In this study, data from the Medical Information Mark for Intensive Care III (MIMIC III) database were collected to investigate the potential association between β-blockers therapy and the short- and long-term survival rates of ESRD patients with CVD who had been admitted to the ICU. We hypothesized that patients with ESRD and CVD who were admitted to the ICU and received beta-blockers were associated with improved 28-day and 3-year survival rates. Our findings may provide a theoretical basis for clinical applications of β-blockers therapy in such patients. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5317/rc).

Methods

Data sources and study design

All the data in this retrospective cohort study were obtained from the MIMIC III database (16). The MIMIC III database contains the information of 46,520 patients admitted to various ICUs of the Beth Israel Deaconess Medical Center (BIDMC) in Boston from 2001 to 2012, and includes data on patients' demographics, vital signs, laboratory tests, fluid balance, and survival status. A local ethics committee's approval was not required for this study, as the disease information of the patients were publicly available, and all the individual information in the database had been anonymized.

To be eligible for this study, patients had to meet the following inclusion criteria: (I) aged ≥20 years; (II) have ESRD; (III) have CVD; (IV) admitted to the ICU; (V) have mortality information. The International Classification of Diseases 9th revision (ICD-9) of ESRD were: 40301, 40311, 40391, 40403, 40413, 40492, 40493, 5856. The CVDs included congestive heart failure, cardiac dysrhythmia, angina, and myocardial infarction. The following disease codes of the ICD-9 were used: heart failure congestive = 4280; cardiac dysrhythmia = 42789, 4279; angina = 4130-4131, 4139; myocardial infarction = 41000-41002, 41010-41012, 41020-41022, 41030-41032, 41040-41042, 41050-41052, 41060-41062, 41070-41072, 41080-41080, and 41090-41092. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had received a kidney transplant; (II) had incomplete baseline data. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Exposure

We extracted information from the MIMIC III database

about whether patients were using β-blockers or not. Patients were distributed to 2 groups depending on whether they received β-blockers therapy: β-blockers therapy group and non-β-blockers therapy group.

Outcomes and follow-up

The outcomes of this study were the short- and long-term survival rates of ESRD patients with CVD, defined as the 28-day and 3-year survival rates of the patients, respectively. Death information of all patients from the MIMIC III database was recorded through the social security account, and the starting time of follow-up was admission to the ICU, and the end point of follow-up was 28-day or 3-year death after admission to the ICU.

Data collection

The following data were extracted (6,15,17)—age, gender, race, diabetes, hypertension, hyperlipidemia, renal replacement treatment (RRT), simplified acute physiological score II (SAPS II), sequential organ failure assessment (SOFA) score, dialysis, use of statins, glucocorticoids and mycophenolate mofetil (MMF), transferrin, hemoglobin, blood urea nitrogen (BUN), creatinine, and 28-day and 3-year survival status.

Statistical analysis

All the statistical analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA) and SPSS 24.0 (IBM Corp., Armonk, NY, USA). The categorical data are presented as the number of cases and percentages, and the χ^2 test or Fisher's exact test were used for the intergroup comparisons. The measurement data with normal distribution data are described as mean and standard deviation (mean ± SD), and the *t*-test was used for the intergroup comparisons. Non-normal measurement data are described as median and interquartile range (IQR), and the comparison between groups was performed by Mann-Whitney U test.

We performed univariate analysis (see Tables S1,S2) to select the potential covariates (P<0.05). A multivariate Cox regression analysis was conducted to explore the effects of β-blockers therapy on the 28-day and 3-year survival rates of ESRD patients with CVD. In addition, subgroup analysis was performed to examine the association between β-blockers therapy and the 28-day and 3-year survival rates in patients stratified by age and gender. A total of 3 models were used for the covariate adjustment: Model 1 was the crude model; Model 2 adjusted for age and gender. Given the small sample size and number of outcomes, the inclusion of too many covariates could lead to model instability and over fitting. Thus, for Model 3, we conducted a stepwise regression to screen the variables that had statistically significant differences in the univariate analysis (P<0.05) Model 3 adjusted for age, race, hyperlipidemia, dialysis, SAPS II, SOFA score, glucocorticoid, hemoglobin, diabetes, hypertension for the outcome of 28-day survival, and adjusted for age, race, hyperlipidemia, dialysis, SAPS II, SOFA score, glucocorticoid, hemoglobin, diabetes, hypertension, creatinine for the outcome of 3-year survival. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The missing values were deleted in this study due to the proportion of missing values more than 30%. We also performed the sensitivity analysis before and after deletion of missing values (Table S3). The survival curves were presented using the Kaplan-Meier method and estimated by the means method for covariates. The statistical significance levels were all 2-sided. A P value <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 1,921 ESRD patients were initially obtained from the MIMIC III database. After excluding 676 patients without CVD, 58 patients who had received a kidney transplant, 31 patients were not admitted to the ICU, and 75 patients with missing baseline data, 1,081 participants were ultimately included in the study, of whom, 248 (22.9%) were treated with β-blockers. The flowchart for patient selection is shown in *Figure 1*. The mean and SD age of the patients was 68 years, and 642 (59.4%) were male. In relation to race distribution, 678 (62.7%) were white, 215 (19.9%) were black, 22 (2.0%) were Asian, and 43 (4.0%) were Hispanic. There were more patients with hyperlipidemia (47.9% *vs.* 30.73%) and those who underwent dialysis (83.1% *vs.* 62.6%) in the β-blockers therapy group compared with the non-β-blockers therapy group. The SAPS II (45.5±13.4 *vs.* 42.5±13.2) and SOFA scores [7 (IQR, 5–10) *vs.* 6 (IQR, 4–9)] of the patients in the β-blockers therapy group were higher than those of patients in the non-β-blockers therapy group. The baseline characteristics of the patients are detailed in *Table 1*.

During the 28 days of ICU hospitalization, 895 (82.8%)

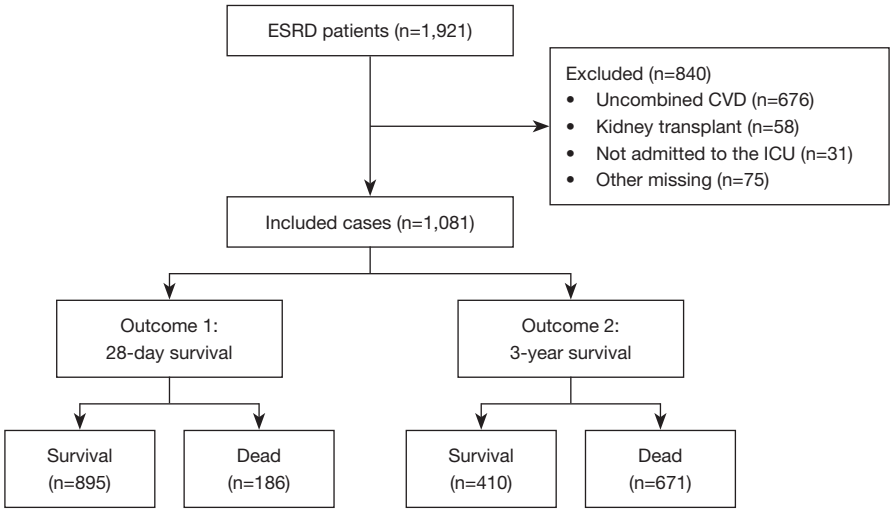

Figure 1 Flowchart for the selection of the ESRD patients with CVD. ESRD, end-stage renal disease; CVD, cardiovascular disease; ICU, intensive care unit.

patients survived, and the patients had a mean inpatient hospital stay of 24.7 days. At 3 years, 410 (37.9%) patients survived, and the patients had a median survival time of 489.2 days.

Short-term (28-day) survival rate

A total of 220 (88.7%) and 675 (81.0%) patients in the β-blockers and non-β-blockers therapy groups survived to 28 days. The patients who received β-blockers therapy had a higher 28-day survival rate than those who did not (Model 1: HR =0.56, 95% CI: 0.38–0.84). In adjusted analyses, patients with β-blockers therapy had a better short-term survival rate than those who did not (Model 2: HR =0.56, 95% CI: 0.37–0.83, P=0.004; Model 3: HR =0.51, 95% CI: 0.33–0.77, P=0.001). The results of the multivariate Cox regression analysis are shown in *Table 2*, and cumulative incidence and Kaplan-Meier survival curves are shown in *Figures 2,3*.

Long-term (3-year) survival rate

A total of 115 (46.4%) and 295 (35.4%) patients in the β-blockers and non-β-blockers therapy groups survived to 3 years. The crude model showed that the patients treated with β-blockers therapy had a higher 3-year survival rate than the untreated patients (Model 1: HR =0.77, 95% CI: 0.64–0.94). In adjusted analyses, the patients who received β-blockers therapy also had a higher long-term survival rate than those who did not (Model 2: HR =0.76, 95% CI: 0.63–0.92, P=0.005; Model 3: HR =0.71, 95% CI: 0.57–0.90, P=0.004). The multivariate Cox regression analysis results are shown in *Table 2*, and cumulative incidence and Kaplan-Meier survival curves are shown in *Figures 2,3*.

Subgroup or exploratory analysis

Additionally, we examined the association of β-blockers therapy and short-term, long-term survival rate based on the subgroup analysis of age and gender (*Table 3*). In adjusted analyses, male patients with β-blockers therapy had a better short-term and long-term survival rate than those who did not (short-term: HR =0.50, 95% CI: 0.30–0.82, P=0.007; long-term: HR =0.73, 95% CI: 0.55–0.98, P=0.038). β-blockers therapy was associated with improved long-term survival rates among female patients (HR =0.67, 95% CI: 0.46–0.98, P=0.037), but not statistically different from short-term survival (HR =0.51, 95% CI: 0.24–1.10, P=0.085). For patients with younger than 65 years, β-blockers therapy was associated with improved short-term and long-term survival rates (short-term: HR =0.20, 95% CI: 0.07–0.60, P=0.004; long-term: HR =0.52, 95% CI: 0.33–0.81, P=0.004); β-blockers therapy was positively related to short-term survival rates for patients with more than 65 years (HR =0.60, 95% CI: 0.38–0.96, P=0.032), but there was no statistically difference in β-blockers therapy and long-term survival (HR =0.78, 95% CI: 0.60–1.03, P=0.076).

Table 1 Comparison of differences between the 2 groups

Variables	Total (n=1,081)	Group		t/χ^2/Z	P
		Non-β-blocker therapy group (n=833)	β-blocker therapy group (n=248)		
Age (year)	68.3±12.8	68.4±12.8	68.3±12.5	0.070	0.943
Gender (female/male)	439 (40.6)/642 (59.4)	345 (41.4)/488 (58.6)	94 (37.9)/154 (62.1)	0.978	0.323
Race				1.726	0.786
White	678 (62.7)	518 (62.2)	160 (64.5)		
Black	215 (19.9)	168 (20.2)	47 (19.00)		
Asian	22 (2.0)	17 (2.0)	5 (2.0)		
Hispanic	43 (4.0)	31 (3.7)	12 (4.8)		
Other	123 (11.4)	99 (11.9)	24 (9.7)		
Diabetes (yes)	394 (36. 5)	309 (37.1)	85 (34.3)	0.656	0.418
Hypertension (yes)	165 (15.3)	130 (15.6)	35 (14.1)	0.330	0.566
Hyperlipidemia (yes)	375 (34.7)	256 (30.7)	119 (48.0)	25.104	<0.001
SAPS II	43.2±13.3	42.5±13.2	45.5±13.4	–3.070	0.002
SOFA score	6 [5–9]	6 [4–9]	7 [5–10]	3.595	<0.001
Dialysis (yes)	727 (67.3)	521 (62.6)	206 (83.1)	36.536	<0.001
Glucocorticoid (yes)	196 (18.1)	155 (18.6)	41 (16.5)	0.554	0.457
MMF (yes)	20 (1.9)	13 (1.6)	7 (2.8)	–	0.189
Statins use (yes)	248 (22.9)	242 (29.1)	122 (49.2)	34.714	<0.001
RRT (yes)	230 (21.3)	83 (10.0)	147 (59.3)	277.421	<0.001
Hemoglobin (g/dL)	10.3±1.9	10.3±1.9	10.1±1.8	1.400	0.163
BUN (mg/dL)	47.0 [32.0–70.0]	48.0 [32.0–72.0]	45.5 [32.5–66.0]	0.723	0.469
Creatinine (mg/dL)	4.0 [2.5–5.9]	3.9 [2.4–5.9]	4.2 [2.8–6.2]	1.018	0.309
28-day vital status				7.907	0.005
Alive	895 (82.8)	675 (81.0)	220 (88.7)		
Dead	186 (17.2)	158 (19.0)	28 (11.3)		
3-year vital status				9.745	0.002
Alive	410 (37.9)	295 (35.4)	115 (46.4)		
Dead	671 (62.1)	538 (64.6)	133 (53.6)		

Data are shown as mean ± standard deviation, number (percentage) or median [interquartile range]. BMI, body mass index; SAPS II, Simplified Acute Physiological Score II; SOFA, sequential organ failure assessment; MMF, mycophenolate mofetil; RRT, renal replacement treatment; BUN, blood urea nitrogen.

Discussion

This study explored the association between β-blockers therapy and the short- and long-term survival of ESRD patients with CVD who were admitted to the ICU, and our results indicated that β-blockers therapy was associated with improved 28-day and 3-year survival rates. In addition, we also found that male patients with β-blockers therapy was related to short-term and long-term survival rates. Among patients younger than 65 years, β-blocker treatment was significantly associated with 3-year survival rates. This

Table 2 Associations between β-blocker therapy and the short- and long-term survival rates of the ESRD patients with CVD

Outcomes	Variables	Model 1		Model 2		Model 3	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Short-term	β-blocker therapy						
	No	Ref		Ref		Ref	
	Yes	0.56 (0.38–0.84)	0.005	0.56 (0.37–0.83)	0.004	0.51 (0.33–0.77)	0.001
Long-term	β-blocker therapy						
	No	Ref		Ref		Ref	
	Yes	0.77 (0.64–0.94)	0.008	0.76 (0.63–0.92)	0.005	0.71 (0.57–0.90)	0.004

Model 1: Crude model. Model 2: adjusted for age and gender. Model 3 (for short-term): adjusted for age, race, hyperlipidemia, dialysis, simplified acute physiological score II, sequential organ failure assessment, glucocorticoid, hemoglobin, diabetes, hypertension. Model 3 (for long-term): adjusted for age, race, hyperlipidemia, dialysis, simplified acute physiological score II, sequential organ failure assessment, glucocorticoid, hemoglobin, diabetes, hypertension and creatinine. ESRD, end-stage renal disease; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval.

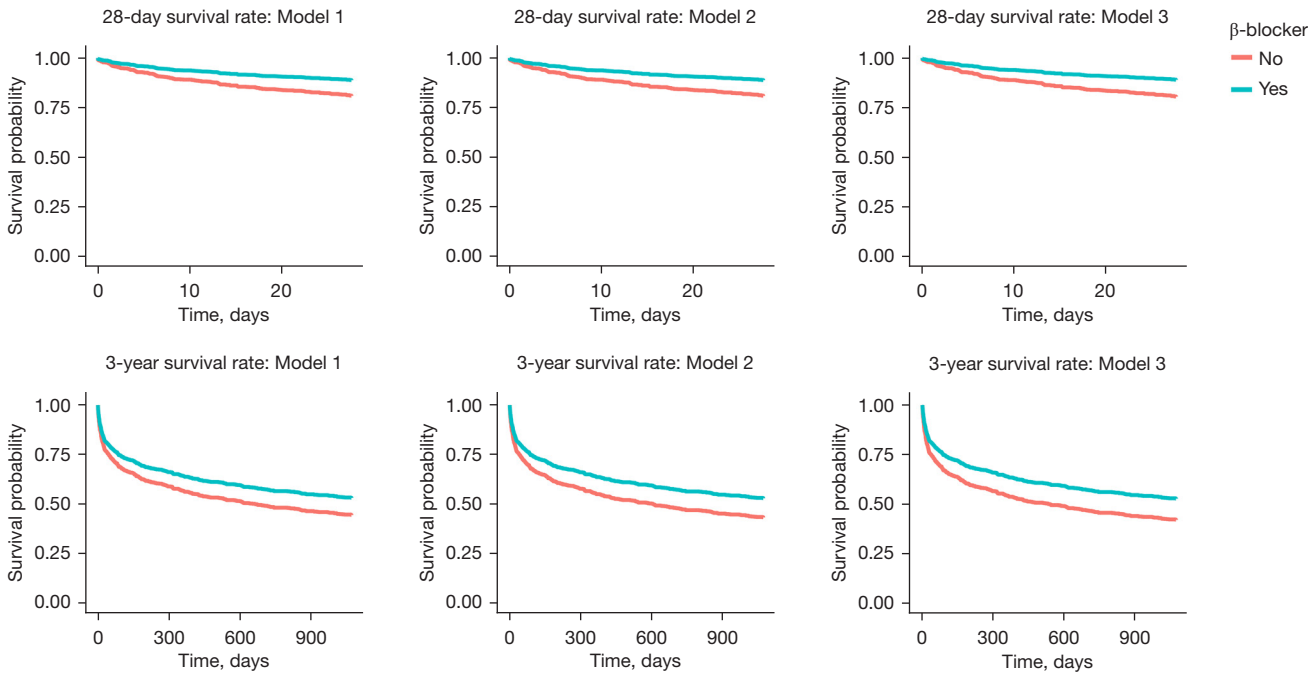

Figure 2 Comparison of 3-year cumulative incidence curves among ESRD patients with CVD who did or did not receive β-blocker therapy. Model 1: crude model; Model 2: adjusted for age and gender; Model 3: adjusted for age, race, hyperlipidemia, dialysis, simplified acute physiological score II, sequential organ failure assessment, glucocorticoid, hemoglobin, diabetes, hypertension and creatinine for the outcome of 28-day survival; Model 3: adjusted for age, race, hyperlipidemia, dialysis, simplified acute physiological score II, sequential organ failure assessment, glucocorticoid, hemoglobin, diabetes, hypertension and creatinine for the outcome of 3-year survival. ESRD, end-stage renal disease; CVD, cardiovascular disease.

finding may provide a theoretical basis for the clinical application of β-blockers therapy in such patients.

A meta-analysis had shown that β-blockers seem to be associated with reduced mortality in patients on dialysis (17). Berger *et al.* found that β-blocker therapy was associated with a 22% lower mortality rate among ESRD patients with acute myocardial infarction after adjusting for baseline variables (18). Additionally, Pun *et al.* showed that among

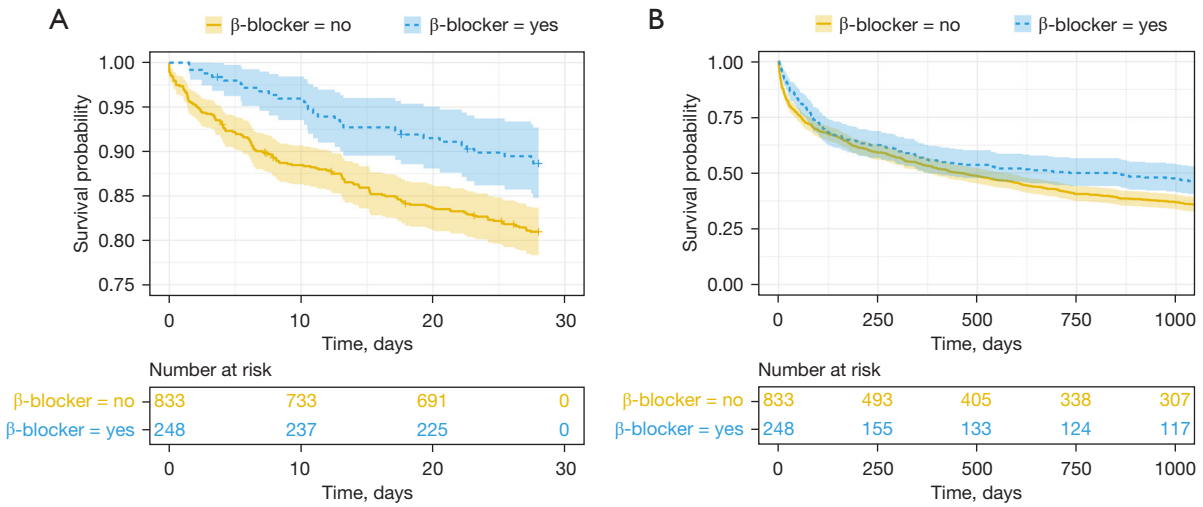

Figure 3 The Kaplan-Meier curves of (A) the 28-day survival rate; (B) the 3-year survival rate of the ESRD patients with CVD. ESRD, end-stage renal disease; CVD, cardiovascular disease.

Table 3 Subgroup analysis based on the age and gender assessed the associations between β-blocker therapy and the 3-year survival rate of the ESRD patients with CVD

Variables	β-blocker therapy	28-day survival rates		3-year survival rate	
		HR[a] (95% CI)	P	HR[b] (95% CI)	P
Age: <65 years	No	Ref		Ref	
	Yes	0.20 (0.07–0.60)	0.004	0.52 (0.33–0.81)	0.004
Age: ≥65 years	No	Ref		Ref	
	Yes	0.60 (0.38–0.96)	0.032	0.78 (0.60–1.03)	0.076
Gender: female	No	Ref		Ref	
	Yes	0.51 (0.24–1.10)	0.085	0.67 (0.46–0.98)	0.037
Gender: male	No	Ref		Ref	
	Yes	0.50 (0.30–0.82)	0.007	0.73 (0.55–0.98)	0.038

[a], adjusted for age, race, hyperlipidemia, dialysis, simplified acute physiological score II, sequential organ failure assessment, glucocorticoid, hemoglobin, diabetes, hypertension. [b], adjusted for age, race, hyperlipidemia, dialysis, simplified acute physiological score II, sequential organ failure assessment, glucocorticoid, hemoglobin, diabetes, hypertension and creatinine. ESRD, end-stage renal disease; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval.

the 43,000 outpatients treated with hemodialysis, 729 of suffered cardiac arrest, and the presence of a β-blocker prescription was associated with increased survival at 24 h and 6 months, and there was a positive correlation between the exposure dose and survival (19). Similarly, this study indicated that β-blockers increased the short- and long-term survival rates of ESRD patients with CVD during critical illness requiring intensive care.

Specific to ICU patients, β-blocker may treat different types of CVD and reduce the risk of myocardial reinfarction and its associated mortality (20). Macchia *et al.* have concluded that β-blockers may be related to a survival advantage for patients who subsequently develop sepsis with organ dysfunction and are admitted to the ICU (21). These findings have suggested a benefit of β-blocker use in ICU patients. Critical illness may also lead to activation of the sympathetic nervous system, which plays a vital role in CVDs in ESRD patients (22). Sympathetic nerve over-activation has been reported to be associated with various CVDs, such as left ventricular hypertrophy

(23,24), arrhythmia (25), and poor survival among patients with heart failure (26,27). Due to associations between sympathetic nerve over-activation and CVDs and ESRD, consideration needs to be given to treatments directed at minimizing the effects of sympathetic nerve over-activation in ESRD patients with CVD. Further, β-blockers have been confirmed to weaken the sympathetic overactivity that links kidney disease with cardiovascular sequelae (28,29), which may explain why β-blockers improved the short- and long-term survival rates of the ESRD patients with CVD admitted to the ICU in this study.

Studies on the treatment of ESRD patients with CVD admitted to the ICU are limited. The strengths of the present study: firstly, the inclusion of the varied ethnic representation and the detailed information available in the MIMIC III database. Secondly, complete long-term follow up data was available. However, this study also had several limitations. We were unable to obtain details of the specific β-blockers regimens from the MIMIC III database, which hindered our ability to further examine the effects of dose, duration and timing of β-blockers therapy on the survival of the ESRD patients with CVD. We also were unable to obtain information on how drug adherence the β-blockers during the 3-year follow-up period. Finally, there were missing information about potential confounders such as history of anticoagulant and antithrombotic drug use, the cause of ICU admission, or smoking status. We were also unable to draw further conclusions about the cause of death as this was not available.

Conclusions

β-blocker therapy was associated with increased 28-day and 3-year survival rates of ESRD patients with pre-existing CVD and who were admitted to ICU. Our findings may provide a theoretical basis for the clinical application of β-blocker treatment in such patients. However, randomized control trials need to be conducted to further investigate and confirm the efficacy of β-blocker treatment on ESRD patients with CVD.

Acknowledgments

The authors appreciate the academic support from AME Critical Care Collaborative Group.

Funding: This research was supported by Shanghai 2021 annual "Science and Technology Innovation Action Plan" Natural Science Foundation Project (No. 21ZR1459400) and Shanghai 2019–2022 Annual Medical Key Disciplines (Class A) Project of Yangpu District (No. YP19ZA07).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5317/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5317/coif). CD received travel support from Nestlè Italia. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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(English Language Editor: L. Huleatt)

Cite this article as: Wang Y, Wu Z, Lu S, Yin L, Chen Y, Qiu C, Ng PY, Durak K, Deana C, Ding F, Zhang Z, Dai L. Effects of β-blockers therapy on the 28-day and 3-year survival rates of end-stage renal disease patients with cardiovascular disease: a retrospective cohort study. Ann Transl Med 2022;10(22):1234. doi: 10.21037/atm-22-5317

