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Heart Failure with Preserved Ejection Fraction in the Elderly: Conventional and Emerging Prognostic Biomarkers in Daily Clinical Practice

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Abstract

Aim: Albumin serum levels and N-terminal pro-brain natriuretic peptide (NT proBNP) have shown to be useful in predicting outcome in patients with heart failure (HF) and systolic dysfunction. Carbohydrate antigen 125 (CA 125) has also been associated to a higher risk of mortality and rehospitalization in patients with HF and impaired left ventricular systolic function. The aim of this study was to evaluate the prognostic role of these biomarkers among acute decompensated HF with preserved ejection fraction (HFpEF) elderly patients.

Methods and results: Data were collected prospectively from 154 consecutive patients with HFpEF admitted to our institution between 2011 and 2012. They were followed for one year after hospital discharge. Average age was 81 years (SD 9) and 63% were female. During follow-up, 37 patients died (mortality rate: 24%). In the multivariable analysis, NT proBNP > 2086 ng/l was identified as an independent predictor of mortality (OR 5.36; 1.84-15.65, CI 95%, p = 0.002). In the same way, hypoalbuminaemia (RR 2.57; 1.46-4.52, CI 95%, p = 0.001) and CA 125 plasmatic concentrations > 31 U/ml (RR 2.58; 1.23-5.43, CI 95%, p = 0.008) also were related to a higher risk of death in the univariable analysis. Finally, we found that the combination of NT proBNP plasmatic concentrations > 2086 ng/l, albuminaemia < 3.5 g/dl and CA 125 > 31 U/ml was associated to a worse outcome among acute decompensated HFpEF patients (RR 3.32; 1.91-5.78, CI 95%, p < 0.0001).

Conclusion: NT proBNP, albuminaemia, and CA 125 could be used as filtering tools to select those with the highest clinical risk among hospitalized HFpEF patients.

Keywords

Heart failure with preserved ejection fraction, Hypoalbuminaemia, CA 125, NT proBNP

Introduction

Heart failure with preserved ejection fraction (HFpEF) prevalence increases with age [1,2]. Furthermore, HF represents a frequent hospitalization cause among elderly patients [3,4]. Classically, albumin serum [5] levels and N-terminal pro-brain natriuretic peptide [6,7] (NT proBNP) have shown to be useful in predicting outcome in HF with systolic dysfunction. Carbohydrate antigen 125 (CA 125) is a biologic marker produced by the serous epithelium in response to several mechanical and inflammatory processes. CA 125 elevated plasma levels have been associated to a higher risk of mortality and rehospitalization in patients with HF and impaired systolic function [8,9]. However, the role of these biomarkers for stratifying prognosis in HFpEF is not so well established. We evaluated the prognostic role of these biomarkers among this specific population.

Methods

Data were collected prospectively from 221 consecutive patients who were admitted to the Cardiology and Internal Medicine Departments of our institution, between 2011 and 2012. All of them had an initial diagnosis of acute decompensated HF and fulfilled the Framingham HF diagnostic criteria. We excluded patients with a history of advanced chronic renal disease (5d stage), high output heart failure (arteriovenous fistulas, hyperthyroidism or severe anemia), congenital heart disease, mitral or aortic prosthesis and those with severe left valvular heart disease. We exclusively included those patients with a left ventricular ejection fraction (LVEF) > 50%, calculated by both Simpson´s and Teichholz´s methods. Finally, 154 patients were enrolled. All patients were followed for one year after hospital discharge. A telephonic interview was performed to collect data related to follow up. Data related to HF rehospitalization and mortality were collected during this period.

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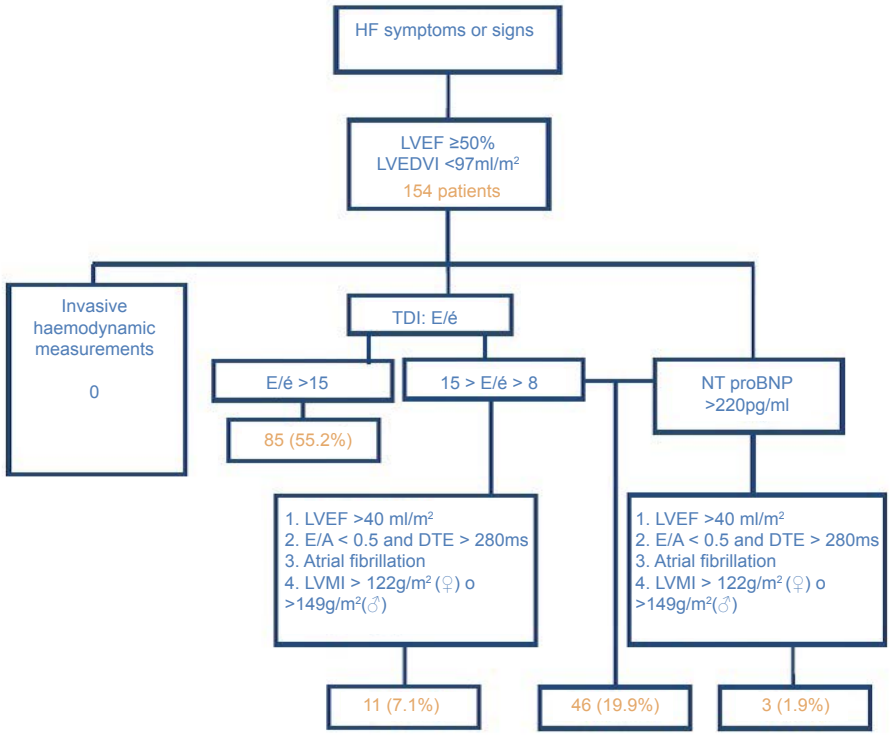

DTE: Deceleration E wave time; TDI: Tissue Doppler Imaging: HF Heart Failure; LAVI: Left Atrial Volume Index; LVEF: Left Ventricular Ejection Fraction; LVMI: Left Ventricular Mass Index; LVEDVI: Left Ventricular End-diastolic Volume Index.

Figure 1: Sample distribution according to the Paulus et al. [11] HFpEF diagnostic criteria.

A transthoracic echocardiography was performed within the first 24 hours after admission. This study included Doppler diastolic echocardiographic parameters (mitral E wave velocity, early diastolic velocity of mitral annulus (e´), E wave deceleration time, E/e´ ratio, left atrial volume index and LV mass index, according to the European Society of Cardiology recommended echocardiographic methods for measurement of diastolic dysfunction [10].

Albumin, NT proBNP and CA 125 plasmatic concentrations were obtained in every patient within the first 24 hours from admission. Hypoalbuminaemia was defined as a plasmatic concentration < 3.5 g/dl. Anaemia was considered if hemoglobin was < 13 g/dl in men and < 12 g/dl in women. Malnutrition was considered if the body mass index was < 18.5 kg/m². The Tricuspid Annular Plane Systolic Excursion (TAPSE) method was applied for the diagnosis of right ventricular dysfunction (TAPSE < 17 mm).

Categorical variables are reported as percentages, and normally distributed continuous variables as mean and standard deviation. For categorical variables, differences between groups were tested with the χ^2 test or Fisher´s exact test where appropriate. For comparison of continuous variables, Student's t-test was employed. A p value < 0.05 was considered significant. All the variables that were statistically significant at univariable analysis and variables considered of relevant clinical interest were included in the multivariable model (logistic regression) to identify the independent predictors of all-cause mortality. Cox proportional hazard models were used to calculate odds ratios (OR) with associated 95% confidence intervals (CI). Correlation coefficients were calculated by Spearman´s linear model. We obtained a prognostic score (PS) based on the factors for predicting 1-year death. It was calculated according to the formula:

*PS: 10x*β coefficient$_1$ *(CA 125)* + 10xβ coefficient$_2$ *(NT proBNP)* + 10xβ coefficient$_3$ *(albumin)*

Where the variables CA 125, NT proBNP and albumin were categorized as 1 for the presence of increased plasmatic concentrations (for NT proBNP and CA 125) or hypoalbuminaemia, and 0 for the absence of these conditions.

Table 1: Baseline characteristics

	Total n (%)	Male n (%)	Female n (%)	p
Age >80 years	93 (60.4)	25 (26.9)	68 (73.1)	0.001
HTA	134 (87.0)	49 (36.6)	85 (63.4)	0.767
Obesity	66 (42.8)	26 (39.4)	40 (60.6)	0.596
Diabetes mellitus	58 (37.6)	25 (43.1)	33 (56.9)	0.224
Anaemia	82 (53.2)	25 (30.5)	57 (69.5)	0.073
Hypertensive cardiomyopathy	99 (64.7)	29 (29.3)	70 (70.7)	0.011
Atrial fibrillation	83 (53.8)	31 (37.3)	52 (62.7)	0.926
Chronic obstructive pulmonary disease	54 (35.1)	28 (51.9)	26 (48.1)	0.005

To assess statistics of variables for mortality, receiver-operating characteristic (ROC) curves were constructed. All analyses were carried out in SPSS software (ver. 15.0; SPSS, Inc., Chicago, IL, USA). The institutional ethics committee approved the study. Every patient signed the informed consent form before being included into the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Results

Average age was 81 years (SD 9) and 63% were female. Out of the 154 patients, 82 had no prior history of HF. Besides the Framingham´s criteria, 97.4% fulfilled the European Society of Cardiology [10] diagnostic criteria and 94.2% accomplished the HFpEF criteria proposed by Paulus et al. [11] (Figure 1). Baseline characteristics are shown in Table 1. Hypertension (87%), atrial fibrillation (53.8%) and anaemia (53.2%) were the most prevalent comorbidities. During follow up, 37 patients died. The mortality rate was 24%. The cause

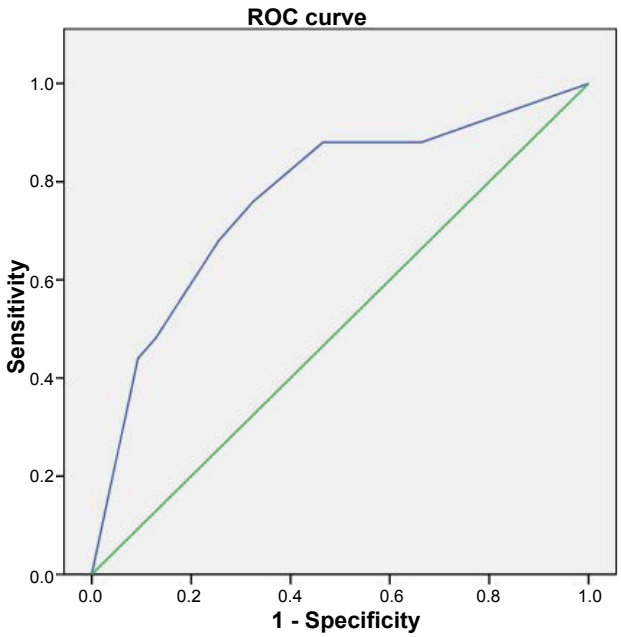

Figure 2: Receiver-operating characteristic analysis of the combined NT proBNP, albumin and CA 125 prognostic score for the prediction of one year mortality.

of death could be ascertained in 25 of the 37 patients and it was attributed to cardiovascular events in 38% of the cases.

At baseline, the NT proBNP median plasma concentration was 1965 ng/l (IQR 4016). NT proBNP values were related to worse diastolic function: there was a significant association between NT proBNP levels and the E/e´ septal ratio (r = 0.25, p = 0.002) and an inverse correlation to the E wave deceleration time (r = -0.28, p = 0.001). The area under curve for NT proBNP > 2086 ng/l to discriminate 1-year-all-cause mortality was 74%. NT proBNP plasmatic levels predicted 1-year all-cause mortality with 77.1% sensitivity and 59.6% specificity. In the multivariable analysis, age > 80 years (OR 5.59; 1.60-22.48, CI 95%, p = 0.008), NT proBNP > 2086 ng/l (OR 5.36; 1.84-15.65, CI 95%, p = 0.002) and the need of chronic oxygen therapy (OR 4.19; 1.51-11.59, CI 95%, p = 0.006) were associated with an increased risk of mortality. Among the 82 patients without a prior history of HF, the Cox regression model identified NT proBNP plasmatic levels > 1822.5 ng/l (HR 3.67; 1.22-11.05, CI 95%, p = 0.021) as the single most important independent predictor of readmission for HF.

The average serum albumin level was 3.7 g/dl (SD 0.4). No association was found between albuminaemia and advanced stages of liver diseases or malnutrition. A consistent association between hypoalbuminaemia and right ventricular dysfunction was demonstrated (p = 0.004). Hypoalbuminaemia was related to a higher risk of death among these patients (RR 2.57; 1.46-4.52, CI 95%, p = 0.001). The area under curve for albuminaemia < 3.5 g/dl to discriminate 1-year-all-cause mortality was 70%, with 71.9% sensitivity and 60.3% specificity.

The CA 125 median plasma concentration was 28.9 U/ml (IQR 65.2). No gender differences were found. There was no relation between a previous history of autoimmune diseases or malignancy and CA 125 concentrations. Increased CA 125 levels were associated to congestive radiologic signs, such as pleural effusion (p = 0.001). Likewise, CA 125 was positively correlated with NT proBNP (r = 0.28, p = 0.002) and inversely related to albuminaemia (r = -0.37, p < 0.0001). A baseline level of CA 125 higher than 31.4 U/ml predicted 1-year mortality with 70.4% sensitivity and 58.9% specificity. Remarkably, CA 125 > 31 U/ml was identified as an independent predictor of mortality (RR 2.58; 1.23-5.43, CI 95%, p = 0.008).

Finally, we found that the combination of NT proBNP plasmatic concentrations > 2086 ng/l, albuminaemia < 3.5 g/dl and CA 125 > 31 U/ml was associated to a worse outcome among acute decompensated HFpEF patients (RR 3.32; 1.91-5.78, CI 95%, p < 0.0001). In the ROC analysis for prediction of death by the score based on these three variables, the area under the curve was 0.76 (0.65-0.87, CI 95%) at one year (Figure 2).

Discussion

Heart failure with preserved ejection fraction is a common reason for hospitalization among old patients. This has been related to the particularities of this population, which usually had left ventricular hypertrophy, diastolic dysfunction, fibrosis or increased prevalence of atrial fibrillation [12].

Multiple biomarkers have been explored to establish a prognostic stratification in HFpEF patients [13]. We have chosen these three laboratory parameters (NT proBNP, albumin and CA 125) because of their widespread use and their relatively low cost, which made them applicable for daily clinical practice. They have demonstrated a prognostic role among HF patients, but their combination in order to stablish a composite predictive measure and its application among a specific population of HFpEF patients has not been studied before.

Despite HFpEF diagnosis is not always an easy task, we have selected a very homogeneous sample, excluding those patients with severe valvular heart disease and those with high-output HF. In addition, every patient who was included in this study really had a preserved left ejection fraction (LVEF > 50%) and accomplished the most standardized HFpEF current diagnostic criteria [10,11].

The role of NT proBNP in these patients is universally recognized [14,15]. In light of our results, however, two considerations should be made. First, we found that the median plasma concentration of NT proBNP of our sample was far superior to the threshold concentration that is generally considered to exclude HF in acute decompensated HFpEF patients [11] (220 ng/l). Berdague et al. [16] had previously described increased NT proBNP plasmatic levels, even among elderly patients with non-cardiac dyspnea. In the light of our results, we suggest that this may not be an optimal decision point to rule out HF among this specific population. On the other hand, NT proBNP appears once again as a very precise marker for stratifying prognosis among HFpEF hospitalized patients, not only for mortality but also for HF readmission.

Albumin is a liver-derived plasma protein. Hypoalbuminaemia can result from hemodilution caused by the HF volume expansion [17]. Congestive right HF may also induce hepatic congestion and cause a decrease in the albumin production [18,19]. Alternative etiologies, as malnutrition [20] or advanced hepatopathy were reasonably excluded in our sample. As far as we know, the association between hypoalbuminaemia and right HF due to right ventricular dysfunction in these patients had not been described before. Further investigations are warranted to confirm the physiopathological mechanisms responsible for this finding. Although hypoalbuminaemia has been related to a poor outcome in HF [17], little is known about its role in HFpEF. Our results are consistent with those reported by Liu et al. [21], who found that albumin values < 3.4 g/dl were related to an increased risk of mortality.

CA 125 is a high molecular weight glycoprotein produced by epithelial serosal cells as a response to mechanical stress and inflammatory processes [22,23]. This could explain the elevated concentrations of CA 125 in congestive conditions, such as HF. Thus, pleural or pericardial effusion, jugular vein distension and peripheral edemas had been related to increased plasmatic CA 125 values. There is a growing interest in the application of the CA 125 as a prognostic marker in HF because of its availability and cost-effectiveness. Hung et al. [24] compared the differences among 3 groups of 158 women which had a preserved LVEF (HFpEF, > 1 cardiovascular risk factors, normal controls). HFpEF patients had increased plasmatic levels of CA 125 and NT proBNP. They also described that CA 125 values > 17.29 U/ml were associated to a higher incidence of HF hospitalization at follow up. In this regard, we have also demonstrated that CA 125

can add prognostic information among acute decompensated HFpEF patients. Even more, elevated concentrations of this biomarker were associated to an increased risk of mortality.

It is particularly interesting to emphasize how the combination of hypoalbuminaemia and higher NT proBNP and CA 125 plasmatic concentrations was associated to a higher risk of mortality (RR 3.32; 1.91-5.78, CI 95%, $p < 0.0001$). This could reflect a severe congestive HF situation because of increased left ventricular filling pressures or an advanced degree of systemic inflammation [25]. Our findings could be helpful to develop prognostic scores for acute decompensated HFpEF hospitalized patients.

Our study has certain limitations. It was a single center observational study. Severely ill patients, like the ones admitted to the Critical Care Unit, were not included. A telephonic interview was performed to collect data at follow up, which may influence in the lack of information about the cause of death at discharge. The small sample size may undermine the reliability of our results. Large prospective randomized trials should be conducted to confirm their clinical applicability.

Conclusion

Conventional and emerging HF biomarkers, such as hypoalbuminaemia or increased NT proBNP and CA 125 plasmatic concentrations, have the potential to become relevant for predicting prognosis in acute decompensated HFpEF hospitalized elderly patients.

Conflicts of Interests

There are no conflicts of interest to declare.

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