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Elevated brain natriuretic peptide predicts mortality in interstitial lung disease

T.J. Corte*,#, S.J. Wort*,¶, M.A. Gatzoulis*,¶, R. Engel*, G. Giannakoulas*, P.M. Macdonald# and A.U. Wells*,¶

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

ILD patients with BNP concentrations performed during 2005–2007 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.

During follow-up (20±9 months) there were 28 deaths (31%). BNP correlated with right heart echocardiographic indices, including right ventricular systolic pressure (RVSP) (R^2=0.18, p=0.0002) but not with parameters of left heart function. Nonsurvivors had higher BNP and RVSP levels than survivors. BNP ⩾20 pmol·L^{-1} (hazard ratio (HR) 2.93, 95% CI 1.28–6.73; p=0.01) and moderate–severe pulmonary hypertension (HR 2.53, 95% CI 1.15–5.57; p=0.02) were associated with increased mortality, independent of age, sex and pulmonary function. Patients with BNP ⩾20 pmol·L^{-1} had a 14-fold increased mortality over those with BNP <4 pmol·L^{-1}.

Increased BNP levels and/or echocardiographic markers of right ventricular dysfunction were associated with increased mortality across ILD. The link between vascular parameters and mortality supports the concept that pulmonary vascular disease contributes to the final common pathway seen across ILD.

KEYWORDS: **Brain natriuretic peptide, echocardiogram, interstitial lung disease, prognosis, pulmonary hypertension, right ventricular function**

AFFILIATIONS
*Royal Brompton Hospital and National Heart and Lung Institute, and ¶Imperial College, London, UK.
#University of New South Wales, Sydney, Australia.

CORRESPONDENCE
A.U. Wells
Interstitial Lung Disease Unit
Royal Brompton Hospital and
National Heart and Lung Institute
Imperial College
Emmanuel Kaye Building
1B Manresa Road
London
SW3 6LP
UK
E-mail: athol.wells@rbht.nhs.uk

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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 by right heart catheter (RHC) strongly predicts rapid mortality across ILD patients [4]. However, RHC is moderately invasive, and not always practicable. Surrogate noninvasive 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 (RV) 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 32–85% [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 RV 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

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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 RV 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, last clinic follow-up or February 1, 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: 1) BNP $\geqslant$4 pmol·L^{-1} and $\geqslant$20 pmol·L^{-1} [20]; and 2) echocardiographic evidence of PH (right ventricular systolic pressure (RVSP) $\geqslant$40 mmHg or right heart dilatation) and moderate–severe PH (RVSP $\geqslant$50 mmHg or right heart dilatation) [12].

Investigations

Brain natriuretic peptide

Venous blood samples were collected for BNP testing into tubes containing potassium EDTA. The BNP samples were analysed within 4 h or, in some cases, whole blood was centrifuged and the plasma stored at -80°C until analysis [21, 22]. The BNP concentrations were quantified using the Beckman Access 2, Triage BNP assay (Biosite Diagnostics Inc., San Diego, CA, USA). 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 ~2 min 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 min, 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 <4 pmol·L^{-1}. Age- and sex-adjusted values are not available for this assay, and so, adjustments for age and sex were performed for each analysis. Thus, we examined BNP $\geqslant$4 pmol.L^{-1} and $\geqslant$20 pmol·L^{-1} 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 (range) from BNP 1 (0–10) months. Right atrial pressure (RAP) was estimated on the basis of inferior vena cava size and movement on respiration [23]. 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 RVSP was $\geqslant$40 mmHg or there was right heart dilatation. Moderate–severe PH was defined as RVSP $\geqslant$50 mmHg or right heart dilatation.

Other investigations

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

$$CPI = 91 - 0.65 \times (D_{L,CO}\ \%) - 0.53 \times (FVC\ \%) + 0.34 \times (FEV_1\ \%)$$

in which FVC is the forced vital capacity and FEV_1 is the forced expiratory volume in 1 s.

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

A 6-min walk test (6MWT) was performed in 55 patients, (median time (range) from BNP 1.4 (0–31) months) was performed by senior personnel in accordance with ATS/ERS guidelines [30] with standardised verbal prompts. The 6MWT was performed on room air or 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, USA). Data are expressed as mean±SD or as median (range), as appropriate. Group comparisons were made using unpaired 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 previously.

Multivariate survival analysis was performed, adjusting for age, sex, 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 Chi-squared test. p-values <0.05 were regarded as statistically significant throughout.

RESULTS

Patient characteristics

90 patients (age 59±12 yrs; 47 (52%) males) fulfilled entry criteria. ILD diagnoses included: IPF (n=16), idiopathic nonspecific interstitial pneumonia (computed tomography 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). 43 patients were life-long nonsmokers, 39 were ex-smokers and five were current smokers (three unknown; mean±SD 25.5±16.6 pack-yrs). 13 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 World Health Organization functional class was 2 (1–4).

79 (88%) had BNP $\geqslant 4$ pmol·L^{-1} and 38 (39%) had BNP $\geqslant 20$ pmol·L^{-1}. 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±9%). On 6MWT, 39 patients (42%) had oxygen desaturation <88%. 13 (14%) patients had elevated creatinine concentrations (>120 μmol·L^{-1}). Other baseline parameters are summarised in table 1.

BNP 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 $D_{L,CO}$ % pred, transfer coefficient of the lung carbon monoxide, arterial oxygen tension measured by pulse oximetry, arterial oxygen tension and the 6MWT distance. BNP did not correlate with echocardiographic parameters of left heart function (table 2). BNP $\geqslant 20$ pmol·L^{-1} was associated with moderate–severe PH on echocardiography ($p<0.0001$).

TABLE 1 Baseline characteristics for the entire population, survivors and nonsurvivors

	Entire group	Survivors	Nonsurvivors
Subjects	90 (100)	62 (69)	28 (31)
Age yrs	59±12	58±14	58±15
Males	47 (52)	29 (47)	18 (64)
Creatinine μmol·L^{-1}	88.5±26.2	87.7±26.0	91.9±27.3
Pulmonary function			
$D_{L,CO}$ % pred	38.0±15.9	39.7±16.6	34.0±13.7
FVC % pred	75.3±22.3	78.6±21.9*	68.1±21.7*
TLC % pred	77.1±19.8	79.3±20.2	71.7±18.1
P_{a,O_2} kPa	9.2±2.3	9.5±2.9	8.5±2.0
6-min walk test$^{\#}$			
End test S_{p,O_2} %	83.3±8.8	84.2±9.1	82.5±9.3
6-min walk distance m	271±127	277±130	258±123
Brain natriuretic peptide pmol·L^{-1}	11 (1.4–377)	9 (3–193.8)¶	22 (1.4–377)¶
Echocardiography			
RVSP mmHg^{+}	49.9±21.7	46.9±21.3*	59.2±19.1*
RAP 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

Data are presented as n (%), mean±SD or median (range). $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; P_{a,O_2}: arterial oxygen tension; S_{p,O_2}: arterial oxygen saturation measured by pulse oximetry; RVSP: right ventricular systolic pressure; RAP: right arterial pressure. $^{\#}$: n=55; $^{+}$: n=63. *: $p<0.05$ (unpaired t-test); ¶: $p<0.05$ (Wilcoxon's rank sum test).

TABLE 2 Correlation of brain natriuretic peptide to parameters of pulmonary vascular impairment

Baseline parameters	Subjects n	R$^{\#}$	p-value
Age yrs	90	0.50	<0.00001
WHO class	90	0.33	0.002
Pulmonary function			
$D_{L,CO}$ %	89	-0.29	0.006
FVC %	86	0.14	0.19
P_{a,O_2} kPa	74	-0.22	<0.05
6-min walk test			
End-test S_{p,O_2} %	55	-0.003	0.98
Distance m	55	-0.35	0.009
Echocardiography right heart indices			
RVSP mmHg	64	0.43	0.0002
Peak tricuspid velocity m·s^{-1}	64	0.39	0.02
Degree of tricuspid regurgitation (scale 1–4)	90	0.34	0.0008
Right atrial pressure mmHg	78	0.27	0.02
Right atrial area cm^2	87	0.42	<0.00001
Longitudinal motion at tricuspid valve annulus cm	84	-0.29	0.008
Right ventricular inlet diameter cm	88	0.36	0.0004
Pulmonary acceleration time ms	88	-0.33	0.002
Echocardiography left heart indices			
Left atrial area cm^2	88	0.02	0.84
Left ventricular end systolic diameter cm	90	0.11	0.32
Longitudinal motion at mitral valve annulus cm	87	-0.20	0.07
Fractional shortening %	87	-0.12	0.26

$D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; P_{a,O_2}: arterial oxygen tension; S_{p,O_2}: arterial oxygen saturation measured by pulse oximetry; RVSP: right ventricular systolic pressure. $^{\#}$: Spearman's rank correlation coefficient.

Characteristics of survivors and nonsurvivors

During the follow-up period of 20±9 months, there were 28 (31%) deaths. Nonsurvivors had higher BNP and RVSP levels and lower FVC % predicted levels than survivors (table 1). Nonsurvivors were more likely to have BNP concentration $\geqslant$20 pmol·L^{-1} (15 out of 28 *versus* 15 out of 62; p=0.006) and to have moderate–severe PH (17 out of 28 *versus* 22 out of 62; p=0.03) than survivors.

Survival analysis

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, sex and pulmonary function. BNP $\geqslant$4 pmol·L^{-1} was not associated with survival. However, patients with BNP $\geqslant$20 pmol·L^{-1} had higher mortality (HR 2.93, 95% CI 1.28–6.73; p=0.01) than those with BNP <20 pmol·L^{-1}, independent of age, sex and pulmonary function (fig. 1a). 1-yr mortality for patients with BNP $\geqslant$20 pmol·L^{-1} was 28.5% compared with 10.1% for those with BNP <20 pmol·L^{-1} (p=0.009). Patients with BNP $\geqslant$20 pmol·L^{-1} had a 14-fold increase in mortality over patients with BNP <4 pmol·L^{-1} independent of age, sex 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^{-1} and <4 pmol·L^{-1}. 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.

Pulmonary hypertension

RVSP was associated with survival (HR 1.03, 95% CI 1.00–1.05; p=0.02) following adjustment for age, sex 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, sex and pulmonary function (table 3; fig. 1b). The 1-yr mortality rate for patients with moderate–severe PH was 20.7% compared to 12.0% for those without moderate–severe PH (p=0.03).

BNP combined with echocardiography

Patients with BNP $\geqslant$20 pmol·L^{-1} 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 $\geqslant$20 pmol·L^{-1} alone. Furthermore, in patients with BNP <20 pmol·L^{-1}, mortality was no higher if there was moderate–severe PH on echocardiography (p=0.58).

Patients with BNP $\geqslant$20 pmol·L^{-1} had lower $D_{L,CO}$ %, 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 pulmonary vascular resistance, which predicts early death [4], elevated BNP and RVSP were predictive of overall, but not short-term, mortality. This suggests that while elevated pulmonary vascular resistance 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 N-terminal pro-BNP 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 20 pmol·L^{-1} had a three-fold increase in mortality over those with BNP<20 pmol·L^{-1} and a 14-fold increase in mortality above those with BNP<4 pmol·L^{-1}. However, when BNP was

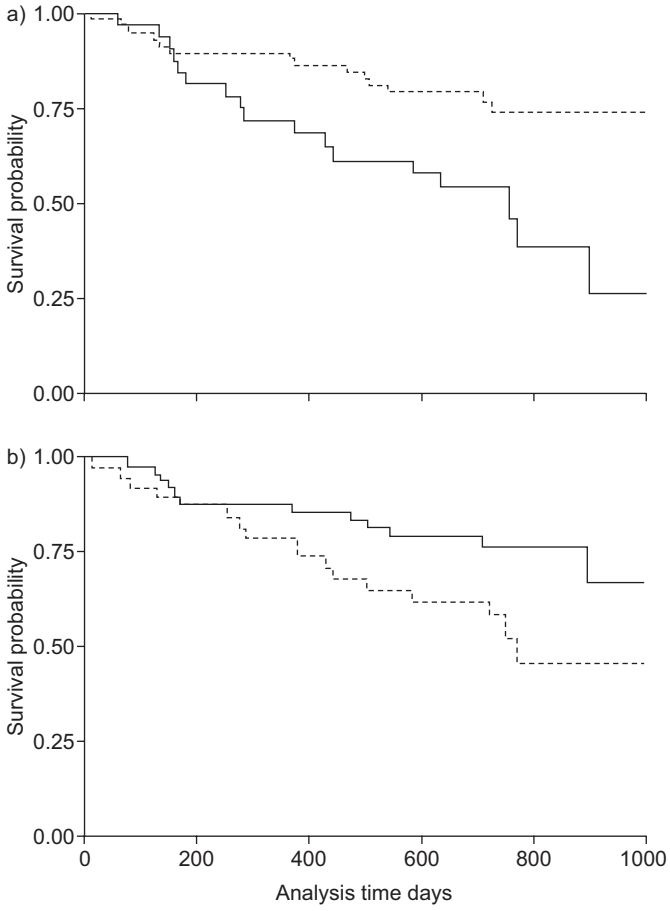

FIGURE 1. Kaplan–Meier survival curve for a) brain natriuretic peptide (BNP) $\geqslant$20 pmol·L^{-1} (– – –: BNP <20 pmol·L^{-1}; ——: BNP >20 pmol·L^{-1}) and b) moderate–severe pulmonary hypertension (PH) (– – – –: with moderate–severe PH; ——: without moderate–severe PH). Patients with BNP $\geqslant$20 pmol·L^{-1} (p=0.009) and moderate–severe PH (p=0.03) had poorer survival than those with BNP <20 pmol·L^{-1} and without moderate–severe PH, respectively.

TABLE 3 Overall and 1-yr survival (for continuous variables and *a priori* thresholds of brain natriuretic peptide (BNP) and right ventricular systolic pressure (RVSP))

	Overall survival[#]		1-yr survival[¶]	
	HR (95% CI)	p-value	OR (95% CI)	p-value
BNP				
BNP continuous pmol·L^{-1}	1.01 (1.00–1.01)	0.004[##]	1.00 (0.996–1.01)	0.35
BNP 4–20 pmol·L^{-1}[§]	2.95 (0.35–24.64)	0.32		
BNP ⩾20 pmol·L^{-1}[§]	13.92 (1.52–127.79)	0.02[##]	No deaths in 1 yr in patients with BNP<4 pmol·L^{-1}	
Echocardiography				
RVSP continuous mmHg[f]	1.03 (1.00–1.05)	0.04[##]	1.01 (0.98–1.06)	0.37
Echocardiography PH	1.99 (0.84–4.71)	0.12	2.64 (0.62–11.36)	0.19
Echocardiography moderate–severe PH	2.53 (1.15–5.57)	0.02[##]	2.18 (0.59–8.09)	0.24
Composite markers				
BNP ⩾20 pmol·L^{-1} and echocardiography moderate–severe PH	3.18 (1.37–7.43)	0.007[##]	2.89 (0.68–12.2)	0.15

PH: pulmonary hypertension. [#]: Cox regression analysis was used for overall survival analysis (adjusted for age, sex and composite physiologic index); [¶]: logistic regression was used for 1-yr survival analysis (adjusted for age, sex and composite physiologic index); [§]: compared with patients with normal BNP concentrations (BNP <4 pmol·L^{-1}); [f]: n=64; [##]: results remained significant following adjustment for serum creatinine concentration (μmol·L^{-1}) and duration of dyspnoea (months).

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.

TABLE 4 Baseline parameters characterised by brain natriuretic peptide (BNP) ⩾20 pmol·L^{-1} and BNP <20 pmol·L^{-1}

	BNP ⩾20 pmol·L^{-1}	BNP <20 pmol·L^{-1}
Subjects	30 (33)	60 (67)
Age yrs	64±11*	56±12*
Males	18 (30)	29 (60)
Pulmonary function		
$D_{L,CO}$ % pred	32.0±14.8*	40.8±15.8*
FVC % pred	78.0±24.3	73.9±21.3
TLC % pred	79.3±17.6	76.0±20.8
P_{a,O_2} kPa	8.6±2.7	9.5±2.1
6-min walk test[#]		
End test S_{p,O_2} %	84.0±8.9	83.4±9.4
6-min walk distance m	214±126*	310±113*
Echocardiography		
RVSP mmHg	61.8±25.8*	42.0±14.0*
RAP mmHg	10.2±0.9*	7.3±2.7*
Pulmonary acceleration time ms	86.2±21.8*	102.1±27.8*
Fractional shortening %	36.1±9.3	37.2±9.3

Data are presented as n (%) or mean±SD. $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; P_{a,O_2}: arterial oxygen tension; S_{p,O_2}: arterial oxygen saturation measured by pulse oximetry; RVSP: right ventricular systolic pressure; RAP: right arterial pressure. [#]: n=55. *: p<0.05 between groups (unpaired t-test).

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 the 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 nonspecific interstitial pneumonia in patients with $D_{L,CO}$ levels <35% pred [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 pulmonary vascular resistance 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.

BNP 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 >20 pmol·L^{-1} 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 analysed the data, excluding each diagnostic subgroup in turn (as the alternative strategy of examining each subgroup in isolation was precluded by small subgroup 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 subgroup numbers. Prospective larger studies with 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 RVSP 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 $\geqslant$20 pmol·L^{-1} and moderate to severe PH on echocardiography were associated with increased mortality. The link between these vascular parameters and mortality supports the concept that pulmonary vascular disease contributes to the final common pathway seen across ILD patients.

STATEMENT OF INTEREST

None declared.

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