International Journal of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Prognostic value of silent myocardial infarction in patients with chronic kidney disease being evaluated for kidney transplantation☆

Ayman A. Farag [a,1], Wael AlJaroudi [c,1], John Neill [a], Harish Doppalapudi [a], Vineeta Kumar [b], Dana Rizk [b], Ami E. Iskandrian [a], Fadi G. Hage [a,d,*]

[a] Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States
[b] Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, United States
[c] Division of Cardiovascular Medicine, Clemenceau Medical Center, Beirut, Lebanon
[d] Section of Cardiology, Birmingham Veterans Affairs Medical Center, Birmingham, AL, United States

ARTICLE INFO

Article history:
Received 20 August 2017
Accepted 18 September 2017
Available online xxxx

Keywords:
Silent
Unrecognized
Clinical
Myocardial infarction
End-stage renal disease
Prognosis

ABSTRACT

Background: Patients with advanced chronic kidney disease (CKD) have increased risk of myocardial infarction (MI). Silent MIs (SMIs) are common in CKD patients and carry increased mortality risk. The prevalence and prognostic value of SMI in advanced CKD has not been evaluated.

Methods: We identified consecutive patients with advanced CKD who were evaluated for renal transplantation at the University of Alabama at Birmingham between June 2004 and January 2006. Clinical MI (CMI) was determined by review of medical records. SMI was defined as ECG evidence of MI without clinical history of MI. The primary end-point was a composite of death, MI, or coronary revascularization censored at time of renal transplantation.

Results: The cohort included 1007 patients with advanced CKD aged 48 ± 12 years (58% men, 43% diabetes, 75% on dialysis). The prevalence of SMI and CMI was 10.7% and 6.7%, respectively. The only independent predictor of SMI was older age (odds ratio for age ≥50 yrs. 2.32, $p < 0.001$). During a median follow-up of 28 months, 376 (37%) patients experienced the primary outcome (33% death, 2% MI, 5% coronary revascularization). In a multivariable adjusted Cox-regression model, both SMI (adjusted HR 1.58, [1.13–2.20], $p = 0.007$) and CMI (adjusted HR 1.67 [1.15–2.43], $p = 0.007$) were independently associated with the primary outcome. Further, both SMI (HR 2.37 [1.15–4.88], $p = 0.02$) and CMI (HR 4.02 [1.80–8.98], $p = 0.001$) were associated with increased risk after renal transplantation.

Conclusions: SMI is more common than CMI in patients with advanced CKD. Both SMI and CMI are associated with increased risk of future cardiovascular events.

Published by Elsevier Ireland Ltd.

1. Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the Western world [1]. Patients with chronic kidney disease (CKD) have increased risk of cardiovascular disease [2,3]. The presence of CKD accelerates atherosclerosis, thrombogenicity of the blood, plaque rupture and acute coronary syndrome, leading to increase incidence of myocardial infarction (MI) and cardiovascular death [4]. In a large population-based study of 18,864 participants, Rizk et al. [5] found that silent MI (SMI) by electrocardiographic criteria was present in 4.5% of the cohort. Importantly, the prevalence of SMI increased with decreasing estimated glomerular filtration rate (eGFR) from 4% in those with eGFR ≥60 ml/min/1.73 m^2 to 13% in those with eGFR <30 ml/min/1.73 m^2. In patients with CKD, SMI was independently associated with worse outcome during follow-up. Since this study excluded patients on dialysis and included only a small cohort of patients with advanced CKD (stages 4 and 5, <1% of the entire cohort), its findings may not extend to these patient groups. Hence, we sought to assess the prevalence and prognostic value of SMI in a large cohort of patients with advanced CKD being evaluated for renal transplantation.

2. Methods

2.1. Patient selection

Patients with CKD presenting at the University of Alabama at Birmingham (UAB) for renal transplant evaluation between June 2004

Abbreviations: CKD, chronic kidney disease; CMI, clinical myocardial infarction; CR, coronary revascularization; HR, hazard ratio; SMI, silent myocardial infarction.

☆ Presented in part as an abstract at the 2016 American Heart Association Scientific Sessions.

* Corresponding author at: University of Alabama at Birmingham, Lyons Harrison Research Building 314, 1900 University BLVD, Birmingham, AL 35294, United States.
E-mail address: fadihage@uab.edu (F.G. Hage).

[1] Both authors contributed equally.

https://doi.org/10.1016/j.ijcard.2017.09.175
0167-5273/Published by Elsevier Ireland Ltd.

and January 2006 were prospectively enrolled in a database as previously described [6–10]. The study was approved by the Institutional Review Board at UAB and was performed according to the standards of the 1964 Declaration of Helsinki and its amendments.

2.2. Clinical definition

Baseline demographics, comorbidities, and medications at time of transplant evaluation were retrospectively retrieved by chart review. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or intake of anti-hypertensive medications. Diabetes mellitus was defined as fasting blood glucose ≥126 mg/dl, A1c ≥6.5% or intake of hypoglycemic agents including insulin. Dyslipidemia was defined as elevated total cholesterol or low-density lipoprotein levels and/or low high-density lipoprotein levels as defined in the ATP III guidelines or intake of lipid lowering agents.

A 12-lead ECG was performed on every patient at the time of transplant evaluation. Automated analysis of the ECGs was conducted by Marquette™ 12SL™ ECG analysis program created by GE Healthcare, revised in 2008, based on the published literature of ECG scoring systems and criteria for infarction. All ECG showing 'possible MI' by the automated software were analyzed by an expert electrophysiologist that was blinded to the baseline characteristics (except for age and gender) and outcomes. The blinded reader used the published ECG criteria for diagnosing prior MI that was adopted by the Third Universal Definition of Myocardial Infarction [11]. An anteroseptal MI was only diagnosed if the criteria were met in leads V1–V3 to avoid false positives resulting from lead misplacement. Clinical MI (CMI) was defined according to the Third Universal Definition of MI and was determined by review of medical records [11]. Patients without prior clinical history of MI but with ECG evidence of MI were defined as having silent MI (SMI). Patients with neither CMI nor SMI were grouped as "No MI".

A subset of patients underwent stress testing with myocardial perfusion imaging (MPI) at the discretion of the clinical team evaluating the patient for renal transplantation. Gated Tc-99m Sestamibi SPECT MPI was performed using stress/rest or stress only one-day protocol according to the American Society of Nuclear Cardiology guidelines and as previously described [12,13]. Image interpretation was done without attenuation or scatter correction. All images were processed by a single investigator who was blinded to the clinical characteristics of the patients (except for gender) and their outcome. The presence and extent of perfusion abnormalities was determined by a software program (Corridor4DM) with visual supervision [14]. A fixed perfusion defect between stress and rest imaging involving >5% of left ventricular myocardium was considered consistent with scar (i.e. MI).

2.3. Endpoints

Patients were followed for all-cause death, MI, and coronary revascularization (CR). All-cause mortality was determined using chart review and by interrogation of the social security death index master data file accessed on February 1, 2014. Events of MI and CR were ascertained following chart review by adjudicators blinded to baseline clinical data and ECGs. The primary endpoint included the composite endpoint of death, MI, or CR. Secondary endpoints were all-cause death and the composite of all-cause death or MI.

2.4. Statistical analysis

Continuous data were expressed as mean ± standard deviation and compared using the two-tailed Student's *t*-test for normally distributed data, and the Wilcoxon test for skewed data. Categorical data were displayed as frequencies and percentages, and compared using Pearson Chi-square test. Binary regression analysis was performed to assess the independent predictors of SMI in patients without evidence of CMI. Variables entered into the model were age, gender, race, hypertension, diabetes, and dialysis.

Kaplan-Meier curves and the log-rank test were used to compare cumulative event rates in the entire cohort. Groups were divided into SMI, CMI, and no MI. Outcome analysis treated the date of renal transplant evaluation as "time 0". Follow-up time was defined by a qualifying event, last event-free encounter, or renal transplantation, whichever occurred first. Risk associated with SMI and CMI was expressed as hazard ratio (HR) with 95% confidence interval (CI), calculated using univariate and multivariate. Cox regression models, adjusting for age, gender, race, diabetes, hypertension, dyslipidemia, dialysis, and medication intake (aspirin, beta-blocker, angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACE-I/ARB), statin, and insulin) at time of evaluation. The proportional hazards assumption with respect to Cox-regression modeling was confirmed using "log minus log" survival plots. To test for incremental value of SMI and CMI, nested Cox models were performed with and without SMI/CMI; the increase in Chi-square value was then reported and the corresponding p value up to 1° of freedom was obtained. Given the higher prevalence of silent MI in patients with diabetes and in men versus women, we analyzed our results stratified by diabetes and gender [15]. Separate analysis was performed in patients who underwent renal transplantation treating the date of renal transplant as "time 0".

All tests were 2-tailed, and a p value < 0.05 (set a priori) was considered statistically significant. All statistical analyses were carried out with SPSS Statistics version 22 (IBM, Inc., Armonk, NY).

3. Results

The cohort included 1007 renal transplant candidates aged 48 ± 12 years. The baseline characteristics and medication intake are listed in Table 1. At the time of evaluation 75% were on dialysis, 44% had diabetes and 12% had a history of coronary revascularization. Of the 1007 patients, 67 (6.7%) had CMI. Of the remaining 940 patients, 73 (7.8%) showed definitive MI and 74 (7.8%) possible MI by the automated software. Of the 74 patients with possible MI by the automated software, 35 (47%) were determined to show MI according to the Third Definition of Myocardial infarction. In total, 108 (10.7%) were determined to have SMI. Therefore, SMI was more prevalent than CMI (10.7% vs. 6.7%. p < 0.001) in our population. Patients with SMI and CMI were older and had more comorbidities than patients without MI (Table 1).

In the 940 patients without CMI, the only independent predictor of SMI was older age (odds ratio for age ≥50 years 2.32, 95% CI 1.47–3.66, p < 0.001). Diabetes (1.40, 95% CI 0.89–2.18, p = 0.14) and male gender (0.83, 95% CI 0.54–1.26, p = 0.8) were not associated with SMI.

3.1. Outcomes prior to renal transplantation

During a median follow-up of 28 months (inter-quartile range 6–59 months), 376 (37%) patients experienced the primary outcome (33% death, 2% MI, 5% coronary revascularization). Compared to patients without evidence of MI (6%, 18%, 27%), patients with SMI (12%, 38%, 53%) and CMI (14%, 41%, 55%) had increased risk of events during follow-up at 1, 3 and 5 years (log-rank p < 0.001) with no statistical difference between the two groups (log-rank p = 0.2) (Fig. 1). Similar associations were seen for the secondary outcomes (Fig. 1). Compared to no MI (reference), SMI (HR 1.58 [1.17–2.13], p = 0.003) and CMI (HR 2.03 [1.45–2.86], p < 0.001) were associated with increased risk of the primary outcome. These results were essentially unchanged when only patients on dialysis at time of evaluation were included (HR for SMI 1.44 [1.03–2.01], p = 0.03 and for CMI 1.98 [1.35–2.89], p < 0.001). When stratified by diabetes status, CMI was significantly associated with increased risk of the primary endpoint in patients with (HR 1.82 [1.17–2.82], p = 0.008) and without (HR 2.45 [1.43–4.20], p = 0.001) diabetes while SMI was associated with

Please cite this article as: A.A. Farag, et al., Prognostic value of silent myocardial infarction in patients with chronic kidney disease being evaluated for kidney transplantatio..., Int J Cardiol (2017), https://doi.org/10.1016/j.ijcard.2017.09.175