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Idiopathic pulmonary fibrosis: BNP and echocardiogram guide difficult but necessary discussions related to prognosis

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ABSTRACT A critical appraisal and clinical application of Song JW, Song J-K, Kim DS. Echocardiography and brain natriuretic peptide as prognostic indicators in idiopathic pulmonary fibrosis. *Respir Med* 2009;103(2):180-186. doi:[10.1016/j.rmed.2008.11.012](https://doi.org/10.1016/j.rmed.2008.11.012).

Keywords: Idiopathic pulmonary fibrosis, brain natriuretic peptide, echocardiography, pulmonary hypertension, IPF, BNP, PH

Clinical Context

A 62-year-old woman presented to the emergency department for shortness of breath. The patient was on home oxygen due to her chronic lung disease, but developed a rapid onset of shortness of breath. After admission to the MICU, the patient's medical records disclosed that she had interstitial lung disease due to idiopathic pulmonary fibrosis (IPF), which was diagnosed by lung biopsy five years prior to this admission. IPF is a diagnosis of exclusion, and the combination of biopsy results and previous work-up ruled-out other lung conditions in this patient. On laboratory workup, the patient's brain natriuretic peptide (BNP) was found to be elevated into heart failure range at 1213 pg/mL (Age and Gender Adjusted Ratio = 19.8)¹ and echocardiography showed minimal left cardiac abnormalities, right atrial and ventricular enlargement, and pulmonary hypertension with a systolic pulmonary artery pressure of 56 mmHg. She was later discharged with recommendations to follow up at an outpatient respiratory clinic for open lung biopsy for two reasons, the first to confirm her diagnosis as it had been five years since her biopsy. The second was that the pulmonary team decided her diagnosis was ambiguous; they were convinced they should further rule-out other chronic lung diseases.

Clinical Question

Do echocardiography and BNP levels help clinicians determine the severity of disease and thus prognosis for patients with interstitial lung disease?

Research Article

Song JW, Song J-K, Kim DS. Echocardiography and brain natriuretic peptide as prognostic indicators in idiopathic pulmonary fibrosis. *Respir Med* 2009;103(2):180-186. doi:[10.1016/j.rmed.2008.11.012](https://doi.org/10.1016/j.rmed.2008.11.012).

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Literature Review

Literature review began with articles found at PubMed.gov and through the Google search engine by combining the keywords “interstitial lung disease” and “brain natriuretic peptide”. Analysis of the resulting literature found multiple prospective and retrospective studies that evaluate the usefulness of BNP and pulmonary artery hypertension as prognostic indicators in chronic lung disease. For example, Leuchte et al. evaluated 176 patients with chronic lung disease and analyzed indicators of mortality such as mean pulmonary artery pressure using pulmonary function testing, cardiac catheterization, and stress testing.² This research included cases of both restrictive and obstructive pulmonary disease. The results of this study indicated that BNP was a good prognostic indicator and screening tool for pulmonary hypertension in patients with chronic lung disease. Likewise, Andreassen et al. evaluated the utility of BNP in an even more heterogeneous group of patients with chronic lung disease, with similar findings.³

However, many of these studies have a small sample size of patients with idiopathic pulmonary fibrosis. Also, these two studies are too generalized to reconcile the prognostic capability of BNP in chronic lung disease; they included patients with both restrictive and obstructive pathologies. Among several similar trials of pulmonary hypertension and BNP measurements, the criteria for excluding/including patients with LV dysfunction were ambiguous.⁴ A further search of PubMed.gov, limited to idiopathic pulmonary fibrosis, determined that the most focused study that defined the prognostic indications of elevated BNP and pulmonary hypertension was written by Song et al. The sample size in this study was relatively large ($n = 131$), and patients with left ventricular dysfunction were excluded based on sound criterion (Ejection Fraction < 50).⁵

Critical Appraisal

The article by Song et al. is a retrospective study of 131 patients with idiopathic pulmonary fibrosis, which falls under level 2B evidence in accord with the Oxford Centre for Evidence Based Medicine. The study excluded all other disorders that could cause secondary pulmonary hypertension and used patients that had BNPs and echocardiography performed within three days of one another. Importantly, patients with a left ventricular ejection fraction less than fifty were excluded from the study.

Despite having patients that fit the criteria for idiopathic pulmonary fibrosis without left ventricular dysfunction, there are admittedly flaws with the patient study group. Patients were selected from the Asan Medical Center in Seoul, South Korea. This geographic distribution of patients makes the results of the study less generalizable as variations in BNP measurements and the correlation to IPF in various races are not well studied. In addition, 73.3% of the patients in the study were males. While IPF is more prevalent in smokers and males, this indicates that the evidence is partially biased to patients already known to have a more severe and dominant presentation in the population. However, what's critical is that the percentage of males with elevated systolic pulmonary artery pressures (sPAP) and BNP ratios was consistent with the percentage of males in the study group (72.7% and 68.4%, respectively). This indicates that there is little confounding bias present.

Furthermore, this study attempted to show an increase in mortality and decreased survival in patients with elevated sPAPs and BNP versus patients without these prognostic indices. However, the study does not indicate whether the data was taken from patients admitted for acute exacerbations of pulmonary dysfunction or from patients undergoing routine management of their condition. The implications of this potential selection bias is less significant considering that the study included follow-up data collection; patients likely returned to their baseline function or were functioning at a more diseased state at follow-up depending on their reference disease state. Therefore, the study adjusted for survival based on disease severity, with data collected at the beginning and end of the study.

While the study predicts increased mortality based on hazard ratios in patients with elevated sPAPs and BNP versus patients with values that fall within normal limits, this type of analysis has its flaws. For example, the hazard ratios for sPAP and BNP ratio were 1.028 and 1.148, respectively (p -values < 0.001). Since the hazard ratio is greater than one, this data indicates that patients with elevated BNP ratios and sPAP are more likely to die compared to patients with values within normal limits. However, the hazard ratio has no implications regarding time to death. With only the hazard ratio at hand, data that better predicts time to death based on survival data from a large study population is necessary for applicability in a clinical setting. While the authors highlight the survival data based on their study population (see Song et al., Table 3), the mean survivals are not generalizable based on the small sample size, which is discussed below.



Upon further consideration of the importance of the small sample size, it is important to note the study's determination of mortality at follow-up in patients with newly developed pulmonary hypertension (PH) as determined by echocardiography. The authors state that there is no significant difference with regard to survival in patients with newly developed PH versus those with persistently normal PH measured at follow-up by echocardiography, which they claim was likely due to the small sample number (9 of the 36 patients found to have normal sPAPs at baseline; $p = 0.061$). However, 13 out of 56 patients were found to have elevated BNP associated with decreased survival at follow-up ($p = 0.005$). As a result, Song et al. could not confirm their hypothesis that a combination of elevated sPAP and BNP were better predictors of mortality over the individual prognostic indices alone. The combination, as noted by the authors, may in fact prove superior to either diagnostic variable alone because of the higher hazard ratio.⁵ As support for this important hypothesis, in comparing groups with zero, one, or two prognostic parameters, the superiority of the combination is highlighted by the decreasing survival rates as the number of abnormal parameters a patient has increases. Therefore, further studies with larger sample sizes that assess the combination of both parameters are warranted.

Clinical Application

In the study by Song et al., it was concluded that patients with no prognostic indicators (elevated BNP or PH) had a mean survival of 25.2 months. Those with one or the other had a mean survival of 14.9 months. Those with both indices had a mean survival of 4.7 months.⁵ The patient previously described had a BNP and BNP ratio of 1213 and 19.8, respectively. In addition, her pulmonary artery pressure was roughly 56 mmHg. Given the two abnormal parameters, the patient has a mean survival of 4.7 months based on the study's survival data.⁵ However, the pulmonary physicians concluded that she would require an open lung biopsy for future management. Retrospectively, the pulmonary physicians could have used the above data to explain that with two abnormal parameters at the patient's baseline level of functioning, survival beyond five months is unlikely when the study's findings are applied to her scenario. Although not absolute, this study provides clinically applicable reasoning regarding prognosis associated with IPF and sets up a theoretical discussion for patients uncertain of the long-term progression of their illness.

I believe there are three points to be made regarding this patient and the above evidence. First, based on the patient's elevated BNP and sPAP, one must surmise that this particular patient has already developed severe, irreversible complications of her respiratory illness and requires no further work-up. Yet, her prognosis was overlooked and further work-up was sought because the pulmonary team decided her diagnosis was ambiguous. Second, and what I took away from this experience, is that when determining future management of patients with idiopathic pulmonary fibrosis and other interstitial lung disease based on BNP and PH, physicians should utilize these indices in the context of the patient's overall physical and mental health. For example, over the course of this patient's hospital stay, her care team discovered that she had poor follow-up with both her primary care provider and specialists for her lung disease. With the pulmonary team unconvinced by a diagnosis of IPF based on previous biopsy results, it was as if her physicians were giving her a false sense of a long life expectancy. Yet, the patient's quickly deteriorating health will likely hinder a follow-up with her respiratory specialist as she will likely need more acute care. Simply put, the team treated the disease, not the patient. Lastly, and as advice for future physicians, utilize these opportunities to build rapport with patients. Evidence-based medicine based on data obtained from studies such as Song et al. allows one to utilize prognostic indices to have difficult conversations with patients. These conversations strengthen the patient-physician relationship. In the case of this particular patient, her prognosis was hampered by a focus on treating her disease and a critical patient-centered discussion was left to follow-up.

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