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Definitions of Stage D heart failure and outcomes among outpatients with heart failure and reduced ejection fraction

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ABSTRACT

Background: An operational consensus definition of Stage D heart failure (HF) is currently lacking.
Methods: We evaluated 512 outpatients (median age, 63 years; 35.0% women; 45.5% white and 45.9% black; median ejection fraction was 25%; 67.4% had coronary artery disease) with HF and reduced (≤40%) ejection fraction. We applied 3 hypothetical definitions for Stage D: (1) designation as "Stage D" or "advanced" HF by treating physician; (2) INTERMACS profiles, defining Stage D as profiles 2–6; and (3) European Society of Cardiology Heart Failure Association (ESC-HFA) criteria.
Results: Physicians, INTERMACS profiles, and ESC-HFA criteria identified 64 (12.5%), 93 (18.2%), and 67 (13.1%) patients, respectively, as Stage D, with modest concordance between definitions ($\kappa = 0.37$). After a median of 3.1 years, 97 patients died (3-year mortality 20.4%). Among patients identified as Stage D by physicians, 3-year mortality was 43.7% vs. 17.0% for non-Stage D patients (age-adjusted hazard ratio [HR] 3.17; 95%CI 1.94–5.18; $P < 0.001$). The corresponding mortalities for the INTERMACS-based definition were 41.0% vs. 16.2% (HR 3.28; 95%CI 2.11–5.11; $P < 0.001$) and for ESC-HFA criteria 33.5% vs. 18.6% (HR 2.02; 95%CI 1.22–3.33; $P = 0.006$); the INTERMACS-based definition provided the best prognostic separation. Results were similar with an alternative INTERMACS-based definition considering only profiles 2–5 as Stage D HF. The INTERMACS-based definition best separated all-cause and HF-specific hospitalization and composite endpoint risk between Stage D and non-Stage D patients also.
Conclusions: INTERMACS profiles provide a practical alternative for the identification of Stage D HF in ambulatory populations with systolic HF. The ESC-HFA criteria offer limited prognostic information.

1. Introduction

Although care for patients with Stage D heart failure (HF) is becoming increasingly complex, an operational consensus definition of Stage D HF is currently lacking [1]. Current estimates of the proportion of patients with Stage D disease among those with HF and reduced ejection fraction (HFrEF) range from 1 to 10% [2–4]. Despite that guidelines highlight the need to define Stage D HF as a distinct entity that needs careful management [4,5], available definitions are mostly descriptive with several subjective elements. Currently, clinicians identify high-risk patients transitioning to Stage D based on clinical judgment. Although the Heart Failure Association of the European Society of Cardiology (ESC-HFA) has previously proposed diagnostic criteria for advanced HF [6], these criteria have not been widely implemented. On the other hand, although the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles carry significant prognostic information for patients receiving advanced HF therapies [7–9], these profiles have not been used to identify Stage D patients in the general HF population. Considering that prognostic implications are a core validity element of any classification system for disease severity, in this work, we compare determination of Stage D ("advanced") HF status

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by the treating physician with definitions of Stage D based on (1) INTERMACS profiles and (2) ESC-HFA criteria, in 512 consecutive outpatients with HFrEF (ejection fraction ≤40%).

2. Methods

2.1. Study population

We evaluated all consecutive adults (age ≥ 18) who received outpatient care with associated International Classification of Diseases, 9th Revision Clinical Modification codes (ICD-9-CM) 402.X1, 404.X1, 404.X3, and 428.XX (Centers for Medicare and Medicaid Services definition [10], Supplemental Table 1) during January 2012 by cardiologists, including HF specialists, at Emory Healthcare (Atlanta, GA). The timeframe was selected to allow for ≥3 years of follow-up. Initially, 930 patients met the ICD-9-CM code criteria. The final cohort consisted of 512 patients (Supplemental Fig. 1). We excluded 56 patients because of unconfirmed HF diagnosis. Subsequently, we excluded 78 patients because of (1) specific cardiomyopathies (e.g. hypertrophic, infiltrative, stress-induced, restrictive, chemotherapy-induced); (2) complex congenital heart disease; (3) primary valvular or right-sided disease; and (4) previous heart transplant or mechanical circulatory support. Among the remaining patients, 264 patients had LVEF >40% and 20 had incomplete data for Stage D classifications.

2.2. Classification of Stage D HF

Patients identified during the index clinic visit by the treating physician as having "Stage D", "advanced", or "end-stage" HF in the medical record and/or were referred for advanced HF therapy evaluation because the treating physician felt that medical therapy was failing to help the patient further, were classified as Physician Stage D HF. For INTERMACS classification (Supplemental Table 2) [4], two investigators (JH and AST), blinded to outcomes data and to each other, independently assigned an INTERMACS profile at baseline to each patient after a detailed review of medical records. For profile 7, in addition to symptomatic limitation with more than mild exertion, we required the absence of recent decompensation (within 6 months) [6]. For profile 6, we required symptomatic limitation with minimal activity (besides activities of daily living) but without overt fluid overload or symptoms at rest. In case of discrepancy, the profile was adjudicated by a third, senior investigator (APK). Patients assigned to profiles 2–6 were classified as INTERMACS Stage D HF, as profile 1 refers to cardiogenic shock (and thus does not apply to outpatients) and profile 7 is not currently approved for mechanical circulatory support [2]. As a sensitivity analysis, we also evaluated an alternative INTERMACS-based definition, in which we considered only profiles 2–5 as Stage D. Every patient was also assessed according to the ESC-HFA criteria (Supplemental Table 3) [6]. To categorize a patient as ESC-HFA Stage D HF, criteria from each major category were required per the original definition [6].

2.3. Baseline characteristics and conditions

Baseline demographic, anthropometric, and vital signs data were collected through the Emory Clinical Data Warehouse from the index (baseline) clinic visit record. Race was self-reported. For laboratory values and medications, we extracted the last information available up to the index visit. The presence of chronic conditions was adjudicated according to the algorithms proposed by the Chronic Conditions Data Warehouse project [11], which is used to analyze Medicare data.

2.4. Outcomes

Outcomes data (death and hospitalizations) were collected through the Emory Clinical Data Warehouse, which is connected to medical records and sources of vital status, and individual review of medical records for all events. We set a minimum of 3 years of follow-up from the index date for each patient who continued to receive care in Emory Healthcare. For patients who were alive until the last encounter but did not continue to receive care in our institution throughout the study period, the last encounter was considered the last date of follow-up for analysis purposes and the patient was censored alive. We further classified all confirmed hospitalizations into HF-related and non-HF-related based on the primary reason for admission.

The primary endpoint was 3-year mortality. The secondary endpoints included (1) time to the composite of death plus all-cause hospitalization and the composite of death plus HF-specific hospitalization (commonly used in clinical trials) and (2) all-cause and HF-related hospitalization rates (i.e., both first and recurrent events). Because physician assessment of Stage D HF is associated with selection for advanced HF therapies (heart transplant and long-term mechanical circulatory support), we did not include these events in the primary endpoint to avoid bias in the comparison of definitions, i.e. only mortality was included for these patients. We did however, as a sensitivity analysis, assess the primary endpoint after censoring patients as alive at the time of heart transplant or ventricular assist device implantation, drawing from previous published experience [12]. All patients were followed up until death or end (or loss) to follow-up. No patient was excluded from the analysis.

2.5. Statistical analysis

We used crude agreement and the kappa (κ) statistic to assess concordance among definitions for Stage D HF, both overall and pairwise. Values for κ range from −1 (complete disagreement) to 1 (complete agreement). For each definition, we used age-adjusted Cox proportional hazards models to calculate hazard ratios (HR) and confidence intervals (CI) for mortality in Stage D vs. non-Stage D patients. We used Royston's R^2 to compare prognostic separation among definitions of Stage D HF for mortality [13]. We used similar models to compare time to the composite endpoints of death plus all-cause hospitalization and death plus HF hospitalization in Stage D vs. non-Stage D patients for each definition, which are commonly used in clinical trials. Rate ratios (RR) for hospitalization rates were estimated with negative binomial regression models. STATA 14.1 (StataCorp LP, College Station, TX) was used for all statistical analyses.

3. Results

3.1. Patient characteristics and disease severity classification

Table 1 summarizes the baseline characteristics, including INTERMACS profiles and ESC-HFA criteria. The number of ESC-HFA criteria met by each patient varied. Specifically, 67 (13.1%) patients met 6 criteria; 130 (25.4%) met 5; 131 (25.6%) met 4; 43 (8.4%) met 3; 103 (20.1%) met 2; 20 (3.9%) met only 1 criterion; and 18 (3.5%) met no criterion for Stage D HF. Physician assessment identified 64 (12.5%) patients as Stage D HF. Using INTERMACS profiles, we identified 93 (18.2%) patients as Stage D HF, defined as profiles 2–6. With the ESC-HFA criteria, we identified 67 (13.1%) patients as Stage D HF. Supplemental Table 4 presents the comparative clinical characteristics of the cohort across the three definitions.

3.2. Concordance between Stage D definitions

Overall concordance between the 3 definitions was low with $\kappa = 0.37$, indicating only modest agreement (complete agreement would be $\kappa = 1.0$). In pairwise comparisons, physician-based and INTERMACS-based definitions had the highest crude agreement (86.5%) and $\kappa = 0.48$. The ESC-HFA criteria and INTERMACS definition had crude agreement 82.4% and $\kappa = 0.34$. Physician-based definition and ESC-HFA criteria had crude agreement 83.8% and $\kappa = 0.27$.

3.3. Mortality according to Stage D definitions

After a median of 3.1 years (1.6–3.3), 97/512 (18.9%) patients died; crude 3-year mortality was 20.4%. In addition, 11 patients received heart transplant and 24 received long-term mechanical circulatory support. The 3-year mortality among patients identified as Stage D HF vs. non-Stage D was 43.7% vs. 17.0% (age-adjusted HR 3.17; 95%CI 1.94–5.18; $P < 0.001$) for physician-based assessment; 41.0% vs. 16.2% (HR 3.28; 95%CI 2.11–5.11; $P < 0.001$) for INTERMACS based definition; and 33.5% vs. 18.6% (HR 2.02; 95%CI 1.22–3.33; $P = 0.006$) for ESC-HFA criteria. INTERMACS profiles provided the best prognostic separation (Fig. 1); Royston's R^2 was 0.121 for INTERMACS definition, 0.088 for physician assessment, and 0.034 for ESC-HFA. The alternative INTERMACS-based definition (only profiles 2–5 considered Stage D), had an even higher age-adjusted HR for mortality (3.85; 95%CI 2.36–6.28; $P < 0.001$) and R^2 (0.124).

In a sensitivity analysis, we explored the discriminatory capacity of the 3 Stage D definitions after censoring patients (i.e. ending follow-up) as alive at the time of heart transplant or ventricular assist device implantation. The results were similar. The 3-year event rates for Stage D vs. non-Stage D patients were 31.9% vs. 14.6% (age-adjusted HR 3.22; 95%CI 1.63–6.34; $P = 0.001$) for physician-based assessment; 31.3% vs. 13.6% (HR 3.28; 95%CI 1.89–5.70; $P < 0.001$) for INTERMACS based definition; and 26.4% vs. 14.8% (HR 2.00; 95%CI 1.07–3.74; $P = 0.030$) for ESC-HFA criteria. The corresponding Royston's R^2 statistics for the 3 Stage D definitions were 0.044, 0.087, and 0.024, respectively.

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