



Role of BNP and echo measurement for pulmonary hypertension recognition in patients with interstitial lung disease: An algorithm application model

This is the peer reviewed version of the following article:		
Original:		
Ruocco, G.M., Cekorja, B., Rottoli, P., Refini, R.M., Pellegrini, M., DI TOMMASO, C., et al. (2015). Role of 3NP and echo measurement for pulmonary hypertension recognition in patients with interstitial lung disease: An algorithm application model. RESPIRATORY MEDICINE, 109(3), 406-415 [10.1016/j.rmed.2014.12.011].		
Availability:		
This version is availablehttp://hdl.handle.net/11365/984378 since 2016-09-11T16:25:24Z		
Published:		
DOI:10.1016/j.rmed.2014.12.011		
Terms of use:		
Open Access The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. Works made available under a Creative Commons license can be used according to the terms and conditions of said license. For all terms of use and more information see the publisher's website.		

(Article begins on next page)

Accepted Manuscript

Role of BNP and Echo measurement for pulmonary hypertension recognition in patients with interstitial lung disease: an algorithm application model

Ruocco Gaetano, MD, Cekorja Behar, MD, Rottoli Paola, MD, Refini Rosa Metella, MD, Pellegrini Marco, MD, Di Tommaso Cristina, MD, Del Castillo Gabriele, MD, Franci Beatrice, PhD, Nuti Ranuccio, MD, Palazzuoli Alberto, MD

PII: S0954-6111(14)00449-1

DOI: 10.1016/j.rmed.2014.12.011

Reference: YRMED 4630

To appear in: Respiratory Medicine

Received Date: 21 August 2014

Revised Date: 19 December 2014

Accepted Date: 28 December 2014

Please cite this article as: Gaetano R, Behar C, Paola R, Metella RR, Marco P, Cristina DT, Gabriele DC, Beatrice F, Ranuccio N, Alberto P, Role of BNP and Echo measurement for pulmonary hypertension recognition in patients with interstitial lung disease: an algorithm application model, *Respiratory Medicine* (2015), doi: 10.1016/j.rmed.2014.12.011.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



1	Role of BNP and Echo measurement for pulmonary hypertension recognition in patients with			
2	interstitial lung disease: an algorithm application model			
3				
4	Ruocco Gaetano MD ¹ , Cekorja Behar MD ² , Rottoli Paola MD ² , Refini Rosa Metella MD ² ,			
5	Pellegrini Marco MD ¹ , Di Tommaso Cristina MD ¹ , Del Castillo Gabriele MD ¹ , Franci Beatrice			
6	PhD ¹ , Nuti Ranuccio MD ¹ , Palazzuoli Alberto MD ¹			
7				
8	¹ Department of Internal Medicine, Cardiology Unit, Le Scotte Hospital University of Siena, Italy			
9	² UO Respiratory Diseases, University of Siena Italy			
10				
11	Short Title: BNP and Echo in interstitial lung disease			
12	Key words: pulmonary hypertension, interstitial lung disease, BNP, diagnostic methods.			
13	Conflict of Interests: None declared			
14	Address for correspondence:			
15				
16	Alberto Palazzuoli MD, PhD			
17	Department of Internal Medicine and Metabolic Diseases, Cardiovascular Diseases Unit			
18	Le Scotte Hospital, Viale Bracci 53100 Siena Italy			
19	Fax: +39577233480			
20	Phone: +39577585363-+39577585461			
21	Email: <u>palazzuoli2@unisi.it</u>			

SUMMARY

Background: This study evaluated the role of echocardiography and BNP in patients with interstitial lung disease (ILD), to identify those with PH and RV dysfunction. The aims of this study were: 1-to evaluate the accuracy of an algorithm including BNP, DLCO and echocardiographic measurements to identify PH and RV dysfunction; 2- to evaluate BNP and Echo values concordance in relation to right catheterization measurement.

Methods: We analyzed 113 patients with diagnosis of ILD. Echo examination included: Pulmonary
systolic, diastolic and mean Arterial Pressure (PAPs, PAPd ,PAP mean), End-Diastolic and EndSystolic right ventricle diameters , Inferior Caval Vein diameter , and Tricuspid Annular Plane
Systolic Excursion (TAPSE). Patients revealing increased PAPs at echocardiography underwent to
catheterization.

Results: Patients with PAPs >40 mmHg (37 patients), PAPmean ≥25 mmHg (23 patients) and 34 PAPd \geq 20 mmHg showed BNP increased (157±96 vs 16±14 pg/ml p=0,004; 201±120 vs 28 ±17 35 pg/mL; 124 ± 88 vs 23 ± 18 pg/ml p<0.001) as patients with TAPSE ≤ 16 mm (25 patients) (145 ± 104 36 vs 26±21 pg/ml p<0,001). In catheterized patients (37 patients) BNP was increased in patients with 37 invasive PAPs > 40 mmHg (165 ± 112 vs 29 ± 14 pg/ml p<0,02), as well as in patients with Wedge 38 pressure > 14 mmHg (199 + 153 vs 54 + 39 pg/mL; p=0,01). ROC Curve analysis showed that 39 elevated values of BNP, PAPs, PAP mean are able to assess PH. On the other hand, lower values of 40 DLCO (<40%) and TAPSE (\leq 16 mm) detect PH. Logistic regression analysis of the previous 41 parameters, confirmed their diagnostic role in PH detection. 42

43 Conclusions: In patients with ILD, an algorithm including BNP, DLCO and echocardiography
44 could be useful for non invasive screening of PH

45

46 **Clinical trial registration name and number:** ARTEMIS-HP trial; ID number: NCT00879229.

47

23

INTRODUCTION

50

49

Laboratory biomarkers approach is becoming a new modality screening to differentiate from 51 cardiac and pulmonary dyspnea where other diagnostic tools are unavailable.[1] B-type natriuretic 52 peptide (BNP) and NT pro-BNP are both useful in order to establish diagnosis and prognosis in 53 patients with congestive heart failure.[2,3] 54 Although their clinical application is accepted for patients with cardiovascular diseases, natriuretic 55 peptides are recently used in respiratory disease, as acute pulmonary embolism and pulmonary 56 hypertension (PH) for an early recognition of right ventricular (RV) overload and hypertension.[4,5] 57 In the setting of interstitial lung disease (ILD) it is often difficult to recognize only by clinical 58 examination PH development: shortness of breath and exercise limitation are common symptoms in 59 both ILD and PH. [6] Physical signs as jugular venous distension, tricuspid murmur regurgitation or 60 61 fixed splitting of pulmonary heart sound, usually appear during advanced stages of PH and have poorly sensibility. Conversely even mild increase of pulmonary pressure may significantly impair 62 the outcome in patients with ILD. Prevalence of PH in ILD ranges from 14% in initial workup to 63 60% in end stage patients. [7,8,9] Because of aspecific symptoms, PH diagnosis is often delayed 64 particularly in patients with concomitant pulmonary diseases. Therefore the recognition of 65 pulmonary arterial pressure (PAP) in ILD patients is very important for clinical assessment and 66 diagnosis. Moreover, poor correlation was reported between lung function impairment and PH 67 severity: in two different studies the diffusing capacity of the lung for carbon monoxide (DLCO) 68 <40%, the percent of predicted forced vital capacity (FVC%) and the ratio FVC/DLCO% revealed 69 70 poor performance to detect PH in this setting.[9,10] Restrictive lung dysfunction is not related to the 71 presence of PH, whereas the need for oxygen supplementation and severe exercise limitation with 72 early oxygen desaturation have been linked to increased pressure. [11] Although the current gold standard for PH assessment is invasive right side catheterization, this procedure should be 73 74 performed only in specific setting for the evaluation of lung transplantation and when gas exchange

75 abnormalities are disproportionate to ventilation defect.[12] RHC should be executed after PH identification by non invasive methods. However the optimal diagnostic algorithm to assess PH in 76 ILD remains to be elucidated; currently, the most common methods is trans-thoracic 77 echocardiography showing a good correlation with invasive measurement. Nevertheless, in some 78 patients it cannot be performed because poor acoustic window and awkwardness to detect a reliable 79 PAP measurement [13,14]; therefore the prognostic value of Echocardiography, in patients awaiting 80 lung transplantation has been debated because of a mild correlation with RHC measurement.[15] 81 Accordingly whit these findings, we suppose that the combination of pulmonary function tests, 82 echocardiography and BNP could be useful for a foremost recognition of PH in patients with ILD. 83 Considering these findings we would to evaluate: 1-to define the prevalence of PH by 84 echocardiographic and RHC assessment in patients affected by ILD. 2-to evaluated the accuracy of 85 an algorithm including BNP measurement, DLCO and echocardiographic signs to identify PH and 86 87 RV dysfunction 3- to evaluate BNP and Echo values concordance in relation to right catheterization measurement. 88

- 89
- 90

METHODS

91

Study design: Patients were enrolled consecutively from the UO of Respiratory Diseases, Le Scotte 92 93 Hospital (Siena, Italy) from March 2011 to August 2013. Patients were included with the following characteristics: 1- clinical signs and symptoms (dyspnea, cough, asthenia, poor exercise tolerance); 94 2- respiratory functional tests alterations (DLCO, Forced espiratory volume [FEV1], FVC); 3-95 radiological findings by chest-ray and computed tomography typical for ILD. We evaluated 113 96 consecutive patients affected by interstitial lung disease. Among these patients we excluded 24 97 98 patients for evidence, at echo-doppler, of left ventricular systolic dysfunction or poor acustic window. Patients with echocardiographic PAPs greater than 40 mmHg (37 patients) underwent to 99 RHC invasive measurement to calculate PAPs, PAP mean and pulmonary vascular resistance 100

(PVR). Written consent was provided by each patient. This sub-study was approved by our
hospital's Institutional Review Board and all patients gave their signed informed consent. Patients
were recruited from ARTEMIS-HP trial; it was registered and regularly updated in
ClinicalTrials.gov with ID number: NCT00879229.

105 **Exclusion Criteria**: patients were excluded if they had left ventricular dysfunction, history of 106 pulmonary embolism or obstructive pulmonary diseases, myocardial infarction and renal 107 dysfunction (creatinine > 1.3 mg/dL). We excluded patients with heart failure and preserved 108 systolic function by E/e¹ ratio analysis (>15). Subjects with sepsis, systemic inflammatory diseases, 109 liver or neoplastic diseases were also excluded.

Laboratory analysis: Within 24 hours from enrolment we measured, in all patients, BNP levels. 110 Plasma BNP was measured with Triage BNP Test (Biosite Inc., San Diego, CA, USA); this test is 111 an immunoassay in a single-use plastic cartridge that contains a fluorescently labeled monoclonal 112 antibody against BNP labeled with a fluorescent dye and BNP. There are built-in control features, 113 including control immunoassays, to ensure that the test performs properly and the reagents are 114 functionally active. The test procedure involves the addition of several drops of whole blood or 115 plasma to the sample port on the test device. After addition of the sample, the cells are 116 automatically separated from the plasma via a filter. The sample reacts with fluorescent antibody 117 conjugates within the reaction chamber and flows down the device detection lane by capillary 118 action. The fluorescent antibody conjugates are captured on discrete solid-phase zones resulting in 119 120 binding immunoassays that are specific for BNP or the control antigens.

Echocardiography: Echocardiography (Hewlett-Packard Sonos 5500 imaging system; Hewlett-Packard Inc) was performed using standard transthoracic windows with a 2.5-MHz transducer. RV dimension was estimated at end-diastole from a right ventricle–focused apical 4-chamber view. Diameter > 42 mm at the base and > 35 mm at the mid level indicates RV dilatation. Right atrial (RA) dimension was calculated by the apical 4-chamber view and considered increased for area >

18 cm² Tricuspid regurgitation flow was identified by color-flow Doppler techniques and the 126 maximum jet velocity was measured by continuous-wave Doppler in all patients. RA pressure was 127 estimated as 5 mmHg, 10 mmHg or 15 mmHg on the basis of the size and respiratory change of the 128 inferior vena cava (complete collapse, 5 mmHg; partial collapse, 10 mmHg; no collapse, 129 15 mmHg).[16] RV systolic pressure was estimated based on the modified Bernoulli equation and 130 was considered to be equal to the Pulmonary systolic Arterial Pressure (PAPs) in the absence of 131 right ventricular outflow obstruction. End-Diastolic Pulmonary Arterial Pressure (PAPd) can be 132 estimated from the velocity of the end-diastolic pulmonary regurgitant jet using the modified 133 Bernoulli equation. Once systolic and diastolic pressures are known, mean pressure may be 134 estimated by the standard formula mean PA pressure = 1/3(PAPs) + 2/3(PAPd). 135

To obtain Tricuspid Annular Plane Systolic Excursion (TAPSE) the apical four chamber view was 136 used, and an M-Mode cursor was placed through the lateral tricuspid annulus in real time. Offline, 137 138 the brightness was adjusted to maximize the contrast between the M-Mode signal arising from the tricuspid annulus and the background. TAPSE was measured as the peak excursion of the tricuspid 139 annulus (millimeters) from the end of diastole to the end of systole, with values representing 140 TAPSE being averaged over three to five beats.[17] We did not calculated pulmonary vascular 141 resistance by echo because its estimation is not adequately established to be recommended for 142 routine .Therefore, Current Guidelines do not include noninvasive measurement as a substitute for 143 the invasive evaluation . [18] 144

145 Echocardiography tapes were reviewed by a cardiologist blinded to other results.

Other investigations: Pulmonary function testing was performed in all patients (and predicted values were calculated according to the American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines.[19-22] Lung volumes (constant volume body plethysmograph), spirometric volumes and DLCO were measured.

Invasive measurement: Patients with echocardiographic PAPs greater than 40 mmHg underwent to RHC in the heamodynamic unit. The RHC was performed with a flow-directed balloon-tipped pulmonary artery catheter leveled to the mid-axillary line and advanced to the pulmonary capillary wedge position. We measured the Pulmonary Artery Pressure (systolic, diastolic, and mean), pulmonary artery WEDGE pressures and Pulmonary Vascular Resistance. [23].

Endpoints: 1- to define the prevalence of PH by echocardiographic and RHC assessment in patients affected by ILD; 2- to evaluate the sensitivity and accuracy power of the Functional Lung test Echocardiographic and BNP assessments (FLEB) Score in detecting PH; 3- to evaluate BNP and Echo values concordance in relation to RHC measurement of PH, defined as PAP mean >25 mmHg.

Statistical analysis: Continuous variables are expressed as mean (± standard deviation or 160 Confidence Interval) and compared using Student's T-test for independent groups if normally 161 distributed; normality was assessed by the Kolmogorov-Smirnov test. Analysis of variance was 162 done by Levene's test, and if it was breached the Welch's correction was used. Spearman's rho 163 correlation coefficient was calculated to determine the relationship among BNP levels, 164 echocardiographic parameters, invasive measurements and DLCO. We also made Receiver 165 Operating Characteristic (ROC) curve analysis to assess the ability of BNP levels, 166 echocardiographic parameters (PAPs, PAP mean and TAPSE) and DLCO to detect PH. For all 167 significant parameters on the ROC Curve analysis we performed logistic regression analysis. We 168 also evaluated the relationship among the score found and the invasive measurements using the 169 concordance analysis and Cohen's "k" index. All reported probability values were two-tailed, and a 170 p value <0,05 was considered statistically significant. Statistical analysis was performed using the 171 SPSS 20.0 statistical software package (SPSS Inc., Chicago, IL, USA). 172

173

RESULTS

176	Patients' characteristics: 89 patients (age 62±11; 46 males) met the inclusion criteria. ILD
177	diagnoses included: Idiopathic Pulmonary Fibrosis (IPF; n= 63), Sarcoidosis (n=11), Systemic
178	sclerosis (n=2), Extrinsic Allergic Alveolitis (EAA; n= 2), smoking-related interstitial lung disease
179	or drug-related interstitial fibrosis (n=10) and Langherans' cell hystiocitosis (n=1). In this
180	population there were: 24% of patients with hypertension, 48% of patients with diabetes, 30% of
181	patients with dyslipidemia and 74% with osteoporosis. 37 of these patients showed
182	PAPs \geq 40mmHg, 23 subjects with PAP mean \geq 25 mmHg and 25 subjects with right ventricular
183	dysfunction (TAPSE ≤ 16 mm). All patients with PAPs > 40 mmHg underwent RHC to measure
184	invasive parameters PAPs, PAPmean, WEDGE pressure and PVR. Of 37 catheterized patients, 31
185	were affected by PH, defined as PAPmean > 25 mmHg. BNP mean in all population was of 60
186	pg/mL [CI: 34-87]. (Table 1)

-BNP and RV parameters: In patients with PAPs >40 mmhg, PAPd>20 mmHg and with PAP mean >25 mmHg, BNP levels were significantly increased compared to patients without pulmonary hypertension (157±96 vs 16±14 pg/ml p=0,004), PAPd > 20mmHg (201±120 vs 28±17 pg/mL p=0,001) and PAP mean < 25 mmHg (124±88 vs 23±18 pg/ml p<0,001). BNP was also significantly increased in patients with right ventricular dysfunction (TAPSE \leq 16 mm) (145±104 vs 26±21 pg/ml p<0,001) and dilatation of RV (End-Diastolic diameter \geq 38 mm) (175±119 vs 27±20 pg/ml p<0,001).

-BNP and RHC measurement: In patients with invasive PAPs > 40 mmHg and with invasive PAP mean > 25 mmHg, BNP levels were significantly increased respect patients with invasive PAPs < 40 mmHg (165±112 vs 29±14 pg/ml p<0,02) and with invasive PAPmean < 25 mmHg (194±133 vs 37±29 pg/ml p<0,005). In patients with Wedge pressure \ge 14 mmHg, BNP levels were significantly higher than patients with Wedge pressure < 14 mmHg (199±153 vs 54± 39 pg/mL; p=0,01). (Table 2)

Correlation echocardiographic, pulmonary, 200 among laboratory tests and invasive measurements: In order to evaluate the relationship between echocardiographic parameters, 201 pulmonary function test parameters and BNP levels we used Spearman' rho correlation coefficient. 202 There were positive significant correlations among BNP and RV DTD (r=0.56; p<0.001), BNP and 203 right atrial area (r= 0.45; p=0.005), BNP and PAPs (r=0.55; p<0.001), BNP and PAP mean (r= 204 0,82; p<0,001), BNP and ICV diameter (r=0,37;p<0,001). An inverse significantly correlation was 205 found between BNP and TAPSE (r=-0,57; p<0,001). The correlations between BNP and 206 pulmonary functional test parameters (DLCO, TLC and FVC) were not significant. 207

In the subgroup submitted to right cardiac catheterization (n. 37) we found a significant correlation between PAPs and PAPm calculated with both methods (r=0,50 and r=0,43 p<0,001 and p<0.01 respectively). (Figure 1) Therefore vascular pulmonary resistance significantly correlates with both PAPs and PAP mean measured non invasively (r=0,49 and r=0,44 respectively). TAPSE values were related to all invasive measurement (r=-070 for PAPs r = -0,61 for PAPmeam, r =-055 for wedge r=-044 for VPR).

Diagnostic prediction for PH: The Roc Curve analysis showed that BNP (AUC 0,85; [CI: 0,74-0,96]; p=0,001), PAP mean (AUC 0,90; [CI: 0,81-0,99]; p=0,001) and PAPs (AUC 0,84; [CI: 0,72-0,97]; p=0,001) were all able to detect PH; lower values of DLCO<40% (AUC 0,73; [CI: 0,60-0,86]; p=0,005) and TAPSE ≤ 16 mm(AUC 0,84; [CI: 0,73-0,96]; p=0,001) also determined PH. (Figure 2). A cut-off BNP value ≥ 50 pg/ml, recognized patients with PH, with good sensitivity (75%) and good specificity (80%).

Regression analysis of the above parameters confirmed that echocardiographic measurements
(PAPs, PAP mean and TAPSE), BNP values and DLCO kept the same trend. (Table 3)

FLEB score index: On the basis of our findings, we built an algorithm including PAPs≥40 mmhg,
PAP mean ≥25 mmhg, TAPSE≤16 mm, BNP > 50 pg/ml and DLCO < 40% giving 1 point value for

each parameter to validate these non invasive parameters for PH detection measured by RHC. We
choose an arbitrary cut-off more than 3 to establish the potential diagnostic value of this score for
PH prediction: patients exceeding 3 points demonstrated an excellent concordance with invasive
measurements (concordance: 0,964; Cohen's K index: 0,825). (Table 4) For these reasons we would
purpose a screening test before to submit ILD patients to RHC. (Figure 3)

229

DISCUSSION

- The prevalence of PH in ILD ranges from 14 to 50 %, depending on the status of disease, 230 fibrosis typology, and timing evaluation. [7,8,9] The measurement of pulmonary pressure is 231 determinant to optimize outcome and possibly to begin a specific treatment. 232 Clinical manifestations of PH are often equivocal, and they could be confused with other cardiac and 233 pulmonary diseases symptoms and signs. For these reasons, current European Society of 234 Cardiology (ESC)/European Respiratory Society (ERS) guidelines recommend an echocardiogram 235 execution every year. [24] Furthermore, the guidelines state that an annual echocardiographic 236 screening "may be considered" in asymptomatic patients; a suggestion that is not substantiated by 237 clinical data, but indeed, by expert opinion. [25, 26] Our Findings confirm an high prevalence of PH 238 in patients affected to ILD (28%) and that most of patients screened by echocardiography revealed 239 increased pulmonary pressure. 240

Although this data is in accordance with previous reports, several unanswered questions remain to be elucidated: which populations should be screened, which tools should be used, which diagnostic protocol is really able to better predict PH recognition. Several non invasive protocols have been recently purposed with different results and opinions. Some Authors [27,28] believe that functional respiratory tests are reliable tools to recognize PH, however recent double blind controlled studies demonstrated that a high percentage of patients without significant reduction of lung function died. [29,30]

Other reports assumed that concomitant use of BNP level measurement and echocardiographic 248 assessment together with six minute walking test and oxygen saturation measurement, could lead 249 with good accuracy to an early detection of PH in patients with ILD. Unfortunately findings of 250 these two single center studies are quite different: Modrykamine et al [31] concluded that PAPs 251 measured by their model is poorly able to detect PH and invite readers to perform invasively 252 measurement of right systolic pressure; conversely Song et al [32] suggest that combined laboratory 253 and echo study is a useful and repeatable tool to evaluated PH and establish a prognosis in this 254 setting. A recent consensus document to detect PH in chronic lung diseases suggested to perform 255 right heart catheterization in specific subgroups of patients in case of: 1-evaluation for lung 256 transplantation; 2-clinical worsening disproportionate to ventilation impairment; 3- prognostic 257 assessment is deemed to be essential; 4-advanced PH is suspected by non invasive diagnostic 258 examinations; 5-suspicion of left ventricle dysfunction or pulmonary artery embolism that could 259 260 alter data interpretation. In all other contexts Authors recommended echodoppler and Natriuretic Peptides measurement for initial non invasive diagnosis. [9] Despite recent improvements in 261 diagnostic tools to detect PH in ILD, the methods used routinely in clinical practice have limitations 262 and it may be that a combination of screening tools or parameters will be required to improve the 263 sensitivity and selectivity of current screening programs. As previously revealed, our findings 264 showed that BNP is significantly increased in patients showing PH and RV dysfunction by non 265 invasive and invasive diagnostic tests (echodoppler and right catheterization measurement) [33]: 266 patients showing PH or RV dysfunction evidenced higher BNP values when compared with 267 patients who experienced normal pressure and RV function. A cutoff BNP value more than 50pg/ml 268 revealed a good accuracy to identify pulmonary pressure increase. Recently a good correlation 269 between hemodynamic and echocardiographic measurements has been evidenced in the ILD 270 patients. [34] Invasive data performed after echocardiographic screening confirmed this analysis. 271 The current protocol adding DLCO, natriuretic peptide to echo measurement appears a good 272

diagnostic algorithm for patients with ILD, so to address and screen those for RCH. Moreover our
findings are confirmatory respect to previous reports evaluating the role of BNP in ILD.[33]

On the opposite, poor correlation between BNP and functional respiratory test has been
revealed. Only DLCO evidenced an inverse correlation with BNP. Univariate analysis including
lung test and risk factors, confirmed that BNP and DLCO are the only two factors for PH
prediction. The latter results are not surprising because they reflect the different development of
lung fibrosis compared to PH. The two pathophysiological processes have different development
and course as demonstrated by the lack of relationship between functional lung parameters PAP and
pulmonary resistances.

Although specific studies about interstitial lymphoproliferation and vascular alteration are lacking, 282 there is a general consensus that lung parenchymal remodeling with accompanying hypoxia is the 283 cause of arteriolar vessels decreased capillarity and increase in pulmonary vascular resistance. Lung 284 285 parenchymal disease is a primary trigger for vascular remodeling and progressive obstruction but it occurs independently of lung impairment. [35] Given the high vasoactive properties, it has been 286 postulated that at least 80% of structural lung lost would lead to PH. A vascular theory directly 287 involving arterial district has been evocated: an increased oxidative stress is the potential trigger for 288 fibroproliferation and vasoconstrictive processes. [36,37] Increased extracellular matrix is 289 associated with reduced synthesis of guanylyl- cyclase and the consequent reduction in nitrix oxide 290 signal transduction. Natriuretic peptide may be partly involved in this process; parenchymal 291 tissue natriuretic peptide receptors alteration involves (NPR) with disruption 292 and downregulation.[38] 293

All these potential factors could explain the good correlation among BNP and pulmonary pressure measurement, but the lack of correlation with respiratory functional parameters reflecting parenchymal status.

The importance of BNP measurement in ILD has been recently demonstrated not only for diagnostic screening but also for risk evaluation: Song et al [31] showed that a combination of BNP

level and non invasive PAPs measurement provide a better prediction of mortality respect to the 299 echo parameter alone. Similarly, Corte et al [39] demonstrated that elevated BNP concentration and 300 pulmonary vascular resistance levels were independently associated to increased mortality. 301 Nevertheless, previous report did not support the contention that pro BNP could be an reliable 302 marker of PH in patients with parenchymal lung disease. [40] Although our study did not provide 303 prognostic data, it is a confirmation of the two more recent studies and it evidenced the accuracy of 304 echodoppler examination for PAP estimation compared with the invasive measurement. [31,34] 305 Therefore we analyzed the role of RV dysfunction with respect to BNP level showing a clear 306 correlation between RV overload and systolic performance and BNP level. We considered it 307 important to establish whether dichotomous BNP values provides diagnostic information on PH: 308 patients with BNP levels above the threshold of 50 pg/ml revealed good specificity for PH and RV 309 dysfunction, confirming that BNP as a dichotomous variable could potentially provide additional 310 311 diagnostic information over echocardiography. Considering that a universal screening method routinely applied in clinical practice does not exist, on the basis of our results we can purpose an 312 algorithm considering BNP assay before echocardiography for a better screening of PH in patients 313 with ILD. Our findings extend the literature by offering a combined evaluation of BNP and 314 echocardiographic measurements of RV dysfunction as predictors of PH. Finally the same 315 dichotomous approach should be used for Echo measurement and DLCO into an algorithm Score 316 including all parameters to better stratify patients with PH needing invasive RHC study: based upon 317 our data features, a score more than 3 points should be a good indicator for PH. If confirmed in a 318 larger population these parameters and cutoff values could be used to identify patients to be 319 submitted to RHC invasive measurements. 320

322 323

LIMITATIONS

Our study was limited by its retrospective design and patient selection evaluated in a single 324 325 tertiary center, therefore this study cannot exactly reflect the all ILD patients. A wide range of disease severity was evaluated, BNP and echocardiography were performed routinely on new 326 referrals. The invasive study was conducted only in patients revealing PH at Echo examination so 327 the exact BNP accuracy in the population unsubmitted to cardiac catheterization cannot be 328 confirmed. We suggest that the resultant range of disease severity and suspicion of PH involvement 329 both reflect real-life clinical practice, and is a representative population in which to explore proof of 330 concept outcome analyses. We did not calculated all the noninvasive echo parameters 331 recommended for PH diagnosis as pulmonary artery dilatation, acceleration time of RV outflow 332 tract. However, our aim would be provide a standard simple method able to identify PH. Our data 333 cannot definitively excluded patients with PH secondary to heart failure with isolated diastolic 334 dysfunction, but an analysis of pulsed Doppler transmitral flow and tissue doppler flow has been 335 performed and we excluded subjects with more advanced dysfunction excluding those with E/e^{1} 336 >15. Exact clinical utility with reference to unselected ILD cases cannot be extrapolated from our 337 data. The algorithm construction purposed by combining BNP and echocardiographic thresholds, 338 was hampered by low subgroup numbers. Besides, even if our score can be considered an accurate 339 index to detect PH, it cannot be applied for outcome assessment. Prospective larger studies with 340 follow-up observation are required to further delineate the relative importance of these prognostic 341 markers alone and in combination, and before these markers can be widely used in clinical practice. 342 Despite these limitations, our study is the first attempt to evaluate the diagnostic role of 343 344 echocardiography and BNP levels in patients with ILD and associated PH.

345

	ACCEPTED MANUSCRIPT		
348	CONCLUSIONS		
349	Our data suggest that an algorithm including BNP DLCO and echocardiography findings is an		
350	useful and repeatable tools for PH detection in patients with ILD. This protocol could help in early		
351	identification of PH and it should be applied in clinical practice as a preliminary screening for		
352	invasive hemodynamic study selection. The current results need to be confirmed in a larger sample		
353	size and validated by follow up data.		
354	Highlights:		
355	1- the prevalence of pulmonary hypertension in ILD is high and echo assessment is a		
356	reliable tool to select this patients for RHC		
357	2- Invasive measurement confirmed that subjects with increased PAP evidenced higher		
358	BNP levels		
359	3- an algorithm including DLCO and BNP measurement to echocardiographic analysis		
360	provide a more detailed screening and accuracy		
361	ACKNOWLEDGEMENTS		
362	GMR has given substantive intellectual contributions to a published study. He has given substantial		
363	contributions to conception and design. He has given final approval of the version to be published.		
364	He is the guarantor of the paper, taking responsibility for the integrity of the work		
365	BC has given substantial contributions to acquisition of data and interpretation of data.		
366	PR has given substantial contributions to acquisition of data and interpretation of data.		
367	RMR has given substantial contributions to acquisition of data and interpretation of data.		
368	MP has given contributions to acquisition of data.		
369	CDT has performed echocardiography examination.		
370	GDC has revised English language of paper.		

371 BF has analyzed the blood samples to measure BNP.

RN has been involved in drafting the manuscript or revising it critically for important intellectualcontent.

AP has been involved in drafting the manuscript or revising it critically for important intellectual content. He has given substantial contributions to conception and design. He has given final approval of the version to be published.

- 377
- 378
- 379
- 380

381 REFERENCES

- Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T,
 Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW,
 Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of Btype
 natriuretic peptide in the emergency diagnosis of heart failure. Breathing Not Properly
 Multinational Study Investigators. *N Engl J Med 2002*; 347:161-7
- 387
- Thygesen K, Mair J, Mueller C, Huber K, Weber M, Plebani M, Hasin Y, Biasucci LM.
 Recommendations for the use of natriuretic peptides in acute cardiac care: a position
 statement from the Study Group on Biomarkers in Cardiology of the ESC Working
 Group on Acute Cardiac Care. *Eur Heart J.2012*; 33: 2001-6
- 392 3. De Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular
 disease. *Lancet 2003*; 362: 316-322
- 4. Pruszczyk P. N-terminal pro-brain natriuretic peptide as an indicator of right ventricular
 dysfunction *J Card Fail 2005*; 11: 65-69

- 5. Krüger S, Graf J, Merx MW, Koch KC, Kunz D, Hanrath P, Janssens U.. Brain natriuretic
 peptide predicts right heart failure in patients with acute pulmonary embolism. *Am Heart J 2004*; 147: 60–65
- 399 6. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. *Eur Resp J 2008*;
 400 31:1357-67
- Kimura M, Taniguchi H, Kondoh Y, Kimura T, Kataoka K, Nishiyama O, Aso H, Sakamoto
 K, Hasegawa Y. Pulmonary hypertension as a prognostic indicator at the initial
 evaluation in idiopathic pulmonary fibrosis. *Respiration 2013*;85:456-463
- 404 8. Andersen CU, Mellemkjær S, Hilberg O, Nielsen-Kudsk JE, Simonsen U, Bendstrup E.
 405 Pulmonary hypertension in interstitial lung disease: prevalence, prognosis and 6 min
 406 walk test. *Respir Med.* 2012;106:875-82.
- Seeger W, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galiè N,
 Ghio S, Gibbs S, Martinez FJ, Semigran MJ, Simonneau G, Wells AU, Vachiéry JL.
- 409 Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol.* 2013;62: 109-16
- 10. Nathan SD, Shlobin OA, Ahmad S, Urbanek S, Barnett SD. Pulmonary hypertension and
 pulmonary function testing in idiopathic pulmonary fibrosis. *Chest 2007*; 131:657-663
- 412 11. Zisman DA, Ross DJ, Belperio JA, Saggar R, Lynch JP, Ardehali A, Karlamangla AS.
 413 Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis. *Respire Med*414 2007; 101:2153-59
- 415 12. Nathan SD, Cottin V. Pulmonary hypertension in patients with idiopathic pulmonary
 416 fibrosis. *Eur Respir Monogr* 2012;57:148-160
- 417 13. Bossone E, Bodini BD, Mazza A, Allegra L. Pulmonary arterial hypertension: the key role
 418 of echocardiography. *Chest 2005*; 127:1836-43
- 419 14. Yock PG, Popp RL. Non-invasive estimation of right ventricular systolic pressure by
 420 Doppler ultrasound in patients with tricuspid regurgitation. *Circulation 1984*; 70:657 421 662

422	15. Homma A, Anzueto A, Peters JI, Susanto I, Sako E, Zabalgoitia M, Bryan CL, Levine SM.
423	Pulmonary artery systolic pressure estimated by echocardiography vs cardiac
424	catheterization in patients awaitinglung transplantation. J Heart Lung Transplant 2001;
425	20:833-39

- 426 16. Arcasoy SM, Christie JD, Ferrari VA, Sutton MS, Zisman DA, Blumenthal NP, Pochettino
 427 A, Kotloff RM. Echocardiographic assessment of pulmonary hypertension in patients
 428 with advanced lung disease. *Am J Respir Crit Care Med.* 2003;167:735-40
- 429 17. Forfia PR, Fisher MR, Mathai SC, Housten-Harris T, Hemnes AR, Borlaug BA, Chamera E,
 430 Corretti MC, Champion HC, Abraham TP, Girgis RE, Hassoun PM. Tricuspid annular
 431 displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med.*432 2006;174:1034-41
- 18. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon
 SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right
 heart in adults: a report from the American Society of Echocardiography endorsed by the
 European Association of Echocardiography, a registered branch of the European Society
 of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr.*2010;23(7):685-713
- 439 19. Macintyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, Burgos F,
 440 Casaburi R, Coates A, Enright P, Gustafsson P, Hankinson J, Jensen R, McKay R, Miller
 441 MR, Navajas D, Pedersen OF, Pellegrino R, Wanger J. Standardisation of the single442 breath determination of carbon monoxide uptake in the lung. *Eur Respir J 2005;* 26:
 443 720–735.
- 20. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P,
 van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R,
 Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force.
 Standardization of spirometry. *Eur Respir J 2005*; 26: 319–338

	ACCLI ILD MANUSCHII I
448	21. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, Casaburi R, Crapo R,
449	Enright P, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson D,
450	Macintyre N, McKay R, Miller MR, Navajas D, Pellegrino R, Viegi G Standardisation
451	of the measurement of lung volumes. Eur Respir J 2005; 26: 511–522.
452	22. Gibson GJ. Standardised lung function testing. Eur Respir J 1993; 6: 155–157.
453	23. Swan HJ, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. Catheterization of the
454	heart in man with use of a flow-directed balloon-tipped catheter. N Engl J Med.
455	1970;283:447-51
456	24. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris
457	P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock
458	A, Rubin L, Zellweger M, Simonneau G; ESC Committee for Practice Guidelines
459	(CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task
460	Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European
461	Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by
462	the International Society of Heart and Lung Transplantation (ISHLT). Eur Heart J.
463	2009;30:2493-537.
464	25. Humbert M, Gerry Coghlan J, Khanna D. Early detection and management of pulmonary
465	arterial hypertension. Eur Respir Rev. 2012;21:306-12.
466	26. Grünig E, Barner A, Bell M, Claussen M, Dandel M, Dumitrescu D, Gorenflo M, Holt S,
467	Kovacs G, Ley S, Meyer JF, Pabst S, Riemekasten G, Saur J, Schwaiblmair M, Seck C,

- 468 Sinn L, Sorichter S, Winkler J, Leuchte HH. Non-invasive diagnosis of pulmonary
 469 hypertension: ESC/ERS Guidelines with Updated Commentary of the Cologne
 470 Consensus Conference 2011. *Int J Cardiol. 2011*;154:S3-12
- 471 27. Gläser S, Noga O, Koch B, Opitz CF, Schmidt B, Temmesfeld B, Dörr M, Ewert R, Schäper
 472 C. Impact of pulmonary hypertension on gas exchange and exercise capacity in patients
 473 with pulmonary fibrosis. *Respir Med. 2009*;103:317-24

474	28. Papakosta D, Pitsiou G, Daniil Z, Dimadi M, Stagaki E, Rapti A, Antoniou K, Tzouvelekis
475	A, Kontakiotis T, Tryfon S, Polychronopoulos V, Bouros D. Prevalence of pulmonary
476	hypertension in patients with idiopathic pulmonary fibrosis: correlation with
477	physiological parameters. Lung. 2011;189:391-9.

- 478 29. Flaherty KR, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, Travis WD,
 479 Flint A, Toews GB, Lynch JP 3rd, Martinez FJ. Prognostic implications of physiologic
 480 and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care*481 *Med. 2003*;168:543-8
- 30. Martinez FJ, Safrin S, Weycker D, Starko KM, Bradford WZ, King TE Jr, Flaherty KR,
 Schwartz DA, Noble PW, Raghu G, Brown KK; IPF Study Group. The clinical course of
 patients with idiopathic pulmonary fibrosis. Ann Intern Med. 2005;142:963-7.
- 31. Modrykamien AM, Gudavalli R, McCarthy K, Parambil J. Echocardiography, 6-minute
 walk distance, and distance-saturation product as predictors of pulmonary arterial
 hypertension in idiopathic pulmonary fibrosis. *Respir Care*. 2010;55:584-8.
- 488 32. Song JW, Song JK, Kim DS. Echocardiography and brain natriuretic peptide as prognostic
 489 indicators in idiopathic pulmonary fibrosis. *Respir Med. 2009*;103:180-6.
- 33. Palazzuoli A, Ruocco G, Cekorja B, Pellegrini M, Del Castillo G, Nuti R. Combined BNP
 and Echocardiographic assessment in interstitial lung disease for pulmonary
 hypertension detection. *Int J Cardiol.* 2014 Oct 22;178C:34-36. doi:
 10.1016/j.ijcard.2014.10.120.
- 494 34. Rivera-Lebron BN, Forfia PR, Kreider M, Lee JC, Holmes JH, Kawut SM.
 495 Echocardiographic and hemodynamic predictors of mortality in idiopathic pulmonary
 496 fibrosis. *Chest. 2013*;144:564-70.
- 497 35. Selman M, King TE, Pardo A; American Thoracic Society; European Respiratory Society;
 498 American College of Chest Physicians. Idiopathic pulmonary fibrosis: prevailing and

	ACCEPTED MANUSCRIPT
499	evolving hypotheses about its pathogenesis and implications for therapy. Ann Intern
500	Med. 2001;134:136-51.
501	36. Cantin AM, North SL, Fells GA, Hubbard RC, Crystal RG. Oxidant-mediated epithelial cell
502	injury in idiopathic pulmonary fibrosis. J Clin Invest 1987;79:1665–1673
503	37. Kinnula V, Fattman C, Tan R, Oury T. Oxidative stress in pulmonary fibrosis: a possible
504	role for redox modulatory therapy. Am J Respir Crit Care Med 2005;172:417-422.
505	38. Behr J, Ryu JH. Pulmonary hypertension in interstitial lung disease. Eur Respir J.
506	2008;31:1357-67
507	39. Corte TJ, Wort SJ, Gatzoulis MA, Engel R, Giannakoulas G, Macdonald PM, Wells AU.
508	Elevated brain natriuretic peptide predicts mortality in interstitial lung disease. Eur
509	Respir J. 2010;36:819-25
510	40. Goetze JP, Videbaek R, Boesgaard S, Aldershvile J, Rehfeld JF, Carlsen J. Pro-brain
511	natriuretic peptide as marker of cardiovascular or pulmonary causes of dyspnea in
512	patients with terminal parenchymal lung disease. J Heart Lung Transplant. 2004;23:80-
513	87
514	
515	
516	
517	
518	
519	
520	

521

- 522
- 523
- 524
- 525

526 TABLES AND FIGURES LEGEND

Table 1. Baseline characteristics of all patients with ILD included in our study. Abbreviations: BNP: B-type
Natriuretic Peptide; DLCO: Diffusing Lung capacity for Carbon Monoxide; FE: Ejection Fraction; FVC:
Forced Vital Capacity; ILD: Interstitial Lung Disease; PAPd: End-Diastolic Pulmonary Arterial Pressure;
PAPs: Pulmonary systolic Arterial Pressure; PAPm: Pulmonary Arterial Pressure mean; PVR: Pulmonary
Vascular Resistance; TAPSE: Tricuspid Annular Plane Systolic Excursion; TLC: Total Lung Capacity.

Table 2. T-test evaluating BNP value changes relation to echocardiographic and invasive parameters.
Abbreviations: BNP: B-type Natriuretic Peptide; PAPd: End-Diastolic Pulmonary Arterial Pressure; PAPs:
Pulmonary systolic Arterial Pressure; PAPm: Pulmonary Arterial Pressure mean; TAPSE: Tricuspid
Annular Plane Systolic Excursion.

Table 3. Logistic regression analysis evaluating ability of echocardiographic parameters (PAPs, PAPm and
TAPSE), DLCO and BNP to detect PH. Abbreviations: BNP: B-type Natriuretic Peptide; CI: Confidence
Interval; DLCO: Diffusing Lung capacity for Carbon Monoxide; OR: Odds Ratio; PAPs: Pulmonary
systolic Arterial Pressure; PAPm: Pulmonary Arterial Pressure mean; PH: Pulmonary Hypertension;
TAPSE: Tricuspid Annular Plane Systolic Excursion.

Table 4. Analysis of concordance between FLEB score and invasive diagnosis of PH. Abbreviations: FLEB:
Functional Lung test, Echocardiographic and BNP assessments; PH: Pulmonary Hypertension.

Figure 1. Spearman's rho correlation between PAPs and PAPm assessed by invasive and echocardiographic
methods. Abbreviations: PAPs: Pulmonary systolic Arterial Pressure; PAPm: Pulmonary Arterial Pressure
mean.

Figure 2. Receiver Operating Characteristic (ROC) curve analysis in predicting patients with PH.
Abbreviations: AUC: Area Under the Curve; BNP: B-type Natriuretic Peptide; CI: Confidence Interval;
DLCO: Diffusing Lung capacity for Carbon Monoxide; PAPs: Pulmonary systolic Arterial Pressure; PAPm:
Pulmonary Arterial Pressure mean; PH: Pulmonary Hypertension; TAPSE: Tricuspid Annular Plane
Systolic Excursion.

Figure 3. Alghoritm model for HP diagnosis in ILD. Abbreviations: BNP: B-type Natriuretic Peptide;
DLCO: Diffusing Lung capacity for Carbon Monoxide; ILD: Interstitial Lung Disease; PAPs: Pulmonary
systolic Arterial Pressure; PAPm: Pulmonary Arterial Pressure mean; PH: Pulmonary Hypertension; RV:
Right Ventricle; TAPSE: Tricuspid Annular Plane Systolic Excursion.

All patients (89)				
Echocardiographic	BNP mean	Echocardiographic	BNP mean	p-values
Parameters	(pg/mL)	Parameters	(pg/mL)	
PAPs < 40mmHg	16 ± 14	$PAPs \ge 40mmHg$	157 ± 96	0,004
PAPd < 20mmHg	28 ± 17	$PAPd \ge 20mmHg$	201 ± 120	0,001
PAP mean < 25 mmHg	23 ± 18	PAP mean $\geq 25 \text{ mmHg}$	124 ± 88	0,001
End Diastolic diameter < 38 mm	27 ± 20	End Diastolic diameter \geq 38 mm	175 ± 119	0,001
TAPSE > 16 mm	26 ± 21	$TAPSE \le 16 \text{ mm}$	145 ± 104	0,001
Catheterized patients (37)				
Invasive BNP mean Invasive BNP mean p-val			p-values	
Measurement	(pg/mL)	Measurement	(pg/mL)	
PAPs < 40 mmHg	29 ± 14	$PAP \ge 40 \text{ mmHg}$	165 ± 112	0,02
PAP mean < 25 mmHg	37 ± 29	PAP mean ≥ 25 mmHg	194 ± 133	0,005
WEDGE pressure < 14 mmHg	54 ± 39	WEDGE pressure $\geq 14 \text{ mmHg}$	199 ± 153	0.01

REPAR

Table 3.

	OR [CI]	p-value
BNP > 50 pg/mL	12.78 [3.83-22.60]	0.001
$PAPs \ge 40 mmHg$	20.08 [4.29-46.61]	0.001
PAP mean $\geq 25 \text{ mmHg}$	9.33 [1.13-26.69]	0.03
$TAPSE \le 16 \text{ mm}$	7.80 [1.68-16.06]	0.009
DLCO < 40%	6.25 [1.32-17.43]	0.02
		6

Table 1.

Number of the patients	89
Age (year):	62 ± 11
Weight (Kg):	75 ± 15
Height (cm):	164 ± 9
Gender (n):	
Male	46
Female	43
Risk factors and comorbidity (%):	
Hypertension	25,8%
Diabetes	48,3%
Dyslipidemia	30,3%
Osteoporosis	74.8%
Interstitial Lung Disease (n):	
Pulmonary Idiopathic Fibrosis	63
Sarcoidosis	11
Extrinsic Allergic Alveolitis	2
Systemic Sclerosis	2
Langherans cell Hystiocytosis	1
Other	1
Lung diseases' treatment (%)	10
Corticosteroids therapy	93
Immunosuppressive therapy	18
Echocardiographic parameters	10
FE (%)	56 ± 3
End-diastolic ventricular diameter (mm)	36 ± 7
Right atrium area (cm ²)	20 ± 3
Caliber Inferior Cave vein (mm)	17 ± 5
PAPs (mmHg)	36 ± 10
$PAPs \ge 40 mmHg (n)$	37
PAPd(mmHg)	17 ± 7
PAPmean (mmHg)	24 ± 8
PAP mean $\geq 25 \text{ mmHg}(n)$	23
TAPSE (mm)	21 ± 4
TAPSE $\leq 16 \text{ mm}(n)$	25
Invasive Measurements (37 patients)	45 . 14
PAPS (MMHg)	45 ± 14
WEDCE program (mmHa)	25 ± 10 12 + 5
WEDGE pressure (mmng)	12 ± 3 2 21 + 2 20
Pulmonary Hypertension defined as invasive $P\Delta Pmean > 25mmHg (n)$	$3,21 \pm 2,20$
$\frac{1}{2} = \frac{1}{2} = \frac{1}$	60 [34-87]
Pulmonary Functional Test parameters (%)	0,0,1,0,1
DLCO	55 + 25
TLC	91 ± 28
FVC	79 ± 27

Table 4.

	Patients with PH	Patients without PH
Patients with FLEB score ≥ 3	29	0
Patients with FLEB score < 3	2	6

Concordance Index: 0,964

Cohen's "k" index : 0,825

Figure 1.



Figure 2.



