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Baconga HS, Resontoc LPR, Castor FRM, Yap JIC, Cordova KAT, Mallari AMC, et al. Diagnostic Performance of Brain Natriuretic Peptide, Bioelectrical Impedance Analysis, and Left Ventricular End-Diastolic Diameter in the Determination of Fluid Overload and Mortality In Pediatric Sepsis
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ORIGINAL ARTICLE

DIAGNOSTIC PERFORMANCE OF BRAIN NATRIURETIC PEPTIDE, BIOELECTRICAL IMPEDANCE ANALYSIS, AND LEFT VENTRICULAR END-DIASTOLIC DIAMETER IN THE DETERMINATION OF FLUID OVERLOAD AND MORTALITY IN PEDIATRIC SEPSIS

Hazel S. Baconga, MD, DPPS, Lourdes Paula R. Resontoc, MD, FPPS, Fides Roxanne M. Castor, MD, FPPS, Justine Iris C. Yap, MD, FPPS, Katrina Anne T. Cordova, MD, DPPS, Ardynne Martin C. Mallari, MD, DPPS, and Mary Mae Catherine N. Yu, MD, DPPS
Philippine General Hospital, Manila, Philippines
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ABSTRACT

Objective: This pilot study investigated whether serum B-type Natriuretic Peptide (BNP), bioelectrical impedance analysis (BIA), and left ventricular end-diastolic diameter (LVEDD) can be used to predict fluid overload and clinical outcomes in pediatric sepsis.

Methodology: Pediatric sepsis patients were enrolled. BNP, BIA, and LVEDD were obtained on admission and on Day 3. Diagnostic performances of BNP, BIA, LVEDD and correlation with fluid status were obtained.

Results: Twenty-two patients were enrolled. Day 3 BNP was higher in non-survivors (9241 vs. 682.2 pg/mL, p=0.04) and day 3 LVEDD Z-score was lower in non-survivors (-3.51 vs. -0.01, p=0.023). There was no difference in the fluid balance between survivors and non-survivors. Admission BNP >670.34pg/mL predicted vasopressor use with a sensitivity of 85.71% and specificity of 86.67% while ΔBNP>5388.13pg/mL predicted mortality with 100% sensitivity. Day 3 LVEDD <22mm predicted mortality with a sensitivity of 94.74%. Cumulative fluid balance was strongly correlated with BIA and LVEDD (r=0.65, p=0.001; r=0.74, p<0.001 respectively). The median length of stay in hospital days for non-survivors was not significantly different from survivors (4 [1-12] vs. 8 [6-12] days, p=0.21).

Conclusion: Rise in BNP levels appear to be independent of fluid status and is a good predictor of mortality, vasopressor, and mechanical ventilator use but not of length of hospital stay. LVEDD and BIA are good estimates of cumulative fluid balance but not as predictors of mortality, vasopressor, mechanical ventilator use, and length of hospital stay. Significance of the outcomes of the study was limited due to the small sample size.

KEYWORDS: *Pediatric Sepsis, Fluid Overload, Brain Natriuretic Peptide, Echocardiography, Bioimpedance Analysis*

Correspondence:
Dr. Hazel S. Baconga
Email: hsbaconga@up.edu.ph

The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and all authors have met the requirements for authorship.

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INTRODUCTION

Sepsis presents a continuing health burden and is part of the top ten leading causes of mortality in the country.[1] There is a trend towards search for biomarkers in pediatric sepsis to help prognosticate and predict medical outcomes. One biomarker being studied is the B-type natriuretic peptide (BNP). BNP physiologically causes diuresis, antagonizes the renin-angiotensin-aldosterone system, and produces vasorelaxation.[2] Recent studies indicate increased BNP levels in pediatric patients with sepsis and septic shock.[3-5] Parker, et al. first reported myocardial dysfunction associated with sepsis back in 1984.[6] With evidence pointing to cardiac dysfunction in sepsis, fluid administration should be monitored and regulated.

Fluid resuscitation has been the cornerstone of treatment for pediatric septic shock to restore circulating filling pressure, guided by clinical markers of cardiac output.[7] There is evidence in a systematic review of pediatric sepsis that positive fluid balance is associated with poorer clinical outcomes.[8] The Fluid Expansion as Supportive Therapy (FEAST) trial challenged the established principles on aggressive intravenous boluses, especially for low-income countries.[9]

There is no consensus or standard method to assess fluid overload (FO) in the pediatric population. A proposed method was to determine % FO by a weight-based technique by taking the difference between the daily fluid intake and output and dividing by the baseline body weight. A value above 10% FO is the level at which clinicians intervene.[10]

There is potential for the use of BNP in guiding fluid therapy in patients with sepsis. A study showed that BNP level was closely correlated with fluid balance and that high levels were associated with mortality.[11] In patients with a high fluid load, BNP is a possible indicator of cardiac preload.[12]

Clinical assessment of a patient's volume status by physical examination provides limited reliability and accuracy. A better measure of total body water (TBW) and the extent of absolute fluid overload (AFO) can be assessed with bioimpedance analysis (BIA). Total body water is composed of intracellular water (ICW) and extracellular water (ECW). Several studies, mostly in the adult population, have already shown its advantage in providing useful information on volume status of certain groups, i.e., dialysis patients, congestive heart failure patients, and those with malnutrition.[13-15]

There are no known published studies, at the time of this research, that assesses the diagnostic performance of BNP, TBW, AFO, and LVEDD in pediatric sepsis patients. This study aimed to determine the diagnostic performance of BNP, TBW, AFO, EF, and LVEDD in predicting fluid overload and clinical outcomes in pediatric sepsis and septic shock. Specific objectives included determining the differences in BNP, TBW, AFO, and LVEDD between survivors and non-survivors; determining the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of BNP, TBW, AFO, and LVEDD with regards to clinical outcomes (mortality, vasopressor use, mechanical ventilator use, length of stay >7 days); and determining the correlation of BNP, TBW, AFO, and LVEDD with fluid status.

METHODOLOGY

Study design

This was a prospective observational cohort pilot study conducted in a tertiary public hospital.

Study population

Patients at the emergency room more than 28 days to 18 years old who fulfilled the criteria for sepsis on admission were included.

A pediatric resident or fellow diagnosed the patient as having sepsis following the definition of Systemic Inflammatory Response Syndrome (SIRS) plus a focus of infection, either clinically, radiologically or microbiologically. The entire clinical spectrum of sepsis, including severe sepsis, septic shock and Multiple Organ Dysfunction Syndrome, was included. Patients who expired within 72 hours of hospital stay were included in the study.

Exclusion criteria

Excluded were cases of traumatic injury, acute gastroenteritis, endocrine disorders, renal disorders, liver disorders, cardiac disorders, autoimmune disorders, burn injury, steroid use, hospital acquired sepsis, and weight and length z-scores below < -2.

Withdrawal criteria

A patient was withdrawn from the study if there was withdrawal of consent and inability to obtain BNP, TBW, AFO, or LVEDD on admission and/or on the third day of admission except for patients who expired within 72 hours of admission.

Sample size

A minimum of 22 patients was required for this study based on an odds ratio of mortality due to 10% fluid overload of 21.1, resulting in an alpha of 0.1, 90% level of significance and 80% power.[10]

Data collection

The principal investigator was not the primary healthcare provider for the patient and served only as a researcher. Eligible subjects were recruited through non-probability sampling as they were admitted to the emergency room. Informed consent was obtained and baseline characteristics were recorded by the principal investigator. If the patient needed resuscitation and emergency care, these were done first before proceeding to discuss the study involving the patient.

Extraction of one sample containing at least 0.5 mL blood for serum BNP was done by the physician on duty within the first hour of admission and on the third day, along with the other necessary blood extractions. Serial monitoring of fluid balance noted as the total daily fluid input (tube feeding, intravenous infusion, oral intake) minus daily fluid output (urine output and drainage of body fluid) was done by the nurse-on-duty assigned to the patient during the first three days of confinement. Fluid overload was computed as the fluid balance divided by the baseline weight.

Serial monitoring of total body water (TBW) and absolute fluid overload (AFO) using bioimpedance analysis (BIA) (Fresenius Medical Care Body Composition Monitor SN 7BJA4849) was taken on admission and on the third day of hospital stay by the pediatric nephrology fellow-on-duty.

Serial monitoring of the cardiac ejection fraction (EF) and left ventricular end-diastolic diameter (LVEDD) via point-of-care echocardiography on admission and on the third day was done by a senior pediatric cardiology fellow. It was done using a phased-array transducer (GE Vscan Extend™, frequency 1.7-3.8 MHz, USA) with the patient in supine position. At least three succeeding cardiac cycles were recorded for each session and it was done on the parasternal short-axis view at the level of the papillary muscle. The true-short axis view of the left ventricle was used to determine the left ventricular internal dimensions at end-diastole (LVEDD) and end-systole (LVESD). Corresponding Z-scores of the dimensions obtained were referenced using age-specific population means. Fractional shortening was determined using the formula: $FS = [(LVEDD-LVESD)/LVEDD] \times 100$.[14] The ejection fraction was determined using the formula: $EF = [(LVEDD^3-LVESD^3)/LVEDD^3] \times 100$.[16]

Direct participant involvement occurred only upon recruitment and during the first 72 hours of admission and ended after extraction of blood and monitoring of fluid balance.

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All other information such as the medical history, interventions and laboratory results were obtained from the patient's chart.

The study did not interfere with management of recruited patients and standard treatment was provided. An intake form that included all the necessary data was filled out by the principal investigator alone. All patient related information were kept confidential and only the principal and supervising investigators had access to the files.

Diagrammatic workflow

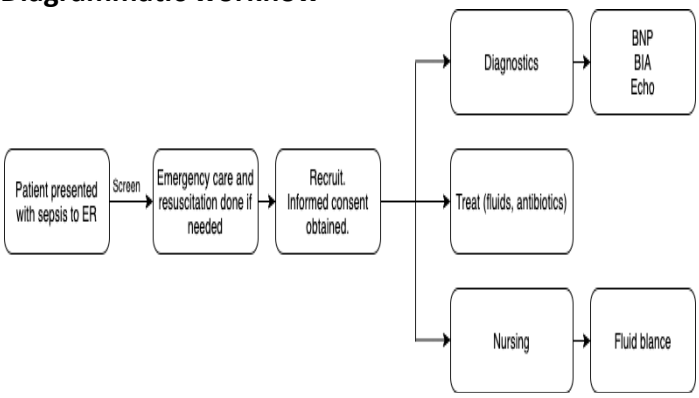

Figure 1. Graphic overview of research workflow at the emergency department

Outcome and Outcome measurements

Baseline characteristics such as patients' demographic and clinical profile were recorded.

Primary and Secondary Outcomes

The primary endpoint of the study was 28-day mortality. Correlation of BNP on admission, ΔBNP, TBW, AFO, EF, and LVEDD with mortality was determined. A patient who expired within 72 hours of admission was included in the analysis.

Secondary outcomes included the following:

1) Diagnostic performance of BNP on admission, ΔBNP, TBW, AFO, and LVEDD with use of vasoactive medications, mechanical ventilator days, and length of stay more than 7days
2) Correlation of ΔBNP, TBW, AFO, and LVEDD with fluid status

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of patients. Frequency and proportion were used for categorical variables and median with interquartile range (IQR) for non-normally distributed continuous variables. Mann-Whitney U test and Fisher's exact test were used to determine the difference of rank and frequency respectively, between survivors and non-survivors.

Cox Proportional Hazard Regression was used to determine significant covariates that were associated with mortality and reported as Hazard Ratio (HR). Death of a participant within 72 hours of admission was accounted for in the statistical analysis.

Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were used to determine the diagnostic accuracy of BNP, TBW, AFO and LVEDD on clinical outcomes. Optimal cut-off values of BNP, TBW, AFO and LVEDD for predicting clinical outcomes (28-day mortality, use of vasoactive medications, mechanical ventilator use and length of stay >7 days) were evaluated using receiver operating characteristic (ROC) curves.

Pearson product moment correlation was used to determine the linear correlation between ΔBNP, Day 3 TBW, Day 3 AFO, and Day 3 LVEDD to cumulative fluid balance and 10% fluid overload.

All statistical tests were two-tailed. Shapiro-Wilk was used to test the normality of continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at 0.05 α-level of significance. STATA 13.1 was used for data analysis.

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RESULTS

Baseline demographic and clinical characteristics were similar for non-survivors (n=3) and survivors (n=19) (Table 1). The median Glasgow Coma Scale (GCS) of non-survivors was significantly lower (p=0.02) with a GCS of 6 (IQR 3 to 15) compared to survivors (GCS of 14, IQR 13-15). The median diastolic pressure of non-survivors versus survivors was statistically lower (48mmHg [IQR 40-56] vs. 65mmHg [IQR 60-69], p=0.05). Sources of infection were the abdomen, lungs, blood, and soft tissues. There was a statistically significant difference (p=0.02) in the sources of infection between non-survivors and survivors. For non-survivors, two patients (66.67%) had clinical sepsis while one (33.33%) had culture confirmed sepsis.

All 3 non-survivors had vasopressor use whereas only 21.05% (p=0.02) of survivors (n=19) used vasopressors. For patients who had vasopressor use, there was no significant difference between vasopressor days (p=0.86). There was also no significant difference between mechanical ventilator use (p=0.23) and mechanical ventilator days (p=0.87) between survivors and non-survivors. No patient in the non-survivor group developed hospital acquired infection compared to 5 patients in the survivor group. Fluid boluses were given to all non-survivors (n=8, 42.11%). Median length of stay in hospital days for non-survivors was not significantly different from survivors (4 [IQR 1-12] vs. 8 [IQR 6-12] days, p=0.21).

Table 1. Characteristics of included patients

Parameter	Total (n=22)	Non-survivors (n=3)	Survivors (n=19)	p-value
	Frequency (%); Median (IQR)			
Age (years)	3.5 (0.67 to 14)	0.67 (0.25 to 13)	4 (0.67 to 14)	0.34
Sex				0.27
Male	14 (63.64)	3 (100)	11 (57.89)	
Female	8 (36.36)	0	8 (42.11)	
Weight (kg)	14 (8 to 36)	8 (6.5 to 36)	13.6 (8 to 37.8)	0.47
Weight Z score	-1 (-1 to 0)	-1 (-1 to 0)	-1 (-1 to 0)	0.68
Height (cm)	98 (66 to 135)	64 (62 to 131)	99 (66 to 149)	0.18
Height Z score	-0.5 (-1 to 0)	-2 (-2 to 0)	0 (-1 to 0)	0.13
Weight at day 3 (kg)	14 (7.6 to 35)	21.25 (6.5 to 36)	14 (7.6 to 35)	0.86
GCS	15 (13 to 15)	6 (3 to 15)	15 (13 to 15)	0.02
Systolic BP (mmHg)	102 (99 to 120)	91.5 (81 to 102)	102 (99 to 120)	0.25
Diastolic BP (mmHg)	63 (60 to 65)	48 (40 to 56)	65 (60 to 69)	0.05
Heart rate (BPM)	133 (121 to 160)	152 (113 to 190)	133 (121 to 160)	0.81
Respiratory rate (RR)	39 (24 to 50)	45 (30 to 60)	39 (24 to 50)	0.59
O2 saturation (%)	98 (95 to 99)	92 (99 to 95)	98 (97 to 99)	0.11
Temperature (C)	37.5 (36.5 to 38)	36.8 (34 to 38.3)	37.5 (36.5 to 38)	0.63
MAP (mmHg)	89.7 (85 to 102)	77 (67.3 to 86.7)	90 (85 to 102)	0.12
Source of infection				0.02
Abdominal	9 (40.91)	0	9 (47.37)	
Blood	4 (18.18)	2 (66.67)	2 (10.53)	
Lung	7 (31.82)	0	7 (36.84)	
Soft tissue	2 (9.09)	1 (33.33)	1 (5.26)	
Diagnosed				0.76
Clinical	9 (40.91)	2 (66.67)	7 (36.84)	
Microbiological	7 (31.82)	1 (33.33)	6 (31.58)	
Radiological	6 (27.27)	0	6 (31.58)	
Vasopressor use	7 (31.82)	3 (100)	4 (21.05)	0.02
Vasopressor days	5 (1 to 7)	5 (0 to 8)	3 (1 to 6)	0.86
Mechanical ventilation use	7 (31.82)	2 (66.67)	5 (26.32)	0.23
Mechanical ventilation days	7 (5 to 9)	7 (5 to 8)	7 (5 to 9)	0.87
Nosocomial infection	5 (22.73)	0	5 (26.32)	1.00
Bolus given	11 (50)	3 (100)	8 (42.11)	0.21
Hospital days	7.5 (5 to 12)	4 (1 to 12)	8 (6 to 12)	0.21

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Table 2. Serum albumin and BNP of included patients

Parameter	Total (n=22)	Non-survivors (n=3)	Survivors (n=19)	p. value
	Median (IQR)			
Albumin (g/L)	36 (31 to 42)	21 (14 to 28)	37 (32 to 43)	0.05
BNP admission (pg/mL)	350 (135 to 3780)	670.34 (213.5 to 3780)	288.14 (91.5 to 5797)	0.53
BNP on Day 3 (pg/mL)	700.85 (274 to 1449)	9241.5 (5601 to 12881)	682.2 (121 to 1432)	0.04
ΔBNP (pg/mL)	450 (-207.7 to 934)	7244.92 (5388 to 9102)	361.87 (-1090 to 750)	0.04

The serum albumin of non-survivors was significantly lower (p=0.05) than survivors (21 [IQR 14-28] vs. 37 [QR 32-43] g/L). Median BNP levels on admission were comparable between non-survivors and survivors (670.34 [IQR 213.5-3780] vs. 288.14 [IQR 91.5-5797] pg/mL, p=0.53). Median serum BNP levels on day 3 of admission were significantly higher in non-survivors compared to survivors (9241.5 [IQR 5601-12881] vs. 682.2 [IQR 121-1432] pg/mL, p=0.04). Subsequently, median ΔBNP levels, which measured the difference between admission and day 3 BNP, were significantly higher in non-survivors compared to survivors (7244.92 [IQR 5388-9102] vs. 361.87 [IQR -1090-750] pg/mL, p=0.04).

Table 3. Echocardiography parameters of included patients

Parameter		Total (n=22)	Non-survivors (n=3)	Survivors (n=19)	p. value
		Median (IQR)			
On Admission	EF (%)	71 (67 to 73)	67.5 (67 to 68)	72 (67 to 74)	0.37
	LVEDD (mm)	32 (25 to 39)	26.65 (19.3 to 34)	32 (25 to 40)	0.40
	Z score	-0.3 (-1.4 to 0.39)	-2.03 (-2.1 to -1.96)	-0.25 (-1.1 to 0.73)	0.07
Day 3	EF(%)	70 (66 to 74)	68.5 (67 to 70)	72 (64 to 74)	0.59
	LVEDD (mm)	31 (26 to 40)	22.5 (19 to 26)	33 (26 to 43)	0.11
	Z score	-0.2 (-0.91 to 0.51)	-3.51 (-4.74 to -2.3)	-0.01 (-0.63 to 0.55)	0.02

Echocardiography parameters of non-survivors and survivors were comparable on admission. None of the patients presented with a decreased ejection fraction characterized as EF <55% at the time of procedure. On day 3 of admission, median LVEDD Z-score of non-survivors was lower than survivors (-3.51 [IQR -4.74 to -2.3] vs. -0.01 [IQR -0.63 to 0.55), p=0.023) and mean LVESD Z-score of non-survivors was lower (-2.3 [IQR -2.9 to -1.71] vs. 0.43 [-0.37 to 0.8], p=0.03). There were no significant differences in bioimpedance analysis (see Table 4) and in the daily and cumulative fluid balance between survivors and non-survivors (see Table 5).

Table 4. Total blood water and absolute fluid overload of included patients

Parameter		Total (n=22)	Non-survivors (n=3)	Survivors (n=19)	P-value
		Median (IQR)			
On Admission	TBW (L)	17 (8.8 to 27.3)	16.15 (7.1 to 25.2)	17 (8.8 to 29)	0.55
	AFO (%)	-13.2 (-40.1 to 5.4)	0.95 (-16.6 to 18.5)	-13.2 (-43.3 to 5.4)	0.34
Day 3	TBW (L)	15.1 (9.7 to 29.6)	27.1 (8.9 to 45.3)	15.1 (9.7 to 29.6)	0.77
	AFO (%)	-5.3 (-13.8 to 3.2)	-5.3 (-13.8 to 3.2)	-1.5 (-13.8 to 10.1)	0.86

Table 5. Percent Fluid Overload of included patients

Parameter	Total (n=22)	Non-survivors (n=3)	Survivors (n=19)	P-value
	Median (IQR)			
Cumulative Fluid balance (mL)	1535 (940 to 2975)	2255 (1535 to 2975)	1500 (940 to 3320)	0.55
10% Fluid overload	0.95 (0.79 to 1.41)	1.59 (0.83 to 2.36)	0.95 (0.73 to 1.41)	0.63

Accounting for the different co-variates affecting survival, there were no significant independent associations between percent fluid overload, BNP, TBW, AFO, and LVEDD with mortality as the primary outcome (see Table 6).

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Table 6. Factors associated with mortality

Parameter	Hazard Ratio (95% CI)	P-value
% Fluid overload		
Cumulative Fluid balance	1.00 (0.98 to 1.01)	0.94
10% Fluid overload	1.42 (0.18 to 11.3)	0.74
BNP		
BNP admission	1.00 (0.98 to 1.01)	0.61
ΔBNP	1.00 (0.99 to 1.02)	0.38
TBW		
TBW on admission	0.99 (0.86 to 1.14)	0.86
TBW on Day 3	1.03 (0.94 to 1.12)	0.53
AFO		
AFO on admission	1.04 (0.96 to 1.14)	0.31
AFO on Day 3	1.01 (0.95 to 1.07)	0.82
LVEDD		
LVEDD on admission	0.96 (0.82 to 1.12)	0.58
LVEDD on Day 3	0.85 (0.64 to 1.14)	0.28

Diagnostic performances of BNP, TBW, AFO, and LVEDD in predicting clinical outcomes are shown in Table 7. BNP levels on admission above the cut-off has high sensitivity for vasopressor use and high specificity for mechanical ventilator (MV) use. ΔBNP above 5388.13 pg/ml and Day 3 LVEDD <22mm as the cut-off had high sensitivity for mortality.

All diagnostic examinations were directly correlated with cumulative fluid balance. ΔBNP levels directly displayed moderate strength of correlation (r=0.43, p=0.04) with cumulative fluid balance, while Day 3 TBW and LVEDD directly displayed strong strength of correlation (r=0.65, p=0.001; r=0.74, p<0.001).

Table 7. Diagnostic performance of BNP, TBW, AFO and LVEDD on clinical outcomes

Parameter	Cut off	Sensitivity	Specificity	PPV	NPV	AU-ROC
BNP on admission	(pg/mL)					
Mortality	≥670.34	66.67%	68.42%	25%	92.86%	0.61
Vasopressor use	>670.34	85.71%	86.67%	75%	92.86%	0.91
MV use	>1211.86	71.43%	86.67%	71.43%	86.67%	0.81
Length of stay >7	≥454.24	63.64%	72.73%	70%	66.67%	0.67
ΔBNP	(pg/mL)					
Mortality	≥5388.13	100%	94.74%	66.67%	100%	0.95
Vasopressor use	≥5388.13	50%	100%	100%	83.33%	0.50
MV use	≥361.87	57.14%	42.86%	33.33%	66.67%	0.53
Length of stay >7	≥450	63.64%	60%	63.64%	60%	0.52
TBW on admission	(L)					
Mortality	≤7.4	94.74%	50%	94.74%	50%	0.63
Vasopressor use	≤8.8	86.67%	50%	81.25%	60%	0.57
MV use	≤15.4	71.43%	71.43%	83.33%	55.56%	0.74
Length of stay >7	≤17	60%	54.55%	54.55%	60%	0.53
TBW on day 3	(L)					
Mortality	≤9.7	78.95%	50%	93.75%	20%	0.43
Vasopressor use	≤9.7	86.67%	50%	81.25%	60%	0.51
MV use	≤10.7	85.71%	57.14%	80%	66.67%	0.65
Length of stay >7	≤11.2	80%	45.45%	57.14%	71.43%	0.53
AFO on admission	(%)					
Mortality	≥18.5	50%	94.74%	50%	94.74%	0.71
Vasopressor use	≥-9.6	66.67%	60%	40%	81.82%	0.76
MV use	≥-30.4	100%	50%	50%	100%	0.71
Length of stay >7	≤-13.2	70%	63.64%	63.64%	70%	0.71
AFO on day 3	(%)					
Mortality	≤-13.6	73.68%	50%	93.33%	16.67%	0.54
Vasopressor use	≤-1.9	66.67%	66.67%	83.33%	55.56%	0.56
MV use	≥-2.9	71.43%	42.86%	38.26%	75%	0.52
Length of stay >7	≤-12.9	80%	45.45%	57.14%	71.43%	0.59
LVEDD on admission	(mm)					
Mortality	≤23	94.74%	50%	94.74%	50%	0.68
Vasopressor use	≤25	86.67%	50%	81.25%	60%	0.56
MV use	≤29	71.43%	71.43%	83.33%	55.56%	0.67
Length of stay >7	≤34	60%	72.73%	66.67%	66.67%	0.58
LVEDD on day 3	(mm)					
Mortality	<22	94.74%	50%	94.74%	50%	0.86
Vasopressor use	≤27	73.33%	66.67%	84.62%	50%	0.69
MV use	≤27	78.57%	71.43%	84.62%	62.5%	0.75
Length of stay >7	≤27	70%	45.45%	53.85%	62.5%	0.58

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Table 8. Correlation of Cumulative Fluid balance to ΔBNP, LVEDD, TBW and AFO

Parameter	Correlation coefficient	Level of association	P-value
ΔBNP	0.43	Directly moderate correlation	0.04
LVEDD on Day 3	0.65	Directly strong correlation	0.001
TBW on Day 3	0.74	Directly strong correlation	<0.001
AFO on Day 3	0.11	Directly weak correlation	0.56

ΔBNP, Day 3 TBW, Day 3 AFO, and Day 3 LVEDD values had no significant correlation with 10% fluid overload.

Table 9. Correlation of 10% fluid overload to ΔBNP, LVEDD, TBW and AFO

Parameter	Correlation coefficient	Level of association	P-value
ΔBNP	0.08	Directly weak correlation	0.72
LVEDD on Day 3	-0.33	Inversely moderate correlation	0.14
TBW on Day 3	-0.36	Inversely moderate correlation	0.11
AFO on Day 3	0.02	Directly weak correlation	0.92

DISCUSSION

Sepsis is one of the leading causes of mortality in the pediatric population. Point of care tests at the emergency department and subsequent monitoring may direct clinicians to make timely interventions to reduce morbidity and mortality, length of stay and improve healthcare costs.

We recruited pediatric patients who were admitted for sepsis at the emergency department, which validated that this pilot study was doable in the critical care setting. Moreover, we were able to monitor their progression in the hospital wards and intensive care unit without problems. Serum BNP determination is readily available in the laboratory of the hospital in which the study was conducted. BIA and point-of-care echocardiography were made available at the emergency department for the duration of the study.

This study was a milestone in the pediatric emergency department on the use of BNP, BIA and point-of-care echocardiography as these were all done in septic pediatric patients.

Serum BNP was included in the standard serum chemistry panel so no additional blood extraction was needed. Moreover, both BIA and point-of-care echocardiography were both non-invasive, quick procedures that did not add any discomfort for patients. BIA is portable, simple to perform, has a lower risk of error from inter-observer variability and is validated for use in children.[17] Point-of-care echocardiography may have inter-reader variability, however, it can be done accurately with proper training.[18] For this study, echocardiography was done by only one experienced cardiologist.

Mortality

Of the 22 recruited patients, non-survivors had severe infections compared to survivors and all patients needed fluid resuscitation and vasopressors. There was no difference between survivors and non-survivors in terms of overall cumulative fluid balance and fluid overload. This is possibly a consequence of judicious fluid therapy practiced in the emergency department and in the hospital wards which adhere to the Surviving Sepsis 2020 Guidelines by Weiss, et al. and the Maitland 2018 findings.[7,9]

This study confirms findings that BNP is elevated in pediatric sepsis and septic shock.[3-5] Median serum BNP levels on day 3 of admission were significantly higher in non-survivors compared with survivors. Subsequently, median ΔBNP levels measuring the difference between admission and Day 3 BNP were significantly higher in non-survivors compared with survivors. However, the BNP level was not a significant risk factor for mortality in pediatric sepsis.

In pediatric patients, increased levels of BNP can also be seen in congenital heart disease with left ventricular overload and cardiomyopathy.[19,20]

The non-survivors did not have significant fluid overload compared to survivors, however, Day 3 BNP values were significantly higher in expired patients, suggesting a different mechanism that is not related to myocardial ventricular stretch from fluid overload but possibly from underlying organ damage.[6,21] In some studies done in adults with sepsis and septic shock, elevated BNP levels have been attributed to cardiac dysfunction, or perhaps build up of inflammatory mediators and endotoxins.[22-26]

TBW and AFO measured by BIA independently were not significant risk factors for mortality in pediatric sepsis. It was surprising to note that all patients had negative AFO values for both survivors and non-survivors. Baseline echocardiography parameters were comparable in both survivors and non-survivors. None of the patients had systolic dysfunction both on admission and day 3 and all EF values were above 50%. Non-survivors had significantly lower diastolic blood pressure, lower Day 3 LVEDD, higher Day 3 BNP, yet with preserved EF. These data are also consistent with the bioimpedance analysis where there were negative AFO percentages, suggesting fluid deficit instead of fluid overload. There was significantly decreased albumin levels in non-survivors. We can infer that with decreased ECW values and decreased LVEDD and LVESD Z-scores, there was low circulating intravascular volume. However, given that BIA only measures ECW and is unable to distinguish between plasma volume and tissue edema components, echocardiography may be helpful to determine effective circulating intravascular volume.

EF was preserved in all patients and even in non-survivors, perhaps due to the use of vasopressors to augment cardiac output. However, there was decreased diastolic blood pressure with increased day 3 BNP levels which might suggest cardiac dysfunction with preserved EF. Studies to determine diastolic function of patients were beyond the scope of this study hence were not performed on patients.

Diastolic function is determined by measuring the ratio between the E wave (early diastolic filling phase) and A wave (atrial contraction) during echocardiography. It is suggested to pursue this study since systolic dysfunction may be foreshadowed or preceded by diastolic dysfunction.[16]

Fluid Overload

Of the three diagnostic tools tested, LVEDD and TBW had direct strong correlations with cumulative fluid balance. All three tests did not have any significant correlation with percent fluid overload and displayed poor accuracy in determining fluid overload. This could be due to the limited subjects in the study. There was a disparity in our results when compared with a similar study by Zhang, et al. in 2012 which looked into 18-80 year old adult patients with sepsis and BNP level & fluid overload in sepsis. Our study had increased BNP values in non-survivors in the absence of significant fluid overload, whereas increase in BNP values was attributed to fluid overload in the study by Zhang, et al.[11] A study by Hartemink, et al. in 2011, which recruited critically ill adult septic patients, implied that increased BNP levels may be indicative of fluid non-responsiveness, regardless of fluid status in critically ill septic patients.[25] As an aid for monitoring and decision-making, increasing BNP levels following fluid resuscitation may guide the clinician to veer away from infusing more fluids and steer towards use of inotropic support.[26]

Other Clinical Outcomes

BNP is a good biomarker for predicting vasopressor use, mechanical ventilator use, and mortality above the cut-off values mentioned. The TBW and AFO levels on admission and day 3 of hospitalization have AU-ROC levels below 0.80 which meant that the discrimination in predicting mortality, vasopressor use, mechanical ventilator use and length of stay of more than 7 days are not excellent.

This is consistent with the demonstrated comparable fluid status of both survivors and non-survivors. The results of this study showed that LVEDD on admission had no diagnostic value in predicting clinical outcomes. However, LVEDD taken on day 3 of admission has excellent diagnostic value in predicting mortality.

This study is limited by the number of patients recruited and may have introduced confounders such as differences in the severity of infection, lack of representativeness of different sources of infection and other unidentified factors. However, in the emergency room and in-patient settings, this would provide vital information to clinicians and might aid in decision-making and in the management of pediatric sepsis.

CONCLUSION

The rise in BNP levels appear to be independent of fluid status and is a good predictor of mortality. LVEDD and BIA are good estimates of cumulative fluid balance, but not as predictors of MV, vasopressor use, and mortality. The utility of these tests is limited to guide fluid therapy.

LIMITATIONS AND RECOMMENDATIONS

There are several limitations to the study. First, this is an observational pilot study and it focused on the feasibility of hypothesis testing. Second, there was an overall decrease in emergency room admissions due to low rates of admission and reduced admitting capacity in the pediatric wards and ICU. Further trials can be performed, such as a cohort study with increased number of participants or a randomized controlled trial utilizing BNP, BIA, or LVEDD to direct fluid administration in pediatric septic patients. Third, there are limitations in the availability of equipment for BIA and echocardiography in the study setting and these equipments are not readily available in the emergency department in all hospitals.

An area for further investigation is the correlation of serum BNP with diastolic dysfunction in pediatric septic patients using spectral doppler assessment. These non-invasive diagnostic tools might aid and augment clinical assessment of pediatric patients who are critically ill.

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