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Original Research Article

Predictors of Heart Failure in Infants with Bronchiolitis

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Abstract

Background: Patients with acute bronchiolitis are more prone to develop heart failure even in those without underlying cardiac diseases. Clinical assessment of heart failure in such subjects is a challenge. Our objective was to evaluate the diagnostic utility of myocardial performance index and B-type natriuretic peptide (BNP) as predictors of Heart failure during acute bronchiolitis and correlate them to clinical manifestation. ***Method:*** 50 subjects with acute bronchiolitis were enrolled in the study over one year duration; 30 healthy subjects of matched age and gender as control group. Heart failure was identified according to clinical, cardiomegaly in X ray and modified ROS classification. We assess the association between clinical manifestations, echocardiographic findings and serum BNP in subjects with bronchiolitis with and without heart failure. ***Results:*** 30% of subjects with bronchiolitis developed heart failure. There is significant decreased tricuspid and mitral annular plane systolic excursion and significant increase in pulmonary artery systolic pressure, myocardial performance index (MPI) and BNP during acute bronchiolitis especially among those who developed heart failure. Regression analysis revealed that MPI and BNP are independent predictors of heart failure during acute bronchiolitis. ***Conclusion:*** MPI is a valuable echocardiographic marker for early detection of heart failure while BNP is a useful circulating biomarker that can be used to differentiate respiratory distress due to heart failure from pulmonary diseases. It can also be used to estimate the prognosis, as well as to predict cardiac complication in infants presented with acute bronchiolitis.

Keywords: Heart failure, bronchiolitis, myocardial performance index, B-type natriuretic peptide.

INTRODUCTION

Acute bronchiolitis is a common cause of hospital admission in young children that account for about 18% of hospital admissions in children [1]. High risk group include preterm infant, those with underlying congenital heart or lung disease, bronchopulmonary dysplasia, malnutrition and immune deficiency disorders [2]. Subtle myocardial dysfunctions in previously healthy children can occur during lower respiratory tract infection that adversely affects the course of the disease [3]. Initial identification and differentiation of congestive heart failure from primary respiratory disorders during infancy represents a diagnostic challenge specially if developed as a complication of acute respiratory illness [4]. Prolonged hospital admission make a burden on the health providing system especially in low resource developing countries. Early identification and proper management of non-traditional risk factors that affect the course of bronchiolitis are required.

Conventional echocardiography provides a non-invasive bedside tool to evaluate cardiac function and identify high risk groups. Most of these cardiac involvements pass uneventfully so it is usually missed to be identified by physicians [5].

Cardiac impairment can occur even in those with preserved ejection fraction. Ejection fraction has low sensitivity for early detection of systolic dysfunction [6]. Otherwise, there are several parameters can be used effectively to evaluate cardiac function including tricuspid annular plane systolic excursion (TAPSE) for right ventricular function and mitral annular plane systolic excursion (MAPSE) for left ventricular function [7]. Myocardial Performance Index (MPI/Tei Index) has been emerged as a simple reliable indicator of the global left ventricular systolic and diastolic function that is better than ejection fraction and E/A ratio [8].

Echocardiography has limited availability in acute care settings. So using cardiac biomarkers is still required as cost-effective tool for evaluation and

monitoring of cardiac function in high risk populations including those with respiratory tract infection [9].

B-type natriuretic peptide (BNP) is a 32-amino acid peptide that released from cardiomyocytes in response to increased ventricular wall tension caused either volume or pressure overload. BNP is a reliable biomarker for detection of myocardial dysfunction in the acute settings both in adults and children. Elevated BNP level might be associated with worse outcome [10]. Adult studies revealed that elevated serum BNP has high sensitivity and specificity for differentiating cardiac from pulmonary etiologies of respiratory distress [11]. Combination of echocardiography with cardiac biomarkers could be a suitable approach to identify myocardial dysfunction in high risk groups including those with acute bronchiolitis.

Feeding difficulties and excessive sweating are the usual presenting features. Tachycardia >150/min is common, and heart rates >180/min are abnormal even in the setting of respiratory distress and suggests congestive heart failure (HF) [12].

New York Heart Association (NYHA) for HF classification is not applicable for young children. The Ross HF classification was developed to assess severity in infants and has subsequently been modified to be applied to all pediatric ages. The modified Ross Classification incorporates feeding difficulties, growth problems, and symptoms of exercise intolerance into a numeric score comparable with the NYHA classification for adults [13].

METHODS

This prospective cross sectional case control study included 50 children with acute bronchiolitis who were admitted to Sayed Galal University hospital Cairo, Egypt. Illegible children are those less than 2 years presented by acute bronchiolitis with respiratory distress that require hospital admission. Bronchiolitis was defined by the clinical evidence of lower airway obstruction (chest wall retractions, wheezing, or ronchi) preceded by upper respiratory infection in children up to the 18th month of age. Additionally, 30 healthy children of matched age and gender were selected from outpatient pediatric clinic of Alzahraa University hospital, Cairo, Egypt to serve as control group. The study was conducted during the period from November 2017 to March 2018. An informed written consent was obtained from all patients and control groups before getting them involved in the study in accordance with the local ethics committee of Al-Azhar University.

Children with structural congenital heart disease, preterm, those with chronic lung disease, infantile asthma, pneumonia, malnutrition, anemia, genetic or skeletal disorders, children with any chronic systemic disorder that affect the cardiac function (e.g. hepatic, renal, endocrinal, neurological, hematological) were excluded from the study.

History and Examination

All studied children were subjected to detailed medical history taking with stress on: the respiratory, cardiac symptoms, history of shocking, perinatal, developmental and dietetic history. Complete general and systemic clinical examination including anthropometric measurement to assess the nutritional status was done. Data on admission including vital signs (heart rate, respiratory rate, temperature), oxygen saturation using pulse-oximeter while the patient is awake on room air, signs of respiratory distress, cyanosis, current medication and oxygen therapy were recorded from patient file. Chest x ray was done at time of admission.

Diagnosis of Heart Failure

Diagnosis of HF was based on clinical evaluation (tachycardia, tachypnea, enlarged tender liver), modified Ross scoring (II-IV), cardiomegaly in X-ray and echocardiographic examination. The modified Ross Classification incorporates feeding difficulties, growth problems, and symptoms of exercise intolerance into a numeric score [13].

Echocardiography

Trans-thoracic echocardiography was performed for all patients in both supine and left lateral position using Philips HD 7xe apparatus. All cases were examined using multifrequency (4-8 Hz) probe. Comprehensive trans-thoracic M-mode, 2Dimensional (2D), and Doppler were done in standard views (parasternal long axis, parasternal short axis, apical four and two chamber views) from all accessible windows with Loop recording of 2-3 cycles to measure left ventricular (LV) dimensions and volumes. Mitral and tricuspid annular systolic velocity was detected by pulsed wave tissue Doppler in lateral position for evaluating RV function. All parameters were taken on the basis of the American Society of Echocardiography [14] to measure left ventricular (LV) dimensions and functions, and right ventricular (RV) functions with special emphasis on tricuspid annular plane systolic excursion (TAPSE), Mitral annular plane systolic excursion (MAPSE). The TAPSE was assessed with M-mode in apical four-chamber view by placing the examination beam on the lateral tricuspid annulus. Measurement was taken as the amplitude of motion from the end of diastole, until maximal excursion in systole. SPAP estimated echocardiographically on the basis of measurement of the velocity of the tricuspid regurgitation jet [15].

MPI (Tei Index) was measured as the time of mitral closure to opening divided by the left ventricular ejection time by pulsed Doppler with the cursor just between mitral inflow and left ventricular outflow. It is inversely related to overall LV function [16].

Measurement of Serum BNP

Two ml of venous blood was drawn and collected in serum separator tubes and centrifuged for serum separation then stored at -20^{o} till the time of assay according to the manufacturer. Quantitative measurement of BDNF was done using competitive enzyme linked immunosorbent assay kits provided by RayBio International Inc., USA.

The kit contains pre-coated micro titer plate with anti BNP antibody. The samples and standards are then added to the plate, where the biotinylated BNP peptide competes with endogenous BNP for binding to the anti- BNP antibody. Before the assay, the standard was diluted 4 times by pipetting 50ul standard dilution in each well. 100 µl of Anti-BNP Antibody was added to each well and incubate for 1.5 hours at room temperature. All samples were washed 4 times by washing solution then we add 100 µl of each standard, positive control and sample to each well and incubated for 2.5 hours at room temperature. All samples were washed again 4 times by washing solution then we add 100ul horseradish peroxidase HRP enzyme to each well and incubated again for 45min at 37C. 100 µl TMB One-Step Substrate Reagent was added to each well and incubated for 30 minutes at 37C. Reaction was stopped by adding stop solution (50ul) and the color change is measured spectrophotometrically at a wavelength of 450 nm ± 2 nm.

Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (version 21; SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± SD and percentages. Differences between groups were analyzed using independent t student test, chi-square test and ANOVA test. Further analysis for difference between groups was done by post hoc analysis (LSD). Correlations between groups were performed using Pearson correlation coefficients. Binary logistic regression models were analyzed for predictors of HF in subjects with acute bronchiolitis. The diagnostic value of BNP and MPI for predicting HF was assessed using receiver operating characteristic (ROC) curve. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value <0.05 were considered significant.

RESULTS

This case control study included 50 infants (28 male and 22 female) with acute bronchiolitis; their age ranged between 4-15 months with mean value of 9.852 ± 3.463. Their duration of hospital admission ranged between 3-8 days. Fifteen out of the fifty included subjects developed heart failure (30%). No statistically significant difference between the studied groups as regard age, gender and anthropometric measurement of weight and length.

Comparison of the clinical and echocardiographic findings between children with bronchiolitis and healthy controls demonstrated significant decreased oxygen saturation on admission, fractional shortening%, tricuspid and mitral annular plane systolic excursion and significant increase in heart rate, respiratory rate, pulmonary artery systolic pressure and myocardial performance index, serum level of BNP during acute bronchiolitis especially in those with HF as shown in table-2.

The correlations between clinical, echocardiographic findings and serum level of BNP in children with bronchiolitis were demonstrated in table 1. There is significant correlation between the severity of clinical manifestations, duration of hospital admission, echocardiographic indices of myocardial dysfunction and serum level of BNP.

Logistic regression analysis revealed that BNP serum level and MPI (Tei index) are independent predictors of HF in infants with bronchiolitis as shown in Table-3.

Table-1: Correlation of clinical manifestations, echocardiographic findings and BNP in children with acute bronchiolitis

	BNP (ng/ml)	
	r	p-value
LVEDD (mm)	0.076	0.564
FS%	-0.146	0.265
SPAP (mmHg)	0.159	0.226
TAPSE (mm)	-0.417	0.001*
MAPSE (mm)	-0.315	0.014*
MPI (Tei index)	0.460	0.039*
Duration of admission (days)	0.757	<0.0001*
HR (beat/min)	0.764	<0.0001*
RR (cycle/min)	0.427	0.001*
Oxygen saturation%	-0.302	0.019*

LVEDD: left ventricle end diastolic dimension; FS%: fractional shortening; TAPSE: tricuspid annular plane systolic excursion; MAPSE: mitral annular plane systolic excursion; SPAP: pulmonary artery systolic pressure; MPI: myocardial performance index; BNP: B-type atrial nautruitic peptide; HR: heart rate; RR: respiratory rate.

At cut off point ≥ 15.5 ng/ml, BNP serum level has 93.33%sensitivity and 93.33% specificity for prediction of HF among subjects with bronchiolitis while MPI (Tei index) has 83. 3%sensitivity and 90% specificity at cut off point ≥ 0.49.5 as shown in Figure-1.

Table-2: Comparison of clinical, echocardiographic findings and BNP of patients with bronchiolitis and healthy controls

	bronchiolitis with HF N=15	bronchiolitis without HF N=35	Healthy control N=30	ANOVA	Post hoc analysis		
				p-value	I	II	III
					p-value	p-value	p-value
Sex (N,%) male/female	9 (60%) /6 (40%)	19 (54.3%) /16 (45.7%)	15 (50%) /15(50%)	0.815‡	-----	----	-----
Age (month)	9.066 ± 3.362	9.200 ± 3.209	9.366 ± 3.316	0.940	0.998	0.980	0.996
Weight (kg)	8.036 ± 1.671	7.9100 ± 1.841	8.363 ± 1.920	0.609	0.990	0.863	0.731
Length (cm)	65.867 ± 66.300	6.563 ± 7.306	67.233 ± 6.995	0.740	0.993	0.943	0.823
HR (beat/min)	170.266 ± 5.030	147.066 ± 7.952	125.40 ± 4.438	<0.0001*	<0.0001*	<0.0001*	<0.0001*
RR (cycle/min)	67.333 ± 1.953	62.200 ± 7.111	34.900 ± 2.056	<0.0001*	0.002*	<0.0001*	<0.0001*
O_2 saturation %	90.633 ± 2.311	93.000 ± 3.841	98.700 ± 0.915	<0.0001*	<0.017*	<0.0001*	<0.0001*
LVEDD (mm)	2.369 ± 0.137	2.328 ± 0.158	2.281 ± 0.147	0.076	0.652	0.060	0.549
FS%	43.966 ± 2.141	44.667 ± 1.806	44.800 ± 1.494	0.173	<0.0001*	<0.0001*	0.370
SPAP (mmHg)	41.033 ± 4.759	38.500 ± 4.606	36.433 ± 3.645	<0.0001*	<0.0001*	<0.0001*	0.067
TAPSE (mm)	14.266 ± 1.257	14.966 ± 1.245	15.600 ± 1.379	0.001*	<0.0001*	<0.0001*	0.759
MAPSE (mm)	10.966 ± 0.927	11.500 ± 0.731	11.800 ± 0.610	<0.0001*	<0.0001*	<0.0001*	0.176
MPI (Tei index)	0.551 ± 0.062	0.487 ± 0.064	0.461 ± 0.051	<0.0001*	0.001*	<0.0001*	0.114
BNP (ng/ml)	18.233 ± 2.011	11.433 ± 1.887	10.767 ± 2.373	<0.0001*	0.017*	<0.0001*	<0.0001*
Duration of admission (days)	7.566 ± 0.773	4.467 ± 0.899	-----	----	<0.0001*†	-----	-----

I: bronchiolitis with HF versus bronchiolitis without HF
II: bronchiolitis with HF versus control
III: bronchiolitis without HF versus control
† Independent T test; *significant
HF: heart failure; HR: Heart rate, RR: Respiratory rate; LVEDD: left ventricle end diastolic dimension; FS%: fractional shortening; TAPSE: tricuspid annular plane systolic excursion ; MAPSE: mitral annular plane systolic excursion ; SPAP: pulmonary artery systolic pressure; MPI: myocardial performance index; BNP: BNP: B-type atrial nautruitic peptide

Table-3: Logistic regression analysis for predictors of heart failure in patients with acute bronchiolitis

	B	S.E.	Wald	P-value	Exp (B)	95% C.I.for EXP(B)	
						Lower	Upper
TAPSE (mm)	-1.022	0.911	1.256	0.262	0.360	0.06	2.149
MAPSE (mm)	-1.045	1.176	0.79	0.374	2.843	0.284	28.487
MPI (Tei index)	1.12	13.761	0.007	0.039*	3.065	0.287	15.324
BNP (ng/ml)	2.674	1.368	3.819	0.021*	14.492	3.992	41.666
Constant	37.825	26.314	2.066	0.151	0.675		

*significant; FS%: fractional shortening; TAPSE: tricuspid annular plane systolic excursion; MAPSE: mitral annular plane systolic excursion; SPAP: pulmonary artery systolic pressure; MPI: myocardial performance index; BNP: P-type nautruitic peptide

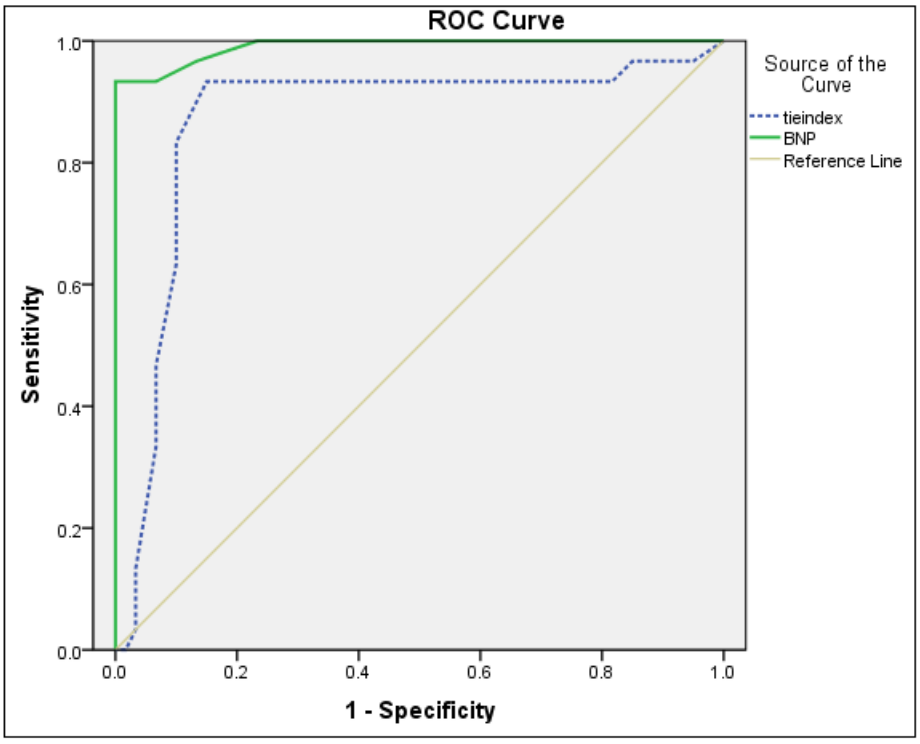

Fig-1: ROC curve of MPI and BNP as predictors for heart failure in patients with acute bronchiolitis

	Cut off point	AUC	Sensitivity	Specificity	PPV	NPV
MPI (Tei index)	≥ 0.495	0.870	83.3%	90%	85.7	95.5
BNP (ng/ml)	≥ 15.5	0.991	93.33%	93.33%	98.2	98.2

AUC: area under curve; MPI: myocardial performance index; BNP: P-type nautruitic peptide

DISCUSSION

Lower respiratory tract infection is a major risk factor for HF in previously healthy subjects that add more burdens to the course of the disease increasing financial cost, duration of hospital admission and increase risk of mortality. In the current study 15 out of 50 infants with acute bronchiolitis developed manifestation of congestive heart failure. This agree with Eisenhut *et al*., [17] systematic review that reported HF and elevated serum troponin levels in 35–54% of ventilated infants with sever bronchiolitis. While Thorburn *et al*., [18] reported right ventricular dysfunction among 20% of cases with severe bronchiolitis.

In spite that echocardiographic ventricular dimension and FS% are within normal limits, however, echocardiographic assessment revealed that those with congestive HF have significant lower FS%, TAPSE and MAPSE and significant higher pulmonary artery systolic pressure and MPI. This agree with previous reports of decreased tricuspid and mitral valves E/A ratios in infants with acute bronchiolitis indicating right and left ventricular diastolic dysfunctions in addition to elevated pulmonary blood pressure and MPI especially in those with acute sever bronchiolitis [19]. Thorburn *et al*., [20] found elevated MPI in patients with acute bronchiolitis however fractional shortening, cardiac ventricular and atrial dimensions had not showed significant difference among those with and without myocardial dysfunction. Bardi-Peti and Ciofu [21] reported elevated pulmonary artery pressure infants with bronchiolitis and attributed this to impact of hyperinflation mechanical forces on pulmonary vessels. MPI simultaneously records systolic and diastolic tissue velocity in the same cardiac cycle providing a reliable, easily applicable tool for assessment of both systolic and diastolic cardiac function [22].

Our study revealed that MPI is an independent echocardiographic predictor of HF with 83.3% sensitivity and 90% specificity. Meric *et al*., [23] reported that standard Doppler assessed MPI has 85.1% sensitivity and 83.1% specificity for evaluation of global cardiac functions in patients with heart failure. The sensitivity and specificity of MPI increased to 92.5 and 91.5%, respectively when assessed using wave Doppler and tissue Doppler.

Regarding BNP, our study demonstrated elevated BNP level in infants with acute bronchiolitis especially those who developed HF with high sensitivity (93%) and specificity (93%) for prediction of HF. In agreement with our findings, Morrison *et al*., [24] concluded that BNP is an accurate predictor of acute HF with 86% sensitivity and 98% specificity for differentiation of HF from pulmonary disease in adult

patients presented with dyspnea. Sahingozlu *et al*., [25] reported in infants presented by respiratory distress, BNP level significantly increased in those with heart rather than lung disease and its level can be used to monitor the response to treatment in infants with heart failure. Up regulation of BNP secretion occurred within 2-12 hours of cardiac strains which explains its high level in those who developed HF [26]. However, hypoxia has been emerged as a stimulus for BNP secretion [27] which explains its higher level in infant with bronchiolitis than healthy controls even in those without HF with significant negative correlation between BNP level and oxygen saturation% on admission of our included infants. Maher [28] reported elevated BNP level in children presented by non-cardiac respiratory diseases however its level was significantly lower, with no overlap to those with cardiac disease. Elevated BNP level represents an adaptive response to myocardial strain; BNP induce natriuresis and diuresis in addition to central inhibition of salt and water intake and suppress antidiuretic hormone secretion leading to decrease volume overload. Furthermore it induces peripheral vasodilatation leading to decrease the pressure overload [29]. BNP may have a role in identification of cardiac impairment in high risk patients who require referral for echocardiography or cardiologist consultation [31].

Several studies both in adult [32] and children [33] demonstrated the diagnostic role of BNP to differentiate cardiac from pulmonary cause of respiratory distress in acute care sitting, however no sufficient data revealed its role as a prognostic marker for identification of cardiac complications including overt or subclinical myocardial dysfunction among subjects presenting with primary lung diseases. Regression analysis demonstrated that elevated BNP is an independent predictor of HF in infants presented with acute bronchiolitis. Furthermore, there was significant positive correlation between the severity of clinical manifestation, echocardiographic indices of myocardial dysfunction and prolonged hospital stay among those infants. Our findings suggest a useful diagnostic role of BNP for identification of pediatric critical heart disease in the acute care setting. Further longitudinal large scale studies will be required to evaluate changes in circulating BNP level and MPI in response to treatment of HF secondary to pulmonary pathology.

The current study revealed a cutoff point ≥15.5ng/ml of BNP for prediction of HF in infants with acute bronchiolitis which is much lower than values reported in adult studies. This difference reflects that BNP production is age specific that increases with age due to age-related changes in ventricular size, subclinical myocardial dysfunction and reduced renal function [32].

CONCLUSION

MPI is a valuable echocardiographic marker for early detection of myocardial dysfunction while BNP is a useful circulating biomarker that can be used to differentiate respiratory distress due to heart failure from pulmonary diseases. It can also be used to estimate the prognosis, as well as to predict cardiac complication in infants presented with acute bronchiolitis.

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