

Elevated Brain Natriuretic Peptide predicts mortality in Interstitial Lung Disease

Authors' Names

Tamera J Corte MBBS, BSc(Med), FRACP*†

Stephen J Wort MA MBBS MRCP PhD*‡

Michael A Gatzoulis MD, PhD, FACC, FESC *‡

Reto Engel MD*

Georgios Giannakoulas MD, PhD, FESC*

Peter M Macdonald MBBS PhD MD†

Athol U Wells MBChb, FRACP, MD, FRCP, FRCR*‡

Institutions

*Royal Brompton Hospital and National Heart and Lung Institute, London, UK.

†University of New South Wales, Sydney, Australia. ‡Imperial College, London, United Kingdom.

Address for Correspondence

Athol U. Wells. Interstitial Lung Disease Unit, Royal Brompton Hospital and NHLI, Imperial College, Emmanuel Kaye Building, 1B Manresa Road, London SW3 6LP, UK.

Telephone number: +44 207 351 8327. Fax number: +44 207 351 8336. Email: athol.wells@rbht.nhs.uk

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STRUCTURED ABSTRACT

Elevated pulmonary vascular resistance portends a poor prognosis across interstitial lung disease (ILD), irrespective of the histospecific diagnosis. Currently no non-invasive surrogate prognostic marker exists. We explore the prognostic value of brain natriuretic peptide (BNP) and echocardiography across ILD.

Methods: ILD patients with BNP concentrations performed during 2005-7 were reviewed (n=90). Echocardiography tapes were reviewed by a cardiologist blinded to other results. Outcome was evaluated for survival against BNP and echocardiograph parameters. *A priori* threshold values and composite markers were evaluated against survival.

Results: During follow-up (20±9months) there were 28 deaths (31%). BNP correlated with right-heart echocardiographic indices, including RVSP ($R^2=0.18$, $p=0.0002$) but not with parameters of left-heart function. Non-survivors had higher BNP and RVSP levels than survivors. $BNP \geq 20 \text{ pmol/L}$ (HR 2.93; CI 1.28, 6.73; $p=0.01$) and moderate-severe PH (HR 2.53, CI 1.15, 5.57, $p=0.02$) were associated with increased mortality, independent of age, gender and pulmonary function. Patients with $BNP \geq 20 \text{ pmol/L}$ had a 14-fold increased mortality over those with $BNP < 4 \text{ pmol/L}$.

Conclusion: Increased BNP levels and/or echocardiographic markers of right ventricular dysfunction were associated with increased mortality across ILD. The linkage between

vascular parameters and mortality supports the concept that pulmonary vascular disease contributes to the final common pathway seen across ILD.

KEY WORDS

Brain Natriuretic Peptide; Echocardiogram; Interstitial Lung disease; Prognosis;
Pulmonary Hypertension; Right Ventricular Function.

ABBREVIATIONS LIST

PH: Pulmonary Hypertension

ILD: Interstitial Lung Disease

IPF: Idiopathic Pulmonary Fibrosis

BNP: Brain Natriuretic Peptide

RHC: Right Heart Catheter

PAH: pulmonary arterial hypertension

RV: right ventricular

EDTA: ethylenediaminetetraacetic acid

RAP: right atrial pressure

RVSP: Right ventricular systolic pressure

PAT: pulmonary acceleration time

CPI: composite physiologic index

6MWT: Six-minute walk test

HR: Hazard Ratio

CI: Confidence Intervals

INTRODUCTION

Across interstitial lung disease (ILD), survival is universally poor when pulmonary hypertension (PH) is present [1-3]. We have recently demonstrated that elevated pulmonary vascular resistance measured at right heart catheter (RHC) strongly predicts rapid mortality across ILD patients [4]. However, RHC is moderately invasive, and not always practicable. Surrogate non-invasive markers of pulmonary vascular compromise are therefore highly desirable in this setting. We explore the prognostic significance of brain natriuretic peptide (BNP) and echocardiographic parameters of right ventricular dysfunction in ILD patients, with reference to both overall and short-term mortality.

PH is not uncommon in patients with ILD, with reported prevalence amongst patients with idiopathic pulmonary fibrosis (IPF) ranging from 32 to 85% [3, 5-10]. PH is more common in patients with severe fibrosis [7, 11], but may develop at any stage of the disease process [2, 12, 13]. In the subgroup of patients with mild underlying fibrosis and poorer prognoses, the poor outcome may be attributed in part to microvascular compromise and subsequent development of PH. Having recently shown that pulmonary vascular resistance is a strong predictor of mortality in advanced ILD [4], we now explore prognostic markers of vascular impairment across a wider range of disease severity.

BNP, a peptide secreted in response to ventricular stretch by the cardiomyocytes of both the right and left ventricles [14], is an important marker of right ventricular dysfunction [15, 16]. BNP concentrations correlate well with RHC parameters in patients with

idiopathic pulmonary arterial hypertension (PAH) and PH associated with chronic lung disease, in which elevated BNP concentrations are associated with a poorer functional capacity and prognosis [17, 18]. In IPF, a study of 39 patients showed that BNP performed well in the identification of PH [19]. A recent IPF study has identified BNP as a marker for poor prognosis (particularly when combined with echocardiographic data) [20].

We hypothesise that markers of right ventricular dysfunction may be identifiable prior to development of overt PH. Furthermore, such markers may be useful in predicting survival. Thus, the goal of this study was to explore the prognostic value of vascular markers (including BNP and echocardiography) across ILD patients.

METHODS

Patient Selection

Plasma BNP was introduced at our institution in 2005, and thereafter performed routinely in all new ILD referrals and in ILD patients being investigated for PH. ILD patients with plasma BNP concentrations performed from 2005 to December 2007 (n=90) were identified from the hospital database. Hospital records were reviewed and demographic and clinical data were recorded.

Patients were followed to death, transplantation or to last clinic follow-up or 1st February 2009. Five patients were lost to follow-up, two underwent pulmonary transplantation and 28 (31%) of patients died during the follow-up period (20 ± 9 months).

***A priori* Thresholds**

As described in our study of severe interstitial disease [4], we studied vascular markers as continuous variables, and according to *a priori* thresholds:

- BNP ≥ 4 pmol/L and ≥ 20 pmol/L [20]
- Echocardiographic evidence of PH (RVSP ≥ 40 mmHg or right heart dilatation) and moderate-severe PH (RVSP ≥ 50 mmHg or right heart dilatation) [12]

Investigations

Brain Natriuretic Peptide

Venous blood samples were collected for brain natriuretic peptide (BNP) testing into tubes containing potassium ethylenediaminetetraacetic acid (EDTA). The BNP samples were analysed within four hours, or in some cases, whole blood was centrifuged and the plasma stored at -80°C until analysis [21, 22]. The BNP concentrations (pmol/L) were quantified using the Beckman Access 2, Triage BNP assay (Biosite Diagnostics Inc., San Diego, California). This BNP assay is a sandwich immunoassay consisting of a disposable device to which 250 μl of EDTA-anticoagulated whole blood or plasma is added. Cells are separated from plasma by a filter, and the plasma (containing BNP) is incubated for around two minutes in a reaction chamber containing fluorescent-tagged BNP antibodies. Finally, the plasma is directed by capillary action to an area of

immobilised antibody that binds the BNP-fluorescent antibody complex, and the remaining fluid is washed away. After 15 minutes, the device is placed in the Triage Meter, the intensity of the fluorescent signal is measured and the BNP concentration calculated by the Triage Meter from an internal calibration curve.

Normal values are <4pmol/L. Age and gender adjusted values are not available for this assay, and so, adjustments for age and gender were performed for each analysis. Thus, we examined BNP ≥ 4 pmol and ≥ 20 pmol/L as *a priori* thresholds (corresponding to one and five times the upper limit of normal) [20]. When multiple BNP levels were available, the BNP concentration closest to echocardiography was employed for analysis.

Echocardiography

All patients underwent two-dimensional echocardiography using Doppler and colour flow imaging (median time from BNP 1month, range 0-10months). Right atrial pressure (RAP) was estimated on the basis of inferior vena cava size and movement on respiration [23]. Right ventricular systolic pressure (RVSP) was calculated as the sum of tricuspid peak gradient (based on the modified Bernoulli equation) [24] and RAP. Pulmonary artery flow velocity was recorded, and pulmonary acceleration time (PAT) was measured as the interval between its onset and peak velocity point. Right atrial dilation, RV dilation and RV dysfunction were scored as present or absent.

All echocardiographic studies were reviewed by an independent and senior operator, who was blinded to patients' clinical characteristics and the results of other investigations.

Specific predetermined right and left ventricular indices were recorded. PH was considered present when the RVSP ≥ 40 mmHg or there was right heart dilatation. Moderate-severe PH was defined as RVSP ≥ 50 mmHg or right heart dilatation.

Other Investigations

Pulmonary function testing was performed in all patients (median time from BNP 1 month, range 0-30 months), and predicted values were calculated according to ATS/ERS guidelines (Jaeger Masterscreen; Cardinal Health UK 240 Ltd) [25-28]. Lung volumes (constant-volume body plethysmograph), spirometric volumes and single-breath diffusion capacity of the lung for carbon monoxide (DLco) were measured. The composite physiologic index (CPI) was calculated according to the following formula [29]:

$$\text{CPI} = 91 - 0.65 * (\text{DLco}\%) - 0.53 * (\text{FVC}\%) + 0.34 * (\text{FEV}_1\%)$$

End capillary (ear-lobe) blood gas analysis was performed on room air (n=74).

Six-minute walk testing (6MWT) was performed in 55 patients, (median time from BNP 1.4 months (range 0-31 months)) was performed by senior personnel in accordance with ATS/ERS guidelines [30] with standardised verbal prompts. 6MWT was performed on room air or on oxygen (n=10) if patients were receiving continuous supplemental oxygen.

Statistical Analysis

All analyses were performed using STATA statistical software (version 10.0; Stata Corp., College Station, TX). Data are expressed as mean and standard deviation or as median

and range as appropriate. Group comparisons were made using Students' t-test or Wilcoxon's rank-sum test.

Outcome was evaluated for overall mortality (Cox regression, with satisfaction of the assumptions of proportional hazards analysis) and death within the first year (logistic regression). Covariates included BNP and the RVSP as continuous variables, as well as the *a priori* thresholds described above. Multivariate survival analysis was performed, adjusting for age, gender, CPI, duration of dyspnoea [31] and creatinine levels. Analysis was repeated with the exclusion of each diagnostic subgroup [4]. Kaplan-Meier curves were generated for categorical variables, and the log-rank test was used to identify significant differences between categories

Univariate relationships were examined using Pearson's or Spearman's rank correlation test as appropriate. BNP thresholds were evaluated against the presence of PH and moderate-severe PH with the Chi² test. P-values less than 0.05 were regarded as statistically significant throughout.

RESULTS

Patient Characteristics

Ninety patients (mean age 59 ± 12 years; 47 (52%) male) fulfilled entry criteria. ILD diagnoses included: IPF (n=16), idiopathic non-specific interstitial pneumonia (CT diagnosis; n=21), connective tissue disease related fibrosis (n=18), sarcoidosis (n=11),

chronic hypersensitivity pneumonia (n=9), smoking related interstitial lung disease (n=8), drug-related interstitial fibrosis (n=2), and other ILD (n=5). Forty-three patients were life-long non-smokers, 39 were ex-smokers and five were current smokers (3 unknown; mean pack years 25.5 ± 16.6). Thirteen patients (14%) had a history of cardiac disease. At the time of assessment closest to the BNP assay, the median duration of dyspnoea was 24 (0-192) months and WHO functional class was two (1-4).

Seventy-nine (88%) had BNP ≥ 4 pmol/L and 38 (39%) had BNP ≥ 20 pmol/L. On echocardiography, PH was evident in 53 (59%), and moderate-severe PH in 39 (43%) of patients. Seven patients had evidence of left ventricular failure (mean fractional shortening $36.7 \pm 9\%$). On 6MWT, 39 patients (42%) had oxygen desaturation below 88%. Thirteen (14%) patients had elevated creatinine concentrations (>120 μ mol/L). Other baseline parameters are summarised in *Table 1*.

Brain Natriuretic Peptide Correlations with Echocardiography

BNP concentration correlated with echocardiographic indices of right heart function, including RVSP ($R^2=0.18$, $p=0.0002$) and PAT ($R^2=0.11$, $p=0.002$), but the relationships were weak (all R^2 values <0.20). BNP also correlated with DLco%, KCO%, SpO₂ and PaO₂ and the 6MWT distance. BNP did not correlate with echocardiographic parameters of left heart function (*Table 2*). BNP ≥ 20 pmol/L was associated with moderate-severe PH on echocardiography ($p<0.0001$).

Characteristics of Survivors and Non-survivors

During the mean follow-up period of 20 ± 9 months, there were 28 (31%) deaths. Non-survivors had higher BNP and RVSP levels and lower FVC % predicted levels than survivors (*Table 1*). Non-survivors were more likely to have BNP concentration ≥ 20 pmol/L (15/28 versus 15/62; $p=0.006$) and to have moderate-severe PH (17/28 versus 22/62; $p=0.03$) than survivors.

Survival Analysis

a) Brain Natriuretic Peptide

Higher BNP concentrations were associated with increased mortality (HR 1.00; 95% CI 1.00, 1.01; $p=0.004$) independent of age, gender and pulmonary function. BNP ≥ 4 pmol/L was not associated with survival. However, patients with BNP ≥ 20 pmol/L had higher mortality (HR 2.93; 95% CI 1.28, 6.73; $p=0.01$) than those with BNP < 20 pmol/L, independent of age, gender and pulmonary function (*Figure 1a*). One-year mortality for patients with BNP ≥ 20 pmol/L was 28.5% compared to 10.1% for those with BNP < 20 pmol/L ($p=0.009$). Patients with BNP ≥ 20 pmol/L had a fourteen-fold increase in mortality over patients with BNP < 4 pmol/L independent of age, gender and pulmonary function (HR 13.92; 95% CI 1.52, 128.79; $p=0.02$, *Table 3*). However, there was no significant difference in mortality between patients with BNP 4-20 pmol/L and < 4 pmol/L. These findings remained significant following adjustment for serum creatinine concentration and duration of dyspnoea, and with the exclusion of each diagnostic subgroup in turn, in separate models, indicating that the overall trends were not overly influenced by one single subgroup.

b) Pulmonary Hypertension

RVSP was associated with survival (HR 1.03; 95% CI 1.00, 1.05; $p=0.02$) following adjustment for age, gender and pulmonary function. The presence of PH on echocardiography was not significantly associated with survival (*Table 3*). However, those with moderate-severe PH had a higher mortality (HR 2.53, 95% CI 1.15, 5.57, $p=0.02$) independent of age, gender and pulmonary function (*Table 3, Figure 1b*). The one-year mortality rate for patients with moderate-severe PH was 20.7% compared to 12.0% for those without moderate-severe PH ($p=0.03$).

c) BNP combined with Echocardiography

Patients with BNP ≥ 20 pmol/L and moderate-severe PH on echocardiography had higher mortality (HR 2.93; 95% CI 1.40, 6.20; $p=0.005$) than patients without both these findings. However, the prognostic distinction of these parameters in combination was no stronger than the simple distinction made from the threshold of BNP ≥ 20 pmol/L alone. Furthermore, in patients with BNP < 20 pmol/L, mortality was no higher if there was moderate-severe PH on echocardiography ($p=0.58$).

Patients with BNP ≥ 20 pmol/L had lower DLco%, 6MWT distance, PAT and higher RVSP and RAP (*Table 4*).

DISCUSSION

The results of the current study demonstrate the prognostic value of BNP and echocardiography over the ILD population as a whole, independent of underlying disease severity. Elevated BNP concentration, and RVSP levels were linked to increased mortality across ILD. When evaluated as a continuous variable, increased serum BNP concentration was the strongest predictor of overall mortality. Unlike PVR, which predicts early death [4], elevated BNP and RVSP were predictive of overall, but not short-term mortality. This suggests that while elevated PVR is a marker of end-stage PH, BNP and echocardiography reflect earlier pulmonary vascular disease.

BNP concentration, as a continuous variable, was the strongest predictor of overall mortality across the ILD population. This finding is in keeping with observations in a recent IPF study [20]. It is not surprising that elevated BNP levels are associated with increased mortality, as both BNP and the more stable NT-proBNP are known to be prognostic markers in idiopathic PAH [17, 32-34] and chronic lung disease [18].

We considered it important to establish whether dichotomous BNP values, above and below *a priori* threshold values, provided equivalent prognostic utility to continuous BNP values. Patients with BNP levels above the threshold of 20pmol/L had a three-fold increase in mortality over those with BNP<20pmol/L and a fourteen-fold increase in mortality above those with BNP<4pmol/L. However, when BNP was considered as a dichotomous variable, it provided no additional prognostic information over echocardiography. Thus, on the basis of the current study, we cannot recommend a

useful threshold BNP level for a prognostic clinical algorithm. However, patient numbers above and below threshold values were small, and larger studies are warranted to further explore this hypothesis before the combination of BNP and echocardiography is dismissed as a potential surrogate prognostic index.

Our results suggest that the clinical utility of serum BNP lies primarily in its superior prediction of mortality when used as a continuous variable. This indicates that advantage of BNP lies, not in defining the presence of pulmonary vascular involvement, using dichotomous threshold values, but in quantifying the degree of pulmonary vascular involvement across the whole spectrum of disease severity. Our results strongly justify the exploration of BNP as a continuous variable in the future formulation of composite prognostic indices.

In contrast to BNP concentrations, RVSP had equivalent prognostic value, whether considered as a dichotomous or continuous variable. Moderate to severe PH on echocardiography was associated with a three-fold increase in mortality, independent of the severity of the underlying ILD. This finding is consistent with previous echocardiography studies in IPF [1].

In advanced ILD there appears to be a final common pathway across the spectrum of ILD disorders. In one study, survival did not differ between biopsy-proven IPF and NSIP in patients with DLco levels below 35% of predicted [35]. In another report, patients with severe hypersensitivity pneumonitis had an outcome similar to that of IPF [36]. We

suggest that pulmonary vasculopathy may contribute to this final common pathway across the ILD population. In support of this hypothesis, we have recently demonstrated that elevated PVR is a marker for early death across the spectrum of ILD patients [4]. Moreover, in the current study we show that elevated BNP levels and echocardiographic parameters of PH, both markers of vascular stress, were indeed linked to increased mortality across ILD independent of the severity of underlying lung disease. These results support the concept that pulmonary vasculopathy has important prognostic implications across ILD, and may contribute to the final common pathway in ILD patients.

Brain Natriuretic Peptide as a Marker of RV dysfunction

In the current study, we show significant, albeit weak, positive correlations between BNP and markers of RV dysfunction. BNP levels above 20pmol/L were associated with moderate-severe PH on echocardiography. Importantly, BNP levels did not correlate with parameters of left heart dysfunction, although left heart dysfunction was not a common finding in our patient population (n=7). However, this study was not designed to evaluate BNP against other indirect measures of PH, but instead, against mortality. In severe ILD, elevated pulmonary vascular resistance strongly predicts mortality [4]. In earlier disease, routine RHC is neither realistic nor desirable. Thus, we evaluated the prognostic implications of pulmonary vascular stress as measured by indirect methods, including BNP. Elevated BNP concentrations have previously been associated with PH on RHC in an IPF population [19], supporting the concept that raised BNP reflects

pulmonary vascular compromise. In our study, raised BNP was associated with markers of right heart dysfunction, suggesting that elevated BNP may be a marker of early pulmonary vascular impairment.

Limitations of the study

In this study we chose to study ILD in general, rather than an individual ILD subgroup, such as IPF. We have previously shown that elevated pulmonary vascular resistance measured at RHC strongly predicts rapid mortality across the ILD population [4] and so we hypothesised that other markers of pulmonary vascular disease may also be prognostic markers across ILD. It was, therefore, important to include the whole ILD population, rather than study a specific ILD subgroup. However, as in our earlier study, we considered it important to establish that our results were not dominated by a single ILD subgroup [4]. Thus, we analyzed the data excluding each diagnostic subgroup in turn (as the alternative strategy of examining each sub-group in isolation was precluded by small sub-group numbers). Results remain highly statistically significant with the exclusion of each diagnostic subgroup, indicating that no ILD subgroup had overly influenced our findings.

Our study was necessarily limited by its retrospective design and patient selection. A wide range of disease severity was evaluated. At the start of the study period, there was a focus on cases with clinical suspicion of PH, but in the latter part of the study period, BNP was performed routinely on new-referrals. We suggest that the resultant range of disease severity and suspicion of PH involvement reflects real-life clinical practice, and is

a representative population in which to explore proof of concept outcome analyses. However, exact clinical utility with reference to unselected ILD cases cannot be extrapolated from our data.

The attempted construction of a staging system, by combining BNP and echocardiographic thresholds, was hampered by low sub-group numbers. Prospective larger studies of longer periods of observation are required to further delineate the relative importance of these prognostic markers alone and in combination, and before these markers can be widely used for prognostic staging in the ILD population

CONCLUSION

Elevated BNP concentration and RSVP levels are linked to higher mortality across the ILD population, independent of the severity of the underlying lung fibrosis. Increased serum BNP concentration was the strongest predictor of overall mortality across ILD patients. BNP ≥ 20 pmol/L and moderate to severe PH on echocardiography were associated with increased mortality. The linkage between these vascular parameters and mortality supports the concept that pulmonary vascular disease contributes to the final common pathway seen across ILD patients.

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FIGURE TITLES AND LEGENDS

Figure 1:

Title: Kaplan-Meier Survival Curve for a) BNP ≥ 20 pmol/L and b) Moderate-Severe Pulmonary Hypertension.

Caption: Patients with BNP ≥ 20 pmol/L ($p=0.009$) and Moderate-Severe Pulmonary Hypertension ($p=0.03$) had poorer survival than those with BNP < 20 pmol/L and without moderate-severe PH respectively.

TABLES

	Entire Group*	Survivors*	Non-survivors*
Number (%)	90 (100)	62 (69)	28 (31)
Age (years)	59 ± 12	58 ± 14	58 ± 15
Male (%)	47 (52)	29 (47)	18 (64)
Creatinine (umol/L)	88.5 ± 26.2	87.7 ± 26.0	91.9 ± 27.3
Pulmonary function			
DLco %	38.0 ± 15.9	39.7 ± 16.6	34.0 ± 13.7
FVC %	75.3 ± 22.3	78.6 ± 21.9 [†]	68.1 ± 21.7 [†]
TLC %	77.1 ± 19.8	79.3 ± 20.2	71.7 ± 18.1
PaO ₂ (kPa)	9.2 ± 2.3	9.5 ± 2.9	8.5 ± 2.0
6 minute walk test (n=55)			
End test SpO ₂ (%)	83.3 ± 8.8	84.2 ± 9.1	82.5 ± 9.3
6 minute walk distance (m)	271 ± 127	277 ± 130	258 ± 123
Brain Natriuretic Peptide			
(pmol/L)	Median 11 Range: 1.4-377	Median 9 Range 3 to 193.8 [‡]	Median 22 Range 1.4 to 377 [‡]
Echocardiography			
RVSP (mmHg; n=63)	49.9 ± 21.7	46.9 ± 21.3 [†]	59.2 ± 19.1 [†]
Right atrial pressure (mmHg)	8.3 ± 3.9	8.0 ± 4.1	8.8 ± 3.4
Pulmonary acceleration time (ms)	96.8 ± 26.9	109.3 ± 32.3	102.2 ± 31.2
Fractional shortening (%)	36.8 ± 9.2	37.6 ± 9.8	35.1 ± 7.9

Table 1: Baseline Characteristics for Entire population, Survivors and Non-survivors.

* Mean ± Standard Deviation or Median and Range, as appropriate.

[†] P value <0.05 (Student's t-test) or Wilcoxon's rank sum test ([‡])

Baseline Parameters*	R	P
Age	0.50	<0.00001
WHO class	0.33	0.002
Pulmonary Function		
DLco % (n=89)	-0.29	0.006
FVC % (n=86)	0.14	0.19
PaO ₂ (kPa, n=74)	-0.22	<0.05
6 minute walk test (n=55)		
End-test SpO ₂ (%)	-0.003	0.98
Distance (m)	-0.35	0.009
Echocardiography Right Heart Indices:		
RVSP (mmHg, n=64)	0.43	0.0002
Peak tricuspid velocity (m/s, n=64)	0.39	0.02
Degree of tricuspid regurgitation (scale 1-4)	0.34	0.0008
Right atrial pressure (mmHg, n=78)	0.27	0.02
Right atrial area (cm ² , n=87)	0.42	<0.00001
Longitudinal motion at tricuspid valve annulus (cm, n=84)	-0.29	0.008
RV inlet diameter (cm, n=88)	0.36	0.0004
Pulmonary acceleration time (ms, n=88)	-0.33	0.002
Echocardiography Left Heart Indices:		
Left atrial area (n=88)	0.02	0.84
LV end systolic diameter (cm)	0.11	0.32
Longitudinal motion at mitral valve annulus (cm, n=87)	-0.20	0.07
Fractional shortening (% , n=87)	-0.12	0.26

Table 2: Correlation of BNP to parameters of Pulmonary Vascular Impairment

(Spearman's Rank Correlation Test)

** n=90 unless otherwise indicated*

	Overall Survival*		One-year survival †	
	HR (95% CI)	P value	OR (95% CI)	P
Brain Natriuretic Peptide				
BNP - continuous (pmol/L)	1.01 (1.00, 1.01)	0.004§	1.00 (0.996, 1.01)	0.35
BNP 4-20pmol/L‡	2.95 (0.35, 24.64)	0.32	No deaths in one year in patients with BNP<4pmol/L	
BNP ≥ 20pmol/L‡	13.92 (1.52,	0.02§		
Echocardiography				
RVSP - continuous (mmHg; n=64)	1.03 (1.00, 1.05)	0.04§	1.01 (0.98, 1.06)	0.37
Echo PH	1.99 (0.84, 4.71)	0.12	2.64 (0.62, 11.36)	0.19
Echo mod-severe PH	2.53 (1.15, 5.57)	0.02§	2.18 (0.59, 8.09)	0.24
Composite Markers				
BNP ≥20pmol/L & Echo mod-severe PH	3.18 (1.37, 7.43)	0.007§	2.89 (0.68, 12.2)	0.15

Table 3: Overall and One-year survival (for continuous variables and a priori thresholds of BNP and RVSP)

* Cox-regression analysis was used for overall survival analysis (adjusted for age gender and composite physiologic index)

† Logistic regression was used for one-year survival analysis (adjusted for age gender and composite physiologic index)

§ Results remained significant following adjustment for serum creatinine concentration (umol/L) and duration of dyspnoea (months).

‡ Compared to patients with normal BNP concentrations (BNP<4pmol/L)

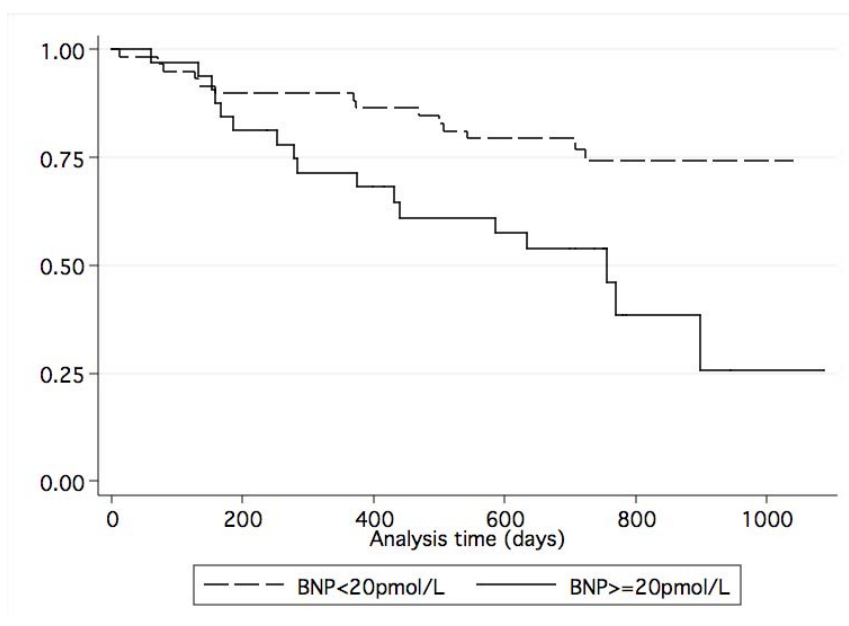
	BNP \geq 20pmol/L [†]	BNP <20pmol/L [†]
Number (%)	30 (33)	60 (67)
Age (years)	64 \pm 11*	56 \pm 12*
Male (%)	18 (30)	29 (60)
Pulmonary function		
DLco %	32.0 \pm 14.8*	40.8 \pm 15.8*
FVC %	78.0 \pm 24.3	73.9 \pm 21.3
TLC %	79.3 \pm 17.6	76.0 \pm 20.8
PaO ₂ (kPa)	8.6 \pm 2.7	9.5 \pm 2.1
6 minute walk test (n=55)		
End test SpO ₂ (%)	84.0 \pm 8.9	83.4 \pm 9.4
6 minute walk distance (m)	214 \pm 126*	310 \pm 113*
Echocardiography		
RVSP (mmHg)	61.8 \pm 25.8*	42.0 \pm 14.0*
Right atrial pressure (mmHg)	10.2 \pm 0.9*	7.3 \pm 2.7*
Pulmonary acceleration time (ms)	86.2 \pm 21.8*	102.1 \pm 27.8*
Fractional shortening (%)	36.1 \pm 9.3	37.2 \pm 9.3

Table 4: Baseline Parameters characterised by BNP \geq 20pmol/L and BNP <20pmol/L

* *P* value <0.05 between groups (Students *t*-test)

[†]Mean \pm standard deviation (unless otherwise specified)

a)



b)

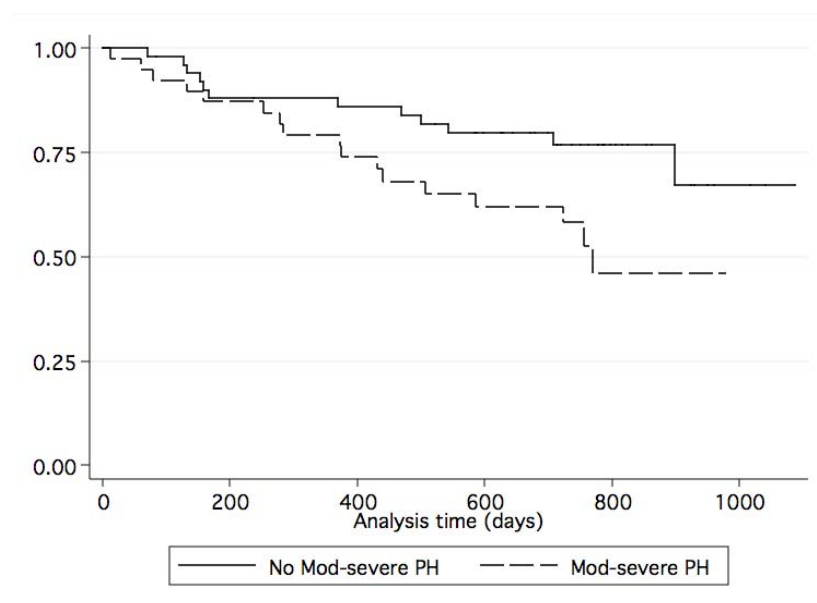


Figure 1: Kaplan-Meier Survival Curve for a) BNP ≥ 20 pmol/L and b) Moderate-Severe Pulmonary Hypertension.

Caption: Patients with BNP ≥ 20 pmol/L ($p=0.009$) and Moderate-Severe Pulmonary Hypertension ($p=0.03$) had poorer survival than those with BNP < 20 pmol/L and without moderate-severe PH respectively.