Functional Mitral Regurgitation Predicts Short-Term Adverse Events in Patients With Acute Heart Failure and Reduced Left Ventricular Ejection Fraction

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Functional mitral regurgitation (FMR) is a common finding in patients with acute heart failure (AHF) and reduced left ventricular ejection fraction (heart failure and reduced ejection fraction [HFrEF]). However, its clinical impact remains unclear. We aimed to evaluate the association between the severity of FMR after clinical stabilization and short-term adverse outcomes after a hospitalization for AHF. We prospectively included 938 consecutive patients with HFrEF discharged after a hospitalization for AHF, after excluding those with organic valve disease, congenital heart disease, or aortic valve disease. FMR was assessed semiquantitatively by color Doppler analysis of the regurgitant jet area, and its severity was categorized as none or mild (grade 0 or 1), moderate (grade 2), or severe (grade 3 or 4). FMR was assessed at 120 ± 24 hours after admission. The primary end point was the composite of all-cause mortality and rehospitalization at 90 days. At discharge, 533 (56.8%), 253 (26.9%), and 152 (16.2%) patients showed none-mild, moderate, and severe FMR. At the 90-day follow-up, 161 patients (17.2%) either died (n = 49) or were readmitted (n = 112). Compared with patients with none or mild FMR, rates of the composite end point were higher for patients with moderate and severe FMRs (p <0.001). After the multivariable adjustment, those with moderate and severe FMRs had a significantly higher risk of reaching the end point (hazard ratio = 1.50, 95% confidence interval 1.04 to 2.17, p = 0.027; and hazard ratio = 1.63, 95% confidence interval 1.07 to 2.48, p = 0.023, respectively). In conclusion, FMR is a common finding in patients with HFrEF, and its presence, when moderate or severe, identifies a subgroup at higher risk of adverse clinical outcomes at short term. **(Am J Cardiol 2017;120:1344–1348)**

In patients with heart failure (HF) and reduced ejection fraction, functional mitral regurgitation (FMR) is a common condition (reported prevalence of about 50%)[1]; however, its clinical implications remain not well clarified.[1–3] Although some previous studies showed that FMR was associated with worse long-term survival rates in chronic HF,[4,5] others failed to show a prognostic role.[6] The evidence in patients with acute heart failure (AHF) is scarcer.[7,8] In this scenario of increased ventricular loading, we postulate that FMR could play a determinant prognostic role. The aim of the present study was to evaluate the association between the severity of FMR after clinical stabilization and short-term adverse outcomes after a hospitalization for AHF.

Methods

We prospectively included a consecutive cohort of 1,180 patients with HF and reduced ejection fraction discharged with the diagnosis of AHF from 2009 to 2015. AHF was defined according to current European Clinical Practice Guidelines.[9] Patients with new-onset or acutely decompensated HF were included in the registry. By design, patients who died during the index hospitalization (n = 51) were not included in the final analysis. To properly define mitral regurgitation as functional, patients with organic mitral valve disease, congenital heart disease, aortic valve disease, and prosthetic heart valves were excluded (n = 242), leaving the study sample with 938 patients (Figure 1).

FMR evaluation was performed by 2 expert sonographers who were blinded to clinical follow-up, and its severity was assessed semiquantitatively by color Doppler analysis of the regurgitant jet area after clinical stabilization was reached (120 ± 24 hours after admission). Clinical stabilization was

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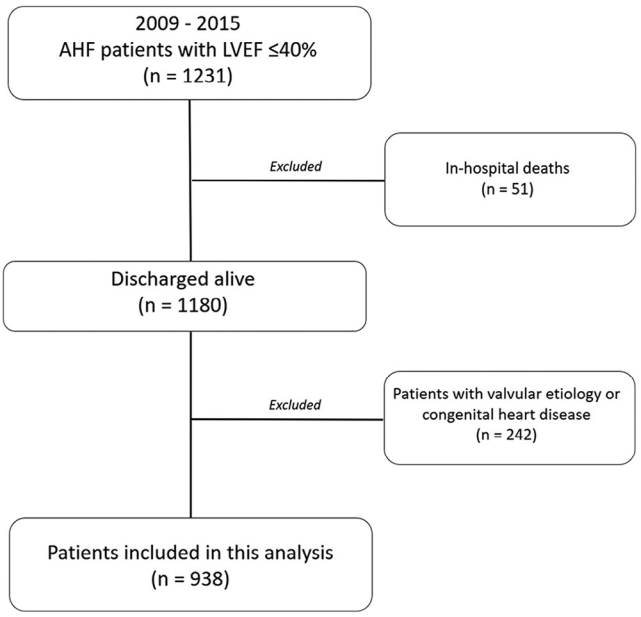

Figure 1. Flowchart.

defined as a cessation of intravenous therapy, a reinstitution of oral diuretics, and hemodynamic stability without the need for mechanical ventilation or ventilator support (other than for sleep apnea, if required). FMR severity was categorized as: none or mild (grade 0 or 1), moderate (grade 2), or severe (grade 3 or 4). Left ventricular ejection fraction (LVEF) was calculated by the biplane Simpson method. Reduced LVEF was defined as an LVEF of ≤40%, based on previously established thresholds.[9] Two commercially available systems were used throughout the study, Agilent Sonos 5500 and ie33 (Philips, Andover, Massachusetts). During the index hospitalization, data on demographics, medical history, vital signs, 12-lead electrocardiogram, laboratory and echocardiographic parameters, and drug use were routinely recorded using preestablished registry questionnaires. Treatment and other therapeutic strategies were individualized after established guidelines that were operating at the time the patient was included in the registry.[9]

The primary end point of the present study was a composite end point (all-cause mortality and/or all-cause readmission) at the 90-day follow-up after discharge. Patients' follow-up was censored if death, cardiac transplantation, or valve replacement occurred. End points were ascertained by a physician blinded to the exposure through a review of hospital and/or outpatient electronic medical records.

The study was prospectively designed, conformed to the principles outlined in the Declaration of Helsinki, and was approved by the institutional local review ethical committee. All patients gave informed consent.

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), as appropriate. Discrete variables were presented as percentages. Comparisons across FMR groups were performed by chi-square test for categorical variables. For continuous variables, 1-way analysis of variance and Kruskal-Wallis test were used for those variables with parametric and nonparametric distributions, respectively. The cumulative probability of the clinical end point was estimated by the Kaplan-Meier method and curves were compared by the log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazards models. For the multivariate regression model, candidate covariates were chosen based on previous medical knowledge and independent of their p value. A reduced and parsimonious model was derived using backward stepwise selection. The covariates included in the final multivariable model for the primary end point were as follows: age, gender, previous AHF hospitalization, length of stay, systolic blood pressure, the interaction between atrial fibrillation and heart rate, N-terminal pro b-type natriuretic peptide (NT-proBNP), urea, hemoglobin, and tricuspid annular plane systolic excursion. The discriminative ability (Harrell C-statistics) and the calibration (Groennesby and Borgan test) of the final model were 0.783 and 0.102, respectively. A 2-sided p value of <0.05 was considered statistically significant for all analyses. All analyses were performed using STATA 14.1 (StataCorp. 2015. *Stata Statistical Software: Release 14.* College Station, TX: StataCorp LP).

Results

The mean age was 70.4 ± 12.2 years, 634 patients (67.7%) were male, the underlying etiology of HF was ischemic in 445 patients (47.4%), and 448 patients (47.7%) had a previous admission for AHF. The mean LVEF was 28.8 ± 1.3% and the median NT-proBNP was 5,206 (6,909) ng/ml.

After clinical stabilization, 533 (56.8%), 253 (27.0%), and 152 (16.2%) patients showed none or mild (grade 0 or 1), moderate (grade 2), and severe (grade 3 or 4) FMRs, respectively. The baseline characteristics according to FMR categories are shown in Table 1.

The composite end point was reached by 161 (17.1%) patients: 49 patients died and 112 were readmitted at 90 days. Patients with a higher degree of FMR showed higher rates of 90-day mortality (none-mild: 16/533 [3.0%], moderate 17/253 [6.7%], and severe 16/152 [10.5%]) and the composite of 90-day death and readmission (none-mild: 71/533 [13.3%], moderate 54/253 [21.3%], and severe 36/152 [23.6%]). Kaplan-Meier curves revealed substantial divergent risk trajectories among FMR groups since the first days after discharge (Figure 2). In the univariate analysis, compared with patients with none or mild FMR, those with FMR grade 2 and grade 3 or 4 showed an almost twofold increased risk of reaching the composite end point at 90 days (unadjusted hazard ratio [HR] = 1.73, 95% confidence interval [CI] 1.22 to 2.47, p = 0.002; and HR = 1.89, 95% CI 1.26 to 2.85, p = 0.002, respectively). After the multivariate adjustment, including well-established prognosticators and potential confounders, a more than mild FMR remained significantly associated with an increased risk of reaching the composite end point (p <0.05). Adjusted HRs for FMR grades 2 and 3 or 4 were 1.50 (95% CI 1.04 to 2.17, p = 0.027 and 1.63; 95% CI 1.07 to 2.48 p = 0.023, respectively.

A subgroup analysis revealed a nonsignificant differential prognostic effect across age (>75 vs ≤75 years: p value for interaction = 0.149), gender (p value for interaction = 0.635), ischemic etiology (p value for interaction = 0.774), previous AHF admission (p value for interaction = 0.418), and LVEF