World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/1949-8462office
wjc@wjgnet.com
doi:10.4330/wjc.v4.i2.23

World J Cardiol 2012 February 26; 4(2): 23-30
ISSN 1949-8462 (online)

EDITORIAL

Predictors of re-hospitalization in patients with chronic heart failure

Melody Zaya, Anita Phan, Ernst R Schwarz

Melody Zaya, Anita Phan, Ernst R Schwarz, Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, United States

Author contributions: Zaya M participated in conception of the topic, literature search and analysis, writing and drafting of the manuscript, and approval of the final manuscript; Phan A and Schwarz ER participated in conception of the topic, drafting and supervision of the review, and approval of the final manuscript.

Correspondence to: Ernst R Schwarz, MD, PhD, FESC, FACC, FSCAI, Cedars-Sinai Heart Institute, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Suite 6215, Los Angeles, CA 90048, United States. ernst.schwarz@cshs.org
Telephone: +1-310-4231876 Fax: +1-310-4231498
Received: August 18, 2011 Revised: December 3, 2011
Accepted: December 11, 2011
Published online: February 26, 2012

Abstract

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.

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

Peer reviewers: Dr. Steven J Haas, National Coroners Information System, Victorian Institute of Forensic Medicine, 57-83 Kavanagh Street, Southbank 3006, Australia; Prashanth Panduranga, Department of Cardiology, Royal Hospital, PB 1331, Muscat 111, Oman

Zaya M, Phan A, Schwarz ER. Predictors of re-hospitalization in patients with chronic heart failure. *World J Cardiol* 2012; 4(2): 23-30 Available from: URL: http://www.wjgnet.com/1949-8462/full/v4/i2/23.htm DOI: http://dx.doi.org/10.4330/wjc.v4.i2.23

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[1,2]. 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[3]. 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[4]. 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[5]. Public reports from Medicare data reported by Ross *et al*[6] revealed 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 better be 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[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[12]. Coronary heart disease and prior pacemaker implantation were also predictors of 90-d readmission[12]. Implantable cardioverter-defibrillator (ICD) insertion and ICD firing has also been found by several groups to be a predictor of re-hospitalization[13,14]. 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[13]. Female sex and age have also been found to be predictors of re-hospitalization[15,16]. Muzzarelli *et al*[12] 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*[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 readmitted had more diabetes, peripheral vascular disease and stroke when compared with HF patients who were not readmitted after their index hospitalization[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[4,7,16-19]. 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[16]. Medicare data reveals average initial HF hospitalization as 5.5 ± 5.4 d[17], 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[4,17,18]. Both length of hospital stay and repeat hospitalization worsened prognosis and increased risk of mortality[20,21]. Findings from the CHARM program reported that the risk of dying increased with each additional HF hospitalization[20]. After discharge from a second or third hospitalization there was an associated 30% cumulative incremental risk of death[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[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[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[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[24].

Serum biomarkers

Studies have shown that renal function worsens dur-

ing hospitalization[25,26]. Findings from Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) demonstrate that during hospitalization, 39% of HF patients had greater than 25% increase in blood urea nitrogen (BUN) and 12% had greater than a 25% decrease in estimated glomerular filtration rate (eGFR)[27]. Worsening renal function during hospitalization has been associated with increased HF hospitalizations[28,29]. Decreased renal function at the time of admission, defined as GFR less than 45 mL/min per 1.73 m^2, has also been found to be an independent predictor of re-hospitalization[16,30]. 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[16].

Patients with HF suffer from vasomotor nephropathy, which can be defined as renal dysfunction that results from afferent/efferent arteriolar perfusion mismatch. In HF patients, this cardiorenal 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[16,31,32], 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[27,33]. BUN is likely a better prognostic indicator because it is more indicative of vasomotor nephropathy rather than an actual measure of renal dysfunction[34]. 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[35,36], 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[35]. 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[35]. While studies have shown that baseline admission serum sodium have been associated with poor prognosis and increased mortality[37], 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[38]. The poor prognosis may also be explained by the correlation of low serum sodium with ventricular ectopy[39], increased sudden death[40], and increased in-hospital mortality[41].

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%[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[42]. 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[42].

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[44]. BNP has been used to help distinguish between cardiac *vs* pulmonary etiologies of dyspnea as well as to act as a guide for therapy in patients with chronic HF. Predischarge BNP has been shown by numerous studies to be a predictor of readmission[19,44-46].

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[47-49], and have also been found to be independent predictors of readmission[45].

Cystatin, which is a serum marker for renal function has been shown to be an independent predictor of HF readmission[45]. Serum cystatin C concentrations have been shown to correlate with serum creatinine and eGFR[45]. Reports show that this marker predicts prognosis better than creatinine and the Modification of Diet in Renal Disease equation in HF patients[45,50], 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[45,51].

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[45]. A significant gradual in-

creased risk of mortality and/or readmission was reported as the number of elevated biomarkers increased[45]. The prognostic value of the multi-marker approach was found to be more powerful that the single-marker approach[45]. 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[52]. 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[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[19,53], while others showed no difference[46,54,55]. 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[19]. 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[56]. 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[46].

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® device has shown a 36% prolongation in the time to first HF hospitalization[57]. Data from the HOMEOSTASIS trial, which evaluated the impact of the left atrial HeartPOD® 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[58]. Results from the CHAMPION trial, which evaluated the effect of the CardioMEMS® Heart Sensor, demonstrated a 30% reduction in HF hospitalizations at 6 mo of follow-up[59]. 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[14]. They found that a positive diagnostic algorithm corresponded to a 5-fold increased risk of HF hospitalization within the following month[14]. 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[60-62]. 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[63]. 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[64]. 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[65]. In an effort to link depression with the increased morbidity associated with HF, investigators have demonstrated that depression increases neurohormonal activation, proinflammatory cy-

Table 1 Risk stratificatio

Predictors	Re-hospitalization risk		
	High risk	Intermediate risk	Low risk
Clinical parameters	3	2	1
Previous hospitalization			
Long hospital stay			
Age			
Sex			
Clinical symptoms			
Low blood pressure			
Comorbid conditions			
ICD, ICD firing			
QRS prolongation			
Elevated heart rate			
Serum biomarkers	3	2	1
Impaired renal function			
BUN			
Persistent hyponatremia			
Anemia			
Pre-discharge BNP			
Cardiac troponin T			
Cystatin			
Hemodynamic parameters	3	2	1
Pre-discharge elevated E/Ea			
IVC > 2.0 cm, collapsibility < 50%			
Abnormalities in implantable intracardiac device parameters			
Psychosocial parameters	3	2	1
Major depression			
Lack of emotional support			
Single marital status			
No occupation			
Race			
Education			
Poor follow-up			
Low income			
Intensity of multidisciplinary support/follow-up/therapy/education	3	2	1

All heart failure patients should be risk-stratified based upon the number of predictors present (those with the highest number of predictors would be considered high risk while those with the lowest number would be low risk). 3 denotes patients with the highest risk or re-hospitalization; 2 denotes an intermediate risk; 1 denotes the lowest risk. While all heart failure patients require comprehensive, multidisciplinary support, the intensity should be adjusted according to their risk of re-hospitalization. 3 denotes that high risk patients should receive the highest intensity of support; 1 denotes that patients with the lowest risk of re-hospitalization should receive lowest intensity of support; and 2 denotes that intermediate risk patients should get intermediate intensity support relative to the highest and lowest risk patients. Also etiology of re-hospitalization must be taken into consideration when customizing intervention to the individual patient. BNP: B-type natriuretic peptide; E/Ea: Early diastolic velocity/tissue Doppler early diastolic mitral annular velocity; IVC: Inferior vena cava; BUN: Blood urea nitrogen; ICD: Implantable cardioverter-defibrillator.

tokines, hypercoagulability, and arrhythmias all of which may contribute to decompensation[60,61,66,67]. Depression may also contribute to poor medical and dietary compliance as well as deconditioning. Hospitalized patients with HF and depression have also been found to experience longer hospital stays and were less likely to receive cardiac procedures, components of HF education, and referral to outpatient disease management programs[65]. These findings together suggest a role for closer depression screening as well as optimized therapy for depression in HF patients.

A strong social network has also been shown to reduce readmission rates in cardiac patients[68]. Among elderly patients with HF, the lack of emotional support was found to be a strong independent predictor of death or re-hospitalization[69]. Correspondingly, single marital status has also been shown to be an independent correlate of readmission[9]. Another independent predictor of readmission was no occupation[18], perhaps owing to increased physical activity and younger age of patients who have an occupation. A recent study also found that low income was an independent predictor or re-hospitalization of HF patients[70]. Several studies have shown that there are differences in HF statistics depending on race[15]. African Americans have a 50% higher incidence of HF compared with the general population and also have higher risk of initial and repeat hospitalization[71]. Poor follow-up was also found to be a strong predictor of HF readmission, with studies showing patients with less follow-up had a 5-fold increase in the risk of HF readmission[18]. These findings highlight the interplay between the social and medical factors that lead to re-admissions 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[72]. 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.

REFERENCES

1 **Dickstein K**, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008; **29**: 2388-2442

2 **Lloyd-Jones D**, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; **119**: e21-181

3 **Lee WC**, Chavez YE, Baker T, Luce BR. Economic burden of heart failure: a summary of recent literature. *Heart Lung* 2004; **33**: 362-371

4 **Krumholz HM**, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, Hennen J. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997; **157**: 99-104

5 A path to bundled payment around a rehospitalization. In: Report to the Congress: reforming the delivery system. Washington DC: Medicare Payment Advisory Commission, 2005: 83-103

6 **Ross JS**, Chen J, Lin Z, Bueno H, Curtis JP, Keenan PS, Normand SL, Schreiner G, Spertus JA, Vidán MT, Wang Y, Wang Y, Krumholz HM. Recent national trends in readmission rates after heart failure hospitalization. *Circ Heart Fail* 2010; **3**: 97-103

7 **Krumholz HM**, Chen YT, Wang Y, Vaccarino V, Radford MJ, Horwitz RI. Predictors of readmission among elderly survivors of admission with heart failure. *Am Heart J* 2000; **139**: 72-77

8 **Philbin EF**, DiSalvo TG. Prediction of hospital readmission for heart failure: development of a simple risk score based on administrative data *Rev Port Cardiol* 1999; **18**: 855-856

9 **Chin MH**, Goldman L. Correlates of early hospital readmission or death in patients with congestive heart failure. *Am J Cardiol* 1997; **79**: 1640-1644

10 **Felker GM**, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams KF, Gheorghiade M, O'Connor CM. Risk stratification after hospitalization for decompensated heart failure. *J Card Fail* 2004; **10**: 460-466

11 **Yamokoski LM**, Hasselblad V, Moser DK, Binanay C, Conway GA, Glotzer JM, Hartman KA, Stevenson LW, Leier CV. Prediction of rehospitalization and death in severe heart failure by physicians and nurses of the ESCAPE trial. *J Card Fail* 2007; **13**: 8-13

12 **Muzzarelli S**, Leibundgut G, Maeder MT, Rickli H, Handschin R, Gutmann M, Jeker U, Buser P, Pfisterer M, Brunner-La Rocca HP. Predictors of early readmission or death in elderly patients with heart failure. *Am Heart J* 2010; **160**: 308-314

13 **Goldenberg I**, Moss AJ, Hall WJ, McNitt S, Zareba W, Andrews ML, Cannom DS. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the multicenter automatic defibrillator implantation trial II. *Circulation* 2006; **113**: 2810-2817

14 **Whellan DJ**, Ousdigian KT, Al-Khatib SM, Pu W, Sarkar S, Porter CB, Pavri BB, O'Connor CM. Combined heart failure device diagnostics identify patients at higher risk of subsequent heart failure hospitalizations: results from PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) study. *J Am Coll Cardiol* 2010; **55**: 1803-1810

15 **Howie-Esquivel J**, Dracup K. Effect of gender, ethnicity, pulmonary disease, and symptom stability on rehospitalization in patients with heart failure. *Am J Cardiol* 2007; **100**: 1139-1144

16 **Komukai K**, Ogawa T, Yagi H, Date T, Sakamoto H, Kanzaki Y, Shibayama K, Hashimoto K, Inada K, Minai K, Ogawa K, Kosuga T, Kawai M, Hongo K, Taniguchi I, Yoshimura M. Decreased renal function as an independent predictor of rehospitalization for congestive heart failure. *Circ J* 2008; **72**: 1152-1157

17 **Aranda JM**, Johnson JW, Conti JB. Current trends in heart failure readmission rates: analysis of Medicare data. *Clin Cardiol* 2009; **32**: 47-52

18 **Tsuchihashi M**, Tsutsui H, Kodama K, Kasagi F, Setoguchi S, Mohr M, Kubota T, Takeshita A. Medical and socioenvironmental predictors of hospital readmission in patients with congestive heart failure. *Am Heart J* 2001; **142**: E7

19 **Dokainish H**, Zoghbi WA, Lakkis NM, Ambriz E, Patel R, Quinones MA, Nagueh SF. Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. *J Am Coll Cardiol* 2005; **45**: 1223-1226

20 **Solomon SD**, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007; **116**: 1482-1487

21 **Setoguchi S**, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J* 2007; **154**: 260-266

22 **Piepoli MF**, Davos C, Francis DP, Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004; **328**: 189

23 **Belardinelli R**, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999; **99**: 1173-1182

24 **Alahdab MT**, Mansour IN, Napan S, Stamos TD. Six minute walk test predicts long-term all-cause mortality and heart failure rehospitalization in African-American patients hospitalized with acute decompensated heart failure. *J Card Fail* 2009; **15**: 130-135

25 **Butler J**, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J* 2004; **147**: 331-338

26 **Forman DE**, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004; **43**: 61-67

27 **Klein L**, Massie BM, Leimberger JD, O'Connor CM, Piña IL, Adams KF, Califf RM, Gheorghiade M. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). *Circ Heart Fail* 2008; **1**: 25-33

28 **Damman K**, Navis G, Voors AA, Asselbergs FW, Smilde

TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. *J Card Fail* 2007; **13**: 599-608
29 **Smith GL**, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol* 2006; **47**: 1987-1996
30 **McAlister FA**, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; **109**: 1004-1009
31 **Akhter MW**, Aronson D, Bitar F, Khan S, Singh H, Singh RP, Burger AJ, Elkayam U. Effect of elevated admission serum creatinine and its worsening on outcome in hospitalized patients with decompensated heart failure. *Am J Cardiol* 2004; **94**: 957-960
32 **Dries DL**, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2000; **35**: 681-689
33 **Filippatos G**, Rossi J, Lloyd-Jones DM, Stough WG, Ouyang J, Shin DD, O'connor C, Adams KF, Orlandi C, Gheorghiade M. Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. *J Card Fail* 2007; **13**: 360-364
34 **Aronson D**, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. *Am J Med* 2004; **116**: 466-473
35 **Schrier RW**, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med* 1999; **341**: 577-585
36 **Schrier RW**. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? *J Am Coll Cardiol* 2006; **47**: 1-8
37 **Klein L**, O'Connor CM, Leimberger JD, Gattis-Stough W, Piña IL, Felker GM, Adams KF, Califf RM, Gheorghiade M. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation* 2005; **111**: 2454-2460
38 **Gheorghiade M**, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Piña IL, Fonarow GC, DeMarco T, Pauly DF, Rogers J, DiSalvo TG, Butler J, Hare JM, Francis GS, Stough WG, O'Connor CM. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. *Arch Intern Med* 2007; **167**: 1998-2005
39 **Dargie HJ**, Cleland JG, Leckie BJ, Inglis CG, East BW, Ford I. Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure. *Circulation* 1987; **75**: IV98-I107
40 **Saxon LA**, Stevenson WG, Middlekauff HR, Fonarow G, Woo M, Moser D, Stevenson LW. Predicting death from progressive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993; **72**: 62-65
41 **Chin MH**, Goldman L. Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. *Arch Intern Med* 1996; **156**: 1814-1820
42 **Felker GM**, Gattis WA, Leimberger JD, Adams KF, Cuffe MS, Gheorghiade M, O'Connor CM. Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. *Am J Cardiol* 2003; **92**: 625-628
43 **Al-Ahmad A**, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001; **38**: 955-962
44 **Dunlay SM**, Gerber Y, Weston SA, Killian JM, Redfield MM, Roger VL. Prognostic value of biomarkers in heart failure: application of novel methods in the community. *Circ Heart Fail* 2009; **2**: 393-400
45 **Manzano-Fernández S**, Boronat-Garcia M, Albaladejo-Otón MD, Pastor P, Garrido IP, Pastor-Pérez FJ, Martínez-Hernández P, Valdés M, Pascual-Figal DA. Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic Peptide and cardiac troponin T in patients with acute heart failure. *Am J Cardiol* 2009; **103**: 1753-1759
46 **Goonewardena SN**, Gemignani A, Ronan A, Vasaiwala S, Blair J, Brennan JM, Shah DP, Spencer KT. Comparison of hand-carried ultrasound assessment of the inferior vena cava and N-terminal pro-brain natriuretic peptide for predicting readmission after hospitalization for acute decompensated heart failure. *JACC Cardiovasc Imaging* 2008; **1**: 595-601
47 **Roger VL**, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004; **292**: 344-350
48 **Levy D**, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; **347**: 1397-1402
49 **Fonarow GC**. Epidemiology and risk stratification in acute heart failure. *Am Heart J* 2008; **155**: 200-207
50 **Shlipak MG**, Katz R, Fried LF, Jenny NS, Stehman-Breen CO, Newman AB, Siscovick D, Psaty BM, Sarnak MJ. Cystatin-C and mortality in elderly persons with heart failure. *J Am Coll Cardiol* 2005; **45**: 268-271
51 **Arimoto T**, Takeishi Y, Niizeki T, Takabatake N, Okuyama H, Fukui A, Tachibana H, Nozaki N, Hirono O, Tsunoda Y, Miyashita T, Shishido T, Takahashi H, Koyama Y, Kubota I. Cystatin C, a novel measure of renal function, is an independent predictor of cardiac events in patients with heart failure. *J Card Fail* 2005; **11**: 595-601
52 **Niizeki T**, Takeishi Y, Kitahara T, Suzuki S, Sasaki T, Ishino M, Kubota I. Combination of conventional biomarkers for risk stratification in chronic heart failure. *J Cardiol* 2009; **53**: 179-187
53 **Gackowski A**, Isnard R, Golmard JL, Pousset F, Carayon A, Montalescot G, Hulot JS, Thomas D, Piwowarska W, Komajda M. Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure. *Eur Heart J* 2004; **25**: 1788-1796
54 **Cheng V**, Kazanagra R, Garcia A, Lenert L, Krishnaswamy P, Gardetto N, Clopton P, Maisel A. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol* 2001; **37**: 386-391
55 **Logeart D**, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, Bouvier E, Solal AC. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol* 2004; **43**: 635-641
56 **Nagueh SF**, Kopelen HA, Zoghbi WA. Relation of mean right atrial pressure to echocardiographic and Doppler parameters of right atrial and right ventricular function. *Circulation* 1996; **93**: 1160-1169
57 **Bourge RC**, Abraham WT, Adamson PB, Aaron MF, Aranda JM, Magalski A, Zile MR, Smith AL, Smart FW, O'Shaughnessy MA, Jessup ML, Sparks B, Naftel DL, Stevenson LW. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. *J Am Coll Cardiol* 2008; **51**: 1073-1079
58 **Ritzema J**, Troughton R, Melton I, Crozier I, Doughty R, Krum H, Walton A, Adamson P, Kar S, Shah PK, Richards M, Eigler NL, Whiting JS, Haas GJ, Heywood JT, Frampton CM, Abraham WT. Physician-directed patient self-manage-

ment of left atrial pressure in advanced chronic heart failure. *Circulation* 2010; **121**: 1086-1095

59 **Abraham WT**, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011; **377**: 658-666

60 **MacMahon KM**, Lip GY. Psychological factors in heart failure: a review of the literature. *Arch Intern Med* 2002; **162**: 509-516

61 **Bosworth HB**, Steinhauser KE, Orr M, Lindquist JH, Grambow SC, Oddone EZ. Congestive heart failure patients' perceptions of quality of life: the integration of physical and psychosocial factors. *Aging Ment Health* 2004; **8**: 83-91

62 **Rozzini R**, Sabatini T, Frisoni GB, Trabucchi M. Depression and major outcomes in older patients with heart failure. *Arch Intern Med* 2002; **162**: 362-364

63 **Rutledge T**, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006; **48**: 1527-1537

64 **Jiang W**, Alexander J, Christopher E, Kuchibhatla M, Gaulden LH, Cuffe MS, Blazing MA, Davenport C, Califf RM, Krishnan RR, O'Connor CM. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Arch Intern Med* 2001; **161**: 1849-1856

65 **Albert NM**, Fonarow GC, Abraham WT, Gheorghiade M, Greenberg BH, Nunez E, O'Connor CM, Stough WG, Yancy CW, Young JB. Depression and clinical outcomes in heart failure: an OPTIMIZE-HF analysis. *Am J Med* 2009; **122**: 366-373

66 **Joynt KE**, Whellan DJ, O'connor CM. Why is depression bad for the failing heart? A review of the mechanistic relationship between depression and heart failure. *J Card Fail* 2004; **10**: 258-271

67 **Parissis JT**, Adamopoulos S, Rigas A, Kostakis G, Karatzas D, Venetsanou K, Kremastinos DT. Comparison of circulating proinflammatory cytokines and soluble apoptosis mediators in patients with chronic heart failure with versus without symptoms of depression. *Am J Cardiol* 2004; **94**: 1326-1328

68 **Berkman B**, Dumas S, Gastfriend J, Poplawski J, Southworthe M. Predicting hospital readmission of elderly cardiac patients. *Health Soc Work* 1987; **12**: 221-228

69 **Krumholz HM**, Butler J, Miller J, Vaccarino V, Williams CS, Mendes de Leon CF, Seeman TE, Kasl SV, Berkman LF. Prognostic importance of emotional support for elderly patients hospitalized with heart failure. *Circulation* 1998; **97**: 958-964

70 **Philbin EF**, Dec GW, Jenkins PL, DiSalvo TG. Socioeconomic status as an independent risk factor for hospital readmission for heart failure. *Am J Cardiol* 2001; **87**: 1367-1371

71 **Alexander M**, Grumbach K, Remy L, Rowell R, Massie BM. Congestive heart failure hospitalizations and survival in California: patterns according to race/ethnicity. *Am Heart J* 1999; **137**: 919-927

72 **Zaya M**, Phan A, Schwarz ER. The dilemma, causes and approaches to avoid recurrent hospital readmissions for patients with chronic heart failure. *Heart Fail Rev* 2011 Jun 5; Epub ahead of print

S- Editor Cheng JX **L- Editor** Cant MR **E- Editor** Li JY