

## Nt-ProBNP, Anaemia and Renal function are independent predictors of hospitalization in outpatients with pulmonary artery hypertension



Dear Editor,

The clinical course of pulmonary arterial hypertension (PAH) is highly variable; therefore, reliable parameters are needed to characterize the severity of the disease and to detect the disease progression sensitively. In recent years, several parameters have been tested.<sup>1</sup> Anaemia and renal function are unspecific markers,<sup>2</sup> while Nt-ProBNP has been extensively studied<sup>3-5</sup> and is recommended in current guidelines.<sup>6</sup> However, renal function may interfere with its levels. We sought to evaluate in patients with PAH, already on specific therapy, which would be the best parameter to predict the long-term hospitalization within the routine laboratory workup.

Thirty consecutive adult patients (73.3% women) with PAH, age of  $63.7 \pm 12.6$  years, Group I PAH, on specific pulmonary vasodilator target therapy >12 months (sildenafil 83.3%, bosentan 60%; both 43.3%), stable outpatients (last hospitalization and diuretic therapy changes >3 months) were included in this 2-year clinical follow-up. Also, at inclusion sPAP and mPAP should be >35 mmHg and >25 mmHg, respectively. Our Unit routine laboratorial workup includes the determination of the Nt-ProBNP, complete blood count including haemoglobin, haematocrit, erythrocyte count, red

cell distribution width, creatinine and estimated glomerular filtration rate (MDRD equation), hepatic enzymes and the ionogram. Outcome: cardiovascular hospitalization.

Besides clinical stability, no recent hospitalization and specific therapy >12 months the sPAP ( $73.9 \pm 24.7$  mmHg), pulmonary vascular resistance ( $3.2 \pm 1.2$  wood) and Nt-ProBNP ( $1021 \pm 1200$  pg/ml) were high. The hospitalization and death rate were 46.7 and 16.7%, respectively. The ROC curve for hospitalization was significant for haemoglobin (AUC=0.75;  $p=0.028$ ), Erythrocytes (AUC=0.76;  $p=0.023$ ), Haematocrit (AUC=0.73;  $p=0.043$ ), Creatinine (AUC=0.74;  $p=0.026$ ), GFR (AUC=0.73;  $p=0.034$ ) and Nt-ProBNP (AUC=0.79;  $p=0.007$ ). The significant cut-off points were calculated from the ROC curve. All these parameters were associated to increased risk of hospitalization (Table 1) and with the hospitalization curve. The multivariate Cox regression ("backward stepwise method) model showed that the Haematocrit <42.4 (HR=11.1;  $p=0.036$ ), Creatinine <1.16 (HR=4.93;  $p=0.022$ ) and Nt-ProBNP >895 (HR=14.9;  $p<0.001$ ) were the independent predictors of hospitalization. Patients with at least one of these parameters above the cut-off had greater risk of hospitalization (HR=5.6; 95% CI 0.73–43.0;  $p=0.097$ ).

In conclusion, the present data showed that the haematocrit, creatinine and Nt-ProBNP, which characterize the anaemia degree, renal function and heart dysfunction; and are included in the routine follow-up of our Unit, are independent predictors of the 2 years hospitalization curve. These data confirm and reinforce previous data on these prognostic markers.

**Table 1** Risk estimate, hospitalization curve; and the univariate and multivariate predictors of hospitalization by Cox regression.

	Fisher exact test with risk estimate			Kaplan–Meier Log-Rank	Cox regression				
	OR	95% CI	P value		Univariate analysis		Multivariate analysis*		
					HR	P value	HR	95% CI	P value
Hb < 14.5 g/dl	2.3	1.3–3.9	0.003	0.006	48.1	0.128	–		
Eryth < 4,710,000	2.2	1.1–4.4	0.023	0.036	4.43	0.055			NS
Ht < 42.4%	2.1	1.2–3.8	0.016	0.021	7.68	0.051	11.1	1.16–106.2	0.036
Rdw > 13.6	1.6	1.1–2.3	0.054	0.047	32.7	0.23	–		
Creat > 1.16 mg/dl	8.0	1.1–57.3	0.012	0.003	4.43	0.006	4.9	1.26–19.3	0.022
GFR < 77.2 cc/min/1.73 m <sup>2</sup>	2.1	1.1–4.2	0.033	0.038	3.59	0.051			NS
Nt-ProBNP > 895 pg/mL	3.43	1.2–10.2	0.024	0.003	4.54	0.007	14.9	3.33–67.2	<0.001

Abbreviations: Hb, haemoglobin; Eryth, erythrocyte count; Ht, haematocrit; Rdw, red cell distribution width; Creat, creatinine; GRF, glomerular filtration rate (MDRD method). \* Multivariate analysis "backward stepwise method". NS, non-significant; OR, odds ratio; HR, hazard ratio; CI confidence interval.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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## Evaluation of clinical presentation and outcome of patients with respiratory bronchiolitis-associated interstitial lung disease



To the Editor,

Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) is a rare interstitial pneumonia that usually affects current smokers in the fourth and fifth decades of life with a history of heavy smoking (usually more than 30 pack-years).<sup>1,2</sup> In most cases the symptoms of RB-ILD are subclinical and detected coincidentally or it is associated with a mild clinical presentation, usually a gradual onset of dyspnea and/or a presence of persistent cough.<sup>1,2</sup> Lung function tests reveal only minor restrictive or obstructive defects in most cases, often combined with hyperinflation. Additionally, carbon monoxide diffusing capacity (DLCO) is often slightly to moderately impaired.<sup>2,3</sup> High Resolution Chest CT-scan (HRCT) classic features are essentially ground glass centrilobular nodules located in the upper lobes which in the appropriate clinical context are normally not difficult to differentiate from other interstitial lung diseases (ILD).<sup>2,4</sup> Bronchoalveolar Lavage (BAL), may help in the differential diagnosis with other ILD and it is characterized by a raised total cell count induced by an increased number of intense brown pigment-laden macrophages, although a mild neutrophilia may also be present.<sup>2,5</sup> The evolution is unpredictable and heterogeneous regardless of smoking cessation and more data are required in order to be precise about the outcome of this disease due the conflicting data published so far.<sup>1,2,5</sup>

The medical records of patients diagnosed with RB-ILD during the period of January 2008 to July 2013, followed in ILD outpatient clinic at Centro Hospitalar S. João, were

retrospectively reviewed. RB-ILD diagnosis was based on 2002 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias.<sup>6</sup> Fifteen patients were included with a mean age of 48 (29–65) years and 13 (86.6%) were male. All of them were heavy cigarette smokers (median: 46.3 pack-year). Most patients (73.4%) have mild symptoms, dyspnea on exertion ( $n=8/53.3\%$ ) and cough ( $n=7/46.6\%$ ) were the only symptoms identified. Typical centrilobular ground-glass nodules predominantly in the upper lobes were the overall pattern on the HRCT (Fig. 1). Concomitant upper lobe centrilobular emphysema was identified in 5 (33.3%) patients. Pulmonary function tests showed a slight obstructive impairment (median FEV1 – 76%) associated with a normal median value in the diffusion capacity (median DL<sub>CO</sub> – 76%), although there was a minor decrease (DL<sub>CO</sub> – 61–75%) in six patients. BAL was performed in 12 patients and besides the increased cellularity associated with the intense brown pigment-laden macrophages (Fig. 2), two (16.6%) had mild neutrophilia and another two mild eosinophilia. Three patients were submitted to surgical lung biopsy, two of them performed during the context of cardiothoracic surgeries not related with RB-ILD and the other one during a video-assisted thoracoscopic surgery for pneumothorax with a persistent air-leak. All patients were referred to smoking cessation programs but only three gave up, the remainder just reduced the amount of tobacco consumption. None of them had any additional therapeutic interventions besides inhaled bronchodilators prescribed to those patients that were more symptomatic. Regardless of whether they maintained smoking habits, after a mean follow-up of 49 (12–72) months, all the patients included remained clinically stable, with similar functional (mean FEV1 – 74% and DLCO – 75%) and radiological features.

This group of RB-ILD patients had the usual characteristic clinical presentation described previously in other series.