Combined use of Lung Ultrasound, B-type Natriuretic Peptide and Echo for Outcome Prediction in Patients with Acute HFrEF and HFpEF

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Running title: B-lines and Prognosis of Acute Heart Failure

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Abstract

Background – Lung ultrasound (LUS) can be used to assess pulmonary congestion by imaging B-lines ('comets') for patients with acute heart failure (AHF).

Objectives- Investigate relationship of B-lines, plasma concentrations of B-type natriuretic peptide (BNP) and echocardiographic left ventricular (LV) function measured at admission and discharge and their relationship to prognosis for AHF with preserved (HFpEF) or reduced (HFrEF) LV ejection fraction.

Methods- Patients with AHF had the above tests done at admission and discharge. The primary outcome was re-hospitalization for heart failure or death at 6 months.

Results:- Of 162 patients enrolled, 95 had HFrEF and 67 had HFpEF, median age was 80 [77-85] years and 85 (52%) were women. The number of B-lines at admission (median 31 [27-36]) correlated with respiratory rate ($r = 0.75$; $p<0.001$), BNP ($r=0.43$; $p<0.001$), clinical congestion score ($r=0.25$; $p=0.001$) and systolic pulmonary artery pressure ($r=0.42$; $p<0.001$). At discharge, B-lines were also correlated with BNP ($r=0.69$; $p<0.001$) and congestion score ($r=0.57$; $p<0.001$). B-line count at discharge predicted outcome (AUC 0.83 [0.77-0.90]; univariate HR 1.12 [1.09-1.16]; $p<0.001$; multivariable HR 1.16 [1.11-1.21]; $p<0.001$). Results were similar for HFpEF and HFrEF.

Conclusions- LUS appears a useful method to assess severity and monitor the resolution of lung congestion. At hospital admission, B-lines are strongly related to respiratory rate, which may be a key component of the sensation of dyspnea. Measurement of lung congestion at discharge provides prognostic information for patients with either HFpEF or HFrEF.

Keywords: LUS; Acute HF; HFpEF; HFrEF; Risk stratification.

Abbreviations

AHF: Acute heart failure;

AF: atrial fibrillation

BNP: B-type natriuretic peptide;

DT: Deceleration time;

EF: Ejection fraction;

HF: Heart Failure;

HFpEF: Heart failure with preserved ejection fraction;

HFrEF: Heart failure with reduced ejection fraction;

IVRT: Isovolumetric relaxation time;

LUS: Lung ultrasound;

LV: Left ventricular;

NP: Natriuretic peptides;

PAPs: Systolic pulmonary artery pressure;

ROC: Receiving operating characteristics.

Introduction

Pulmonary congestion, either due to redistribution or retention of water, is a common reason for admitting patients with heart failure to hospital and accounts for high rates of readmission and death. [1] Persisting symptoms and signs of congestion at discharge or amongst out-patients are strong predictors of an adverse outcome. [2-6] Although, symptoms and signs (clinical or radiological) are often obvious when pulmonary congestion is severe, they may not detect milder degrees of congestion. [7,8] Better methods of detecting and quantifying congestion and its resolution could improve management and outcomes.

Plasma concentrations of natriuretic peptides (NP), especially at discharge or in the out-patient setting, when patients are on stable doses of diuretics, reflect the severity of congestion and predict outcome.[9] However, plasma concentrations of NP are influenced by several factors other than cardiac dysfunction (eg:- heart rhythm, renal dysfunction and body mass index). Ultrasound can be used to assess atrial, ventricular and valvular structure and function, pulmonary artery pressure, inferior vena cava distension and, most recently, the lung itself. The synergistic application of biomarkers and imaging enable a detailed assessment of the pathophysiology and cause of heart failure as well as the severity of systemic and pulmonary congestion. [10]

B-lines or lung ‘comets’ on lung ultrasound (LUS) are caused by ultrasonic reverberations arising from extra-vascular lung water. The number of B-lines (ultrasound lung comets) is directly proportional to the severity of lung congestion. [11] LUS could be a simple, accurate, fast and economic tool to assess pulmonary congestion and detect milder degrees of congestion that might benefit from an intensification of therapy. [12] Although B-lines improve diagnostic accuracy, studies reporting their relationship to other non-invasive measures of congestion, such as respiratory rate, B-type natriuretic peptide (BNP) or E/e’, their evolution during treatment, especially for patients with heart failure with preserved ejection fraction (HFpEF) and their prognostic significance are scarce. We set out to address these issues in a prospective, cohort study.

Methods

Population

Consecutive patients admitted to the Cardiology Unit in Siena with dyspnea and subsequent a clinical diagnosis of new-onset or worsening chronic heart failure (HF) and in sinus rhythm were enrolled within 12 hours of hospital admission. HF diagnosis was performed on the basis of the presence of at least two typical AHF signs and symptoms (third heart sound, pulmonary rales, jugular venous distention, hepatomegaly, peripheral edema, lung congestion on chest X-ray and BNP levels greater than 100 pg/dl). Exclusion criteria were 1) patients with a poor acoustic window on echocardiography; 2) pulmonary disease as the dominant cause of dyspnea (eg:- bronchial asthma or chronic obstructive pulmonary disease by clinical history of beta agonist administration and chest signs examination); 3) a history of pneumothorax, lobectomy or lung cancer; 4) myocardial infarction within the last 6 months; 5) atrial fibrillation (AF), because this reduces the accuracy of Doppler measurements; 6) patients with unstable cardiogenic shock (arterial systolic pressure <90 mmHg); 7) patients with infection or inflammatory, autoimmune or neoplastic diseases. This study was approved by our hospital's Institutional Review Board of Siena (CEAVSE) and all patients gave their signed informed consent.

Physical examination and Blood Tests

Patients were evaluated by two physicians at admission and discharge to assess grade of clinical congestion (congestion score) giving 1 point for each of following signs: pulmonary rales, third heart sound, jugular venous distention, peripheral edema and hepatomegaly (5 total points).[13] Blood was taken for the measurement of BNP ((Biosite Inc., San Diego, CA, USA) at admission and discharge into sterile tubes containing EDTA.

Echocardiography

Echocardiography (HP Sonos 5500) was performed within 12 hours of admission by one of two

experienced cardiologists following the recommendations of the American Society of Echocardiography.[14] Systolic and diastolic volumes and left ventricular (LV) ejection fraction (EF) were determined using apical two-and four chamber views by Simpson biplane formula. We evaluated three consecutive cardiac cycles to obtain average pulsed Doppler trans-mitral flow velocity signals. The isovolumetric relaxation time (IVRT) was obtained in the apical five chamber view. Medial and lateral mitral annulus movement was measured using apical four-chamber Tissue Doppler Imaging. Recordings of peak systolic velocity (S'), early diastolic myocardial velocity from both lateral and septal walls (e') and atrial systole velocity (A') were made for three consecutive cardiac cycles. Systolic pulmonary artery pressure (PAPs) was measured by continuous Doppler from the tricuspid regurgitation signal. Tricuspid Annular Plane Systolic Excursion was obtained from M-mode recordings of the lateral tricuspid annulus. Results were normalized for body surface area (in square meters) where appropriate. Patients were classified as heart failure with reduced ejection fraction (HFrEF) [EF<50%] or HFpEF [EF≥50%].

We assessed the diastolic pattern using the following criteria: Impaired relaxation (E/A <1, deceleration time [DT] > 240 msec, IVRT> 90 msec, E/e'<15); pseudo-normal filling (E/A 1-1.5, DT 140-200 msec, IVRT <90 msec, E/e' <15); restrictive filling (E/A> 1.5, DT <140 msec, IVRT <70 msec E/e' ≥15). LV filling pressure was considered normal when the ratio E/e' was ≤ 8; in a grey zone when E/e' was >8 but < 15 and raised when E/e' ≥15. [15] Combination of the current measurements has recently demonstrated to provide a good estimation of LV filling pressure. [16,17]

Lung Ultrasound

LUS was contemporary performed by two physicians within 12 hours of hospital admission and before discharge. Patients were placed in a semi-recumbent position (45°) and scanned using the same probe as for echocardiography, in eight predefined lateral and anterior thoracic zones. [16] We

measured the number of B-lines in parasternal, midclavicular, anterior axillary and midaxillary lines and summed the B-lines in each zone at admission and at discharge. B-lines were defined as discrete laser-like vertical hyperechoic reverberations extending from the pleura to the bottom of the screen and moving synchronously with respiration. [18-19] Intra- and inter-observer variability were respectively 6% and 7%.

Follow-up & Endpoint

Patients were followed for six months after discharge at a clinic or by telephone. The principal outcome of interest was the composite outcome of re-hospitalization for acute heart failure (AHF) or all-cause mortality.

Statistical analysis

Continuous variables were expressed as median (25^{th}-75^{th} percentile) and categorical variables as count or percentage and differences for patients with HFrEF compared to HFpEF tested using Mann-Whitney non-parametric test and X^2 tests. Spearman's rho correlation coefficient was used to assess relationships for continuous variables; in particular BNP was analysed after logarithmic transformation. Receiving Operating Characteristic (ROC) curve were used to assess the relationship between variables and outcome. Cox regression analysis was used to assess the independent and the dependent relationship between variables (B-lines, BNP, age, sex, cardiovascular risk factors, including hypertension, diabetes, dyslipidemia, smoking, coronary artery disease and outcome. All reported probability values were two-tailed, and a p value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 20.0 statistical software package (SPSS Inc., Chicago, IL, USA).

Results

Of 162 patients enrolled, 95 had HFrEF and 67 had HFpEF, median age was 80 [77-85] years and

85 (52%) were women. A history of hypertension (68%), dyslipidemia (53%), ischemic heart disease (38%) and valvular disease (30%) were common. Rales were present in 89% of patients at admission and peripheral edema in 63%. Overall, the median number of B-lines at admission was 31 [27-36], the median BNP was 1,007 [768-1540] ng/L and median PAPs 45 [40-55] mmHg by echocardiography.

Compared to patients with HFrEF, patients with HFpEF were more likely to be women and had lower plasma BNP on admission and at discharge. [Table 1] Compared to patients with HFpEF, those with HFrEF had more B-lines and congestion at admission and discharge. By 180 days, the composite endpoint had occurred more often for HFrEF than HFpEF (44% vs 28%; p=0,04).

Overall, B-lines at admission correlated with respiratory rate (r=0.75; p<0.001), BNP (r=0.43; p<0.001), PAPs (r=0.42; p<0.001), atrial size (r=0.42; p<0.001), clinical congestion (r=0.25; p=0.001) and measures of diastolic dysfunction. [Table 2] Findings were similar for HFrEF and HFpEF. There was also a strong relationship between B-lines and BNP (r=0.69; p<0.001) and congestion (r=0.57; p<0.001) at discharge, especially for patients with HFrEF. [Figure 1-2]

In our sample, 61 patients (38%) developed adverse events during 180 days of follow-up. 45 [28%] patients were re-hospitalized and 16 [10%] died. HFrEF patients showed a significantly higher rate of adverse events with respect to HFpEF patients (42[44%] vs 19 [28%]; p=0.04).

B-lines measured on admission did not predict the composite outcome (AUC 0.52 [0.43-0.61]; p=0.59) with admission BNP faring little better (AUC 0.62 [0.53-0.71]; p=0.01). In contrast, B-lines measured at discharge predicted the composite outcome for the overall population (AUC 0.83 [0.77-0.90]; p<0.001) and appeared superior to discharge BNP (AUC 0.68 [0.59-0.77]; p<0.001). For discharge B-lines, a (Youden) cut-point of 22 identified patients at high risk with fair accuracy (Sensitivity 70%, Specificity 81%, Accuracy 76%). [Figure 3] B-lines measured at discharge (median 20.0 IQR [13.7-26.0]) predicted the composite outcome similarly well for HFrEF (AUC

0.81 [0.72-0.89]; p<0.001) and HFpEF (0.87 [0.78-0.95]; p<0.001). [Figure 4]

B-lines reduction (%) from admission to discharge was significantly correlated with increased congestion score at discharge (r=-0.55; p<0.001). [Supplementary Figure 1 and 2]

At discharge, on univariate analysis, the number of B-lines (HR 1.12 [1.09-1.16]; p<0.001), Log BNP (4.34 [2.06-9.14];p<0.001), congestion score ≥ 2 (HR 5.03 [2.93-8.64]; p<0.001), E/A (HR 1.55 [1.12-2.17]; p=0.009) and E/e'(HR 1.08 [1.01-1.16]; p=0.04) all predicted outcome at 180 days but only the first three contributed independent information in a multivariable model. [Table 3] [Figure 5] The association between B-lines at discharge and outcome was similar for patients with HFrEF (univariate HR 1.10 [1.06-1.14], p<0.001; multivariable HR 1.16 [1.10-1.23], p<0.001) and HFpEF (Univariate HR 1.18 [1.10-1.26], p<0.001; multivariable HR 1.17 [1.06-1.29], p=0.001).

Discussion

To the best of our knowledge this is, to date, the largest and most comprehensive study showing the prognostic importance of B-lines for patients in hospitalized with decompensated heart failure. Several papers demonstrated the additive diagnostic power of LUS in the early diagnosis of HF and its application has been inserted in the guidelines recommendation. [20-25] Current findings has been reported by Gargani et al. and recently confirmed by Coiro in 60 patients during shorter follow up period. [20,21] Anyway no data are currently reported about the building of specific score counting clinical signs, echo and BNP data together with LUS measurement in either HFrEF and HFpEF [Table 4]

In our study protocol B-lines on LUS, measured prior to discharge were a powerful marker of the subsequent risk of readmission for heart failure or death for patients with either HFrEF or HFpEF. However, B-lines measured on admission were only a weak marker of prognosis. This is logical.. The symptomatic efficacy of diuretic treatment in this setting precludes confirmatory randomized controlled trials. Accordingly, any test that can monitor the changing severity of congestion is

unlikely also to be a good test of prognosis in the acute setting. On the other hand, residual congestion at discharge may be strongly linked to re-admissions and death and, therefore, a sensitive and accurate measurement of congestion at the time of discharge should be a powerful prognostic and clinical tool for guiding management.

B-lines measured on LUS were related to clinical evidence of pulmonary congestion, raised plasma BNP, increased echocardiographic measures of left ventricular filling pressure, left atrial dilatation, raised pulmonary artery pressure and inferior vena cava distension. [5,23-28] Many of these features were related to a poor outcome when measured at discharge, but not when measured at admission. [26-29] Accordingly, B-lines appear useful, in addition to BNP and chest X-ray, for the differential diagnosis of suspected AHF as suggested by current guidelines. [9,30,31]

The relationship between the number of B-lines at admission and respiratory rate was remarkably strong. Indeed, we believe this is a unique and important finding of this study. Although tachypnoea is associated with lung congestion and a useful measure of its severity it may not be a reliable, objective diagnostic measure . Nonetheless, this observation suggests that respiratory rate might be a useful, simple measure of dyspnea and lung congestion.

In the setting of chronic heart failure, the pathophysiology and treatment of HFpEF and HFrEF may differ markedly but the mechanisms of congestion and decompensation may be rather similar for each phenotype. [32] In either case, renal retention of water and salt may precipitate fluid overload or activation of the sympathetic nervous system and systemic vasoconstriction may lead to an increase in LV afterload and pulmonary congestion without fluid retention. Alternatively, myocardial ischemia or the onset of atrial fibrillation may cause a sudden deterioration in cardiac function. [33] Pulmonary hypertension secondary to left atrial hypertension and pulmonary congestion may have deleterious effects on right ventricular function, with peripheral organ congestion creating a downward spiral of further cardiac dysfunction and congestion. If LUS are indeed a direct, quantifiable measure of lung congestion then they are likely to be agnostic to its

cause. The speed with which B-lines develop and resolve requires further research.. Many studies in acute HF focused on pulmonary and systemic congestion resolution providing negative results. [34,35] This is probably due to the methods currently employed for congestion evaluation mostly based on symptoms improvement, chest radiography and BNP decrease, rather than a more detailed evaluation of fluid retention in different districts and detailed measurement of effective LV filling pressure. [36] Our data seems to reflect the current view indeed we found poor concordance between congestion sign and number of B-lines. Current analysis did not include patients with AF, representing about one third of patients admitted with AHF. Different studies highlighted the prognostic role of this arrhythmia. [36,37] Nevertheless, diastolic function (e.g. E/A, E/e') cannot be easily assessed in this setting. Thus, our results without AF patients underlined the real prognostic power of BNP, B-lines and clinical congestion. In these subjects in which the diastolic function is poorly detectable

Studies of AHF have had disappointing results. Failure is likely to be multifactorial. Most patients admitted to hospital with peripheral congestion will also have pulmonary congestion. Persistent congestion, pulmonary and/or peripheral, despite standard initial measures identifies patients with greater unmet needs who might benefit from experimental interventions. [36-41]. Although B-lines recruitment is not a specific sign for etiology determination ,and it does not explain the pathopyisiologic mechanism, it appears just a marker of pulmonary congestion independently from HF subtype.

Otherwise, clinical evaluation, based on symptoms and signs, and chest radiography are insensitive measures both of raised LV filling pressures and of residual congestion, which may be particularly important during the early post- discharge vulnerable phase of AHF. [42-46] In our study, although few patients displayed persistent systemic congestion at discharge, around 50% were readmitted within 6-months. Pre-discharge LUS identifies patients with residual, subclinical lung congestion: This appears confirmed by the relation found between residual B-lines and clinical congestion signs Moreover, these two items identify the success of decongestion therapy together with less adverse

events occurrence. Congestion plays a central role in neuro-endocrine and cytokine activation and the development and progression of heart failure. [41] Congested lungs contribute to pulmonary hypertension and are more prone to infection. Renal congestion contributes to water and salt retention. [47,48] Hepatic congestion impairs synthesis of albumin and degradation of aldosterone. In this context, the evaluation of vena cava diameter could be of interest for assessing abdominal congestion. [29,49]

. Objective evidence of freedom from congestion, either the absence of 'comets' or a normal BNP, indicates that at least some aspect of the disease is under control. .

Even if the previous purposed scores demonstrated a good prognostic indicator for short term outcome, they do not appear accurate enough in identification of silent congestion particularly during the early post discharge vulnerable phase. [41,42] Similarly chest radiography does not guarantee an adequate sensitivity and specificity to detect pulmonary congestion particularly in patients developed a chronic pulmonary hypertension. [43,44] An integrated evaluation of decongestion in AHF patients is a future challenge. Our findings highlighted a novel prognostic algorithm including either echo parameters, BNP, clinical score, and lung ultrasound evaluation for a more precise detection of congestion status .

Limitations

This is a single center study with a relative small sample size although it is larger than previously published series. The scan protocol employed used a simplified 8-quadrant protocol that is more practical for clinical use, rather than the full 28 view protocol. Other conditions, such as pulmonary fibrosis, acute respiratory distress syndrome and interstitial pneumonia can cause B-lines Patient cohort included is older than usual population admitted with CHF exacerbation, so extrapolation of these findings to the general population may not be appropriate. For the opposite reason, our sample was previously selected by Chest radiography and BNP measurement and this is not completely representative of general population admitted for dyspnea into emergency department. The

diagnostic accuracy of B-lines may depend not only on the availability of equipment and the skill of the operator but also clinical context, chest X-rays and measurement of BNP as was the case for our study. The persistence of pre-discharge B-lines may reflect sub-optimal medical treatment. However, we cannot be sure that more aggressive treatment to reduce B-lines will improve outcome. An ongoing study is evaluating the potential role of B-lines guided therapy for AHF. [50] Finally, we excluded patients with atrial fibrillation that may confound interpretation of Doppler measures of diastolic function thus our data cannot be extended to the patients affected by this arrythmia in which E/A ratio is not detectable, and E/e' ratio strictly depends on heart rate.

Conclusions

B-lines or 'comets' on LUS are strongly associated with other measures of congestion: clinical assessment, biomarkers or echocardiography. LUS is potentially a readily-available method of assessing pulmonary congestion that may be used to assess and monitor pulmonary congestion. Residual pulmonary congestion at the time of discharge identifies patients with HFrEF or HFpEF at high risk of readmission or death. B-lines at discharge add important information regarding risk stratification and patients with a cut-off value >22 demonstrated impaired outcome. Current findings cannot be extensible to all patients and needto be confirmed in larger, multi-centre studies, . With better standardization, measurement of B-lines might be useful for selecting patients, for therapeutic monitoring and as a surrogate endpoint for clinical trials.

AUTHOR CONTRIBUTIONS

AP and GR helped conceive and design the study and interpreted the results AP supervised the research and wrote the first draft of the manuscript. GR provided statistical analysis and revised the manuscript. MB helped acquire data. RN and JGC contributed to data interpretation and revision of

the manuscript. All authors gave final approval of the version to be published.

TABLES HEADING AND FIGURES LEGEND

Table 1. Differences in patient characteristics between HFrEF and HFpEF.

Table 2. Spearman rho correlation coefficient amongst B-lines, BNP, Respiratory rate, PAPs, E/A, E/e' and congestion score at admission.

Table 3. Univariate and multivariable analysis for 180 days composite outcome.

Table 4. Main studies regarding lung ultrasound in heart failure.

Figure 1. Correlation between admission B-lines and respiratory rate in the overall population and in patients with HFrEF (circles) or HFpEF (diamonds). *Abbreviations: B-type natriuretic peptide (BNP); Heart failure with preserved ejection fraction (HFpEF); Heart failure with reduced ejection fraction (HFrEF).*

Figure 2. Correlation between discharge B-lines and discharge BNP in the overall population and in patients with HFrEF (circles) or HFpEF (diamonds). *Abbreviations: B-type natriuretic peptide (BNP); Heart failure with preserved ejection fraction (HFpEF); Heart failure with reduced ejection fraction (HFrEF).*

Figure 3. ROC curve showing the relationship between the primary outcome and plasma BNP and B-lines for all patients, at admission and at discharge. *Abbreviations: B-type natriuretic peptide (BNP).*

Figure 4. Percentage of adverse events occurrence according discharge B-lines quartiles. *Abbreviations: Heart failure with preserved ejection fraction (HFpEF); Heart failure with reduced ejection fraction (HFrEF).*

Figure 5. Kaplan Meier event curves according to quartile of B-lines at discharge (Median 20.0; quartile range [13.7-26.0]).

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