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Clinical Study

Predictive Value of Admission N-Terminal Pro-B-Type Natriuretic Peptide and Renal Function in Older People Hospitalized for Dyspnoea

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Background. We investigated the relationship between NT-pro-BNP, glomerular filtration rate (GFR), and all-cause mortality rates in a cohort of older people discharged from an internal medicine unit after admission for dyspnoea. *Patients and Methods*. NT-pro-BNP was evaluated in serum samples of 134 patients aged 80 ± 6 years who presented to a single academic centre with worsening dyspnoea. History data and anthropometric, clinical, and biochemical parameters including GFR were collected at the time of admission. 119 out of 134 were discharged alive from hospital and were included in the follow-up of 779 ± 370 days. *Results*. 35 out of 119 subjects died after a follow-up of 266 ± 251 days. Cox proportional hazards model showed that GFR and Ln (NT-pro-BNP) were predictors for all-cause mortality with estimated hazard ratios of 0.969 (95% confidence interval: 0.950–0.988; $P = 0.001$) and 2.360 (95% confidence interval: 1.208–4.610; $P = 0.012$), respectively. Patients characterized by high NT-pro-BNP levels and GFR ≥ 60 mL/min/1.73 m^2 showed a dramatic reduction in survival duration compared with the groups with different combinations of the two variables ($P = 0.008$). *Conclusions*. In the elderly, NT-pro-BNP and GFR are predictors of all-cause mortality after admission because of dyspnoea. Since the fact that subjects with high NT-pro-BNP and GFR ≥ 60 mL/min/1.73 m^2 exhibited a reduced survival, high admission NT-pro-BNP suggests future negative outcome.

1. Introduction

N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) plasma levels are assessed in patients who present acutely with dyspnoea. NT-pro-BNP plasma levels are related to the severity of congestive heart failure (CHF) [1], and they are evaluated in order to diagnose CHF in older subjects aged 70 years [2]. Moreover, NT-pro-BNP levels have been found to predict incident disability in older people. In a recent Japanese study, participants were classified into five groups based on their NT-pro-BNP plasma levels (<47, 47–77, 77–133, 133–241, and >241 pg/mL, resp.), and the authors demonstrated that the combined rate of incident disability/death was higher in those with high NT-pro-BNP values [3]. Again, assessment of natriuretic peptide after myocardial infarction is a good indicator of infarct size and left ventricle function [4], probaly due to its overexpression in the ischemic myocardium [5]. Nevertheless, not all patients with symptomatic CHF have high NT-pro-BNP plasma concentrations, and not all asymptomatic patients have low NT-pro-BNP values. Furthermore, plasma NT-pro-BNP provides prognostic information in patients with acute and chronic CHF and, in short-of-breath patients, it may be predictive of 1-year all-cause mortality independently of the baseline diagnosis of acute CHF [6]. Age, gender, and body mass index (BMI) are known determinants of NT-pro-BNP plasma levels, and the normal values tend to increase with age. We have previously shown that, in older people, diseases different from CHF affect NT-pro-BNP plasma levels [7], so that determination of NT-pro-BNP levels does not seem to help

clinicians in definition of dyspnoea. Moreover, Vaes et al. [8] performed a systematic review to evaluate the diagnostic accuracy of natriuretic peptides in older subjects from the general population and found limited evidence supporting their use for diagnosis of cardiac dysfunction or heart failure.

The aim of this study was to investigate the relationship between NT-pro-BNP, glomerular filtration rate (GFR), comorbidities, and two-year all-cause mortality rates in a cohort of older people consecutively discharged from an internal medicine unit after admission for dyspnoea.

2. Methods

In the present study we evaluated with a two-year follow-up 134 patients, aged 65 to 90 years, previously enrolled in a cross-sectional study [7]. All these subjects had been admitted along a complete calendar year to our medical unit because of shortness of breath. They were suspected of having CHF and were studied with NT-pro-BNP assessment [7]; subjects with pulmonary infections and cancer were also included into the study. CHF was diagnosed according to the European Society of Cardiology criteria [9], and dyspnoea was assessed on the basis of Medical Research Council (MRC) breathlessness scale [10] plus the objective sign of increased use of respiratory accessory musculature. In particular, the study included only patients in grade 5 of the MRC breathlessness scale and those with evidence of increasing use of respiratory accessory musculature, whereas subjects with pulmonary embolism were excluded. Age, sex, body mass index (BMI), and serum creatinine were recorded at the time of admission. Serum creatinine levels assays were all performed with the Jaffe method on a Hitachi Modular (Roche Diagnostics, Mannheim, Germany). Renal function was also assessed as GFR evaluated by CKD-EPI formula [11]; patients were classified into the five stages of chronic kidney disease (CKD) [12]. GFR < 60 mL/min/1.73 m^2 defined impaired renal function [12]. As regards comorbidities, history of hypertension, diabetes mellitus, ischaemic heart disease, CHF, cerebrovascular disease, peripheral vascular disease, and chronic obstructive pulmonary disease were considered.

As for NT-pro-BNP plasma levels, patients were classified into subgroups, according to the Januzzi cut-off levels (i.e., age < 50 years: upper normal value 450 pg/mL; age 50–75 years: upper normal value 900 pg/mL; age > 75 years: upper normal value 1,800 pg/mL) [13].

This cohort of patients was followed up for 779 ± 370 days (maximum 1181 days). Cases of inhospital death were excluded, and the rate of death from all causes occurring after discharge was determined. Out of 134 patients, 119 were discharged alive from hospital and were included in the follow-up.

The study was approved by the local ethics committee.

2.1. Statistical Analysis. The results are presented as mean ± SD or percentage as appropriate. NT-pro-BNP values were log transformed [Ln (NT-pro-BNP)] prior to the analysis, in order to approximate normal distribution. Patients were classified into the deceased and survivors, and clinical parameters were compared in the two groups by t-test, chi-squared test, and Mann-Whitney U test, as appropriate. Survival analysis of parameters independently associated with all-cause mortality was performed by Kaplan-Meier survival curve, by classifying the patients on the basis of GFR (<60 and ≥ 60 mL/min/1.73 m^2) and NT-pro-BNP plasma levels (normal and high). A value of $P < 0.05$ was considered statistically significant. Because of the limited absolute number of events (35 deaths) and in order to avoid an overparameterized model, Cox regression analysis, with a backward stepwise selection method to eliminate unnecessary control variables, was carried out to evaluate the effect of the biochemical and clinical variables for all-cause mortality, and hazard ratios (HR) were calculated. SPSS for Windows was used as a statistical system (SPSS, version 13, SPSS Inc., Chicago, IL, USA).

3. Results

We analyzed 119 patients aged 79 ± 6 years (70, 58.8% females; 49, 41.2% males). Hypertension was diagnosed in 67.2% of cases, diabetes mellitus in 36.1%, ischaemic heart disease in 36.1%, CHF in 30.3%, chronic obstructive pulmonary disease in 23.5%, peripheral vascular disease in 25.2%, and cerebrovascular disease in 19.3%. Mean BMI was 28 ± 7 Kg/m^2, serum creatinine 1.32 ± 0.63 mg/dL, GFR 52 ± 21 mL/min/1.73 m^2, and NT-pro-BNP 5.576 ± 8.638 pg/mL (range 60–56,829). Mean Ln (NT-pro-BNP) was 3.37 ± 0.64. Classification of patients based on GFR levels showed that 8 (6.7%) were in CKD stage 1, 34 (28.6%) in CKD stage 2, 57 (47.9%) in CKD stage 3, 18 (15.1%) in CKD stage 4 and 2 (1.7%) in CKD stage 5. Thirty-five (29.4%) patients died after a followup of 266 ± 251 days. The main clinical parameters of the deceased and survivors are shown in Table 1. Cardiovascular therapy administered during admission in deceased and survivors was not statistically different (data not shown). Similarly, the percentage of the deceased and survivors treated with ace inhibitors and angiotensin receptor blockers was not statistically different (34.3 versus 51.2% and 8.6 versus 11.9%, resp.). Multivariate Cox proportional regression analysis (backward selection model) showed that only GFR (HR: 0.969, 95%CI: 0.950–0.988; $P = 0.001$) and Ln (NT-pro-BNP) (HR: 2.360, 95%CI: 1.208–4.6108; $P = 0.012$) were predictors of total mortality. Other variables initially forced in the survival model (age, sex, history of hypertension diabetes, CHF, ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, and cardiovascular therapy) were not statistically associated with the risk of death over the follow-up.

Figure 1 shows the survival analysis of subjects with NT-pro-BNP lower or higher than Januzzi cut-off levels ($P = 0.05$), and Figure 2 shows the cumulative survival in patients with GFR (<60 and ≥ 60 mL/min/1.73 m^2) and normal or high NT-pro-BNP. Patients characterized by high NT-pro-BNP levels and normal renal function showed a dramatic

Table 1: Main clinical parameters of the deceased and survivors.

	The deceased $n = 35$	Survivors $n = 84$	P
Age (years) at admission	81 ± 5	79 ± 6	0.070
BMI (Kg/m^2)	27 ± 6	28 ± 7	0.573
Serum creatinine (mg/dL)	1.66 ± 0.79	1.18 ± 0.49	<0.001
GFR (mL/min/1.73 m^2)	39.8 ± 18.4	57.1 ± 20.4	<0.001
NT-pro-BNP (pg/mL)	9809 ± 13113	3812 ± 4995	0.004
Ln (NT-pro-BNP)	3.66 ± 0.58	3.24 ± 0.62	0.001
Follow-up (days)	266 ± 251	992 ± 111	<0.001
Diabetes (n (%))	14 (40)	29 (34.5)	0.571
Pulmonary disease (n (%))	13 (37.1)	15 (17.9)	0.024
Congestive heart failure (n (%))	12 (34.2)	24 (28.6)	0.536
Cerebrovascular events (n (%))	8 (22.9)	10 (11.9)	0.129
Peripheral vascular disease (n (%))	11 (31.4)	19 (22.6)	0.313
Ischaemic heart disease (n (%))	17 (48.6)	26 (30.9)	0.068

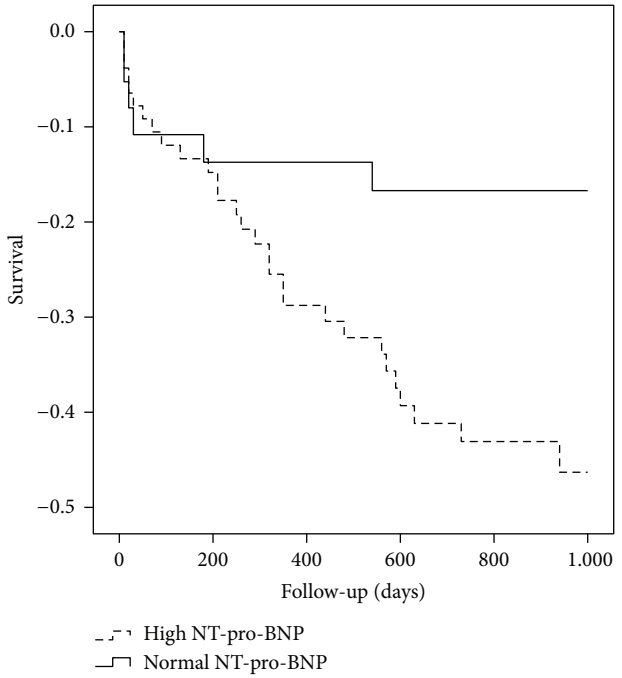

Figure 1: Cumulative survival curves in patients with NT-pro-BNP lower and higher than Januzzi cut-off levels.

reduction in survival duration compared with the other three groups ($P = 0.008$).

4. Discussion

We found that, in a cohort of older people hospitalized for dyspnoea, GFR < 60 mL/min/1.73 m^2 and high NT-pro-BNP levels measured at admission were independently

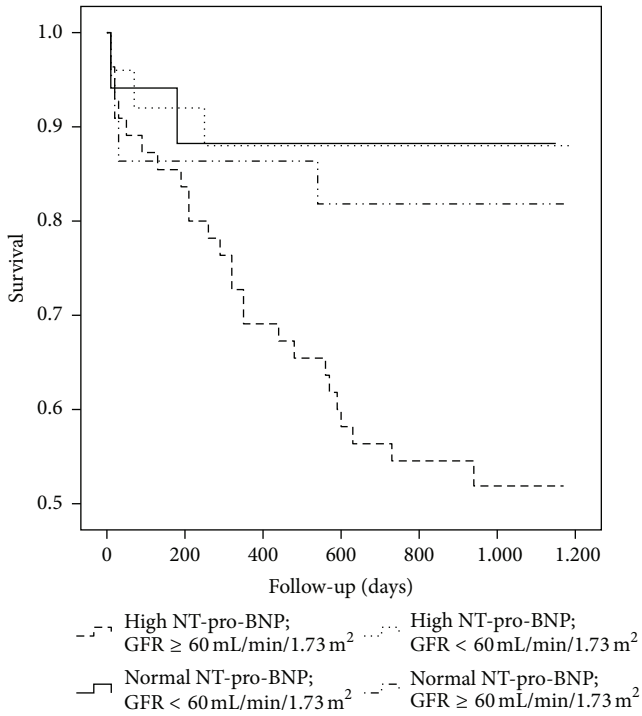

Figure 2: Cumulative survival curves in patients with combined different degrees of renal function (GFR <60 or >60 mL/min/1.73 m^2) and normal or high NT-pro-BNP.

associated with total mortality rate after two years of follow-up. Nevertheless, when these two parameters were combined, only NT-pro-BNP values above the Januzzi cut-off levels had a significant impact on survival.

It has been shown that discharge levels of NT-pro-BNP predict poor cardiovascular outcome in hospitalized diabetic patients with a broad spectrum of cardiovascular disease [14]. Again, NT-pro-BNP levels are strong and independent predictors for long-term mortality in unselected dyspnoeic patients presenting to the emergency department, independent of the cause of dyspnoea [15]. In patients with advanced left ventricular dysfunction, the relationship between NT-pro-BNP and mortality is known since more than one decade [16]. Moreover, in subjects with advanced CHF, natriuretic peptide is a powerful predictor of functional status deterioration [17] and an independent predictor of sudden death [18]. Recently, Idris et al. [19] suggested that high NT-pro-BNP plasma levels, determined in the acute phase of stroke, were an important predictor of mortality. In patients with CHF, it has been estimated that every 100 pg/mL increase in plasma natriuretic peptide was associated with a 35 percent increase in the relative risk of death [20].

In short-of-breath patients, NT-pro-BNP may be predictive of 1-year all-cause mortality, independently of the baseline diagnosis of acute heart failure [6]. In fact, mortality was higher in patients with baseline NT-pro-BNP concentrations above the cut-off levels of 2060 ng/L [21]. The correlation between NT-pro-BNP and mortality has been confirmed also by long-term studies. Data on a cohort of older people with

symptoms of CHF, followed in primary health care, showed that high NT-pro-BNP plasma concentrations, together with diabetes and New York Heart Association class III, were predictors of cardiovascular mortality up to 10 years [22]. Again, a prospective study on more than 3500 men (aged 60–79 years) followed for 9 years, including records on all major cardiovascular disease events (i.e., fatal and nonfatal coronary heart disease, stroke, and cardiovascular death), showed that NT-pro-BNP was more strongly associated with outcomes than C-reactive protein in subjects with and without preexisting cardiovascular disease. Moreover, the raise of NT-pro-BNP was strongly associated with GFR [23].

The relationship between renal function and NT-pro-BNP represents pivotal question, since NT-pro-BNP undergoes renal clearance, and a decreased GFR is associated with increased NT-pro-BNP levels. Thus, both GFR and NT-pro-BNP could represent risk factors for increased mortality. Reny et al. [24] assessed NT-pro-BNP in 254 patients over 70 years hospitalized because of dyspnoea, and kidney function was evaluated with Cockroft-Gault formula. Fifty-five percent of patients died, and the median survival was about 750 days. Cox analysis showed that NT-pro-BNP higher than 2856 pg/mL, creatinine clearance lower than 30 mL/min, and age higher than 80 years were predictors of all-cause mortality [24]. Also in patients with end-stage renal disease, in spite of generally elevated NT-pro-BNP levels, the latter remains an independent predictor of mortality [25].

5. Limitations

The analysis considering only all-cause mortality, and not cardiovascular mortality as a separate outcome, represents a first limitation. Nevertheless, the small number of patients did not allow further multiple grouping. Moreover, since cardiovascular treatment in the deceased and survivors was not significantly different, a certain degree of homogeneity may be hypothetically presumed. Second, dyspnoea is usually associated with an acute condition, and renal function evaluated by equations would require clinically stable conditions. In our study, we decided to exclude patients with acute kidney injury, since they are more likely to die during hospitalization. Third, in our study we did not systematically consider cardiac function in all patients. On the other hand, Lee et al. [26] reported that NT-pro-BNP values progressively increase with worsening renal function, independent of the value of ejection fraction. We are aware that it is somewhat difficult to draw conclusions about CKD stage 5, due to the very limited number of such patients enrolled in our study. Thus, data should be taken with caution, but this study was focused on the real world of elderly comorbid subjects admitted to internal medicine wards, also because patients with severe CKD on stage 5 are usually managed by nephrologic units. Fourth, we did not consider urine abnormalities and imaging studies for classification of CKD stages. However, in our opinion this approach is more appropriate for stable patients managed into ambulatory setting, since it is difficult to correctly classify CKD in acute patients, especially when GFR is higher than 60 mL/min/1.73 m^2. Finally, not being strictly related to the aims of our study, we did not assess systematically functional and cognitive status of the patients; these parameters might have influenced the development of diseases which may give dyspnoea as main clinical symptom.

Study strengths included well-defined and precise parameters of evaluation of NT-pro-BNP and renal function. As for the former, in fact, high NT-pro-BNP plasma levels were defined on the basis of the internationally validated Januzzi cut-off levels [13]. Moreover, we measured serum creatinine with a standardized method and estimated GFR with a validated equation. In fact, the choice of the formula used to assess renal function is not a secondary point, especially when such assessment is used to make long-term evaluations of different diseases [27]. A recent cross-sectional study on a cohort of older people with and without cognitive impairment reported significant differences in the evaluation of GFR with different equations [28]. Again, Earley et al. [29] reviewed the performance of GFR estimating equations derived or reexpressed and validated by using creatinine measurement traceable to the standard reference material and concluded that, in a general practice and public health perspective, the CKD-EPI equation represents the best instrument. The same consideration was reported by Corsonello et al. [30], after a multicentre observational study on more than ten thousand hospitalized older people, who were evaluated for their incident adverse drug reactions during hospital stay and for ability of different equations to calculate GFR. In a previous study, we analyzed the relationship between NT-pro-BNP and kidney function and found that reduced renal function may correspond to increased NT-pro-BNP concentrations, and this could represent an interfering factor when high NT-pro-BNP plasma levels are to be interpreted. Moreover, the different formulae used to evaluate GFR could differently stratify NT-pro-BNP in older adults [31].

6. Conclusions

In conclusion, we found that, in a cohort of older comorbid patients consecutively hospitalized for shortness of breath (representative of the *real world* of everyday patients of internal medicine wards), admission renal function and NT-pro-BNP were independently associated with long-term mortality. In particular, subjects with high NT-pro-BNP and GFR $\geq$ 60 mL/min/1.73 m^2 exhibited a reduced survival of about 20% compared with the other groups. In these subjects, elevated admission NT-pro-BNP levels could represent an important predictor of mortality.

Disclosure

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