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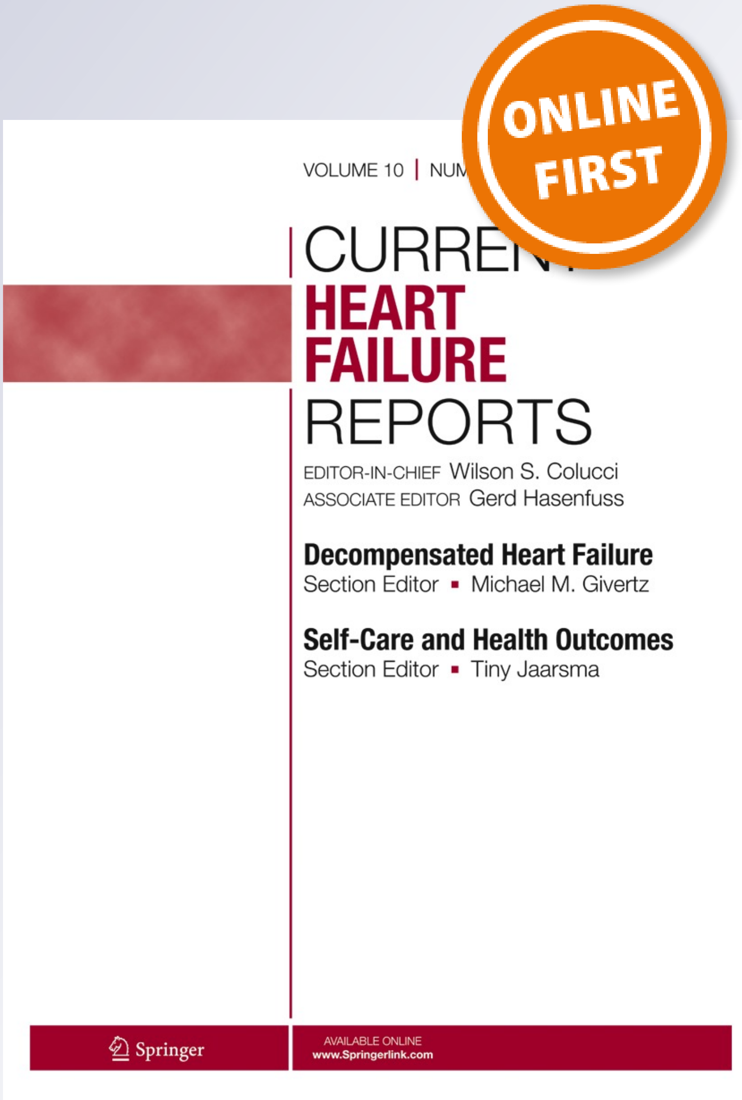

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EPIDEMIOLOGY OF HEART FAILURE (J BUTLER, SECTION EDITOR)

Prognostic Factors in Patients Hospitalized for Heart Failure

Lakshmi Sridharan · Liviu Klein

Abstract Each year, there are over one million hospitalizations for heart failure in the United States, with a similar number in Western Europe. Although these patients respond to initial therapies, they have very high short and intermediate term (2-6 months) mortality and readmission rates, while the healthcare system incurs substantial costs. Several risk prediction models that can accurately identify high-risk patients have been developed using data from clinical trials, large registries or administrative databases. Use of multi-variable risk models at the time of hospital admission or discharge offers better risk stratification and should be encouraged, as it allows for appropriate allocation of existing resources and development of clinical trials testing new treatment strategies for patients admitted with heart failure.

Keywords Heart failure · Hospitalizations · Prognostic factors · Risk factors

Introduction

Hospitalizations for heart failure (HFH) are a considerable health care burden, with over one million annual hospital discharges in the United States [1, 2••], a number that has not decreased in the last decade. The 30-day readmission rate approaches 25 % [3, 4••], the subsequent one-year mortality rate is nearly 30 %, and hospital costs carry a price tag of $30 billion dollars [5, 6], most of which is directly absorbed by the Medicare health system.

In this context, much attention has been paid to the ability of finding prognostic factors during the index HFH that can potentially be addressed and lead to prevention of rehospitalizations. Understanding the relevant predictors of HFH is an important step in defining individual risk, building risk models and pursuing preventive strategies that can help contain costs and improve morbidity and mortality in this patient population.

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Definition

A HFH is defined as an unplanned visit to a healthcare facility for which HF symptoms (dyspnea on exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, cough, fatigue, leg edema, nausea/ vomiting, poor appetite, abdominal bloating, right upper quadrant pain) are the main reasons for presentation and for which HF is recorded as the primary or secondary diagnosis at the time of discharge.

Due to the different setup specific to individual healthcare facilities, as well as to various administrative and reimbursement issues, patients presenting to medical attention with HF symptoms may be treated in the Emergency Department and subsequently released, admitted for a short period (less than 48 hrs) in Observation/ Short Stay Units, or admitted to the hospital for a longer duration of treatment. This concept is particularly important as it may have an effect on the ability to identify prognostic factors, may influence readmissions and may influence patients' selection for HF clinical trials.

In general, HFH can be divided in three groups: acute worsening of chronic (stage C) HF (70-80 % of HFH), de novo diagnosis of HF (20-25 % of HFH), or acute worsening of advanced (stage D) HF refractory to traditional therapies (less than 5 % of HFH) [1, 7]. Irrespective of the group, all patients presenting with HF symptoms share one thing in common: they all have elevated ventricular filling pressures leading to pulmonary and/or systemic congestion [8].

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Burden and Costs

The growing health care burden of HFH has been well described. In the United States, HFH nearly tripled between 1979 and 2004, and have remained constant at approximately one million discharges for the past decade [9]. Heart failure is the most common reason for hospital admission amongst the Medicare population (not surprisingly, since the mean age at HF diagnosis is around 74 years), with an average length of stay of 6 days [2••, 10]. Hospitalization costs account for the majority of the $40 billion dollars spent yearly in the United States on HF treatment [2••, 11]. Similar HFH trends are observed in Europe [7], where the mean age at diagnosis is 71 years and where the mean length of stay is 11 days [12].

Epidemiology

In the last decade, multiple large registries have described the demographic and clinical characteristics of HFH. From American and European populations, the Acute Decompensated Heart Failure National Registry (ADHERE), the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF), the Get with the Guidelines Heart Failure (GWTG-HF), and the Euro Heart Failure Survey (EHFS) I and II, have shed light on the epidemiology of HFH [12–17].

Demographics

In the United States, slightly more women (55 %) than men are hospitalized for HF [13, 16, 17], with temporal data (from 1990 to 1999) showing a rise in age-specific rates for women compared to men [18]. By contrast, men are more likely to be admitted for HF in Europe, with a widening gender gap over time as demonstrated by EHFS I in 2003 (53 % men) and EHFS II in 2006 (61 % men) [12, 14, 15]. The mean age of hospitalized patients is between 70 and 73 years, and is similar between continents. The risk of rehospitalization amongst patients in this age group is at least three fold higher than those younger than 65 years [19, 20••], with the risk for rehospitalization increasing with increasing age [19].

Clinical Classification

Heart failure is associated with a broad spectrum of left ventricular function and can be further classified as HF with preserved ejection fraction (HFpEF, > 40-45 %) or HF with reduced ejection fraction (HFrEF, < 40-45 %). In the United States, the incidence of HFH due to HFpEF has been increasing over time, accounting for 50-55 % of all HFH in the most current statistics [7, 13, 16, 17, 21–23]. Similarly, earlier European data from EHFS I suggested that 55 % of HFH were due to HFpEF [12, 14], although, more recently, EHFS II has put that number much lower at 34 % [15].

With respect to rehospitalization, rates are similar between HFrEF and HFpEF patients [16, 23], although HFpEF patients may be at higher risk for non-cardiac and non-HF hospitalizations [24•]. Lastly, patients hospitalized for HFpEF are more likely to be female and of an older age than HFrEF patients [16, 17].

Effect on Survival

Although the reasons are still poorly understood, the index HFH increases mortality in the immediate (30-60 days) and intermediate (up to 6 months) post-discharge period [12, 25, 26]. While the in-hospital mortality during a HFH has declined since 1979 (currently at 2-3 %) [9], approximately 15 % of patients die within 2-3 months of the index admission [12]. The mortality risk is greatest in the first 30 days after discharge and is estimated to be six times greater than those HF patients who have never been hospitalized. A HFH doubles the risk of death even two years after the incident hospitalization [25]. Notably, the increase in mortality is independent of the cause of death and persisted whether the cause was identified as HF, cardiovascular, or all-cause [26]. An increase in the number and duration of HFH has also been associated with an increased mortality, with a second or third HFH leading to a 30 % increase in the cumulative incremental mortality risk [25]. Finally, the clinical subtype of HF may have a differential risk on in-hospital versus post-discharge mortality. When compared to HFrEF patients, HFpEF patients tend to have decreased in-hospital mortality but roughly equivalent post-discharge mortality rates in the three months following index hospitalization [16, 17].

Prognostic Factors

Etiology of HF

Acute coronary syndromes are the leading precipitant of de novo HFH [15]. Ischemic etiology of HF predicts increased post-discharge mortality and rehospitalization [27–29]. Estimates of the increased risk of rehospitalization in ischemic HF range from 1.25 to 2 times greater than of non-ischemic HF in the 2 to 6 months post-discharge [7, 20••, 27]. The in-hospital mortality, however, is similar regardless of etiology [27].

Furthermore, severe presentations of HF at the time of admission are more likely to be associated with acute coronary syndromes. According to EHFS II, in over 70 % of cases, the etiology of HFH for cardiogenic shock is ischemia. Independent of acute coronary syndromes, coronary artery disease can precipitate comorbidities that can worsen the degree of HF [29]. For instance, ventricular arrhythmias often present in the setting of ischemia can amplify the hemodynamic consequences of HF [15].

Comorbidities

The comorbid burden of patients hospitalized for HF is significant and is growing with age [2••, 20••, 30]. Hospitalized HFpEF patients may have a larger comorbid burden than HFrEF patients [31]. Non-cardiac (e.g., diabetes, anemia, renal insufficiency) and cardiac (e.g., arrhythmias, valvular disease) conditions are widely co-prevalent in these patients [7, 13, 20••, 32, 33]. Several of these diagnoses are important prognostic factors for HFH and associated mortality.

Diabetes has been repeatedly shown to increase the risk of HFH [33, 34]. The increased risk of HFH and mortality is 1.5 to 2 times greater in diabetics [32]. The effect on HFH seems to be more pronounced among HFpEF patients even when the prevalence of diabetes is similar to HFrEF patients [34]. Hospitalized diabetics with HFpEF have a 60 % increase in their five-year mortality compared to non-diabetic HFpEF patients [35].

Similarly, anemia increases the risk of rehospitalization and in-hospital mortality among HF patients [20••, 28, 36]. The rates of anemia in patients hospitalized for FH are estimated at 30 % [12–17] with comparable rates among HFpEF and HFrEF patients in smaller analyses [37]).

A history of renal insufficiency related to intrinsic renal disease (a distinct entity from the cardio-renal syndrome that occurs during a HFH or from the renal effects of medications during a HFH) is estimated at 20 % [12–17] and negatively impacts the HFH prognosis.

With respect to cardiac comorbidities, valvular heart disease may be seen in up to one-third of patients hospitalized for FH [15] and increases the risk of readmission and mortality [31, 38]. One small cohort study suggested that it nearly quadrupled the risk of readmission regardless of ejection fraction [31], while other data suggest a more modest increase in HFH and mortality of approximately 20 % [38].

Arrhythmias are seen in over 60 % of elderly hospitalized for HF [4••] and new arrhythmias are common [20••]. Atrial fibrillation is present in nearly 40 % of patients hospitalized for HF [13, 39] and can develop during admission [40]. A new occurrence of atrial fibrillation during the index HFH appears to increase the risk of rehospitalization and mortality. A history of arrhythmias in general may confer an additional risk of rehospitalization and mortality [40].

Hemodynamic Profile

The hemodynamic profile is an important factor of a patient's presentation at the time of HFH. Hemodynamics that prognosticate hospitalization and mortality in HFH include heart rate, systolic blood pressure, diastolic blood pressure, and ventricular filling pressures.

Higher heart rate increases the risk of HFH and in-hospital mortality, though the clinical effect is small [32, 41]. Lower diastolic blood pressure has been shown to predict an increase in mortality and HFH [32]. Similarly, a lower systolic blood pressure at the time of HFH predicts higher in-hospital and post-discharge mortality [28, 41–43]. However, systolic blood pressure has no effect on rehospitalization [42].

Prior to a HFH, patients develop an increase in ventricular filling pressures that present clinically as congestion [7, 8]. Observational data demonstrates an increase in right ventricular filling pressures that begins several days before a HFH [44]. Reducing filling pressures (as approximated by the pulmonary capillary wedge pressure) prior to hospital discharge may portend improved mortality up to two years post-discharge. Notably, an improvement in the cardiac output does not appear to affect post-discharge mortality [45, 46].

Symptoms and Signs at Presentation

A higher New York Heart Association (NYHA) functional class is in itself a predictor of increased mortality and rehospitalization [28, 32, 47]. Dyspnea at rest has also been shown to increase the risk of mortality and rehospitalization by 20 % [32]. An increase in body weight after HFH for HFrEF predicts readmission but not post-discharge mortality [48].

The physical examination can provide useful information about perfusion and state of congestion. Cool extremities, a sign of decreased tissue perfusion, can predict a 2.5-fold decrease in hospital-free survival [20••, 49]. Peripheral edema, elevated jugular venous pressure, and crackles on pulmonary exam are signs of volume overload and at the time of discharge, such findings portend up to a two-fold increase in risk of rehospitalization [32, 50].

Laboratory Data

Various laboratory data, including biomarkers, sodium, and measures of renal function, have been studied for their prognosticating ability in HFH and related mortality. The biomarkers with the best predictive abilities are troponin and natriuretic peptides.

Troponin elevation may be detected in up to 75 % of patients hospitalized for HF [51, 52•], and regardless of HF etiology; troponin leak during HFH has consistently predicted readmission. Troponin elevation in the context of HFH is commonly due to ischemic injury related to elevated ventricular filling pressure and is independent of ongoing coronary ischemia. Estimates suggest a tripled risk of rehospitalization and a double risk of 60-day post-discharge mortality when troponins are detected during a HFH [7, 20••, 51, 52•, 53, 54].

Natriuretic peptides (BNP and NT pro-BNP) may have prognostic value in HFH as well. As hormones of ventricular origin, BNP and NT pro-BNP are typically released as response to an increased ventricular wall stress. A greater than 30 % increase of NT pro-BNP from admission to discharge during a HFH predicts a six-fold increase in readmission risk [50]. Observational data suggest that high admission NT pro-BNP levels predict an increased risk of mortality [55]. Similar data demonstrate that discharge BNP levels after HFH can stratify patients at risk for further rehospitalization [55, 56].

Sodium levels, as markers of neurohormonal activation, are yet another predictor of HFH and mortality. Nearly a quarter of HFH are associated with hyponatremia (sodium level less than 135 mEq/L), and the condition often persists throughout hospitalization [57]. Lower levels of sodium at admission or during HFH portend an increased in-hospital mortality, 60-day post-discharge mortality, and rehospitalization [28, 41, 57, 58].

Finally, increased creatinine and blood urea nitrogen (BUN) associated with HFH predict worse outcomes. As described above, intrinsic renal insufficiency in the context of a HFH can be difficult to parse from transient elevations in creatinine and BUN secondary to the cardio-renal syndrome or acute changes in medications (e.g., diuretics, ACE inhibitors, non-steroidal agents). Regardless of etiology, elevations in BUN, creatinine, and BUN/creatinine ratio predict worse survival and increased readmission risk [28, 59–61]. BUN and the BUN/creatinine ratio are good markers of renal dysfunction in patients hospitalized for HF [62]. Specifically, BUN is a better predictor of post-discharge mortality than glomerular filtration rate [63]. High admission BUN levels lead to a three-fold increase in the risk of in-hospital and post-discharge mortality [7, 28, 59–61]. In addition, the change in BUN and creatinine from admission to discharge strongly predicts readmission and 6-month mortality [63–65].

Pharmacologic Therapy during a HFH

Although patients hospitalized for HF are often managed with intravenous medications, hospitalized patients requiring intensive management often suffer from more severe HF and consequently, data regarding the prognostic effects of in-hospital therapies can be confounded. For instance, the use of intravenous diuretics has been associated with increased mortality [66, 67]. Similarly, intravenous inotrope use portends worse outcomes, particularly in ischemic HF patients [27, 68, 69]. Lastly, use of intravenous vasodilator has not demonstrated a clear mortality benefit and can precipitate worsening hypotension and renal dysfunction, exacerbating hemodynamic aberrations in these patients [70, 71].

Risk Prediction Models

Given the high rate of HFH and the multitude of relevant predictors, it is not surprising that several multivariate risk

Table 1 Risk prediction models of heart failure hospitalizations

Risk Prediction Models[†]	Registry/Trial	Predictors*		Predictive Performance**
Model 1 *Felker M, et al. 2004* [28]	OPTIME-CHF	HFH in prior 12 months History of PCI Admission hemoglobin	Admission SBP Admission BUN	0.68
Model 2[‡] *Pocock SJ, et al. 2006* [32]	CHARM	Age Diabetes LVEF<45 % Prior HFH	Cardiomegaly Longer duration of HF NYHA class DBP	0.75
Model 3 *O'Connor CM, et al. 2010* [72•]	ESCAPE	Age SBP BUN Sodium B-natriuretic peptide	Use of a beta-blocker Use of a high-dose diuretic 6-minute walk distance In-hospital mechanical ventilation In-hospital CPR	0.803

BUN blood urea nitrogen, *CHARM* Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity, *CPR* cardiopulmonary resuscitation, *DBP* diastolic blood pressure, *ESCAPE* Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness, *HF* heart failure, *HFH* heart failure hospitalization, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *OPTIME-CHF* Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure, *PCI* percutaneous coronary intervention, *SBP* systolic blood pressure

*All listed predictors have a p-value≤ 0.05 unless otherwise indicated

**Predictive performance as indicated by c-statistic in which 0.5 indicates no discriminative power and 1.0 indicates perfect discrimination

[†] All models use data from the indicated registry/trial. Models 1, 2, and 3 use a composite endpoint of risk of mortality and rehospitalization (at 60 days in model 1, and at 6 months for models 2 and 3). The endpoint for model 4 is rehospitalizations at 6 months

[‡] Twenty-one variables were identified as independent predictors in this model; here are only the top eight predictors (highest chi-square in the multivariate model)

models of HFH have been created. In general, in order to assess their predictive ability and superiority a c-statistic is reported with each risk model, with 0.5 meaning no discriminative power and 1.0 indicating perfect discrimination.

Three sets of predictive models from registries and randomized control trials are well described (Table 1). One comes from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) and assesses the composite of time to death or rehospitalization at 60 days with a c-statistic of 0.68 [27, 28]. The five identified predictors were HFH in the prior 12 months, systolic blood pressure value on admission, admission BUN, admission hemoglobin, and history of percutaneous coronary intervention.

The second model comes from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program and estimates the time to cardiovascular death or first HFH with a c-statistic of 0.75 [32]. Twenty-one variables are assessed in this risk score, with eight of the strongest predictors being prior HFH, longer duration of HF, diastolic blood pressure, age, diabetes, decrease in left ventricular ejection fraction below 45 %, cardiomegaly, and NYHA class.

The third model comes from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE) trial and assesses the 6-month risk of death or rehospitalization, with a c-statistic of 0.803 [72•]. All patients in this study had HFrEF with ejection fraction less than 30 %. The nine identified predictors were age, BUN, sodium, BNP, systolic blood pressure, use of a beta-blocker, use of high-dose diuretics, 6-minute walk distance, and a need for mechanical ventilation or in-hospital cardiopulmonary resuscitation.

Models discussed above are specific to rehospitalization, but several more models exist when risk scores are broadened to in hospital or post-discharge mortality [41, 73, 74].

Conclusions

Hospitalizations for HF represent a significant and growing health care burden. Although the vast majority of patients improve symptomatically during hospitalization, the post-discharge rehospitalization and mortality rates continue to be extremely high. Strategies to reduce readmission rates after HFH need to target primarily the identification of modifiable risk/ prognostic factors. Use of multi-variable risk models at the time of hospital admission or discharge offers better risk stratification and should be encouraged, as it allows for appropriate allocation of existing resources and development of clinical trials testing new treatment strategies for patients admitted for HF.

Compliance with Ethics Guidelines

Conflict of Interest Lakshmi Sridharan and Liviu Klein declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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