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B-type Natriuretic peptide Levels and Outcome in Children With Severe Acute Malnutrition With Co-morbidity

We studied the ability of B-type natriuretic peptide (BNP) in predicting mortality among 86 in-patients with severe acute malnutrition presenting with co-morbidity, and found that cut-off level of BNP ≥201 pg/mL in Receiver operating characteristics curve [AU-ROC 0.96 (95% CI 0.92,1.003, P<0.0001)] had high discriminative ability to distinguish between survivors and non-survivors.

Keywords: *Cardiac failure, Mortality, Under-nutrition.*

Pneumonia presenting with respiratory failure is associated with heart failure, even in healthy children without cardiac risks, and high mortality [1]. However, risk of mortality and cardiac morbidity is further increased in pneumonia occurring in children with severe acute malnutrition (SAM).The accuracy of diagnosing heart failure in children with presenting with respiratory distress is difficult clinically, as signs of heart failure are subtle and mimic the features of SAM. Prior studies revealed increased levels of BNP in pneumonia complicated with heart failure which returned to lower levels with control of heart failure [2,3]. However, there is paucity of data on BNP levels in children with SAN with pneumonia. Present study, aims to identify levels BNP that predict mortality in children with SAM with co-morbidities.

This case-control study was conducted from September, 2016 to May, 2018 in a tertiary care hospital in Northern India. Consecutive children, aged 6 to 60 months fulfilling the WHO criteria of SAM were enrolled as cases [4]. Age- and sex-matched children of age group 6 to 60 months with weight for length/height >1SD, and mid upper arm circumference >13.5 cm and without pitting edema were recruited as controls from well-baby clinic of the department of pediatrics. The study was approved by the Institutional ethics committee, and informed consent was obtained from the parents before the study. Detailed history, clinical examination, socio-demographic variables, anthropometry, laboratory results, diagnosis and outcome were recorded on pre-designed form.

Co-morbidity was defined as presence of one or more additional conditions co-occurring in SAM children. Tachypnea was defined as respiratory rate >50/minute in 6-12 months children and more than 40/minute in children 13-60 months. Tachycardia was defined as pulse rate >160/minute in children up to one year and more than 140/minute in children 13-60 months [4]. Clinical heart failure was defined as the presence of tachycardia, tachypnea, triple rhythm, tender hepatomegaly and engorged jugular veins [5]. Biochemically heart failure was defined as BNP levels >300 pg/mL [6]. Investigations included arterial blood gas analysis, serum electrolytes, calcium, serum albumin, blood sugar, *X*-ray chest, and any other as per indication. The Alere Triage Cardio 3 panel was used to estimate levels of BNP in SAM children and age- and sex-matched healthy children as per manufacture's guidelines.

For sample size calculation, we measured BNP levels in 16 children with SAM and found that mean (SD) BNP level was 22.6 (25.27) and ranged from 1.8 to 103 pg/mL. Considering ≤100 pg/mL as normal levels, and assuming 20% increase in BNP levels in SAM children with co-morbidity, with power of study as 90% and with alpha error of 0.05, a sample size of 75 SAM children with SAM was required.

Data were analyzed by using SPSS (version 16.0). The Receiver operating characteristic (ROC) curve analysis was performed to obtain the area under the curve (AUC)

as well as the recommended cut-off point. Sensitivity, specificity, positive predictive value, and negative predictive value was calculated.

Of the 86 children (65.1% males), the mean (SD) age of study population were 28.8 (15.2) months and edematous children constitute 60.4% of cases. Thirty-two (37.2%) presented with tachycardia, 53 (61.6%) tachypnea, 31 (36%) with hypoxia (SpO2 <90%), and 18 (20.9%) with hypotension. The co-morbidities were pneumonia 52 (60.4%), acute diarrhea 54 (62.7%), and meningitis 18 (20.9%). Nine (10.4%) children died and rest were discharged from hospital. SAM children dying in hospital were more likely to have tachycardia and hypotension (P<0.001). Among those dying in hospital, 7 presented with septic shock and 9 had pneumonia with diarrhea. Of the 86 children, 32 had BNP levels >100pg/mL and among increased BNP levels, 25 children had tachycardia. The median (IQR) value of BNP in SAM children was 88 (31,117.5) pg /mL, in healthy control children it was 14 (11.23, 18.62) pg/mL and in SAM children without co-morbidity it was 14.5 (11.3, 25.18) pg/mL. There was no difference observed in median (IQR) BNP levels between edematous and non-edematous children [87 (26,111) *vs* 88 (28,109), P=0.69]. There was a significant difference in BNP levels between children who survived and those died, with respect to edema, tachycardia, tachypnea, and hypoxia (***Table* I**). AU-ROC curve revealed a cut-off levels of BNP ≥ 201 pg/mL to discriminate between survivors and non-survivors and this value had sensitivity of 100%, specificity of 90.9%, positive predictive value of 56.2%, negative predictive value of 100%, and accuracy of 91.8%. AU-ROC curve was 0.96 (95% CI 0.92, 1.003, P<0.001) (***Fig.* 1**).

Among clinical signs tachycardia had area under curve, 0.88 (95% CI 0.76, 1.002, P<0.001), revealing a cut-off levels of BNP ≥201 pg/mL to discriminate between survivors and non-survivors and this value had sensitivity of 100% and specificity of 69.6%.

The main finding of the present study is that BNP levels increase significantly in pneumonia with heart failure in children with SAM, and a cut-off levels ≥201 pg/mL has the ability to differentiate between surviving children and those dying in hospital. Similar observations have been reported previously [2,7]. The increased levels of BNP in pneumonia with heart failure are because of stimulation of sympathetic nervous system, pro-inflammatory cytokines, and further compounded by cardiac dysfunction [8]. There was no difference between healthy controls and children with SAM without co-morbidity, signifying that increased BNP levels may be because of co-morbidity in children with SAM. The present study showed that early clinically recognizable parameters like tachycardia in heart failure and shock has good discriminative ability to differentiate between survivors and non-survivors at cut-off levels of BNP ≥201 pg/mL. Echocardiography demonstrated cardiac dysfunction correlates with BNP levels, and a cut-off level ≥140 pg/mL in children with moderate heart failure is associated with a higher risk for death [9]. A single BNP cutoff value of 100 pg/mL had of an accuracy of 83% for differentiating cardiac dyspnea from non-cardiac dyspnea in adults [10]. However, in children, a single BNP assay prior to treatment with values >550 ng/L may indicate the presence of CCF in a child with pneumonia, this might be because of lower age group in study cohort by Sadoh, *et al* [7], as age has impact on BNP levels. In the present study, lower cut-off of BNP to predict mortality may be because of least variability of BNP levels in age group of 1- 5 years.

We had few limitations in our study, as we could not correlate the levels of BNP with ventricular functions of heart and the cardiac mass. Our study in an Indian setup, adds to the growing evidence all over the world that in inconclusive clinical state of heart failure in pneumonia, subtle features of heart failure and the BNP levels ≥201 pg/mL with tachycardia in SAM children warrants the clinicians to suspect and manage heart failure appropriately.

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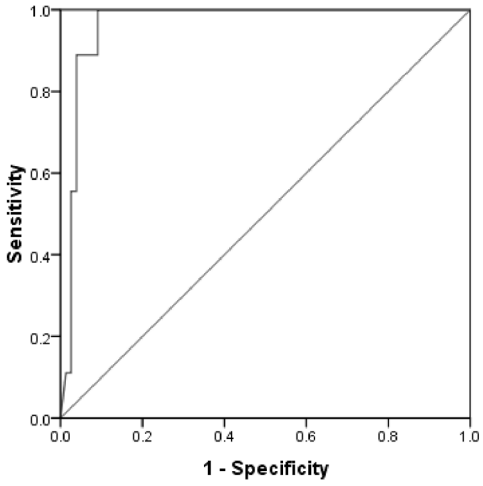

Fig.1 *Receiver operating characteristic curve for BNP levels to predict the death of hospitalized children with SAM. The area under the curve was 0.96 (95% CI, 0.92 to 1.003,P<0.001*) for a level of ≥201 pg/mL.

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Web Table I B-type Natriuretic Peptide Levels Among Inpatients With Severe Acute Malnutrition (*N*=86)

Variables	*BNP levels (pg/mL), median (IQR)*				*P value*
	No.	*Survived (n=77)*	*No.*	*Died (n=9)*	
SAM children	77	79 (27,106)	9	667 (453,931.5)	<0.001
Edematous	50	78.5 (22.75,101.5)	5	689.2 (508.5,1050)	<0.001
Non- edematous	27	86 (33,101)	4	561.5 (273.75,832)	0.001
Tachycardia	23	112 (90,256)	9	667 (453,931.5)	<0.001
Hypotension	9	256 (161.5,786.5)	9	667 (453,931.5)	0.13
Tachypnea	46	86.5 (22.75,109)	7	689 (456,667)	<0.001
Hypoxia (SpO2<90%)	23	80 (23.5,100)	8	678.1 (479.25,953.75)	<0.001
Heart failure(n=17)*					
Clinical	3	223 (189,256)	3	67(213,689.2)	0.40
Biochemical[#] (BNP>300 pg/mL)	5	590 (332,1053)	8	678.1(483.75,953.75)	0.71

**Median (IQR) BNP in heart failure, 567(293,931.5); [#]includes both clinical and biochemical heart failure.*