Review

Paolo Mastandrea*

The diagnostic utility of brain natriuretic peptide in heart failure patients presenting with acute dyspnea: a meta-analysis

Abstract

Heart failure with normal ejection fraction (HFNEF) accounts for approximately 50% of heart failure (HF) cases. To establish the utility of brain natriuretic peptide (BNP) in differentiating HF-related severe dyspnea from non-HF-related acute dyspnea, we used an estimation formula (eF) that was obtained from a series of three meta-regressions. We selected 60 out of 2721 case-control and follow-up studies that were published from 1998 to 2010. The heart failure levels (HFLs) were assessed using the New York Heart Association (NYHA) criteria. Random-effects meta-regression analyses of the natural logarithm (ln) of the BNP odds ratio (OR) were performed on the HFLs. The ln of the median BNP values (lnmBNP) was meta-regressed over the laboratory method (LM). A third meta-regression was performed on the HFLs to account for only the lnmBNP in the homogeneous LM subgroups. To determine the eF, the data from the diseased and control subjects were combined. The Bland-Altman method was used to detect eF bias. The overall BNP(OR) in the subgroup with severe HF was 35. The lnmBNP analysis showed that LM was a significant heterogeneity factor in the meta-regression (slope $-0.38; \text{CI} -0.59$ to $-0.16$). The meta-regression of lnmBNP on the HFL resulted in the following calculation for eF: estimated HFL ($e_{HFL}$) = (lnmBNP $-3.157$)/0.886. The Bland-Altman test revealed no significant difference (0.0997; 95% CI $-2.84$ to $3.06$) between HFL and $e_{HFL}$. The severe $e_{HFL}$ showed a 78% accuracy. Based on the eF obtained from this meta-analysis, the BNP outcomes were shown to reliably diagnose severe dyspnea in HF and differentiate this condition from non-HF acute dyspnea.

Keywords: brain natriuretic peptide; heart failure; meta-analysis.

Introduction

Heart failure (HF) is a major health burden for the Western world, with an increased prevalence in elderly individuals [1]. HF represents an end-stage complication of several pathologies, including both cardiac and extracardiac pathologies. The most common HF diagnostic test is the measurement of reduced left ventricular ejection fraction (LVEF) using echocardiography [1]. An evaluation of the circulating levels of brain natriuretic peptide (BNP) is considered to be a first-step triage test, and BNP measurements have been shown to have high specificity (Sp) but low sensitivity (Se) [2]. Echocardiography has been used as a second-step triage test because it is considered to be more specific [1]. Nevertheless, several recent studies indicate that approximately 50% of patients with HF have normal or near-normal LVEF or fractional shortening, although a variety of cut-off (CO) LVEF values have been applied unsuccessfully. Moreover, in these false-negative cases, additional diastolic dysfunction assessments do not provide additional clarity, because these readouts are weakly correlated with symptomatic or latent HF [1]. Thus, it is clear that the currently available tests for HF greatly need improvement.

Using the most up-to-date laboratory methods to diagnose acute dyspnea, circulating BNP values can rule-out HF at values lower than 100 pg/mL [2]. Only a few authors have diagnosed HF with BNP CO values between 300 [3] and 400 [4] pg/mL. However, both in acute cases and in those that fall within the BNP gray zone (100–400 pg/mL), which mainly correspond to patients with chronic, mild or latent HF, the LVEF and diastolic dysfunction assessments are reported to have a sensitivity of approximately 50%. Maisel et al. suggested that the presence of a large proportion of patients with acute breathlessness and BNP values in the gray zone could reduce the clinical utility of BNP; however, in practice, 75% of patients have values above 400 pg/mL or below 100 pg/mL [4]. Nevertheless, these authors do not clarify what percentage of the BNP values...
were above the high CO point in acute HF breathlessness. HF can occur in the absence of cardiac ejection fraction reduction; in some subjects with true HF, such as in some cases of acute pulmonary edema, the presentation can be dramatic. These patients exhibit physiological and neurohumoral patterns similar to those of patients with HF and reduced LVEF, including impaired oxygen consumption and elevated circulating levels of BNP [1]. However, there is still controversy surrounding the underlying pathophysiology of these cases. Recently, the use of physiological descriptors such as “diastolic HF” has declined, and the more descriptive term “heart failure with normal ejection fraction (HFNEF)” has been adopted [2]. The differential diagnosis between HF-associated acute dyspnea and other cardiac or non-cardiac dyspneas cannot be easily or quickly made at the point-of-care or in an emergency department [5]. For HF diagnosis in emergency departments, echocardiography is challenging because it generally requires a longer turn-around time and advanced operator skills, which are disadvantages compared with the BNP test.

Thus, the objective of this meta-analysis of case-control and follow-up studies was to estimate a formula that can reliably predict HF in the widest possible range of levels. To achieve this goal, we utilized the New York Heart Association (NYHA) classifications and incorporated the simple BNP test. A similar approach was used in the study by Levey et al. [6], which opted not to utilize 24-h urine samples from nephrology patients to obtain creatinine clearance rates, as these measurements are time-consuming and difficult to obtain. Instead, these authors estimated the glomerular filtration rate (eGFR) using their Modification of Diet in Renal Disease (MDRD) formula, that was obtained by regressing serum creatinine levels according to age, gender and ethnicity in a sample of 1628 patients who had been randomized at 15 clinical centers. To test the data accuracy, these authors further compared the estimated values with the urinary clearance of I-125 iothalamate (reference method).

We used the meta-regression results of blood BNP as the most significant determinant of HFL. Traditionally, CO is determined from receiver operating characteristic (ROC) curve, that is a non-parametric model. As regression (and meta-regression) is a parametric linear model, it should obtain a higher Se and accuracy than non-parametric models. Using an estimation formula (eF) that was derived from the meta-regression, the current study aimed to determine whether and in which cases BNP should rule in the diagnosis of HF. This aim was successfully achieved due to the following factors: 1) the high number of subjects and the absence of evident biases in this meta-analysis; and 2) the use of BNP levels to provide diagnostic accuracy, which was shown to be reliable because it was assessed in both diseased and control subjects.

Methods

Preliminary assessments

Studies published from 1998 to 2010 were selected from PubMed using the keywords “brain natriuretic peptide AND heart failure” and the limitations of “human species”, “age >18 years” and “English, French or Italian language”. Other publications were also identified in the references of the selected articles (Supplemental Data Figure 1, which accompanies the article at http://www.degruyter.com/view/j/cclm.2013.51.issue-6/issue-files/cclm.2013.51.issue-6.xml). The guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [7] were followed in performing this meta-analysis. Each study was reviewed twice, and the studies with discordant findings were reviewed a third time. The following inclusion criteria were applied: 1) studies that enrolled healthy subjects, and/or controls, and diseased subjects spanning the entire range of HF stages using the NYHA classification; 2) studies that used subjects without interfering pathologies (renal failure, pulmonary or systemic hypertension, obesity, and anemia); 3) studies that assessed HF levels in diseased (HFLd) and control (HFLc) subjects and BNP Se and Sp in all patients; 4) studies that used whole blood or plasma BNP samples; 5) studies with a declared number of diseased and non-diseased subjects; 6) studies that used the maximum diagnostic accuracy to determine the CO; 7) studies that were not duplicates; 8) studies in which all of the subjects were present in no more than one sample group; 9) case-control or follow-up observational studies; 10) studies in which the subjects were consecutively enrolled; 11) studies that used BNP outcomes in a non-Gaussian distribution expressed in terms of median and inter-quartile ranges and that were reducible to a Gaussian distribution by transformation to the natural logarithm (ln); 12) studies with sample sizes of at least 30 patients; and 13) studies in which the right ventricle was not evaluated for HF.

First, the Gaussian distributions of BNP Se and Sp and the ln of the odds ratio (OR) were tested using the D’Agostino (1990) method [8]. The OR was calculated as follows: (true positives/false negatives)/(false positives/true negatives). To normalize the distribution, the BNP outputs that were expressed as continuous data (i.e., the median, 25th percentile and 75th percentile BNP values...
for the diseased patients and controls, separately) were natural log-transformed to obtain the ln of the median BNP value for the diseased patients (lnmBNPd) and the controls (lnmBNPc). The extracted inter-quartile ranges were converted to one In standard deviation by dividing them by 1.35 [8].

When the BNP blood values were expressed in pmol/L, they were multiplied by 3.46 so that all of the BNP values were uniformly expressed in pg/mL [9]. A continuity correction was applied by adding 0.5 to the true-positive, true-negative, false-positive and false-negative data when the original values were equal to zero. HFLs were classified and subsequently scored according to the NYHA criteria [HFL0: subjects at risk, HFL1: latent dysfunction, HFL2: dyspnea from effort exceeding usual activities (mild HF), HFL3: dyspnea during usual activities (moderate HF), and HFL4: dyspnea at rest (severe HF)]. An additional HFL level, HFL(-1), was included in the meta-analysis to represent healthy subjects. When more than one HFL was considered in the study (with relative percentages), the mean value was obtained, and this value resulted in the generation of continuous HFL values (Supplemental Data Table 1). These HFL values were also categorized using the meta-ANOVA.

Subsequently, a subgroup random-effects meta-analysis and summary ROC curves, which were stratified by HFLd, were obtained to assess the Se, Sp, diagnostic BNP ln OR and the degree of heterogeneity across various subgroups (i.e., the variation in effect size that was attributable to heterogeneity [I2], with 0% – 25% indicating homogeneity, 26% – 50% indicating mild heterogeneity, 51% – 75% indicating moderate heterogeneity, and 76% – 100% indicating severe heterogeneity) [10].

### Random-effects meta-regressions and meta-analyses of variance (meta-ANOVAs)

Compared with continuous lnmBNP data, binary BNP ln OR data are more reliable for detecting associations with HFLs in meta-regressions and meta-ANOVAs [10]. Continuous lnmBNP data are not adjusted according to the BNP CO, which is specific to the study method and the laboratory method (LM) that was used. In contrast, the binary data are constitutionally adjusted for the CO values because the data represent the disease ratios, which reflect the frequencies of positive and/or negative results; therefore, these data are reliable outcomes for ascertaining the significance of HFLs as a disease-constitutive determinant or constitutive heterogeneity factor (HeF) in a first-order meta-regression and meta-ANOVA (Table 1, Step 1-A).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The three-step random-effects meta-regression analysis performed to obtain the estimation formula for heart failure levels at patient point-of-care centers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>aData selected only within homogeneous 2HeF levels. BNP ln OR, natural logarithm of the BNP odds ratio; c1HeF, disease-constitutive heterogeneity factor in diseased and control subjects (i.e., heart failure levels); c1HeFd, disease-constitutive heterogeneity factor in diseased subjects (i.e., heart failure levels); ec1HeF, estimated disease-constitutive heterogeneity factor in diseased and control subjects (i.e., estimated heart failure levels); ef, estimation formula; i1, intercept of the step-specific regression line; lnmBNP, natural logarithm of the median BNP values in both diseased and control subjects; lnmBNPd, natural logarithm of the median BNP values in diseased subjects; 1HeFd, disease-conditioning heterogeneity factor in diseased subjects (candidate factors: age, gender, disease prevalence, LVEF, sample size, publication year, and study design); 2HeF, methodological heterogeneity factor in both diseased and control subjects (i.e., laboratory methods); 2HeFd, methodological heterogeneity factor in diseased subjects (i.e., laboratory methods); s1, slope of the step-specific regression line.</td>
<td></td>
</tr>
</tbody>
</table>

Subsequently, all of the candidate first-order disease-conditioning HeFs (Table 1, Step 1-B), including age, gender, disease prevalence, LVEF, sample size, publication year, and study design, were assessed in relation to the BNP ln OR using the same statistics. With the meta-ANOVAs, significant heterogeneity among studies was considered as true heterogeneity only when the corresponding heterogeneity within the studies was insignificant [11]. Only the concordant results of the meta-regression and the meta-ANOVA were accepted, because both meta-regressions and meta-ANOVAs can provide spurious results that become evident if they are compared with each other [10].

After the importance of HFL and the absence of disease-conditioning factors had been ascertained, the methodological factors were tested as candidate conditioning second-order HeFs; lnmBNPd was the response variable in the second-order meta-regression and meta-ANOVA (Table 1, Step 2). The LM levels were as follows: level 1, chemi-luminescent immunoassay (CLIA) produced by Biosite-Beckman; level 2, microparticle-enhanced immunoassay (MEIA); level 3, CLIA, using a fully automated ADVIA Centaur Bayer; level 4, immuno-radiometric assay (IRMA); and level 5, radio-immunoassay (RIA). In the LM scoring, the level functions as an indicator that has no ordinal meaning. If the lnmBNPd regression on the second-order HeFs was significant, further meta-regressions were performed to identify the homogeneous subgroup.
Furthermore, with the meta-ANOVA, the mean values of the levels within the LM variable were compared with each other, using the tests of Bonferroni, Scheffé, and post-hoc comparisons with “dummy variables” [11]. Next, only the homogeneous lnmBNPd and lnmBNPc data were combined and regressed on the corresponding HFLd and HFLc data. This step was performed to obtain a wide range of data to analyze in the subsequent third-order (or HF-scoring) meta-regression. Once the linear equation was obtained, the estimated HFL (eHFL) values were calculated (Table 1, Step 3).

**Assessment of estimation formula (eF) performance**

The following items were evaluated: 1) total bias (the mean difference between eHFL and HFL); 2) total precision [standard deviation (SD) of the total bias [12]; and 3) accuracy (the percentage of eHFL that was equal to HFL).

**Sensitivity analysis**

The bias assessment was conducted on the binary data set as follows: 1) the Begg and Egger tests were both applied [13] for the publication bias assessment; and 2) the methodological quality items were evaluated according to the recommendations of the Cochrane Collaboration [14] (Supplemental Data Figure 2). The bias estimation was accomplished as follows: 1) using a meta-regression of the BNP ln OR over every bias factor (bias score: 1=absent, 2=present, 0=undetectable); 2) repeating the meta-regression after excluding the biased studies (i.e., the studies with a significant meta-regression); and 3) using box-and-whisker plots to reevaluate the BNP ln OR after excluding the outliers (i.e., outcomes more extreme than 1.5 times the 25th or 75th percentile values) [11].

The meta-ANOVA was performed using SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, USA). The other statistics and the graphics were obtained using Stata 10 (Stata Corp., College Station, TX, USA).

**Results**

**Preliminary assessments**

A total of 71 samples were included from 60 studies [4, 15–74]; the total meta-analysis included data from 26,485 subjects (Supplemental Data Figure 1; Supplemental Data Table 1). One study provided four samples [16], and seven studies each provided two samples [17–22, 49].

In the analysis, ln Se and ln Sp were not considered because of their non-Gaussian distributions (p<0.001 and p=0.006, respectively); conversely, ln OR (n=71, χ²=0.18, p=0.915), lnmBNPd (χ²=2.44, p=0.295) and lnmBNPc (χ²=1.41, p=0.493) were normally distributed.

**Random-effects meta-regressions and meta-ANOVAs**

For the assessment of the disease-conditioning first-order HeFs (Table 1, Step 1-B), only disease prevalence demonstrated a concordant positive result in both the meta-regression and the meta-ANOVA. In addition, age was only significant in the meta-ANOVA, and EF was only significant in the meta-regression.

The constitutive first-order HeF HFL was a significant regressor (Table 1, Step 1-A) (n=71; slope 0.56, CI 0.24–0.88; residual I²=87%), and the LM served as the methodological second-order HeF (Table 1, Step 2). The regression was significant (n=71; slope −0.38, CI −0.59 to −0.16; residual I²=83.81%).

Within the LM, there was homogeneity among levels 1–3. In fact, using the meta-ANOVA mean comparison, a difference resulted between the first three levels and the last two. Furthermore, taking into account only the first three levels, lnmBNPd, regressed on HFLd, was homogeneous (n=48, slope 1, CI 0.7–1.32; residual I²=3%). When the meta-regression accounted for LM levels 4–5, the resulting model was heterogeneous and non-significant (n=23; slope 0.6, CI −0.1–1.3; residual I²=88%).

The third-order meta-regression was significant (n=94; slope 0.886, CI 0.72–1.05; residual I²=0.00%). The eF was determined as follows: eHFL=(lnmBNP–3.157)/0.886 (Table 1, Step 3). Consequently, the resulting BNP CO for HFL4 was 530 pg/mL. In fact, [ln(530)–3.157]/0.886=3.51=HFL4 CO (Table 2).

**Assessment of eF performance**

The total bias of 0.0097 was insignificant (n=94; SD=0.926, CI −2.84 to 3.06). For accuracy, the percentage
Figure 1  A forest plot of the odds ratios of brain natriuretic peptide, which were sub-grouped according to the heart failure levels defined by the New York Heart Association criteria.

CIE, clinical indication for echocardiography; DD, diastolic dysfunction (degree of severity from 1 to 3); ES, effect size of the BNP odds ratio natural logarithm; LVH, left ventricular hypertrophy; PS, patient sample (for studies with more than one sample); RN, reference number; SD, systolic dysfunction (degree of severity from 1 to 3); SDD, systo-diastolic dysfunction.
HFL (range) & eHFL values within the HFL range (frequency) & BNP value, pg/mL & Mean (confidence interval) \\

<table>
<thead>
<tr>
<th>eHFL</th>
<th>HFL</th>
<th>eHFL =± 1 HFL</th>
<th>eHFL =HFL</th>
<th>Mean (confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1 (&lt; −0.49) &amp; 4/4 (1) &amp; 0/4 (0) &amp; 14 (6–32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (−0.49 to 0.5) &amp; 11/22 (0.5) &amp; 8/22 (0.36) &amp; 40 (7–226)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (0.51−1.5) &amp; 12/22 (0.55) &amp; 7/22 (0.32) &amp; 74 (13–420)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (1.51−2.5) &amp; 7/18 (0.38) &amp; 9/18 (0.5) &amp; 134 (30–596)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (2.51−3.5) &amp; 10/19 (0.53) &amp; 7/19 (0.37) &amp; 365 (60–2208)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (&gt;3.5) &amp; 7/9 (0.78) &amp; 2/9 (0.22) &amp; 665 (123–3604)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Evaluation of the estimation formula accuracy in terms of the frequency of eHFL equal to HFL or ±1 HFL, along with the corresponding median values and the confidence intervals of the blood BNP outcomes.

eHFL, estimated heart failure level; HFL, heart failure level.

of eHFL that was equal to HFL was 54%, and the percentage of eHFL that was equal to ±1 HFL was 35%; for HFL4, these values were 78% and 22%, respectively (Table 2).

**Sensitivity analysis**

Regarding publication bias, neither BNP ln OR nor lnmBNPd were significant in the Begg and Egger tests (n=71; z-test (1.14; p=0.255) and bias coefficient (1.36; CI −1.29 to 4) for BNP lnOR; z-test (1.06; p=0.29) and bias coefficient (−1.99; CI −10.39 to 6.41) for lnmBNPd). No significant methodological bias was detected (Supplemental Data Figure 2). Regarding the excluded outliers, the BNP ln OR values of the studies [33, 34] and of the sample with severe systolic dysfunction in the study [16] were considered outliers. The complete results were confirmed after excluding the outliers.

**Discussion and conclusions**

In this random-effects meta-analysis, Table 2 shows that only HFL(-1) and HFL4 revealed good diagnostic performance for BNP. HFL(-1) showed total agreement between the real and estimated HFL results, and the BNP values remained below the negative CO values. HFL4 showed 78% reliability when comparing eHFL and HFL. Therefore, according to the three-step meta-regression method used here, HFL4 severe dyspnea can be more easily differentiated from non-HF acute dyspnea using eHFL, and HFL4 can be reliably “ruled in” using eF BNP CO (i.e., 530 pg/mL) and eHFL. Furthermore, BNP test is also useful as a point-of-care test in emergency departments because it is performed on whole blood. Conversely, NT-proBNP, a hormonalinactive form, works only on serum samples. In my previous meta-analysis [75], I found that, while BNP heterogeneity was explained by some heterogeneity factors (therefore making it useful), NT-proBNP was associated with unaccountable heterogeneity and therefore was not included in the current meta-analysis. However, NT-proBNP has been shown to have an excellent reliability in vitro [76]; in vivo this pro-hormone was sensitive in diagnosing acute heart failure, but less sensitive than BNP in detecting rapid variations in the pathophysiological changes in the patients [77, 78].

Table 2 shows that the BNP mean level at HFL4 was 665 pg/mL (CI 123–3604). By normalizing this outcome with the ln transformation, a value of 6.45 (4.8–8.2) was obtained, and 6 was the ln of 400 (i.e., the ln of the rule-in CO value by the method of the ROC curve); however, this value corresponds to approximately one-third of the half-standard deviation on the left-hand side of the mean value, meaning that it covers only the mean minus 14% of the possible BNP outputs of HFL4. Therefore, the rule-in ROC-curve CO has an accuracy of approximately 64% in detecting HFL4. With the three-step meta-regression method, 78% of the eHFL4 cases correctly estimated the corresponding HFL; this is also the accuracy of the CO found with eF. In previous studies and reviews [2, 4], only the rule-out CO (that optimized Sp) was adopted. Using the higher CO value assessed with the ROC curve, the Se and accuracy were unsatisfactory. The current study was the first to attempt to improve the HFL4 diagnostic accuracy of BNP using a meta-analysis. In this meta-analysis: 1) regression was used as a statistical model with parametric assumptions, which is more powerful to assess HFL4 than CO with the ROC curve; 2) eHFL was not determined using a single-study BNP CO and outcome value; and 3) concerning I² and only considering the second-generation LM in the third-order meta-regression, the lnmBNP F was absent from this second-generation LM, and the study homogeneity contributed to the higher eF performance for HFL4. Furthermore, 1) the extreme eHFLs were one-side bounded, which contributed to the higher performance of the eF for these levels (Table 2); 2) among the negative and positive COs, the extreme HFLs were the farthest from the BNP “gray zone”. Other favorable conditions in this meta-analysis included the absence of relevant biases, the large sample size, and the wide observation range for BNP that covered both normal and diseased subjects. Diseased and control subjects were each considered at every possible HFL. In the Levey study [6], the
mean difference between eGFR and GFR was 0.2, which is twice the mean difference between HFL and eHFL that was found in the current HF meta-analysis. Nevertheless, the Levey confidence interval was narrower (−0.08 to 0.48) because the trial samples in their study were more homogeneous (although multicentric) than ours. Conversely, in the current meta-analysis, the eHFL presented a higher accuracy of the mean but a wider standard deviation. One limitation of our study was that the highest and lowest HFL sample sizes were half the size of other HFLs, which spuriously reduced the subgroup $I^2$ value (Figure 1) for HFL 1 and 4. However, the highest HFL minimized the confounding effect of the first-order conditioning factors on the BNP. The HFL4 eF can be usefully applied to the point-of-care, and in emergency departments it can quickly differentiate (using whole blood) HF-associated acute dyspnea from other severe forms of dyspnea that do not have an HFL4 component. The 22% incorrect diagnosis probability obtained in the current study is the lowest value for HFL4 diagnosis to date. The 78% accuracy of the eF needs to be confirmed in the Emergency Department practice. For example [4], dyspnea in a patient at rest could be caused by: 1) a significant pulmonary embolus or edema; or 2) a sudden HFL4 with another acute cause (that could be extra-cardiac). In the latter case, a normal ejection fraction could be present with the HF; if the extra-cardiac pathology has suddenly developed and the heart is not yet stressed enough to decrease its ejection fraction, but is operating insufficiently for an intrinsic reason (diastolic dysfunction [1]). In the condition described at the point 1) the heart could be a) normal; b) mildly or moderately insufficient; or c) suddenly severely insufficient in non-HF severe dyspnea, but this occurrence is very unlikely. In the cases of a) and b), we conclude that severe dyspnea is of non-HF origin. Only in HFL4 with severe dyspnea, can non-HF acute dyspnea be excluded. In practice, in non-HF severe dyspnea, a) and b) are always the cases. In mitral stenosis and/or insufficiency, that is a cause upstream of the left ventricle, BNP levels may not be very high despite severe symptoms [4]. In fact, the mitral steno-insufficiency, if not yet complicated with HF, is another non-HF condition of severe dyspnea. The non-HF causes of acute dyspnea may be extra-cardiac (pulmonary embolus or edema) or cardiac (mitral non-complicated steno-insufficiency). The rule remains that an eHFL outcome of $<4$ (i.e., $<3.51$) indicates non-HF acute dyspnea (Table 2). However, which is the “gray zone” of this new CO has to be determined in the future. The main exceptions to this rule appear to be when the pathologies of severe renal failure and obesity interfere [4]. Obesity spuriously decreases the levels of BNP [4]; furthermore, in advanced renal failure, that interferes increasing the BNP outcome, the clinical assessment is crucial [4], as eHFL results are inaccurate in 22% of cases. A higher eF accuracy could be achieved by performing an individual patient data meta-analysis.

In this review, it was not possible to compare HFL4 patients with and without preserved ejection fractions, because subjects with normal ventricular ejection at this HFL were absent from the included studies. The reasons for this absence could be that the majority of patients with normal ejection fractions presented with HF of extra-cardiac origin that had not yet strongly compromised the cardiac structure. The second inclusion criterion of this review was “studies that considered subjects without interfering pathologies”; the “interfering” pathology could be the pathology causing the HFNEF, particularly in the very old subjects with significant co-morbidities. Furthermore, there should be a different distribution of the HFNEF across HFLs, and its prevalence at HFL4 should be significantly lower than in HFL2 and HFL3. In fact, HFNEF is synonymous with diastolic HF, that is characteristic of non-acute HF stages. Consequently, the roles of advanced age and co-morbidities require special attention in the future, as both of these factors are likely to occur.

Intermediate eHFLs appeared to have a trend of decreasing accuracy toward the middle level of eHFL2 (Table 2). The low percentage of reliable eHFLs at levels 0–3 (the “gray zone” of diagnostic outcomes) likely depends on the cardiac and/or extra-cardiac BNP conditioning factors, such as arrhythmias, coronary ischemia, valvular dysfunctions, age, gender, disease prevalence, renal failure, pulmonary or systemic hypertension, anemia, and body mass index [5]. These first-order conditioning HeFs can be more exhaustively explored through a large, multicenter follow-up study or an individual patient meta-analysis [79].

In conclusion, the eF CO, which was determined using the BNP ln OR, lnMBNP and HFL values with a three-step meta-regression method, was shown to “rule in” a severe HF diagnosis. Compared to the 50% accuracy of LVEF measured with echography and the 64% accuracy of the “rule in” ROC BNP CO, the HFL CO estimation procedure by the three-steps meta-regression performed significantly better by reliably estimating approximately 78% of severe HF cases. HFL eF could therefore be helpful in the differential diagnosis of severe dyspnea from HFL4 or other acute cardiac or non-cardiac pathologies. Concerning the large “gray zone” between the negative and positive COs, further research is needed on the intermediate HFL HeFs.
Conflict of interest statement

Authors’ conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Received August 3, 2012; accepted October 3, 2012; previously published online November 5, 2012

References


Dr. Paolo Mastandrea is a Clinical Pathologist and Biostatistician, and Assistant Director in the Laboratory Medicine Department, Azienda Ospedaliera S. G. Moscati- Avellino (Italy). He is particularly experienced in the area of the Laboratory Emergency Medicine; other areas of his interest are the Clinical Biochemistry and Metabolism. He is author of several publications, particularly in the field of the laboratory test meta-analysis, cardiac markers, biochemistry of metabolism and laboratory test diagnostic accuracy. He is active member of the SIBioC (Italian Society of Clinical Biochemistry) group of study in Biostatistics.