Abstract: When considering the appropriate disposition plan in a patient presenting to the emergency department (ED) with acute heart failure (HF), the range of options includes discharge home to intensive care unit (ICU) admission. Unfortunately, there are few objective measures to insure optimal choices, and the currently available science is scant at best. The consequences of a lack of a standardized approach are nowhere more evident than as demonstrated by the worldwide 90-day heart failure rehospitalization rate that exceeds 25%. New strategies to address this important gap in clinical care are sorely needed. The measurement of galectin-3 may represent a new alternative to the historical standard of gestalt-based clinical disposition decisions. Elevated galectin-3 can identify patients at very high risk for short-term adverse outcomes, while low levels identify a population with essentially no 90-day revisits. This prospective objective measure of illness severity may aid in clinical decision making and thus represent a future where rehospitalization after HF is an unusual event.

Keywords: acute heart failure; emergency medicine; galectin-3.

Introduction

In the emergency department (ED) critical decisions must occur in a temporally sensitive climate that is intolerant of errors and inefficiency. Objective measures for diagnosis and prognosis are of particular value by assisting the practitioner to optimize clinical outcomes while controlling hospital admission costs. This may be of unique utility in patients with suspected acute decompensated heart failure (ADHF) as early treatment is associated with reduced short-term mortality and shorter in-hospital stays [1].

More than 1 million patients are hospitalized with acute HF each year in the USA. Of these, 80% are managed in the ED. After stabilization, the emergency physician must ensure ongoing clinical improvement and determine an appropriate disposition location. The latter decision may range from early discharge home, observation unit placement, hospitalization on a regular floor, or intensive care unit (ICU) admission. Which is most appropriate is determined by the available resources and an estimate of the patient’s illness severity. Until recently, determining the severity of illness and the short-term risk of adverse outcomes was a subjective exercise, defined by the response to therapy, traditional biomarkers (e.g., natriuretic peptides, troponin), presenting blood pressure, and chest radiographs.

The diagnosis of HF is that of a syndrome, with no specific objective finding as a definition. It is commonly defined by the patient’s presenting symptoms, history, physical exam, chest X-ray, and potentially echocardiography (although not routinely available in all EDs). Unfortunately, clinical impression and chest X-rays provide a diagnostic accuracy of about 75% [2]. In addition, consideration of natriuretic peptide testing can increase the probability of a correct diagnosis to nearly 82%. However, at this point in their ED clinical course, a disposition to decide patient placement is required. Unfortunately, no objective measure to define disposition need is available, and this task must be accomplished based upon the impression of the patient’s symptom severity and physician gestalt. In other words, a decision is required to determine where the patient’s needs would be best matched to the available resources for the particular hospital environment. For this task, biomarkers have great utility, and in this role galectin-3 offers substantial promise.

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Galectin-3 physiology

Galectin-3, the levels of which are associated with risk for short-term adverse events, is now available to assist in early ED decision making. A member of the β-galactoside-binding lectin family, galectin-3 is expressed in the failing heart [3], where it binds to ligands in the extracellular matrix, including laminin, synexin, integrins, and collagen [4]. Previously performed animal work indicates that activated cardiac macrophages produce galectin-3 and recognize its binding sites in cardiac fibroblasts and the extracellular matrix [3]. Galectin-3 may actually have a pathologic role in HF genesis, as an intra-pericardial infusion in rats results in a depressed ejection fraction and increased myocardial collagen deposition [3].

Mortality

Galectin-3 may play an important role in myocardial fibrosis, inflammation, and myocardial remodeling. Elevated levels are associated with elevated short-term mortality and 30-day re-hospitalization. Van Kimmenade [5] evaluated approximately 600 patients, and reported the combination of NT-proBNP and galectin-3 identified those at greatest death risk (see Figure 1). Patients with the highest quartile of both markers had mortality rates as high as 15% within 10 days of presentation, and twice the 30-day mortality rate versus the cohort with both markers being low. Overall, galectin-3 was an independent predictor of 60-day mortality (odds ratio 10.3, p<0.01) and for the combined endpoint of 60-day death/recurrent HF (odds ratio 14.3, p<0.001). Thus, it is reasonable to consider that when HF patients present with both markers elevated, because of the high short-term mortality rate, ICU admission may be warranted.

Rehospitalization

Galectin-3 also identifies a cohort of patients at higher risk of short-term re-hospitalization. Thus, the knowledge of its levels may provide an opportunity for interventions known to decrease subsequent unplanned re-hospitalizations. The availability of ED risk stratification tools predicting the probability of re-hospitalization would enable more effective methods to direct resource-intensive HF disease management efforts. Conversely, the identification of lower risk patients might facilitate ED discharge with close follow-up.

A number of recent studies suggest that galectin-3 in excess of 17.8 ng/mL may identify patients at high risk of 30-day revisits. DeBoer reported on 892 patients in a three study meta-analysis [6]. This included the 582 patient Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure (COACH) study with galectin-3 measured at hospital discharge, the 181 patient Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, with a galectin-3 sample obtained at the time of hospitalization, and the 129 patient University of Maryland Pro-BNP for Diagnosis and Prognosis in Patients Presenting with Dyspnea (UMD H-23258) study that had galectin-3 measured at admission. Using a cut-off value of 17.8 ng/mL Kaplan-Meier curves demonstrated the relationship between elevated galectin-3 and the timing of re-hospitalization, as presented in Figure 2. Patients with galectin-3 levels >17.8 ng/mL were nearly three times as likely to suffer short-term re-hospitalization (odds ratio 2.80, 95% CI 1.41–5.57, and 3.01, 95% CI 1.79–5.05, for 30- and 90-day readmissions, respectively). Also, baseline galectin-3 was a predictor of re-hospitalization even after adjustment for age, gender, estimated glomerular filtration rates, New York Heart Association class, left ventricular ejection fraction and NT-proBNP levels. The authors of this meta-analysis concluded that in acute HF, an elevated galectin-3 during an ED visit, hospital admission, or at hospital discharge is independently associated with early HF readmission.

These results suggest galectin-3 may identify ADHF patients with elevated risk for death and re-hospitalization independent of the severity of signs and symptoms at presentation. As revisit rates are a major determinant of economic efficiency and quality of life, identifying those requiring more intensive therapy could be of significant
value. Simultaneously, identifying those at lowest risk could select patients appropriate for either observation unit care, or early ED discharge with close follow-up [7]. Although not validated, an ED disposition approach that considered galectin-3 combined with natriuretic peptides (with consideration of the known BNP limitations) would be reasonable [8, 9] (see Figure 3).

Conclusions

Galectin-3 appears to discriminate ED ADHF risk profiles. This may have application in identifying those ED patients at highest risk of adverse outcomes and those most likely to benefit from ICU therapy. Conversely, it may determine which patients have the lowest risk of 30-day revisits and thus aid in the selection of early discharge candidates.

Conflict of interest statement

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