Role of galectin-3 and plasma B type-natriuretic peptide in predicting prognosis in discharged chronic heart failure patients

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Abstract
Galectin-3 demonstrated to be a robust independent marker of cardiovascular mid-term (18-month) outcome in heart failure (HF) patients. The objective of this study was to analyze the value of a predischarged determination of plasma galectin-3 alone and with plasma brain natriuretic peptide (BNP) in predicting mid-term outcome in frequent-fliers (FF) HF (≥2 hospitalization for HF/year)/dead patients discharged after an acute decompensated HF (ADHF) episode.

All FF chronic HF subjects discharged alive after an ADHF were enrolled. All patients underwent a determination of BNP and galectin-3, a 6-minute walk test, and an echocardiogram within 48 hours upon hospital discharge. Death by any cause, cardiac transplantation, and worsening HF requiring readmission to hospital were considered cardiovascular events.

Eighty-three patients (67 males, age 73.2 ± 8.6 years old) were analyzed (mean follow-up 11.6 ± 5.2 months; range 4–22 months). During the follow-up 38 events (45.7%) were scheduled: (13 cardiac deaths, 35 rehospitalizations for ADHF). According to medical history, in 33 patients (39.8%) a definition of FF HF patients was performed (range 2–4 hospitalization/year). HF patients who suffered an event (FF or death) demonstrated more impaired ventricular function (P = 0.037), higher plasma BNP (P = 0.005), and Gal-3 at predischarge evaluation (P = 0.027). Choosing adequate cut-off points (BNP ≥ 500pg/mL and Gal-3 ≥ 17.6 ng/mL), the Kaplan-Meier curves depicted the powerful stratification using BNP + Gal-3 in predicting clinical course at mid-term follow-up (log rank 5.65; P = 0.017).

Adding Gal-3 to BNP, a single predischarge strategy testing seemed to obtain a satisfactorily predictive value in alive HF patients discharged after an ADHF episode.

Abbreviations: ADHF = acute decompensated heart failure, BNP = brain natriuretic peptide, FF = frequent-fliers, HF = heart failure, LOS = length of hospital stay, LVEF = left ventricle ejection fraction, NYHA = New York Heart Association.

Keywords: b type-natriuretic peptide, chronic heart failure, galectin-3, prognosis

1. Introduction
Risk stratification in patients suffering from heart failure (HF) is based on a variety of clinical and laboratory variables. Indeed, several prognostic parameters have been identified, including age, New York Heart Association (NYHA) class, renal function, comorbidity such as atrial fibrillation, diabetes mellitus, and ischemic heart disease.[1] In acute decompensated heart failure (ADHF) episodes, the degree of renal dysfunction and arterial hypotension easily stratified patients with worse clinical outcome.[2] A single determination of brain natriuretic peptide (BNP) plasma level represents a reliable risk stratification procedure and its increase is considered a sensitive diagnostic marker of left ventricular dysfunction[3–4] having a clear prognostic relevance in predicting cardiovascular events in HF patients.[5–7] In discharged HF patients the combination of galectin-3 and NT-proBNP seemed to be the best predictor for short-term (60-day) mortality in the PRIDE study.[8] Furthermore, in the substudy of COACH[9] galectin-3 demonstrated to be a robust independent marker of cardiovascular mid-term (18-month) outcome in HF patients with much stronger relevance to be a robust independent marker of cardiovascular mid-term outcome.

In discharged HF patients the combination of galectin-3 and NT-proBNP seemed to be the best predictor for short-term (60-day) mortality in the PRIDE study.[8] Furthermore, in the substudy of COACH[9] galectin-3 demonstrated to be a robust independent marker of cardiovascular mid-term (18-month) outcome in HF patients with much stronger relevance to be a robust independent marker of cardiovascular mid-term outcome (in 63% being above the median value) in a longer follow-up (4-year) independently of echocardiographic parameters of HF severity.

Advanced HF patients constitute a challenge for cardiologists according to their high mortality and rehospitalization rate.[11,12] Therefore, a strategy for stratifying planning tailored clinical follow-up in those patients seems to be mandatory. The objective of this study was to analyze the value of a single, predischarged determination of plasma galectin-3 alone and in...
correlation with plasma BNP in predicting mid-term clinical outcome in worst clinical outcome [frequent-flyers (FF) + death] chronic HF patients discharged after an ADHF episode.

2. Methods

All chronic HF subjects discharged after an acute episode of cardiac decompensation were enrolled in an out-patient clinic follow-up. Patients were classified as having CHF according to the criteria commonly accepted in literature,\(^{[13]}\) namely the presence of 2 major criteria or 1 major criterion +2 minor criteria according to the Framingham score and an NYHA functional class II, III, or IV, due to an exacerbation of symptoms with at least 1 class deterioration. The presence of inadequate echo images or no adherence to the therapy and disagreement with the periodical follow-up were considered exclusion criteria. All patients underwent a clinical examination, a 12-lead electrocardiogram, plasma determination of BNP, water composition (on admission and at discharge), 6-minute walk test, noninvasive cardiac output, and a transthoracic echocardiogram within 48 hours upon hospital discharge. The criteria for discharging HF patients were the following: subjective improvement on the basis of NYHA class, cardiovascular events. The Spearman rank-order correlation with plasma BNP in predicting mid-term clinical outcome [frequent-flyers (FF) + death] chronic HF patients discharged after an ADHF episode.

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direction of association between galectin-3 and glomerular filtrate and between galectin-3 and BNP. Event-free survival was estimated by Kaplan–Meier method, and curves were compared with the log-rank test. A P value < 0.05 was considered significant. All statistical calculations were performed on STATA software (version 11.0 STATA Corporation, College Station, TX).

3. Results

Eighty-three patients (67 males, age 73.2 ± 8.6 years old) were discharged after a new diagnosis of CHF or for acute decompensation in chronic CHF and were requested to enter the study, signing an informed consent and were enrolled (mean follow-up 11.6 ± 5.2 months; range 4–22 months). The etiology of HF was interpreted as: 35 ischemic (42.1%), 23 cardiomyopathy (28%), 22 hypertensive (26.5%), and finally 3 others (3.6%). During the follow-up 48 events (57.8%) were scheduled (13 cardiac deaths, 35 rehospitalizations for HF). Twenty-eight HF patients were hospitalized ≥ 2 times/year (range 2–4 times/year) and were defined FF (8 patients out of 28 died because of a cardiac death). Therefore, the group with a worst clinical prognosis (FF + cardiac death) was formed by 33 patients (39.8%). Main differences between the events group versus control group are described in Table 1. Although the events group population seemed to be not older or hyponatremic, the pre-discharge value of galectin-3 and plasma BNP were significantly higher (P = 0.027 and 0.005, respectively). In HF patients with worst clinical outcome a more severe impairment in LV systolic function (P = 0.0037) emerged, without a significant LV enlargement or a right ventricular involvement. However, the diastolic filling pattern evaluated with echocardiography seemed to be not different in the 2 groups. At univariate analysis, a negative Spearman coefficient (rho) of −0.38 indicates a moderate decreasing monotonic trend between galectin-3 and glomerular filtrate (P = 0.0055), while a positive correlation (rho = 0.44, P = 0.002) between galectin-3 and BNP was detected. At multivariate analysis, only galectin-3 showed a significant correlation with worst clinical prognosis (P = 0.047; odds ratio 1.05, confidence interval 1.001–1.10), independently to age and renal function, being for each galectin-3 increment of 1 ng/mL determined an increase of 3% in probability of cardiovascular events. Choosing adequate cut-off points, the Kaplan–Meier curves depicted the powerful stratification using a galectin-3 level of 17.6 pg/mL (Fig. 1) added to plasma BNP level of 500 pg/mL (log rank 5.65; P = 0.017).

4. Discussion

Elderly patients with chronic HF represent most of subjects (70%) admitted to hospitals for acute cardiac decompensation; the length of hospitalization lasts usually > 2 weeks in geriatric wards and readmissions are frequent.[17] Recently, the OPTIMISE-HF study[11] included more than 30,000 HF patients discharged from 215 hospitals, described a short length of hospitalization (4 days) but a 21.3% of rate of readmission within 30-day. This study evidenced as an early (1-week) outpatient clinical follow-up after discharged helped HF patients

![Figure 1.](image)

**Figure 1.** the Kaplan–Meier event-free curve (with the log-rank) according to the selected cut-off values for galectin-3 (17.6 ng/mL) and brain natriuretic peptide (BNP) (500 pg/mL).

| Table 1 | Differences between main parameters in event group (FF + death) versus control group. |
|------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Control group (50 pts) | FF + death (33 pts) | P |
|------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Age | 73.8 ± 6.9 | 72.8 ± 11.5 | 0.6 |
| Sodium, MEq/L | 140 ± 3.5 | 140 ± 3.2 | 0.9 |
| Galectin-3, pg/mL | 19.4 ± 10.3 | 24.8 ± 11.2 | 0.027 |
| LVEF, % | 40.7 ± 15.8 | 32.9 ± 16.2 | 0.037 |
| LVEDD, mm | 44.8 ± 14.9 | 49 ± 17.9 | 0.3 |
| LVEDD, mm | 58.7 ± 12.9 | 60.5 ± 11.3 | 0.5 |
| TAPSE, mm | 17.9 ± 4.3 | 16.9 ± 5.1 | 0.4 |
| PAP, mm Hg | 38.1 ± 10 | 38.9 ± 9.2 | 0.7 |
| Creatinine | 1.29 ± 0.9 | 1.3 ± 0.9 | 0.6 |
| Atrial fibrillation | 22 (44%) | 17 (51.5%) | 0.5 |
| Diastolic pattern (II/III) | 28/658 | 18/10/5 | 0.8 |
| 6minWT, m | 362.3 ± 119.7 | 302.4 ± 70.7 | 0.09 |
| GFR | 68.7 ± 17.9 | 60.2 ± 23.1 | 0.1 |
| LOS, days | 11.9 ± 6.6 | 10.6 ± 5.4 | 0.3 |
| Hb, g/dL | 13.1 ± 6.1 | 12.8 ± 2.1 | 0.7 |
| BNP, pg/mL | 725.1 ± 594.3 | 1391.17 ± 1288.5 | 0.005 |

BNP = brain natriuretic peptide, FF = frequent flyers, GFR = glomerular filtration rate, Hb = hemoglobin level, LOS = length hospital stay, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-systolic diameter, 6minWT = 6 minute walking test, PAP = pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion.
to undergo to a lower probability to be readmitted within 30-day. In the IN-HF outcome, an Italian nationwide registry, the 30-day mortality after discharging for an acute episode of HF proved to be 2.8% and hospital readmission 6.2%.11,12 Older age, longer in-hospital stay, the necessity of intrope use, and worsening NYHA class identified HF patients discharged home who are at highest risk of death or readmission. Multiple interventions such as patients education, discharge planning, complete adherence to a correct and tailored medical therapy, scheduling follow-up after discharge, attention to caregivers, and follow-up telephone calls might be useful in reducing the 30-day risk of readmission and, generally, more comprehensive interventions reported greater success.13,18 According to the huge number of HF patients discharged from our hospitals, easy and practical prognostic parameters able to predict adverse outcome are mandatory in order to allocate correctly our resources and established tailoring specific follow-up.

The analysis of this single-center HF clinic experience demonstrates as in older systolic HF patients discharged after an ADHF episode, the single determination of galectin-3 and BNP permitted to predict worst clinical outcome (death or multiple hospital admissions) at mid-term (11 months) follow-up. Galectin-3 is a lectin secreted in plasma usually at low levels but increased substantially the secretion under conditions like injury or stress, having a biological role in cell adhesion, inflammation, and above all, tissue fibrosis.19 A single value of galectin-3 in patients admitted for an episode of ADHF clearly demonstrated a powerful prognostic power in predicting mortality and rehospitalization at short- or long-term follow-up.8-10 On the contrary, a low plasma level of galectin-3 (<11.8 ng/mL) proved to be an independent predictor (odds ratio 20.9, P=0.003) for the absence of mortality and rehospitalization at a short-term follow-up (6 months) suggesting that a reclassification of the alive HF patients at discharge might help in planning an adequate clinical follow-up.20 However, NT-ProBNP did not add an incremental value in order to predict risk-low events outcome postulating as natriuretic peptide, exploring hemodynamic loading conditions, might be less specific in detecting HF patients with favorable outcome. Moreover, the pooled analysis of 3 clinical trials including 902 HF patients21 demonstrated as HF patients with galectin-3 >17.8 pg/mL had more risk (2.6-3 times) to be readmitted for ADHF from 30 to 120 days after discharge.

In our experience, none of other demonstrated parameters (renal function, length of hospital stay [LOS], and hemoglobin) seemed to correlate with an unfavorable outcome. In particular, the LOS was not different in the 2 groups, being prolonged (>10 days) according to the older age and the presence of comorbidity in a real-world population. In fact, while in OPTIMIZE-HF11 the LOS was documented very short, in IN-HF outcome,12 based on data coming from Cardiology Department, a prolonged LOS (10 days) emerged and significantly correlated with the risk of 30-day readmission. Data coming from the EVEREST Trial13 suggested as a longer LOS was associated with cardiovascular and all cause hospital admissions, but indicated a lower risk of HF readmissions for HF within 30 days after discharging. In our experience, the limited series and the prolonged LOS did not permit to observe an influence by LOS in clinical outcome.

Finally, in a paramount of interesting predicting parameters in HF, clinicians should concentrate their attention on the most specific and cheapest at the moment of discharging your patients. Therefore, chronic HF patients discharged alive after an ADHF with an elevated predischarge value of galectin-3 (≥17.6 ng/mL) together with BNP (≥500 pg/mL) might be inserted into a rigid clinical follow-up, performed by the general practitioner or the HF out-clinic ambulatory, providing a strict control of body weight, hydration status, pharmacological adherence, and clinical status in order to prevent multiple readmissions.

5. Limitations
The main limitation of this study was the small sample size observed that might reduce the power of some consolidated prognostic parameters (as renal function). Moreover, the sample size did not permit a correct distinction between HFpEF and HFrEF. Finally, the risk of multiple rehospitalization for HF has normally correlated to the severity of cardiac condition as well as other non tested patient-related factors (social status, cognitive performance, and presence/absence of caregiver) that might significantly influence the rate of readmissions. In fact, it has been documented23 in the DIG TRIAL, as about 58% of the nation variations in hospital readmission were correlated with socioeconomic factors.

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