



Cardiovascular risk prediction in the elderly

Kartik Kumar, Luis Afonso

Division of Cardiology, Wayne State University, Detroit Medical Center, Detroit Michigan, Detroit, MI 48201, USA

Abstract

Heart failure (HF) in the elderly, besides being a leading cause of mortality and morbidity, is rapidly increasing in prevalence with patients aged 65 and older accounting for more than 75% of heart failure hospitalizations. Elderly patients have historically been unrepresented in clinical HF trials and often present with multiple comorbidities, including frailty, depression, nutritional, functional and cognitive impairments. Additionally, pharmacologic challenges such as adherence to therapy, polypharmacy, altered drug pharmacokinetics and/or renal derangements make them less likely to receive guideline-directed medical therapies for HF. Recognition of these various interrelated domains is key and should prompt a multidisciplinary, holistic management approach so as to optimize prognosis in this vulnerable subset of the population.

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1 Background

The United States (US) has > 5.7 million individuals suffering from heart failure with > 915,000 newly diagnosed cases annually and an expected increase in prevalence by 46% to > 8 million individuals by 2030.^[1] In 2012, the total cost for HF was estimated to be approximately 31 billion dollars and is projected to increase by 127% to 70 billion dollars in 2030.^[2]

Age is inarguably an important risk factor for the development of congestive heart failure (CHF). The average age of adults with HF exceeds 70 years with the prevalence of HF doubling from 6% (age 60–79 years) to 14 % in those > 80 years.^[3] Between the 1970s and 1990s, there was an increase in mortality, hospitalization, and prevalence of heart failure. Of note, the increases in HF mortality and morbidity rates were confined to those over the age of 65 years, who accounted for > 80% of deaths and prevalent cases.^[4] Based on Medicare data from 1994 to 2003, the overall incidence of heart failure has declined, however, survival has increased slightly, which resulted in an increase in number of elderly living with heart failure.^[5] The geriatric population is expected to increase nearly two-fold by 2050 and thus the burden of cardiovascular disease, including heart failure, is

expected to also rise proportionately. With increasing prevalence of traditional risk factors for HF such as diabetes, hypertension, and tobacco use, as well as improved survival with CHF, the geriatric population living with HF is expected to increase significantly.

While coronary artery disease and hypertension are generally the more common underlying etiologies for HF, disparate maladaptive mechanisms peculiar to the elderly may be operant and contribute to the development of HF in this population. These include reduced left ventricular compliance and diastolic dysfunction, diminished aortic elasticity, deranged cardiovascular coupling, increased dependency of left atrial contraction for diastolic filling and increase in variability of cardiac output according to volume status.^[6] Accurate prognostic stratification of elderly stable patients with HF is imperative to better inform management decisions related to pharmacotherapy or device-based treatments. A brief overview of clinical predictors and the role of established as well as emerging biomarkers for prognostication of HF in the elderly is provided.

2 Clinical risk predictors

2.1 Frailty

Frailty is a geriatric syndrome characterized by a decrease in physiological activity of organ systems as a result of aging, causing a vulnerability to adverse outcomes such as falls, hospitalizations and mortality.

The elderly population represents a very high-risk group

Correspondence to: Luis Afonso, MD, Division of Cardiology, Wayne State University, Detroit Medical Center, Detroit Michigan, Detroit, MI. 48201, USA. E-mail: lafonso@med.wayne.edu

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for falls given age, frailty, and cognitive impairment. The addition of HF and its changes in the cardiovascular structure can also lead to frailty and predispose the elderly to falls. Likewise, impaired baroreceptor and autonomic reflexes also increase the risk for syncope.^[7] Multiple co-morbidities and polypharmacy (defined as the use of ≥ 5 medications) encountered in the vast majority of elderly HF patients are also risk factors for falls.^[8]

The prevalence of frailty in patients living with heart failure was demonstrated by McNallan, *et al* in 2010.^[9] Among 448 patients with a mean age of 73 ± 13 years, 74% had some degree of frailty. Frailty was associated with a 92% increased risk for emergency department visits and a 65% increase for hospitalization.^[9]

Typical clinical markers of frailty include low physical activity, weight loss (more than 4.5 kg in one year), slow walking speed, weak grip strength and exhaustion by self-report or measured low physical activity. The FRAIL-HF trial, a prospective cohort study, included 450 non-dependent patients ≥ 70 years old hospitalized for HF. Frailty was screened according to the above clinical markers. One-year survival was significantly lower in the frail group at 75% compared to 89% in the non-frail group. After adjusting for age, gender and other co-morbidities, frail patients also had a higher risk for 30-day functional decline, 1-year all-cause mortality, and 1-year readmission. Slow walking speed was the most discriminative component between frail and non-frail patients.^[10]

The importance of frailty is also reflected by age groups. In a recent study by Bottle, *et al.*,^[11] first hospitalization had the highest hazard ratio for those aged < 65 years and frail as compared to age < 65 years and fit. Importantly, being aged 65–84 years and being fit conferred similar hazard to being < 65 years and fit. However, being aged > 85 appeared to have the same hazard irrespective of frailty level.^[11]

Multiple clinical scoring systems can be utilized to assess for frailty in the elderly population including walking speed, timed up-and-go test, PRISMA 7 questionnaire and the Frail Score.^[12] Although there is no acceptable gold standard to measure frailty, a recent study compared various frailty screening and assessment tools and suggested that a simple to use clinical frailty scale (CFS) had the highest diagnostic accuracy and lowest misclassification rate.^[13]

A current on-going trial, the FLAGSHIP trial, is a multi-center prospective cohort study which seeks to develop frailty-based prognostic criteria in heart failure patients. The trial has enrolled 2650 patients to date and will further give diagnostic criteria on frailty as a novel method to risk stratify patients for best practices in long-term management of HF.^[14]

2.2 Cognitive and behavioral derangements

The brain is susceptible to reduced cerebral blood flow which is a proposed mechanism for brain injury in HF. Deep brain structures lack collateral blood flow and are often supplied at the junction of major cerebral arteries and hence are susceptible to watershed phenomena. Thus, these areas are prone to ischemic injury during conditions of hypoperfusion from a reduced cardiac output such as in HF. A study by Jefferson, *et al.*^[15] examined brain magnetic resonance imaging, neuropsychological data, and Alzheimer's disease in the Framingham Offspring Cohort participants. The concluded cardiac index was positively related to total brain volume and information processing speed and inversely related to lateral ventricular volume.^[15]

The prevalence of cognitive impairment in HF is estimated to be 40%.^[16] The elderly with HF are at risk not only for age related cognitive decline such as Alzheimer's disease and other types of dementia, but also for HF-related cognitive impairment. A recent study alluded to this entity as "cardio cerebral syndrome" and may be one of the presenting symptoms of acute HF. In addition, it is suggested that a Mini-Mental Status Exam (MMSE) be conducted in all HF patients.^[17] In fact, the European Society of Cardiology 2016 guidelines recommend a HF team approach to elderly patients which includes dementia specialists.^[18]

The importance of adopting a multidimensional, holistic approach to address the biopsychosocial complexities of caring for the elderly patient with HF is elegantly highlighted in a recent document from the Geriatric Cardiology Section Leadership Council of the ACC, titled, a 'Domain Management Approach to Heart Failure in the Geriatric Patient'. Amongst the many conditions and syndromes encountered in older patients, mind and emotion was cited as being equally as important as medical evaluation.^[19]

3 Biomarkers

Biomarkers play an important role in the management of heart failure and have shown utility to confirm or exclude a diagnosis of HF, guide therapy, help establish prognosis and potentially provide mechanistic insights into molecular and cellular processes that lead to HF. The American College of Cardiology and American Heart Association have recommendations on the appropriate use of many of the biomarkers.^[20] A summary of indications, class of recommendation, and level of evidence are presented in Table 1. While an exhaustive review of all biomarkers is beyond the scope of this article, the authors would refer readers to a recent review by Ibrahim, *et al.*^[21] A comprehensive list of

Table 1. HF Biomarkers endorsed by the American College of Cardiology/American Heart Association.

Biomarker	Indication for use	Class of recommendation	Level of evidence
BNP or NT-proBNP	Diagnosis	I	A
	Hospital admission	I	A
	Prognosis	Ia	B
	Prevention	Ia	B
	Hospital discharge prognosis	Ia	B
Troponin T or I	Guided therapy (chronic HF)	IIb	B
	Hospital admission prognosis	I	A
sST2, Galectin-3	Prognosis (Chronic HF)	IIb	B

HF: heart failure; sST2: soluble suppression of tumorigenicity 2.

biomarkers is displayed in Table 2, categorized according to implicated mechanism.^[21]

3.1 Natriuretic peptides

Natriuretic peptides (NP), especially B-type natriuretic peptide (BNP) and the N-terminal fragment of the proBNP (NT-pro BNP), have been demonstrated to correlate with HF severity and provide both diagnostic and prognostic value in HF.

Unlike atrial natriuretic peptide that is stored as granules in the atria, BNP and NT-proBNP are synthesized in bursts (cleaved from pro-BNP) and released into the circulation directly from the myocardium in response to elevated end diastolic wall stress ensuing from increases in volume or pressure. While renal clearance of both natriuretic peptides is comparable, the half-life of NT-proBNP is longer than that of BNP (120 vs. 20 min).^[22]

In patients presenting with unexplained dyspnea, measurement of natriuretic peptide biomarkers is useful to support a diagnosis or exclusion of HF. Several landmark studies, namely the Breathing Not Properly Multinational study and the ProBNP Investigation of Dyspnea in the Emergency Department study have found that BNP and NT-proBNP respectively, were the single most accurate predictor of a diagnosis of acute decompensated HF.^[23,24] Measurement of BNP and NT-pro BNP levels are useful for prognostication in chronic HF and have been shown to parallel functional NYHA Class, filling pressures and reflect extent of hemodynamic derangements.

Obesity is known to decrease levels of natriuretic peptides and modestly reduce the diagnostic sensitivity in morbidly obese individuals. Along these lines, relative increases of BNP and NT-proBNP with increasing age are observed^[25]

Table 2. HF biomarkers classified according to implicated mechanism.

Myocardial stretch biomarkers
BNP & NT-proBNP
MR-proANP
Myocardial necrosis biomarkers
High-sensitivity troponin
Myeloperoxidase
Uric Acid
Neurohormonal
Norepinephrine
Adrenomedullin
Arginine vasopressin & copeptin
Endothelin-1
Myocardial remodeling
sST2
Galectin-3
Matrix metalloproteinases and tissue inhibitors of metalloproteinases
MicroRNA
Growth differentiation factor-15
Insulin-like growth factor binding protein-7
Biomarkers of co-morbid conditions
Inflammation
IL-6
TNF- α
Renal function & injury
Serum creatinine
eGFR
Blood urea nitrogen
Cystatin C
Neutrophil-gelatinase-associated lipocalin
Kidney injury molecule
Hematologic
Anemia
Liver function tests and albumin
Adipokines
Nephrilysin

BNP: brain natriuretic peptide; eGFR: estimated glomerular filtration rate; HF: heart failure; IL-6: interleukin 6; MR-proANP: MR-pro-atrial natriuretic peptide; NT-proBNP: N-terminal pro b-type natriuretic peptide; sST2: soluble suppression of tumorigenicity 2; TNF: tumor necrosis factor.

with the former having a larger increase.^[26] Despite the confounding influences of advancing age and other comorbidities on the interpretation NP levels, the prognostic value of both BNP and NT-proBNP in chronic HF is maintained at both 1 year and 5 year follow up in the elderly, as well as very elderly.^[27]

NP's have been also shown to have predictive value for incident HF. In a study by Choi, *et al.*,^[28] 5597 asymptomatic

matic multi-ethnic participants were divided into quartiles. Importantly, participants in the 4th quartile, mean age of 69 years, had higher NT-proBNP and a higher incidence of HF compared to those in lower quartiles, which persisted after adjusting for traditional risk factors. Pre-discharge BNP levels have also been shown to be stronger predictors of post-discharge outcomes than admission BNP levels of percent change in BNP during hospitalization.^[22]

Of note, it is important to be aware that ARNI's (angiotensin receptor-neprilysin inhibitor) elevate BNP but not NT-proBNP levels; accordingly, the type of natriuretic peptide assay performed has to be taken into account when interpreting natriuretic peptide levels in patients on ARNI's.^[1] Aside from obesity, lower than expected NP levels may be encountered in patients with flash pulmonary edema and end-stage cardiomyopathy, whereas NP levels may be higher than expected in the setting of renal insufficiency, anemia, sepsis, pulmonary embolism, mitral regurgitation and atrial fibrillation.^[22]

3.2 Troponins

Cardiac troponin T and troponin I are biomarkers released in response to cardiac myocyte necrosis. They have been independently associated with adverse outcomes following acute coronary syndromes, chronic heart failure and in the general population. The introduction of highly sensitive new assays, cTn levels are detectable in the large majority of patients with HF and are predictive of adverse outcomes and mortality.^[22]

High sensitivity cardiac troponin measured serially in an elderly population without known HF are significantly associated with incident HF and cardiovascular death.^[29] The Atherosclerosis Risk in Communities Studies also found cTnT with high sensitivity assay to be associated with incident coronary heart disease, mortality, and heart failure in patients aged 54 to 74 years.^[30]

More recently and specific to the elderly population, a study by Alehagan, *et al.*,^[31] combined high-sensitivity cardiac troponin T and NT-proBNP measures in elderly patients presenting with symptomatic HF. Of the 470 patients aged 65–86 years, 80.4% had a hs-cTnT assay > 99th percentile of a healthy population. These patients had an approximately 2 fold increase risk for cardiovascular mortality.^[31]

3.3 Galectin-3

Galectin-3 is a beta-galactoside binding lectin known to impair cardiac function. It is produced by cardiac macrophages which are activated in response to inflammation. It is thought that this inflammation is another mechanism or

pathway which may play a role in HF.^[32] While galectin-3 is not as useful in the diagnosis of HF as compared to NT-proBNP, it has been shown to have superior ability to predict 60-day prognosis in terms of mortality as well as readmission in acute HF as compared to NT-proBNP. When used in combination with NT-proBNP this had significantly better predictive power for rates of death.^[33] In a sub study of the Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure (COACH) trial, De Boer, *et al.*^[34] evaluated galectin-3 and found it to be an independent prognostic marker at a longer interval of 18 months. In addition, a correlation with left ventricular ejection fraction (LVEF) was reported and the prognostic value of galectin-3 appears to be strongest with the subset of patients with HF with preserved ejection fraction.^[34]

More recently, in a study evaluating galectin-3 in the elderly population with a mean age of study participants of 77.5 ± 5.9 years, a pre-discharge galectin-3 was significantly associated with total events, including death and re-hospitalization for HF. In addition, patients with higher galectin-3 also had a higher level of frailty and functional impairment.^[35]

3.4 sST2

Soluble suppressor of tumorigenicity2 (sST2) is a protein member of the interleukin-1 receptor family released during conditions of myocardial or vascular strain. Endothelial cells appear to be the main source of sST2 in addition to contributions from the heart and peripheral tissues. Two isoforms of ST2 exist, with the soluble component isoform—sST2, having a Class IIb recommendation from the AHA/ACC.^[20] These biomarkers play a role in the mediation of cardiovascular remodeling, early atherosclerosis, hypertension, and fibrosis.^[36]

sST2 appears to be emerging as a promising biomarker in chronic HF, associated with inflammatory and profibrotic pathways. Importantly, plasma levels of sST2 appear to be relatively unencumbered by influences of age, sex, BMI or comorbidities such as chronic kidney disease that often confound interpretation of natriuretic peptide levels. Although the diagnostic utility of ST2 has not been promising, the prognostic value afforded in both acute and chronic HF has been extensively studied. In the PRIDE study, elevated sST2 concentrations strongly predicted death at one year in dyspneic patients as well as in those with acute decompensated heart failure above and beyond NT-proBNP.^[37,38] The combination of sST2 and NT-proBNP more accurately identified patients with the highest risk for death.^[39] Of note, a study by Pacho, *et al.*^[40] evaluating predictive biomarkers for death and rehospitalization in comorbid frail elderly HF

patients found that ST2 to be the strongest predictor in both univariate and multivariate analysis outperforming NT-proBNP for both all-cause mortality or HF-related rehospitalizations.^[40] In a similar study of HF patients (mean age: 68 years, $n = 4268$), sST2 emerged as a strong, independent predictor (independent of NT-proBNP and hs-TnT) of all-cause and cardiovascular mortality and HF hospitalization^[41] across a wide range of patient subsets using a plasma sST2 cut off value of > 28 ng/mL.

3.5 Estimated glomerular filtration rate (eGFR) & Creatinine

Chronic kidney disease (CKD) is a common co-morbidity in patients with acute decompensated HF and has been associated with an increased risk of adverse cardiovascular events and mortality. In a study by Hillege, *et al.*^[42] eGFR was found to be a significant independent predictor for adverse outcomes. The risk for HF hospitalization and cardiovascular death as well as all-cause mortality increased significantly below an eGFR of 60 mL/min per 1.73 m².^[42]

3.6 Albumin

Malnutrition is common in patients with HF and predicts adverse outcomes.^[43] It may manifest as low body mass index (BMI) or sarcopenic obesity in Western populations (increased BMI despite muscle wasting) or hypoalbuminemia, a frequent finding in elderly patients with acute HF. A study led by Arques, *et al.*^[44] evaluated 64 consecutive patients with a median age of 86 who were admitted for acute HF. Serum albumin concentration, age, blood urea nitrogen, and systolic blood pressure were independent predictors of in-hospital mortality. Albuminuria is associated with subsequent heart failure even when the patients urine albumin creatinine ratio is within the normal range.^[45] Importantly, nutritional intervention in malnourished hospitalized patients with heart failure has been shown to reduce the risk of death from any cause and the rates of readmission for worsening of heart failure.^[46]

3.7 Uric acid

Uric acid is an important and easily obtainable biomarker and is an important predictor of mortality in HF. In a landmark study by Anker, *et al.*,^[47] high serum uric acid levels were found to be a strong and independent marker of poor prognosis in patients with moderate to severe CHF. The study found that uric acid ≥ 565 $\mu\text{mol/L}$ strongly related to increased mortality. In addition, for every 100 $\mu\text{mol/L}$ increase in UA, the risk of death increased by 53%. However, the mean age of patients was 59 ± 12 years in the derivation study and 63 ± 12 years in the validation study.

More recently, a study published in 2018 found that a high serum uric acid concentration at discharge was a strong predictor of adverse outcomes in a population of elderly patients with acute heart failure. Importantly, addition of serum uric acid to other traditional predictors of outcomes can improve risk classification of elderly patients with acute heart failure.^[48]

4 Prognosticating HF outcomes in the elderly

The long-term prognosis of HF in the elderly is generally poor. Prognostic instruments used to predict rehospitalization and mortality have been a major challenge in the management of HF, especially in the elderly. The Seattle Heart Failure Model is a well-recognized tool that estimates 1-, 2-, and 3-year survival with the use of easily obtained clinical, pharmacological, device, and laboratory characteristics.^[49] However, the performance of this instrument was shown to be suboptimal in the elderly.^[50] The Multidimensional Prognostic Index (MPI) derived from a comprehensive geriatric assessment (CGA) is an instrument that demonstrates powerful predictive capabilities for 30-day mortality in elderly patients but is particularly cumbersome to use.^[51]

Manzano, *et al.*,^[52] using the SENIORS trial cohort of patients, created a model to predict mortality and morbidity in the elderly population. Many factors which were identified in studies of younger patients (anemia) were not significant independent factors in the elderly, whereas other novel factors such as uric acid and left atrial dimension were.^[52]

Many of the currently used prognostic models include patients younger than 70 years of age and focus primarily on heart failure with reduced ejection fraction.^[49] The prevalence of heart failure with preserved ejection fraction increases relative to reduced ejection fraction in the elderly. In addition, it is the HFpEF population that lacks specific recommendations on optimal management. In addition, this population appears to be less likely to be discharged with blood pressure at goal, despite the known contribution of HTN to poor cardiovascular outcomes and diastolic dysfunction.^[53] Future research efforts need to focus on developing more robust risk prediction instruments for prognostication of HFpEF and HFrfEF in the elderly.

5 Conclusion

Compared to younger patients with HF, elderly patients tend to be underrepresented in clinical trials and are plagued by multiple comorbidities, frailty, polypharmacy, pharmacokinetic/pharmacodynamic imbalances, dementia, depres-

sion and cognitive impairments. These disparate complexities call for a multidimensional approach to management of HF in the elderly. Strategies adopting a domain-based approach, centered around modifiable biomarkers coupled with the judicious adoption of cost effective, evidence-based pharmacologic and non-pharmacologic therapies, may help stem the rising cost burden of HF on our health care-system in the years ahead.

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