European Journal of Internal Medicine 29 (2016) 78–87

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Renal insufficiency and mortality in coronary artery disease with reduced ejection fraction

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ARTICLE INFO

Article history:
Received 1 September 2015
Received in revised form 15 December 2015
Accepted 3 January 2016
Available online 20 January 2016

Keywords:
Coronary artery disease
Renal insufficiency
Cardiac function
Prognosis

ABSTRACT

Background: Despite strong evidence linking decreased estimated glomerular filtration rate (eGFR) to worse cardiovascular outcome, the impact of eGFR on mortality in coronary artery disease (CAD) patients with different left ventricular ejection fraction (EF) is not well defined.

Methods: A retrospective cohort study. From Jul. 2008 to Jan. 2012, consecutive patients with CAD of West China Hospital were enrolled and were grouped into 3 eGFR categories: ≥90, 60–90, and <60 mL/min/1.73 m^2. Patients with EF ≥ 50% or <50% were defined as preserved EF or reduced EF, respectively. The endpoints were all-cause mortality and cardiac mortality.

Results: There are 2161 patients according to the inclusion criteria and follow-up requirement. The mean follow-up time was 30.97 ± 11.70 months. Cumulative survival curves showed that in patients with reduced EF, renal insufficiency significantly increases all-cause mortality and cardiovascular mortality in a graded fashion (mortality rate, moderate or severe *vs.* normal: 29.3% *vs.* 5.4%, $p < 0.001$; cardiac mortality rate, moderate or severe *vs.* normal: 18.2% *vs.* 4.5%, $p = 0.001$, respectively). Cox regression analysis showed that in CAD patients with reduced EF, moderate to severe renal insufficiency increased all-cause mortality by 6.10-fold (HR 6.10, 95% CI 2.50 to 14.87) and cardiac mortality by 4.10-fold (HR 4.10, 95% CI 1.51 to 11.13). Use of beta-blockers, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and statins was associated with decreased risk of mortality, but the use was lower in renal insufficiency patients, especially in combination of reduced EF.

Conclusion: This study has found that the effect of renal function on prognosis in patients with CAD is closely related to cardiac function. In patients with reduced EF, renal insufficiency accompanies the higher risks of all-cause mortality and cardiovascular mortality. A higher number of treatments from beta-blocker, ACEIs or ARBs, and statin therapy were associated with decreased risk of mortality, even in the combination of renal insufficiency or declining cardiac function.

1. Introduction

The correlation between chronic renal insufficiency and cardiovascular disease (CVD) has received longstanding attention. On the one hand, renal impairment is an important risk factor for the incidence of cardiovascular events [1,2]; on the other hand, CVD is the leading cause of death in patients with chronic kidney dysfunction [3,4], and mortality from CVD in these patients is approximately 9% per year, which is about 30 times the risk in the general population [5,6]. Coronary artery disease (CAD) and chronic kidney dysfunction share a number of arteriosclerotic risk factors, including older age, hypertension, diabetes, dyslipidemia, and physical inactivity [1–3,6,7]. Therefore, patients with CAD often suffer complications from renal insufficiency. Chronic kidney dysfunction (from mild renal insufficiency to end-stage renal disease (ESRD)) is associated with a high prevalence of CVD and the association of renal insufficiency with risk for adverse outcomes is strongly related to coexisting CVD and CVD risk factors [4,5,8]; meanwhile, the studies have well demonstrated that renal insufficiency is associated independently with mortality and complications after myocardial infarction [9–11]. A recent study indicates that even mild renal insufficiency can drastically increase the risk of death in patients with CAD or suspected CAD [12]. Clinical studies have confirmed that patients with CAD, especially patients with myocardial infarction, frequently suffer complications from cardiac dysfunction, whereas renal insufficiency increases the risk of death in patients with heart failure

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http://dx.doi.org/10.1016/j.ejim.2016.01.002
0953-6205/

[13,14]. Therefore, renal insufficiency would further increase the risk of death in CAD patients with reduced ejection fraction (EF). However, to date, relevant research is still insufficiency.

This study recruited patients with CAD complicated by renal insufficiency as research subjects to investigate the different effects of renal insufficiency on the prognosis of CAD patients with different cardiac functions (preserved or reduced EF).

2. Methods

2.1. Study population

The data source for this investigation was the West China Hospital CAD database. This single center database includes all the CAD or high risk patients undergoing angiography in West China Hospital, a 4950-bed teaching hospital affiliated to Sichuan University. For this analysis, we prospectively enrolled consecutive patients with CAD from Jul. 2008 to Jan. 2012 of the database. Patients with CAD were eligible for inclusion if they were restricted to participants with angiographic evidence of ≥50% stenosis in ≥1 coronary vessels. Patients with AMI were eligible for inclusion if they had the following criteria: (1) ischemic chest discomfort that increased or occurred at rest; (2) elevated cardiac troponin I levels (≥0.03 μg/L) or elevated cardiac troponin T levels (≥42 ng/L); and (3) new or presumably new electrocardiographic deviation in at least two contiguous leads (either pathologic Q waves (≥0.04 s in duration), ST segment dynamic horizontal/down-sloping depression ≥ 0.05 mV, or persistent ST segment elevation ≥ 0.1 mV in ≥2 contiguous precordial leads or ≥2 adjacent limb leads or new left bundle branch block (LBBB)). The exclusion criteria included malignancies, pregnancy, end stage renal disease (ESRD) with hemodialysis or renal transplant and severe liver or hematological diseases. The study protocol was approved by the local institutional review boards in accordance with the Declaration of Helsinki. All subjects provided written informed consent before enrolment.

2.2. Baseline characteristics

Demographic data, medical history, cardiovascular risk factor, vital signs at admission, medication at discharge, and final diagnosis were obtained from the patients' electronic medical records and reviewed by a trained study coordinator. Blood sample was collected before angiography, and plasma biomarkers including liver and kidney functions (including the admission serum creatinine levels), blood glucose, serum lipid, *etc.* were analyzed in the Department of Laboratory Medicine, West China Hospital, accredited by the College of American Pathologists. Hypertension was defined as those with systolic blood pressure (SBP) greater than 140 mm Hg and/or diastolic blood pressure (DBP) greater than 90 mm Hg and/or those receiving antihypertensive medications. Diabetes was diagnosed in patients who had previously undergone dietary treatment for diabetes, had received additional oral antidiabetic or insulin medication or had a current fasting blood glucose level of ≥7.0 mmol/L or random blood glucose level ≥ 11.1 mmol/L. Dyslipidemia was defined as fasting serum total cholesterol (TC) level of ≥5.18 mmol/L, and/or fasting serum low-density lipoprotein-cholesterol (LDL-C) level of ≥3.37 mmol/L, and/or fasting serum high-density lipoprotein-cholesterol (HDL-C) level of <1.04 mmol/L, and/or fasting serum triglycerides (TG) level of ≥1.70 mmol/L, and/or those receiving treatment with drugs or therapeutic life-style change (TLC) for dyslipidemia. Patients received care according to the usual practice; treatment was not affected by participation in this study.

2.3. Renal function assessment and echocardiographic examinations

Serum creatinine was finished before the angiography within first 24 h after admission and assessed by a nonkinetic alkaline picrate (Jaffe) method. The Modification of Diet in Renal Disease (MDRD) equation was used to estimate glomerular filtration rate (eGFR) in milliliters per minute per 1.73 m^2 [15]. Patients were divided into 3 eGFR groups corresponding to strata used to define CKD stages [16]: normal renal function group (eGFR ≥ 90 mL/min/1.73m^2), mild impaired renal function group (eGFR: 60 to <90 mL/min/1.73m^2), and moderate or severe impaired renal function group (eGFR < 60 mL/min/1.73m^2). Baseline two-dimensional echocardiographic examinations were performed in all subjects before discharge according to the American Society of Echocardiography (ASE) recommendations. LV volume and ejection fraction (EF) were calculated by modified biplane Simpson method. Patients with a EF ≥ 50% and <50% were defined CAD patients with preserved EF and CAD patients with reduced EF, respectively.

2.4. Follow-up and endpoints

The follow-up period ended on Jan. 2013. Follow-up information was collected through contact with patients' physicians, patients or their family. Patients who were lost to follow-up were considered at risk until the date of last contact, at which point they were censored. All data were corroborated with the hospital records. The endpoints in this study were all-cause mortality and cardiac death, as documented in the database. Death was considered cardiac when it was caused by acute MI, significant arrhythmias, or refractory heart failure. Sudden unexpected death occurring without another explanation was included as cardiac death.

2.5. Statistical analyses

We conducted the post-hoc analysis on a retrospective basis. Baseline demographics and clinical characteristics were compared among patients categorized by the admission eGFR levels in 3 groups. Continuous variables are expressed as the mean ± standard deviation (SD), and categorical variables are reported as counts and percentages. Analysis of variance (ANOVA) and chi-squared tests were used to test for differences between groups for continuous and categorical variables, respectively. Follow-up of patients was censored at the occurrence of a study endpoint. Kaplan–Meier survival curve of the 3 eGFR groups in relation to all-cause mortality and cardiac mortality in CAD patients was constructed and examined using the log-rank test for overall comparison and pairwise comparison. To assess the potential effect of heart failure on patients with different renal function, we performed Kaplan–Meier survival curves of renal function in relation to all-cause mortality and cardiac mortality in CAD and AMI patients by EF stratum and examined using the log-rank test for overall comparison and pairwise comparison, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on Cox proportional hazards regression models, which was used to investigate the independent effect of renal function on the outcome events. Adjustments were made for the possible confounding effects of age, gender, current smoking, medical history (prior diabetes mellitus, prior hypertension, and prior dyslipidemia), and discharge medication (aspirin, clopidogrel, statin, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), beta-receptor blockers). An interaction testing between cardiac function and renal function was performed in the Cox-regression analysis. Cardiac function and renal function were both presented as categorical variables. As mentioned above, cardiac function was defined as preserved EF and reduced EF; and renal function was stratified into 3 groups: normal, mild impaired, and moderate or severe renal function group. Increasingly adjusted models for composite effect of discharged medication on mortality were built for all-cause mortality to assess the three evidenced-base medicines (EBMs): ACEIs or ARBs, beta-receptor blockers, and statin. Model 0: no medication; model 1: prescribed 1 type of EBMs; prescribed 2 types of EBMs; model 3, prescribed all 3 types of EBMs. Two-sided