Predictors of re-hospitalization in patients with chronic heart failure

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Heart failure (HF) is a chronic, progressive illness that is highly prevalent in the United States and worldwide. This morbid illness carries a very poor prognosis, and leads to frequent hospitalizations. Repeat hospitalization in HF is both largely burdensome to the patient and the healthcare system, as it is one of the most costly medical diagnoses among Medicare recipients. For years, investigators have strived to determine methods to reduce hospitalization rates of HF patients. Despite such efforts, recent reports indicate that re-hospitalization rates remain persistently high, without any improvement over the past several years and thus, this topic clearly needs aggressive attention. We performed a key-word search of the literature for relevant citations. Published articles, limited to English abstracts indexed primarily in the PubMed database through the year 2011, were reviewed. This article discusses various clinical parameters, serum biomarkers, hemodynamic parameters, and psychosocial factors that have been reviewed in the literature as predictors of re-hospitalization of HF patients. With this information, our hope is that the future holds better risk-stratification models that will allow providers to identify high-risk patients, and better customize effective interventions according to the needs of each individual HF patient.

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Key words: Heart failure; Readmission; Predictors; Re-hospitalization; Chronic heart failure; Hospitalization

INTRODUCTION

Heart failure (HF) is a prevalent and morbid chronic illness. According to the European Society of Cardiology and the American Heart Association, HF affects approximately 15 million Europeans and over 5 million Americans[3,4]. HF is not only taxing to the patient, but also to the healthcare system. Studies evaluating the economic burden of HF among several countries reveal estimated direct HF costs of 1%-2% of total healthcare expenditures, with approximately two-thirds of costs attributable to hospitalization[1]. While HF poses a significant burden to healthcare systems worldwide, the most abundant data and literature comes from the United States. In the United States a reported $37.2 billion was spent in direct and indirect costs in 2009, with $20.1 billion dollars of the expenditure relating to hospitalization[2]. Repeat hospitalization contributes significantly to the hospitaliza-
tion expenditure as HF patients are re-hospitalized at an alarmingly high rate, with approximately 50% of patients requiring readmission in the 6 mo after initial hospitalization\cite{1,6}. Reports from the Medicare Payment Advisory Commission reported that Medicare expenditures for potentially preventable re-hospitalizations may be as high as $12 billion a year\cite{5}. Public reports from Medicare data revealed by Ross et al\cite{12} showed that all-cause 30-d readmission rates after HF hospitalization have shown no improvement over the past several years with rates of 23.0% in 2004, 23.3% in 2005, and 22.9% in 2006, indicating that this persistent public health problem must be addressed more aggressively. In this article, we aim to discuss the predictors of re-hospitalization in patients with chronic HF, with the hope that providers will be better able to identify their patients who are at highest risk of repeat hospitalization, and customize their care accordingly.

**PREDICTORS OF HEART FAILURE HOSPITAL READMISSIONS**

Numerous studies have been conducted in order to identify factors associated with readmission of HF patients. In order to identify such relevant studies, we performed a key-word literature search using the PubMed database. Examples of key words used were “heart failure”, “heart failure readmission”, “heart failure hospitalization”, “predictors of heart failure”. Only English citations were searched and reviewed through 2011. We found that with the vast and diverse HF population as well as the differences in study characteristics, many predictors have been identified, however not all factors have been consistently found to be predictors among all studies. Several groups of investigators have presented statistical models and risk scores in order to determine patient risk of readmission after HF hospitalization\cite{7-11}. Identifying predictors among HF patients will help physicians to improve risk stratification and to determine the optimal post discharge plan for preventing readmission. Many predictors of readmission have been recognized and can be organized into (1) clinical parameters; (2) serum biomarkers; (3) hemodynamic parameters; and (4) psychosocial factors.

**Clinical parameters**

Patients with chronic HF may present to the hospital with various symptoms that represent volume overload and/or hypoperfusion. One study found several clinical predictors of early re-hospitalization (within 30 d) including angina, lower systolic blood pressure, and more extensive edema, while clinical predictors of later (within 90 d) of re-hospitalization included pulmonary rales, high jugular venous pressure, depressive symptoms and old age\cite{13}. Coronary heart disease and prior pacemaker implantation were also predictors of 90-d readmission\cite{13}. Implantable cardioverter-defibrillator (ICD) insertion and ICD firing has also been found by several groups to be a predictor of re-hospitalization\cite{13,4}. The Multicenter Automatic Defibrillator Implantation Trial II randomized control trial also found atrial fibrillation and diabetes to be predictors of HF re-hospitalization as well as a prolonged QT interval, and elevated heart rate\cite{3}. Female sex and age have also been found to be predictors of re-hospitalization\cite{15,16}. Muzzarelli et al\cite{13} highlighted that patients with chronic HF have significant comorbidities and demonstrated that 45% of re-hospitalization was secondary to non-cardiovascular conditions. According to a Medicare analysis reported by Aranda et al\cite{17}, HF accounted for 28% of all hospital readmissions in the 6-9 mo following the initial (index) HF hospitalization, followed by pneumonia and chronic obstructive pulmonary disease. Patients who were re-admitted had more diabetes, peripheral vascular disease and stroke when compared with HF patients who were not readmitted after their index hospitalization\cite{17}. These studies indicate that comorbid conditions may be significant predictors of repeat hospitalization of HF patients.

Several studies have shown that previous hospitalization is a powerful independent predictor of readmission\cite{4,17-19}. One study from Japan showed that prior hospitalization was the strongest predictor of HF re-hospitalization in a mixed population of HF with preserved and depressed ejection fraction patients\cite{16}. Medicare data reveals average initial HF hospitalization as 5.5 ± 5.4 d\cite{4}, although there exists some variation, longer hospital stays were commonly described as more than 7 d. Increased length of initial hospital stay has been shown to be a predictor of future readmission\cite{3,17,18}. Both length of hospital stay and repeat hospitalization worsened prognosis and increased risk of mortality\cite{20,21}. Findings from the CHARM program reported that the risk of dying increased with each additional HF hospitalization\cite{20}. After discharge from a second or third hospitalization there was an associated 30% cumulative incremental risk of death\cite{20}. Reports also indicate that the risk of death was highest in the immediate post-discharge period, with an estimated 6-fold excess risk in the first month after discharge compared to a 2-fold increased risk of death 2 years after discharge\cite{20}. These reports not only highlight the morbidity and mortality associated with hospitalization but also suggest an important role for increased surveillance in the immediate post-discharge period.

The etiology of worsened prognosis with hospitalization itself has not been fully elucidated. Some attribute the worsened prognosis to the use of intravenous diuretics and catecholamine release\cite{21}, while others have proposed that hospitalization leads to deconditioning and decreased exercise tolerance, which have been associated with increased likelihood of re-hospitalization and poorer prognosis\cite{22,23}. A recent prospective study among African American patients with acute decompensated HF revealed that a distance of less than 200 m on the 6-min walk test was found to be a strong and independent predictor of mortality and HF re-hospitalization\cite{24}.

**Serum biomarkers**

Studies have shown that renal function worsens dur-
persistent hyponatremia predicts both 6-mo mortality and increased mortality associated with poor prognosis and increased mortality,

shown that baseline admission serum sodium have been shown to be independent predictors of re-hospitalization. One study reported that at 1 year, 67% of HF patients with preserved renal function remained hospitalization-free compared with only 42.5% of HF patients with renal dysfunction.

Patients with HF suffer from vasomotor nephropathy, which can be defined as renal dysfunction that results from efferent arteriolar perfusion mismatch. In HF patients, this cardiovascular interaction at least in part occurs as a result of a distinct neurohormonal activation. While decreased renal function characterized by increased creatinine levels and lower eGFR have been associated with poor outcome, findings from the activ in CHF study and OPTIME-CHF indicate that the BUN level is a better predictor of both mortality and re-hospitalization at 60 d. BUN is likely a better prognostic indicator because it is more indicative of vasomotor nephropathy rather than an actual measure of renal dysfunction.

In HF, the renin-angiotensin-aldosterone system and sympathetic nervous system are activated, causing afferent arteriolar vasoconstriction and resulting reduction in renal perfusion pressure and increase in water reabsorption. This results in more filtered urea being absorbed along with water and sodium in the proximal tubule of the nephron. Vasopressin release also causes increased urea reabsorption in the distal nephron. These changes result in elevated BUN often independently of changes in GFR, as creatinine is secreted and not reabsorbed by the kidney.

Activation of the renin-angiotensin-aldosterone system may also explain the low serum sodium levels, defined as ≤ 134 mEq/L, seen in HF patients. The increased proximal tubular sodium and water retention that occurs as a compensatory mechanism for decreased renal perfusion, results in decreased sodium and water delivery to the collecting duct of the nephron, which, combined with resistance to the action of natriuretic peptides, results in impairment of free-water excretion and hyponatremia. Increased vasopressin levels in HF contribute to the development of hyponatremia by increasing the number of aquaporin water channels in the collecting duct of the kidney. While studies have shown that baseline admission serum sodium have been associated with poor prognosis and increased mortality, findings from the ESCAPE trial indicate that only persistent hyponatremia predicts both 6-mo mortality and re-hospitalization when compared to patients with corrected hyponatremia or normonatremia. The poor prognosis may also be explained by the correlation of low serum sodium with ventricular ectopy, increased sudden death, and increased in-hospital mortality.

Anemia, defined by the World Health Organization as hemoglobin (Hb) < 12 g/dL in females and < 13 g/dL in males, is quite prevalent in HF patients. Studies have demonstrated varying prevalence, ranging from 4% to 50%.[33,42,43]. Low serum Hb in HF patients is likely related to hemodilution secondary to volume overload. This patient population suffers from a high number of comorbid chronic diseases, which also likely contribute to the high prevalence of anemia. Findings from the OPTIME-CHF study, which reported a prevalence of anemia of 49%, show that, after adjusting for confounding variables associated with volume overload, anemia remained an independent predictor of death or re-hospitalization. These investigators reported a 12% increase in the probability of death or re-hospitalization within 60 d for every 1 g/dL decrease in admission Hb.

B-type natriuretic peptide (BNP) is a commonly measured serum biomarker that is released from the cardiac ventricles and promotes vasodilatation, natriuresis, and diuresis in response to pressure and volume overload. BNP has been used to help distinguish between cardiac and pulmonary etiologies of dyspnea as well as to act as a guide for therapy in patients with chronic HF. Pre-discharge BNP has been shown by numerous studies to be a predictor of readmission.

Cardiac troponin T has also been used as a prognostic cardiac biomarker as it represents cardiomyocyte injury. In patients with HF, cardiac troponins are often found to be detectable, and elevated values have been associated with poor prognosis in both ambulatory and hospitalized patients, and have also been found to be independent predictors of readmission.

Cystatin, which is a serum marker for renal function, has been shown to be an independent predictor of HF readmission. Serum cystatin C concentrations have been shown to correlate with serum creatinine and eGFR. Reports show that this marker predicts prognosis better than creatinine and the Modification of Diet in Renal Disease equation in HF patients, perhaps because this serum marker appears to be independent of age, sex and muscle mass and is able to detect early renal dysfunction. Reports have shown that HF patients with elevated cystatin C levels exhibited higher cardiac event rates compared with patients with normal cystatin C levels, even in patients with normal serum creatinine.

Several studies have assessed multiple cardiac biomarkers simultaneously in order to gain complementary prognostic information that could be used to improve risk stratification of HF patients. A recent prospective study incorporated NT-pro BNP, cardiac troponin T and cystatin C and, after multivariate regression analysis, found that independent and complementary prognostic information was gained. A significant gradual in-
creased risk of mortality and/or readmission was reported as the number of elevated biomarkers increased\cite{49}. The prognostic value of the multi-marker approach was found to be more powerful than the single-marker approach\cite{50}. Another recent prospective study evaluated the incremental usefulness of multiple conventional biomarkers that have been known to have prognostic value in HF patients including elevated BNP, uric acid, high sensitivity C-reactive protein, decreased levels of serum sodium and Hb, and renal insufficiency\cite{51}. Patients were given 1 point for each abnormal biomarker, then organized into 3 strata according to multi-marker score. Patients in the high strata (5-7 abnormal biomarkers) were found to have significantly higher rates of re-hospitalization than those in the low strata (0-3 abnormal biomarkers). After multivariate Cox proportional hazard regression analysis, only multimarker score was found to be an independent predictor of cardiac death or re-hospitalization among all the variables\cite{52}. These findings suggest that the multi-marker approach may be a simple, objective way to improve risk stratification of HF patients for the prediction of readmission.

**Hemodynamic predictors**

HF patients commonly are readmitted with signs and symptoms of volume overload. While clinical parameters and laboratory findings are useful, these values are not always specific thus several studies have sought to investigate more accurate ways to determine volume status in an effort to prevent premature hospital discharges and reduce readmissions. Invasive measurements of right heart pressures and pulmonary capillary wedge pressures are gold standard methods of determining intravascular volume status but are not always practical for most patients. Conventional echocardiographic parameters that are measured in HF are left ventricular ejection fraction (LVEF) and mitral flow, which is an index of left ventricular filling pressure. LVEF has been an inconsistent predictor of readmission, with some studies suggesting patients with lower LVEF were more likely to be readmitted\cite{53,54}, while others showed no difference\cite{49,55,56}. One novel study performed comprehensive 2-dimensional echo-Doppler examination prior to discharge and found that early diastolic velocity/tissue Doppler early diastolic mitral annular velocity (E/Ea), as a measure of left ventricular filling pressure, in combination with elevated pre-discharge BNP levels were powerful and incremental predictors of cardiac death or re-hospitalization for HF, to which the conventional predictors did not add\cite{57}. Because of the cost and inconvenience of large full-featured ultrasound platforms, a more recent study evaluated the use of hand-carried ultrasound devices. In addition to pre-discharge BNP, this prospective study evaluated pre-discharge inferior vena cava size and collapsibility as these are known predictors of right atrial pressure\cite{58}. Patients requiring repeat hospitalization were found to have abnormal inferior vena cava diameter (≥ 2.0 cm) and collapsibility indices (< 50%), 3 times and 1.5 times as often, respectively, when compared with patients who did not require hospitalization\cite{59}.

Most recently, investigators have been evaluating the effect of implantable hemodynamic devices that detect rising intracardiac pressures and therefore help predict future hospitalization, allowing the provider the chance to titrate diuretics and neurohormonal antagonists prior to clinical deterioration and hospitalization. Retrospective analysis of data from the COMPASS-HF trial which evaluated the impact of continuous monitoring of the Chronicle\textsuperscript{®} device has shown a 36% prolongation in the time to first HF hospitalization\cite{60}. Data from the HOMEOSTASIS trial, which evaluated the impact of the left atrial HeartPOD\textsuperscript{®} device, found improvement in hemodynamics, symptoms, quality of life, as well as reduction in death and decompensated HF events, once left atrial-pressure guided therapy was initiated\cite{61}. Results from the CHAMPION trial, which evaluated the effect of the CardioMEMS\textsuperscript{®} Heart Sensor, demonstrated a 30% reduction in HF hospitalizations at 6 mo of follow-up\cite{62}. The recent Partners HF study evaluated patients with cardiac resynchronization therapy implantable cardioverter-defibrillators which have been programmed with a diagnostic algorithm on an independent dataset\cite{63}. They found that a positive diagnostic algorithm corresponded to a 5-fold increased risk of HF hospitalization within the following month\cite{64}. These devices may be beneficial options in ambulatory HF patients with advanced symptoms that are refractory to optimal medical therapy and are at high risk for re-hospitalization as well as those with co-morbidities such as pulmonary disease or morbid obesity.

**Psychosocial parameters**

The morbidity associated with HF causes significant psychological distress, thought to be associated with changes in functional status, work status, and increased relationship strains\cite{65,66}. Studies have demonstrated the prevalence of depression among HF patients to be quite high, ranging from 9%-60%, with large variation likely owing to the method of diagnosis, with prevalence estimates being lower with medical record diagnosis vs diagnosis via patient questionnaires\cite{67}. One study showed that patients with major depression, diagnosed by initial screening with the Beck Depression Inventory followed by an interview using a modified National Institute of Mental Health Diagnostic Interview Schedule, had readmission rates 3 times that of patients with only mild depression or no depression\cite{68}. Similarly, findings from OPTIMIZE-HF analysis show that depression was associated with increased mid (3-6 mo after discharge) and late (1 year after discharge) re-hospitalization, but not early re-hospitalization (within 3 mo of discharge), likely indicating that hospitalization immediately post discharge can be attributed to other factors\cite{69}. In an effort to link depression with the increased morbidity associated with HF, investigators have demonstrated that depression increases neurohormonal activation, proinflammatory cy-
Intensive care unit (ICU) hospitalization and poor follow-up were also found to be strong independent predictors of readmission risk (Table 1). These findings highlight the interplay between the social and medical factors that lead to readmissions as well as indicate the need for establishing adequate social support and medical follow-up for HF patients.

We feel that all patients that are hospitalized for HF should be risk stratified as high risk, intermediate risk, or low risk of re-hospitalization according to the number of predictors of re-hospitalization they possess (Table 1). Also, the etiology of re-hospitalization must be evaluated, addressed, and taken into consideration when determining re-hospitalization risk. Those patients who are at highest risk for re-hospitalization should be given the highest intensity of multidisciplinary support, education, follow-up, therapy, and access to resources, while those at lower risk should be given less (Table 1). This customized approach is crucial when resources are sparse and finances limited and may lead to reduced re-hospitalization of HF patients.

### CONCLUSION

As investigators gain a more complete understanding of the pathophysiology of HF, more novel predictors of poor outcome are being identified. Extensive research has revealed a variety of promising predictors of re-hospitalization in HF patients including clinical parameters, serum biomarkers, novel hemodynamic approaches, and psychosocial factors. We hope the future holds the development of an effective, universally applicable risk stratification model utilizing the numerous predictors of readmission that have been identified. Perhaps better risk models will allow providers to better tailor comprehensive HF management programs, therapies, follow-up, and allocation of resources according to the needs of each individual patient and thus lead to reduced re-hospitalization of patients with chronic HF.
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