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Markers of severity of heart failure in the elderly

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Abstract. Objective: To determine the possible correlation of NYHA classification with clinical and paraclinical parameters in elderly diagnosed with heart failure. Material and methods: Patients aged over 65 years, diagnosed with heart failure, were included in study. Clinical data, biochemical markers and imagistic parameters were determined, and the presence or absence of comorbidities was noted. Results: A number of 178 patients were included in study. In univariate analysis, NYHA classification was associated with: orthopnea, jugular venous distention, rales, bilateral ankle edema, pleural effusion, hepatomegaly, atrial fibrillation, estimated glomerular filtration rate (eGFR), blood urea nitrogen (BUN), C-reactive protein (CRP), high-density lipoprotein cholesterol (HDL-cholesterol), and left ventricle ejection fraction (LVEF). The multivariate analysis showed the independent markers linked to NYHA classification: presence of orthopnea ($p<0.001$), bilateral ankle edema ($p=0.05$), chronic kidney disease ($p=0.05$), high levels of CRP ($p=0.04$) and altered LVEF ($p=0.02$). Conclusion: Orthopnea, bilateral ankle edema, renal dysfunction, inflammation and low LVEF are correlated with NYHA classification.
Key Words: elderly, heart failure, NYHA classification, clinical and paraclinical markers.

Rezumat. Obiectiv : Determinarea unei posibile corelaţii între clasificarea NYHA şi parametri clinici şi paraclinici la vârstnicii diagnosticaţi cu insuficienţa cardiacă. Material şi metodă : Pacienţii cu vârsta peste 65 ani, diagnosticaţi cu insuficienţa cardiacă, au fost incluşi în studiu. Date clinice, biochimice şi parametrii imagistici au fost determinaţi, iar prezenţa sau absenţa comorbidităţilor a fost notată. Rezultate : Un număr de 178 pacienţi a fost inclus în studiu. La analiza univariată, clasificarea NYHA a fost asociată cu ortopneea, jugularele turgescente, ralurile crepitante, edemul gambier bilateral, revărsatul pleural, hepatomegalia, fibrilaţia atrială, rata de filtrare glomerulară estimată (RFGe), ureea sangvină, proteina C reactivă (PCR), HDL-colesterolul şi fracţia de ejecţie a ventriculului stâng (FEVS). Analiza multivariată a arătat markerii independent asociaţi cu clasificarea NYHA : prezenţa ortopneei ($p<0,001$), edemul gambier bilateral ($P=0,05$), boala renală cronica ($p=0,05$), niveluri mari de PCR ($p=0,04$) şi FEVS alterată ($p=0,02$). Concluzie: Ortopneea, edemul bilateral gambier, disfuncţia renală, inflamaţia şi FEVS redusă sunt corelate cu clasificarea NYHA.
Cuvinte cheie: vârstnici, insuficienţă cardiacă, clasificarea NYHA, markeri clinici şi paraclinici.

Introduction. Heart failure is a major health problem, whose incidence rises continuously, despite numerous means of diagnostic and treatment. A highly accepted definition of heart failure is difficult to formulate, and that is because there are many etiological factors implicated, complex physiopathological mechanisms and because the evolution of disease has extended effects on every major organs of the body.

Heart failure is a complex progressive disease that is caused by the alteration of the structure or function of the heart, with a direct effect on the contraction or relaxation of the ventricles (Hunt et al 2009). Heart failure is characterized by elevated filling pressures and inadequate periphery distribution of oxygen. In the early stages of the disease, these changes appear only during effort, and later they are present even when the patient rests (Kliger et al 2006).

The incidence of heart failure is high in the elderly, this social category being the most affected. The existence of some chronic diseases in the elderly, of special social conjuncture, makes the management of heart failure extremely difficult. There are other factors that contribute to the low impact of heart failure therapy in the elderly: the

noncompliance of the patients to the treatment, the restrictive diet, the physical activity, and the low adherence by the physicians to new guidelines of disease management.

Currently, the severity of heart failure is quantified by the NYHA (New York Heart Association) classification. The NYHA classification is correlated with mortality and morbidity in patient with heart failure (Muntwyler et al 2002; Lewy et al 2006; Macarie et al 2009). However, NYHA classification is not always correlated with clinical status in the elderly. That is because elderly have a limited physical autonomy due to some noncardiac pathologies (arthrosis, fractures, and strokes). Therefore, it is necessary to study the factors that are associated with NYHA classification in elders with heart failure, without the presence of physical disabilities.

Aim. We evaluated the association between some clinical and paraclinical parameters and the severity of the heart failure, quantified by NYHA classification, in patients aged over 65.

Material and Method. The study included consecutive patients hospitalized in the 5th Medical Clinic, Municipal Clinic Hospital of Cluj-Napoca, from November 2006 to November 2008, diagnosed with heart failure. The study was observational. We followed the evolution of the patients for a period of six months.

The diagnosis of heart failure was established by the use of major Framingham criteria (nocturnal paroxysmal dyspnea, orthopnea, jugular venous distention, rales (crackles) or acute pulmonary edema, cardiomegaly, Z_3 cardiac sound) and minor criteria (nocturnal cough, bilateral ankle edema, exertional dyspnea, pleural effusion, hepatomegaly, tachycardia (>120 bpm) (European Society of Cardiology guideline 2008). The presence of two or more major criteria, or one major and two or more minor criteria, was used to establish the clinical diagnostic of heart failure. We also used imagistic methods to confirm the diagnostic: echocardiography, pulmonary radiological exam and electrocardiography.

The patients suffering from following diseases were not included in study: COPD (chronic obstructive pulmonary disease), pneumonia (or other severe infections), hepatic cirrhosis, chronic renal disease stage V (KDOQI), specified anemia (autoimmune, leukemia, lymphoma, recent hemorrhages, cancer, chronic inflammatory diseases), fractures of lower limbs, obstructive peripheral arterial disease, paralysis, lower limb advanced arthrosis.

We acquired several general and specific data. The age and sex of the patients were recorded. From the clinical exam and anamnesis we obtained the necessary elements for the diagnosis of heart failure and for NYHA classification: acute pulmonary edema, nocturnal paroxysmal dyspnea, orthopnea, exertion dyspnea (mild, moderate, and severe), nocturnal cough, jugular venous distention, rales, Z_3 cardiac sound, pleural effusion, bilateral ankle edema, tachycardia, hepatomegaly.

From the history of the patient we noted the presence of arterial hypertension, ischemic cardiac disease, diabetes, atrial fibrillation, valvular diseases, and chronic renal disease. We established NYHA class for every patient, in accordance with criteria described in table 1 (The Criteria Committee of the New York Heart Association 1994).

Table 1

NYHA classification

NYHA Class	*Symptoms*
I	Patient has no symptoms and his daily activity is not limited.
II	Mild symptoms (mild dyspnea) and mild limitation of daily activity.
III	Marked limitation of activity due to symptoms, even during minimal effort.
IV	Severe limitation of activity. The symptoms are present even when patient is resting.

Echocardiography was performed in order to quantify the left ventricular ejection fraction (LVEF), the presence and severity of diastolic dysfunction and valvular heart diseases. The assessment of diastolic dysfunction was made using the E/A ratio (E=early filling,

A=atrial filling). An E/A ratio less than 0.75 was designated as mild dysfunction or impaired relaxation, while an E/A ratio more than 1.5 was defined as severe dysfunction or restrictive disorder (Redfield et al 2003). Abdominal ultrasonography determined the presence of hepatomegaly.

We measured a series of blood markers: hemoglobin (g/dl), urea (blood urea nitrogen – BUN - normal values (NV) – 30-40 mg/dl), creatinine (NV – 0.5-1.2 mg/dl), C-reactive protein (CRP – NV <0.5 mg/dl), uric acid (NV – 2.4-7.5 mg/dl), total cholesterol (NV – 140-200 mg/dl), triglycerides (NV – 50-150 mg/dl), high-density-lipoprotein cholesterol (HDL – NV > 40 mg/dl for males, > 50 mg/dl for females), low-density-lipoprotein cholesterol (LDL – NV - < 100 mg/dl), Na^+ (NV – 135-145 mEq/L) and K^+ (NV – 3.5-5 mEq/L). Anemia was defined, in conformity with World Health Organization, as the hemoglobin value less than 12 mg/dl in women, and less than 13 mg/dl in men (WHO 2005). Estimated glomerular filtration rate (eGFR) was calculated with Modification of Diet in Renal Diseases (MDRD) formula (Levey et al 2003). Chronic kidney disease is defined as kidney damage for more than 3 months (structural damage or functional abnormalities) with or without decreased GFR, manifest by either: pathological abnormalities or markers of kidney damage (abnormalities of the blood or urine, imagining tests), or a GFR lower than 60 ml/min/1.73 m^2 for more than 3 months, with or without kidney damage.

The statistical analysis was performed using the SPSS software version 17. For the basic comparison of the primary variable we used the T test for independent variables (continuous variables with normal distribution (Kolmogorov-Smirnov test)), Mann-Whitney test (continuous variables with non-normal distribution), Chi square test (dichotomic variables), ANOVA test (ordinal variables), Pearson or Spearman's correlations (depending of normality of distribution of continuous variables). The multivariate analysis was performed with the ordinal regression (Tabachnik et al 1996; Whitley et al 2002; Băicuş 2007). The statistic significance was established by calculating the p parameter and a value less than 0.05 was considered statistically significant.

Results. We included 178 patients in study. Mean age was 77.9 years, and the median age was 77 years. 50 (33.3%) patient were men and 118 (66.7%) were women.

We only observed NYHA class II, III and IV, and no patients had NYHA class I. There were 39 (22%) patients in NYHA class II, 88 (49.75) in NYHA class III and 50 (28.2) were in NYHA class IV. We did not observed an association between NYHA classification and age (T test for independent variables; p=0.7) or sex (Chi square test; p=0.44).

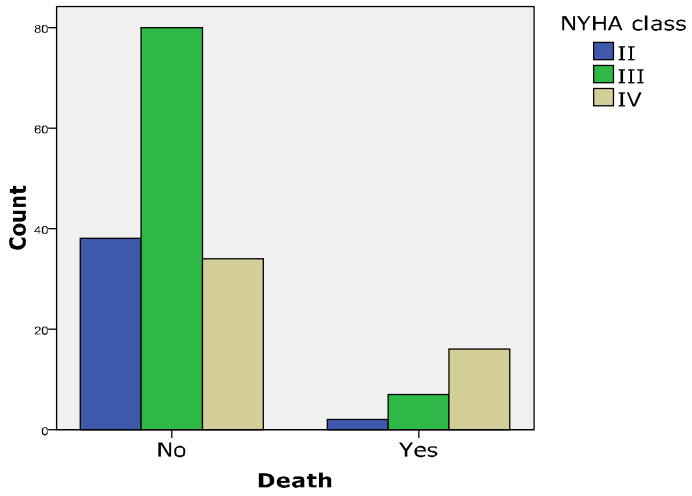

Figure 1. Association deaths – NYHA classification

For the duration of the study there were 26 (14.7%) deaths. 18 patients were females, and 8 males. We analyzed the relationship between deaths and NYHA classification and we found and association statistically significant ($p<0.001$). Figure 1 show the association.

Valvular heart disease was diagnosed in 134 (75%) patients. We observed an association between NYHA classification and the severity of mitral regurgitation ($p<0.001$), and none with other valvular diseases.

Arterial hypertension was detected in 118 (66.6%) patients. Ischemic cardiac disease was observed in 144 (85%) patients. Atrial fibrillation was determined in 89 (33.3%) patients, and diabetes was found in 42 (23%) patients. We found an association between NYHA classification and the presence of atrial fibrillation ($p=0.01$).

Nocturnal paroxysmal dyspnea was encountered in 40 (22.2%), orthopnea in 103 (58%) patients, jugular venous distention in 30 (16%) patients, cardiomegaly in 81 (45%) patients, rales in 106 (59%) patients, bilateral ankle edema in 115 (64%) patients, pleural effusion in 51 (28%) patients, nocturnal cough in 24 (13%) patients and hepatomegaly in 74 (41%) patients. We determined that NYHA classification was associated with orthopnea ($p<0.001$; Figure 2), jugular venous distention ($p<0.001$; Figure 3), rales ($p<0.001$), bilateral ankle edema ($p<0.001$), pleural effusion ($p=0.003$), hepatomegaly ($p=0.001$).

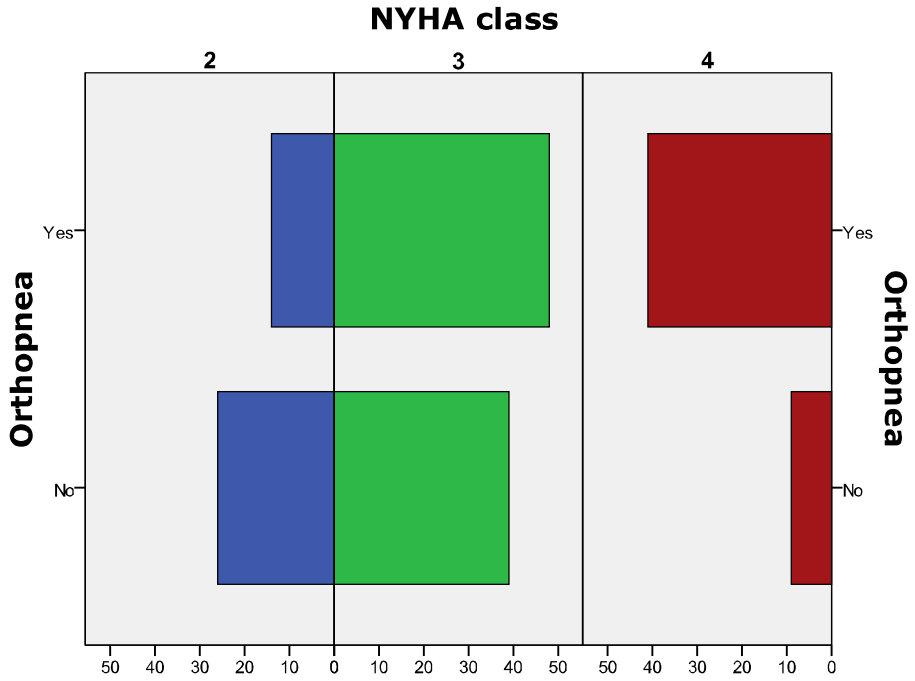

Figure 2. Association between orthopnea – NYHA classification

Anemia was detected in 74 (41.2%) patients. Chronic renal disease was diagnosed in 100 (56.6%) patients. We divided the values of CRP by levels of cardiovascular risk: mild (CRP less than 1 mg/dl), moderate (CRP between 1 and 3 mg/dl) and severe (CRP higher than 3 mg/dl). 58 (32.8%) patients were at mild risk, 49 (27.7%) at moderate risk and 70 (39.5) at severe risk. Hiperuricemia was detected in 108 (61%) patients. We recorded high values of BUN in 116 (65.5%) patients.

In order to evaluate the relationship between blood parameters and the severity of heart failure, as quantified by NYHA classification, we used the analysis of variances the parametric alternative: ANOVA test. We did not found any association between NYHA class and hemoglobin ($p=0.08$). The difference of means for eGFR (Figure 4) was highly

statistically significant associated for NYHA class III and IV (15.2 ml/min; p<0.001), and statistically significant associated for NYHA class II and IV (14.5 ml/min; p=0.004). The association was a moderate one (the η^2 coefficient = 0.1), so a higher NYHA class explain 10% of the variation of eGFR levels. The difference of means for BUN was highly statistically significant associated for NYHA class III and IV (25 mg/dl; p<0.001), and highly statistically significant associated for NYHA class II and IV (29 mg/dl; p<.001). CRP was statistically significant associated with NYHA classification (Figure 5). The post hoc Tukey analysis revealed that the difference of mean of CRP was statistically significant for NYHA class II and III (0.45 mg/dl; p=0.03) and for NYHA class II and IV (0.5; p=0.003). We did not found an association between uric acid and NYHA classes, but we demonstrated a negative relationship between HDL-cholesterol and NYHA classes (p=0.002).

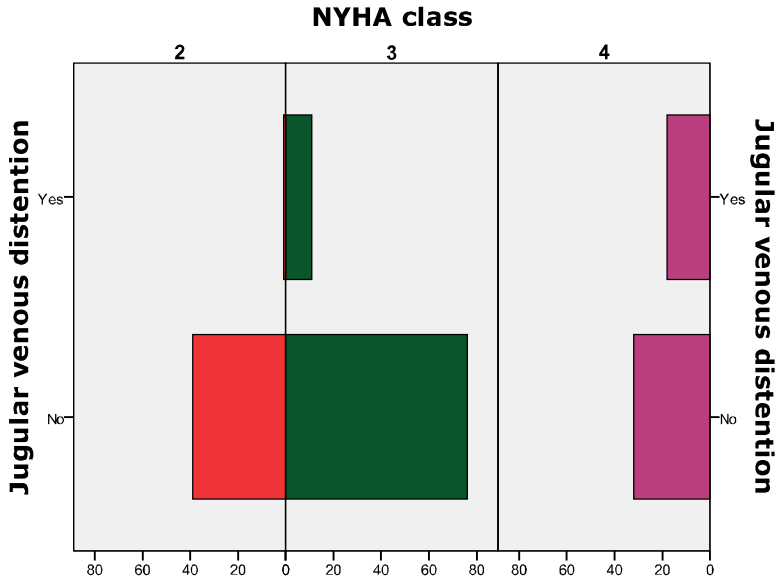

Figure 3. Association between jugular venous distention – NYHA classification.

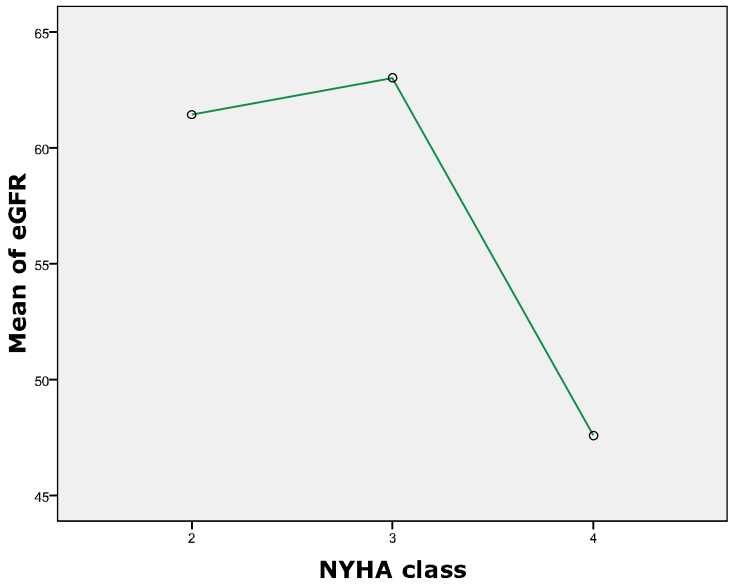

Figure 4. Means of eGFR as reflected by NYHA classification.

We used the Chi square test to investigated the association between NYHA classification and anemia (p=0.24), chronic kidney disease (p=0.007), levels of risk (CRP) (p=0.007), hiperuricemia (p=0.06).

A highly statistically significant association between NYHA classification and the ejection fraction of left ventricle (EFLV) was found using the ANOVA test (p<0.001; Figure 6). The difference of means for EFLV was 12.9 for NYHA class II and IV (p<0.001), 6.8 for NYHA class II and III (p=0.001) and 6 for NYHA class III and IV (p=0.003). We did not determine a correlation between NYHA classification and diastolic dysfunction.

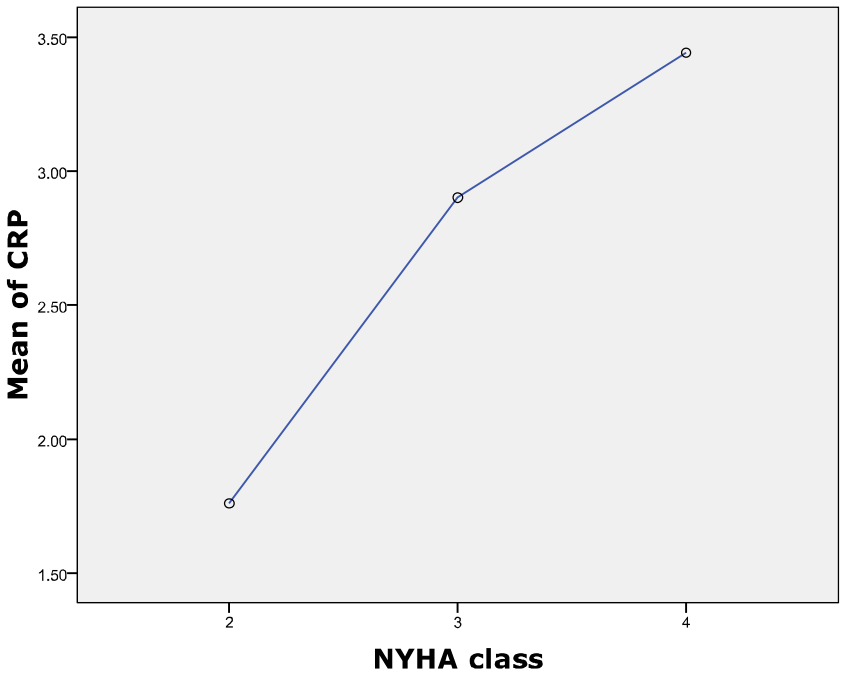

Figure 5. Means of CRP as reflected by NYHA classification.

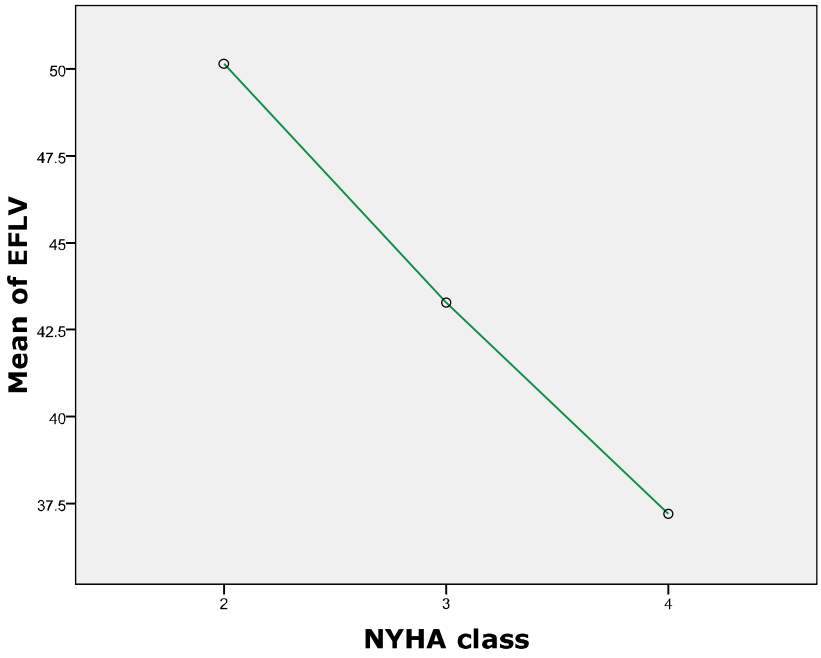

Figure 6. Means of LVEF as reflected by NYHA classification.

Table 2

Ordinal regression for NYHA classification

		Std. Error	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
						Lower Bound	Upper Bound
Threshold	[NYHA = 2]	.666	51.188	1	.000	-6.073	-3.461
	[NYHA = 3]	.558	9.826	1	.002	-2.841	-.655
Location	[LVEF (>50)]	.366	4.963	1	.026	-1.534	-.098
	[LVEF (<50)]	.	.	0	.	.	.
	[CKD=0]	.350	2.986	1	.050	-1.290	.081
	[CKD=1]	.	.	0	.	.	.
	[Age (<69 years)]	.540	1.229	1	.268	-1.656	.460
	[Age (70-70 years)]	.342	1.096	1	.295	-.313	1.030
	[Age (> 80 years)]	.	.	0	.	.	.
	[Female]	.351	.337	1	.562	-.484	.892
	[Male]	.	.	0	.	.	.
	[CRP (mild)]	.385	4.217	1	.040	-1.543	-.036
	[CRP (moderate)]	.403	2.337	1	.126	-1.405	.174
	[CRP (severe)]	.	.	0	.	.	.
	[Uric acid (N)]	.344	2.428	1	.119	-1.209	.138
	[Uric acid (high)	.	.	0	.	.	.
	[Atial fibrillation absent]	.338	.026	1	.872	-.718	.608
	[Atial fibrillation present]	.	.	0	.	.	.
	[Orthopnea absent]	.353	13.081	1	.000	-1.968	-.585
	[Orthopnea present]	.	.	0	.	.	.
	[Jugular venous distention absent]	.486	2.929	1	.087	-1.786	.121
	[Jugular venous distention present]	.	.	0	.	.	.
	[Rales absent]	.340	.320	1	.572	-.859	.475
	[Rales present]	.	.	0	.	.	.
	[Ankle edema absent]	.365	3.562	1	.050	-1.406	.027
	[Ankle edema present]	.	.	0	.	.	.
	[Pleural effusion absent]	.383	.859	1	.354	-1.106	.396
	[Pleural effusion present]	.	.	0	.	.	.
	[Hepatomegaly absent]	.366	2.172	1	.141	-1.256	.178
	[Hepatomegaly present]	.	.	0	.	.	.

The multivariate analysis was created using an ordinal regression (Table 2). We obtained a $p<0.001$ at the Chi square test, so we reject the null hypothesis that the model without predictors is as good as the model with the predictors. The value of R-square parameter obtained at Cox-Snell test was 0.352, at Nagelkerke test 0.402 and at McFadden test 0.208. The value of p in the Goodness-of-Fit section was 0.66 for Person statistic and 0.9 for Deviance statistic. The variables associated independently with NYHA class were: low

EFLV, high levels of CRP, the presence of chronic kidney disease, orthopnea and bilateral ankle edema.

Discussion. The NYHA classification is a simple modality used to quantify the heart failure based on the limitation of the physical activity by dyspnea. The classification is an easy to apply instrument, that should not miss from the evaluation of heart failure, and that is the reason for which many studies include NYHA classes as predictor factors for the mortality and morbidity in heart failure. The value of NYHA classification is less studied in the elderly mainly because the majority of trials include adults and not older people.

Most people in our study were in NYHA class III, followed by NYHA class IV and then NYHA class II. We did not found any relationship between advanced age and NYHA classification. There were no differences in sex distribution related to NYHA class. We found that a more severe NYHA class was prognostic for the deaths of the patients in our study. Only the severity of mitral regurgitation, from all valvular diseases present in our study, was linked to a higher NYHA class. The presence of atrial fibrillation was correlated with a more severe NYHA class.

The NYHA classification sensitized extremely well the complexity and number of signs and symptoms of heart failure. A higher NYHA class was, not at all surprising, statistically significant associated with the presence of orthopnea, jugular venous distention, rales, bilateral ankle edema, pleural effusion, and hepatomegaly.

Although we observed a reduction in levels of hemoglobin in patients with a higher NYHA class, it was not statistically significant. A lower value of eGFR was correlated statistically significant with NYHA classification. The alteration of eGFR was more pronounced in patients from NYHA class IV. Also NYHA classes were predicted by BUN levels. NYHA classes were also associated with the levels of CRP. There were no correlations between NYHA class and uric acid. A low LVEF was associated with a high NYHA class.

The multivariate analysis showed that only few parameters were correlated independently with NYHA classification: orthopnea, bilateral ankle edema, altered eGFR and LVEF, high levels of CRP.

The studies found in literature showed the predictor role of NYHA class for the infaust prognostic of patients with heart failure (Studies of Left Ventricular Dysfunction (SOLVD), Improvement program on evaluation and management of heart failure (IMPROVEMENT of HF), Prospective Randomized Amlodipine Survival Evaluation Study Group (PRAISE), Digitalis Investigation Group (DIG) (Packer et al 1996; Villacorta et al 1999; Muntwyler et al 2002; Levy et al 2006).

Like our study, the PRAISE TRIAL did not found any association between anemia and NYHA classification (Packer et al 1996). However, Silverberg et al have demonstrated repeatedly that correction of anemia, using erythropoietin or iron, improves the quality of life and clinical status (Silverberg et al 2000; Silverberg et al 2001).

Postorino et al showed that NYHA is a powerful predictor of clinical status in chronic kidney disease (Postorino et al 2007). Other studies revealed the correlation between NYHA class and renal function in elderly with heart failure (Stanojević et al 2007). Data form Valsartan Heart Failure Trial (Val-HeFT) showed that higher levels of CRP were associated with poorer clinical status in patients with heart failure (Anand et al 2005).

There are studies that did not showed a link between NYHA class and altered LVEF (Levy et al 2006). Solomon et al showed an association between higher NYHA class and lower LVEF (Solomon et al 2005). The correlation between LVEF and NYHA classification in our study was independent and cannot be explained by the presence of any signs or symptoms, because none were associated with LVEF.

The limitations of our study include: we could measure natriuretic peptides only in a small number of patients; therefore we did not include this important marker in our analysis; we included a relatively small number of patients in our study because of numerous exclusion criteria.

Conclusions. The primary univariate analysis of our study showed the association of NYHA classification with many clinical and paraclinical parameters: orthopnea, jugular venous distention, rales, bilateral ankle edema, pleural effusion, hepatomegaly, atrial fibrillation, eGFR, BUN, CRP, HDL-cholesterol and LVEF. The complex final multivariate analysis revealed the independent markers linked to NYHA classification: presence of orthopnea, bilateral ankle edema, chronic kidney disease, high levels of CRP and altered LVEF.

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