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ORIGINAL ARTICLE

Relative value of amino-terminal pro-B-type natriuretic peptide testing and radiographic standards for the diagnostic evaluation of heart failure in acutely dyspneic subjects

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Abstract

To define more clearly the relationship between the information provided by the chest radiograph (CXR) and the natriuretic peptide (NT-proBNP) test as part of the evaluation of dyspneic patients presenting to the emergency department with suspected acute heart failure (HF), we evaluated the PRIDE cohort of 599 patients with and without HF, focusing on blinded NT-proBNP and unblinded CXR information. Clinical characteristics and diagnostic performance for each test were compared. We found that NT-proBNP measurement is superior to routine CXR interpretation for diagnosis or exclusion of acute HF and that normal CXR results should not be used to exclude HF in this population.

Keywords: *Dyspnea; heart failure; diagnosis; natriuretic peptides; biomarkers; chest radiograph*

Introduction

Recent estimates place the prevalence of heart failure (HF) at 5.3 million patients in the USA (AHA 2008), about one-third of them are admitted annually to the hospital, most through the emergency department (ED) (Graff et al. 1999). Optimizing the evaluation process as these patients pass through the ED is a key strategy in reducing hospitalization rates, shortening the length of hospital stay and minimizing adverse outcomes among those with HF, with associated goals of reducing the high cost of healthcare for these patients with HF (Weintraub 2002, Siebert et al. 2006).

The challenge of evaluating those with acute dyspnea – the most common symptom of acutely destabilized HF – is considerable. As has been demonstrated, the patient with dyspnea is often evaluated with some degree of uncertainty, even by highly skilled clinicians (Maisel et al. 2002, McCullough et al. 2002, Januzzi et al. 2005). The optimal evaluation of the dyspneic patient includes a balance of history, physical examination and adjunctive testing; traditionally, the chest radiograph (CXR) has been a reliable, inexpensive tool commonly used in the ED for the evaluation of dyspnea (Marantz et al. 1990, Badgett et al. 1996), and has a time-tested role in this setting.

Natriuretic peptide (NP) (including B-type natriuretic peptide BNP, and its amino terminal cleavage fragment, NT-proBNP) testing is a recent strategy that has consistently been shown to be useful for assisting clinicians in the early diagnosis and triage of dyspneic patients (Maisel et al.2002, Januzzi et al. 2005), with a role that may supersede that of CXR for diagnosis and prognosis (Dao et al. 2001, Ogawa et al. 2002).

It has been suggested that the accuracy of CXR is low for HF (Chakko et al. 1991, Collins et al. 2006); however prospective data examining this assertion are relatively lacking. In addition, physicians place inordinate value on the CXR in the ED setting for acute HF evaluation. In this context, confusion is not infrequent if testing for NPs is

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abnormal but a normal CXR is obtained. Furthermore, the converse – a normal NP with a CXR suggestive of HF – is similarly confusing. Accordingly, a better understanding of the individual and combined value of NPs and chest radiography is relevant. Using data from a previously conducted clinical trial of acute dyspnea (Januzzi et al.2005), we sought to analyse the relationship between the information provided by the routine interpretation of the CXR and the results of NP testing in these patients, in order to further redefine their role as complements to the clinical impression of the ED clinician, particularly in discordant clinical scenarios. We hypothesized that NP testing – in the form of NT-proBNP – would be more sensitive and specific for acute HF than interpretation of the CXR by on-duty radiologists, but suggestive results from both modalities would be present in a correct diagnosis of acute HF.

Methods

The ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study

The PRIDE study was a prospective, blinded study of 599 dyspneic subjects presenting to the ED of the Massachusetts General Hospital, and was performed for the purpose of validation of the diagnostic and prognostic use of NT-proBNP testing for the diagnosis or exclusion of HF. The results and methods of the PRIDE study have been reported (Januzzi et al. 2005).

Briefly, patients were included if they were 21 years of age or older and presented with a chief complaint of dyspnea. Exclusion criteria included severe renal insufficiency (serum creatinine level >2.5 mg dl^{-1}), dyspnea after chest trauma, dyspnea secondary to severe coronary ischemia (>0.1 mV ST-segment elevation or ST-segment depression on a 12-lead ECG if performed at presentation), >2-h delay after urgent intravenous loop diuretic administration and unblinded NP level measurement. At the conclusion of ED evaluation, in order to understand better the role of clinical judgment in the correct diagnosis or exclusion of HF, the attending ED physician was asked to render on a scale of 0–100%, the likelihood for acute HF as the cause of dyspnea (thus, 0% would be 'absolutely no likelihood', while 100% would be 'absolutely definite likelihood').

After enrolment, clinical information for all patients was recorded, along with information from diagnostic studies performed in the ED including standard-of-care routine CXR interpretation by attending radiologists blinded to the results of NT-proBNP testing.

All patients consented to use of clinical and laboratory information gathered at the time of initial enrolment. The institutional review board (IRB) approved the use of the data gathered in PRIDE for the current evaluation.

Radiographic standards

Radiographic reports produced by NT-proBNP-blinded on-duty staff radiologists were reviewed on each subject, and the radiologist interpretation was entered into a database by PRIDE study ancillary staff who were not involved in the care of the patients and were blinded to both NT-proBNP and gold-standard review results. All radiographic evidence pertaining to HF pathophysiology was recorded; findings that were observed in <5% of the patients (such as Kerley B-lines) were not included in the present analysis.

CXR information was classified as normal or abnormal; an abnormal CXR was defined as containing one or more of the following: cephalization of vessels, interstitial edema, alveolar edema, pleural effusion(s) and cardiomegaly.

NT-proBNP testing

Blood samples were collected for NT-proBNP measurement at the time of enrolment. These were then processed and frozen at –80°C for later analysis with a commercially available immunoassay (Elecsys proBNP, Roche Diagnostics, Indianapolis, IN, USA) on an Elecsys 1010 analyzer according to established methods. Table 1 provides the standard age-stratified NT-proBNP cut-off points used for the diagnosis of HF.

Gold standard for diagnosis of HF

In the PRIDE study, the gold standard for the diagnosis of acute HF was based on the impression of two independent reviewing cardiologists. By using all available data from presentation through a 60-day review (including radiographic results, but excluding NT-proBNP data), a clinically rendered diagnosis for each patient was assigned. In the 10% of cases in which the diagnosis was unclear or in doubt or when disagreement as to the final diagnosis existed, an adjudicated diagnosis was rendered in accordance with Framingham Heart Study criteria for diagnosis of CHF (Kannel et al. 1999). The IRB approved the use of the data gathered in PRIDE for the current evaluation.

Statistical analysis

Comparisons of clinical characteristics between patients with normal CXR and abnormal CXR were performed with χ^2 tests for categorical data and Wilcoxon's rank-sum test for continuous data, as interval variables were found to be non-normal by the Wilk–Shapiro test.

Sensitivity, specificity, predictive values and positive/negative likelihood ratios were calculated for radiographic variables and NT-proBNP concentrations.

Table 1. Comparative diagnostic performance characteristics for chest radiography and natriuretic peptide (NT-proBNP) for the evaluation of heart failure.

Characteristic	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	LR+	LR–
Radiograph						
Cephalization of vessels	1 (0.3–4.1)	99.5 (98–100)	60	65	2.80	0.99
Pleural effusion	34 (28–41)	92 (89–95)	70	72	4.33	0.71
Cardiomegaly	17 (12–23)	96 (94–98)	70	68	4.35	0.87
Alveolar edema	15 (11–21)	86 (83–90)	38	66	1.13	0.98
Interstitial edema	42 (35–49)	96 (94–98)	86	76	11.6	0.61
Any abnormality	64 (57–71)	73 (68–77)	56	79	2.36	0.49
NT-proBNP						
'Rule in cut-off points'[a]	90 (83–94)	86 (82–90)	84	90	5.98	–
'Rule out cut-off point'[b]	–	–	–	99	–	0.20

[a]450/900/1800 p ml^{-1} for ages <50/50–75/>75 years. [b]<300 pg ml^{-1}, age independent. CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

Receiver-operating characteristic curve analyses with estimation of an area under the curve (AUC) were also performed (Analyze-It software; Analyze-It Ltd, Leeds, UK). The final blinded diagnosis was used as the reference standard.

Results

Of 599 patients evaluated, 359 had a normal CXR result and 240 had an abnormal result. A comparison of the baseline characteristics of our population stratified by normal versus abnormal radiographic results is depicted in Table 2. The median age of the patients with an abnormal CXR was 12 years older than the age of patients with a normal CXR result, 71 years (interquartile range (IQR) 58–80) vs 59 years (IQR 47–72) (p <0.001).

As expected, a higher number of patients with an abnormal CXR were more likely to have a history of prior HF, hypertension, diabetes mellitus, coronary artery disease or myocardial infarction, and more use of loop diuretics, β-blockers and angiotensin-converting enzyme inhibitors; however both groups had similar numbers with a history of obstructive airways disease (11% vs 13%, normal vs abnormal CXR). Patients with a normal CXR had a higher glomerular filtration rate (GFR) (78.3 ml min^{-1} m^{-2} (IQR 57.7–96.3) vs 63.3 ml min $^{-1}$ m^{-2} (IQR 45.2–83.7); p <0.001). Notably patients with an abnormal CXR result had a much higher NT-proBNP level 1919 pg ml^{-1} (399–7167) than those with a normal CXR, 190 pg ml^{-1} (56–967) (p <0.001). Lastly, clinicians were more likely to assign a diagnosis of acute HF to those with an abnormal CXR.

The influence of radiographic results as a function of clinician confidence for the diagnosis of HF was examined. Interestingly, when examining those patients who were ultimately diagnosed with acute HF by the gold standard, but for whom the attending physician in the ED had judged the likelihood for HF to be ≤50% (i.e. 'favouring a diagnosis other than HF'), the prevalence of an abnormal CXR was low, at 34.2%. In contrast, among those correctly judged as having a higher likelihood for HF (i.e. >50%), the prevalence of CXR abnormalities was considerably higher (95%). The ED physicians formulated their assessment using all the clinical information available at the time of evaluation in the ER, including history and physical, laboratory and CXR results.

Table 1 details the performance of radiographic standards for the diagnosis of acute HF, relative to NT-proBNP results. While radiographic cephalization of vessels and alveolar edema were insensitive and non-specific with lower positive and negative likelihood ratios, respectively, the radiographic finding of interstitial edema had a sensitivity of 42% and a specificity of 96% for acute HF with correspondingly high positive likelihood ratio; cardiomegaly also showed a poor sensitivity of 17%, but good specificity of 96%, with the same being true for pleural effusion (sensitivity 34%; specificity 92%). The presence of any radiographic abnormality had a sensitivity of 64% and a specificity of 73% for acute HF but an overall lower positive and negative likelihood ratio.

Among all comers, as reported by Januzzi et al. (2005), NT-proBNP had a sensitivity of 90% and specificity of 86% (Table 1) with reasonable positive likelihood ratio and excellent negative likelihood ratio.

Among those with a normal CXR, ROC curve analysis demonstrated that NT-proBNP had an AUC of 0.94 (CI 0.91–0.96) and was not significantly different to the AUC produced by the curve of NT-proBNP results and an abnormal CXR (0.92, CI 0.89–0.96; p = 0.45). These curves are shown in Figure 1.

The probability of HF was higher in all patients who had a positive NT-proBNP determination regardless of the radiographic finding. Figure 2 provides an overview of these comparisons across groups stratified by radiographic findings and NT-proBNP levels.

A total of 390 patients were judged to be without acute HF; patients in this group with a normal CXR (n = 284)

Table 2. Baseline characteristics in patients with normal vs abnormal chest radiography (CXR) findings.

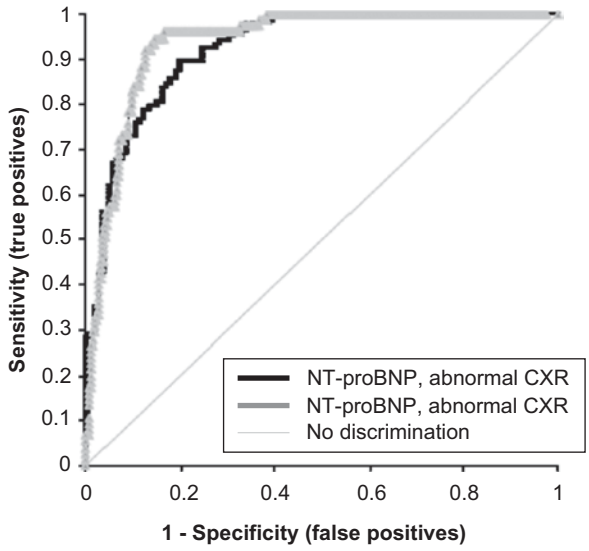
Patient characteristics	Normal CXR (n = 359)	Abnormal CXR (n = 240)	p–Value
Age (years)	59 (47–72)	71 (58–80)	<0.001
Male gender, %	52	50	0.64
Body mass index	27.7 (23.9–31.7)	26.5 (22.9–31.2)	0.14
Symptoms, %			
Paroxysmal nocturnal dyspnea	10	16	0.034
Orthopnea	14	22	0.013
Lower extremity edema	13	24	<0.001
Chest pain	46	38	0.05
Cough	34	41	0.10
Fever	9	10	0.46
Prior medical history, %			
Hypertension	44	56	0.005
Diabetes mellitus	23	31	0.02
Coronary artery disease	24	34	0.005
Myocardial infarction	11	16	0.10
Asthma	19	11	0.009
Chronic obstructive pulmonary disease	11	13	0.50
Medications at presentation, %			
β-Blocker	32	47	<0.001
Loop diuretic	24	38	<0.001
ACEI	16	28	<0.001
ASA	28	34	0.11
Vital signs			
Temperature (°F)	97.7 (97.0–98.3)	97.8 (97.0–98.4)	0.28
Pulse (beats min^{-1})	84 (70–103)	87 (73–104)	0.40
Systolic blood pressure (mmHg)	134 (118–150)	136 (120–152)	0.67
Respirations per min	20 (18–24)	22 (20–28)	<0.001
Physical examination			
Jugular venous distension	8	11	0.15
Murmur	9	15	0.015
Edema	20	32	<0.001
Rales	17	40	<0.001
Wheezing	26	23	0.40
Heart failure (HF)-related variables			
Cardiomyopathy	9	13	0.12
Last known EF (%)	63 (51–69)	58 (39–67)	<0.002
History of prior HF	19	34	<0.001
Suspected acute HF by ED physician	66	95	<0.001
Laboratory testing			
Creatinine clearance (ml min^{-1} 1.73 m^{-2})	78 (58–96)	63 (45–84)	<0.001
NT-proBNP (pg ml^{-1})	190 (56–967)	1919 (399–7167)	<0.001

Continuous variables expressed as medians with interquartile ranges. ACEI, angiotensin converting enzyme inhibitor; ASA, aspirin; EF, ejection fraction; ED, emergency department.

had a median NT-proBNP level of 105 pg ml^{-1} (IQR 41–304), those with CXR abnormalities (n = 106) had a median NT-proBNP value of 334 pg ml^{-1} (IQR 67–994; p = 0.18). For the 209 patients who were evaluated to have acute HF, those with a normal CXR (n = 75) had a median NT-proBNP level of 2664 pg ml^{-1} (IQR 1157–6899), and those with an abnormal CXR (n = 134) had levels of 5564 pg ml^{-1} (IQR 2212–12065; p <0.001). These results are summarized in Figure 3. Lastly, among those with acute HF, but with an NT-proBNP that was below the threshold for the diagnosis ('false negatives'), the proportion of patients with an abnormal CXR was significantly smaller than among those with a 'true positive' NT-proBNP result (39% vs 69%, p <0.001).

Discussion

Chest radiography is a crucial part of the complete evaluation of the acutely dyspneic patient in the ED. Quick



Group	Area under the curve	95% CI
Normal CXR	0.94	91-96%
Abnormal CXR	0.92	89-96%

Not a statistically significant difference.

Figure 1. Comparison of the receiver operating characteristic curves produced by the addition of radiographic information to the natriuretic peptide (NT-proBNP) diagnostic performance analysis. CXR, chest radiograph; CI, confidence interval.

and inexpensive, common sense dictates CXR to be a useful test to evaluate the broad differential diagnosis of shortness of breath, and as a modality for imaging, the CXR will not soon be replaced by any new technology; however, as newer tests for evaluating dyspnea come into use, the additive value of such modalities to chest radiography is important to understand, particularly should emerging data suggest that radiographic standards may be less sensitive or specific for important diagnoses such as acutely destabilized HF.

As an example, when evaluating the relationship between findings on history and physical examination, CXR and cardiac catheterization, radiographic signs of congestion are common in patients with elevated pulmonary capillary wedge pressures, but CXR cannot be used reliably to separate patients with different filling pressures and has poor negative predictive value for excluding significantly elevated filling pressures, which may lead to inaccurate diagnosis and inadequate therapy (Badgett et al. 1996, Chakko et al. 1991). Indeed, in a large registry of 85 376 patients with CXR results, approximately one in every five patients admitted from the ED with acute decompensated HF had no signs of congestion on CXR (Collins et al. 2006).

On a clinical level, the ramifications of these results are important, as data clearly suggest that clinicians may overly rely on the CXR to rule out HF in patients (Collins et al. 2006). Consistent with these findings, in our study, ED physicians (with CXR results available at the time they formulated a diagnosis) were less likely to suspect acute HF when a patient in our cohort had normal CXR interpretation, irrespective of the correctness of the diagnosis; this implies that clinicians place an inordinate value on the ability of CXR to – in particular – exclude the diagnosis of HF. Conversely, in the presence of an abnormal CXR, clinicians were more likely to have the impression that acute HF was present, yet, in those patients, a wide variety of symptoms and signs were present to support the diagnosis.

Similar to a prior meta-analysis (Badgett et al. 1996), our data demonstrated that interstitial edema, cardiomegaly and pleural effusion were the findings with the best diagnostic performance for acute HF, but each had disappointing sensitivity and predictive values and this performance is likely grossly affected by patient selection and pretest probability for acute HF. Indeed, the other radiographic findings occasionally associated with HF on CXR, cephalization and alveolar pulmonary edema, were even less sensitive. Cephalization relies on observing the redistribution of pulmonary blood flow into upper lung zones, and is dependent on the patient positioning. In fact, cephalization may not be reliably diagnosed in supine radiographs, a commonly used technique in portable radiographs performed in the ED setting, as the pulmonary blood flow distributes equally in all lung zones (Collins et al. 2006). This may in part relate to the low sensitivity and specificity of cephalization in our results, but nonetheless reflect the outcome of testing in a routine ED setting. The most likely explanation for the poor diagnostic performance of alveolar edema includes the fact that it is a manifestation of extreme and sustained elevation of left atrial pressure, which may also be caused by processes other than HF, such as pneumonia (van Kimmenade et al. 2006, Cotter et al. 2008).

These findings resemble those of a recent European study evaluating the performance of CXR accuracy for the diagnosis of HF (Studler et al. 2008), where most individual radiographic signs only had moderate diagnostic performance and particularly limited sensitivity, but in contrast to our results, the strategy of grouping signs into an overall radiological impression did outperform individual radiographic signs and achieved a similar accuracy to that provided by BNP testing (Studler et al. 2008).

Still, it is incorrect to assume that the application of CXR is the sole purpose of diagnosis or exclusion of HF in a dyspneic patient, when in fact, it is important to consider the broader differential diagnosis of dyspnea, where the value of CXR has been clearly established (Janower et al. 1984, Collins et al. 2006). This broader view also necessarily highlights the fact that the comprehensive evaluation of the dyspneic patient in the ED includes more than the use of chest radiography.

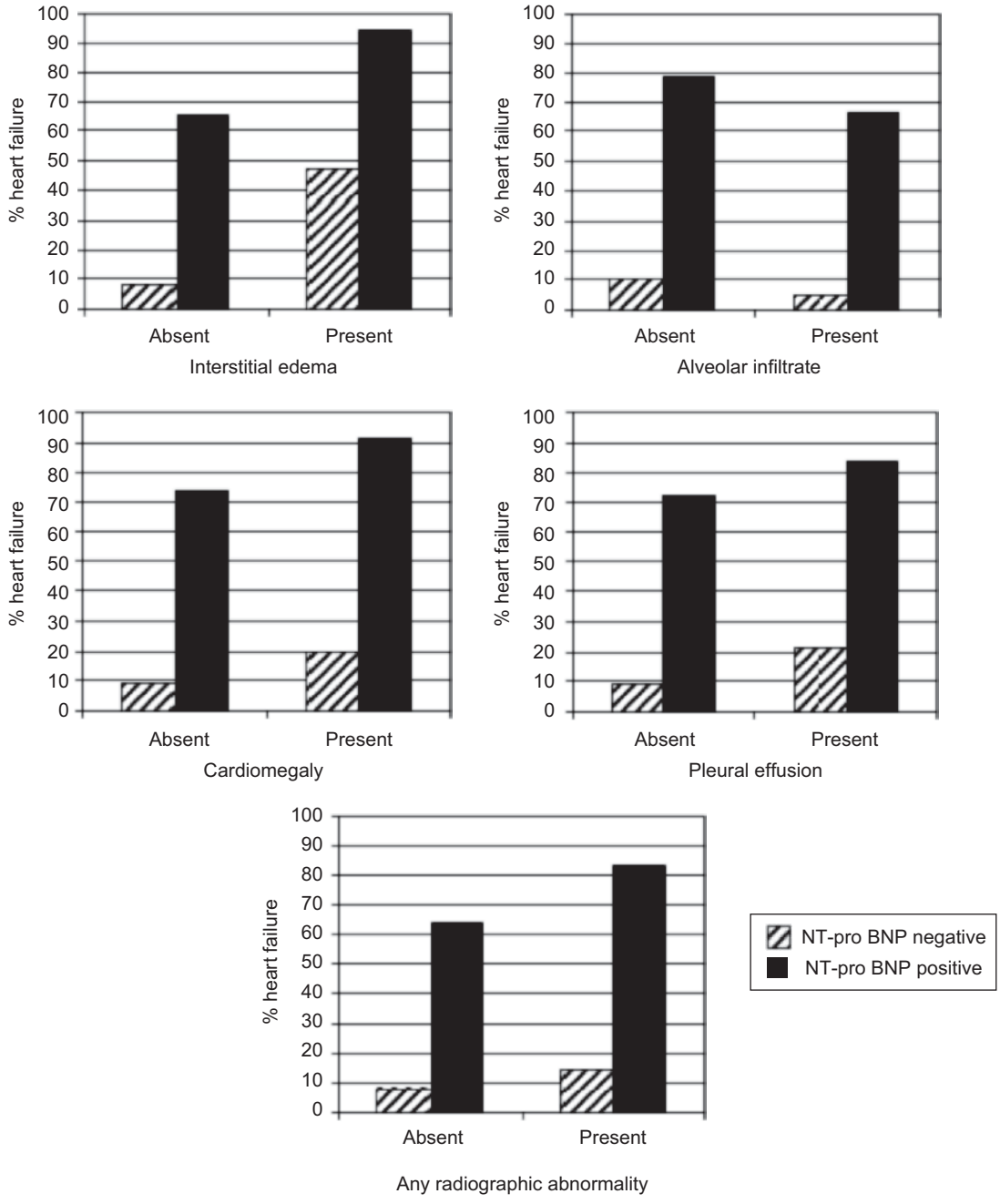


Figure 2. Comparisons across groups stratified by radiographic findings and natriuretic peptide (NT-proBNP) results. Among those with diagnostic NT-proBNP values (solid), the percentage with acute heart failure (HF) was considerably higher, irrespective of the results of chest radiography (CXR); in those with lower NT-proBNP (striped), the prevalence of HF was considerably lower, even if the CXR was positive.

Among the recent advances in diagnostic testing for dyspnea is a better understanding of the role of NP testing in this field. Our data and others demonstrate the extreme sensitivity of NPs for diagnosis or exclusion of acute HF, with superior performance to routine CXR interpretation.

On the one hand, incorporating CXR results into our ROC curve analysis of NT-proBNP, did not improve the diagnostic performance of NP testing for acute HF, which argues for a superior role of NT-proBNP for diagnosis in this setting. On the other hand, on a case-by-case basis, CXR findings are obviously still useful to evaluate those with dyspnea, particularly those with a negative NT-proBNP (where another diagnosis is operative), for those with a positive NT-proBNP (to evaluate for the presence/severity of pulmonary congestion) or intermediate concentration for NP (in order to identify or exclude HF correctly) (Gehlbach & Geppert 2004).

Focusing solely on the question of HF however, our analysis of NT-proBNP levels in groups stratified by

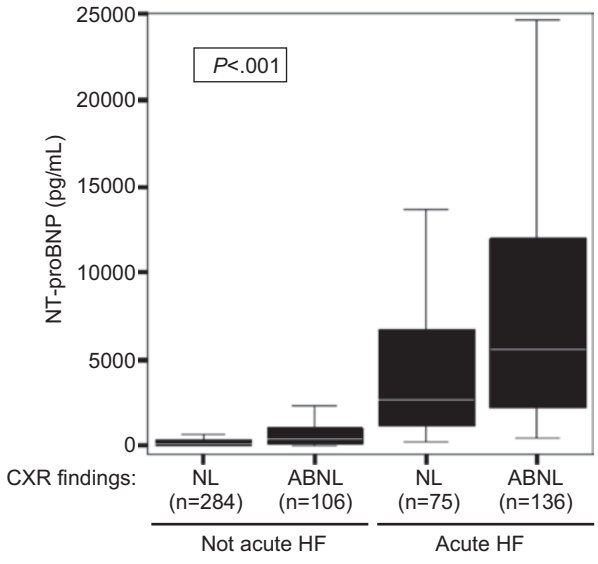


Figure 3. Natriuretic peptide (NT-proBNP) levels stratified across four possible clinical scenarios. The box and whisker plots represent median NT-proBNP levels with their respective interquartile range in the four different groups. CXR, chest radiograph; NL, normal; ABNL, abnormal; HF, heart failure.

the presence and absence of CXR abnormalities and diagnosis of HF suggest that clinicians should expect higher NT-proBNP concentrations in the context of an abnormal CXR, but must also realize that NT-proBNP will still be significantly higher in a patient with acute HF, even in the setting of a normal CXR result. Our subanalyses for each radiographic finding support this concept, showing higher probabilities of HF for the groups with 'positive' NT-proBNP measurements regardless of the radiographic finding. In short, a normal CXR in the presence of abnormal NT-proBNP does not exclude HF, and depending on other clinical findings, further investigation may still be required.

Limitations of our study include the fact that the physicians rendering a final adjudicated diagnosis in the PRIDE study were not blinded to CXR results as variables in their assignment of diagnosis. Nevertheless, we believe it is reasonable to assume that reviewing cardiologists were biased by the CXR results in the same way that ED physicians were (towards assigning more weight to the routine interpretation of the CXR), which in turn would have strengthened the diagnostic value of CXR for the diagnosis of HF and biased towards a null difference. In spite of this, our results still show NT-proBNP to be superior. Furthermore, the radiologists reviewing the CXR may have had access to clinical information regarding the presentation of subjects, which may have biased them towards assigning a diagnosis based on 'incorporation bias' using such information. In addition, CXR interpretation was done as part of standard of care, rather than a blinded, multiple observer method; thus, we lack data regarding interobserver variation. It is possible that combining the more obvious radiographic findings such as pleural effusion(s), pulmonary edema and cardiomegaly into one variable, may increase the diagnostic accuracy of CXR. Unfortunately, in our study there are only a handful of cases where this can be done reliably, and this small number does not allow for a statistically robust analysis. Also, the limitations of ED-based radiography (i.e. the widespread use of portable CXR) may have biased the results against CXR, but we argue our study reflects a 'real-world' comparison of tests. Lastly, the cohort had an exclusion criterion of a serum creatinine >2.5 mg dl^{-1}; as such patients more often present a diagnostic dilemma than less medically complex patients, this may reduce the clinical applicability of our results, particularly given the effects of renal failure on NT-proBNP results.

For a clinician faced with the discordant scenario of a positive NT-proBNP result and absent CXR findings our results suggest the importance of assigning appropriate weight to the NP result, leading to a higher suspicion for HF. As for a scenario where the CXR is suggestive of HF but the NT-proBNP measurement is either negative (<300 pg ml^{-1}) or in the 'grey zone', a more exhaustive consideration of other etiologies of dyspnea is recommended, given that HF will be much less likely, although still possible. Thus, careful clinical judgment, rendered from an excellent history and physical examination is necessary in order to ascertain the diagnosis correctly. Lastly, it is important to emphasize that even in the setting of an elevated NT-proBNP and a strong clinical suspicion, the CXR will always be needed to assess for concomitant non-cardiac causes of dyspnea, and the clinician should always be aware of non-HF pathologies that may cause dyspnea and elevation of NT-proBNP – such as acute coronary syndromes (deLemos et al. 2001), acute pulmonary embolism (Binder et al. 2005) and acute respiratory distress syndrome (Januzzi et al. 2006) to name a few.

In summary, CXR analysis and NP measurements are both useful modalities for evaluating the patient with undifferentiated dyspnea presenting to the ED. Our data suggests that when the CXR lacks congestion and NT-proBNP is elevated, acute HF must still be considered in the differential diagnosis.

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