Study of NT-proBNP and Hs-Troponin I biomarkers for early detection of children's heart function of protein-energy malnutrition

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Abstract

The Protein Energy Malnutrition (PEM) is the condition of a lack of carbohydrate and protein stores in the body that trigger chronic failure nutrient intake and body maintenance function caused to impact the heart functions. The NT-pro-BNP and Hs-Troponin I proteins were found as the indicator of cardiac dysfunction. The sixty subjects of PEM, analyzed by standard of Indonesia Healt Ministry as well as nutritional status. The blood electrolytes examined by laboratory assay and the levels of Hs-Troponin 1 and NT-Pro-BNP were analyzed by Immune-Chromatography method. Assessing of the ventricular mass with the seeing the peak of the diastolic flow rate of left ventricular that estimated by the curve of the receiver operating characteristic and the area under the curve ($P<0.05$). The result has shown that the PEM decreased in the left ventricular mass for impaired heart function and systolic disorder. The Hs-Troponin I (90.9%) has better sensitivity than NT-pro-BNP (85.5%) if the merger of those markers possesses the lowest sensitivity (81.8%). These proteins have good biomarkers in heart function, mainly in cases where PEM is present.

Introduction

The Protein Energy Malnutrition (PEM) condition in children is still a public health problem in many developing countries, including in Indonesia.[1] The PEM implies a condition of a lack of carbohydrate and protein stores in the body with or without a body fat reduction that triggers chronic failure in which there is insufficient nutrient intake and body maintenance function.[2] The effects of PEM are liver diseases, alterations of cardiovascular structures and functions, a decrease in the thickness of the inter-ventricular septum, and the posterior wall of the left ventricle. It was last reported that the rate of hypotrophy in the left ventricle was linear with the PEM severity.[3]

The Cipto Mangunkusumo Hospital, in Jakarta, Indonesia found that the left ventricular mass from conditions in PEM children was lower than in children with normal nutrition.[4] Studies of echocardiography have also found that children with PEM have a decreased left ventricular function, both systolic and diastolic. In another study, age was an influence in nutrition status as it continued to be an indicator of ejection and left ventricular shortening fractions of children with malnutrition.[5]

The NT-pro-BNP protein reported as the best single marker for the detection of the dysfunction of systolic and diastolic of left ventricle (LV). The research conveyed that the NT-pro-BNP was considered for detection of both structural and functional cardiac abnormalities.[6] The PEM will cause a disturbance in heart function and changes of myocyte structure, which will cause the Troponin release in the blood circulation and increase the permeability of the cell wall. The concentration of 1.0 ng/mL Troponin I already has the sensitivity and specificity that is necessary to detect the damage of the heart muscle. There are at least five pathobiological pathways for releasing the Troponin into blood circulation. In the case of PEM, it occurs through the apoptotic pathway.[7]

A different study of early diagnosis of myocardial damage used the sensitivity and specificity values of Troponin, while NT-pro-BNP was used to diagnose or judge the effectiveness of cardiovascular therapy. This marker was also considered the single best marker of left ventricular systolic and diastolic dysfunction, as well as a marker of left ventricular hypertrophy. These markers had good diagnostic values with positive sensitivity, specificity, and predictive value to detect systolic dysfunction, because both markers of Troponin I and NT-pro-BNP have high sensitivity charges in myocardial injury and can be used as promising biomarkers.[8] This study investigates the possibility of using these biomarkers as an alternative diagnosis to the rapid and inexpensive examination of emergency health services of heart failure in hospitals which do not have an expert to diagnose of heart disease or echocardiography which currently as the gold standard. The purpose of this study is to analyze the NT-pro-BNP and Troponin I biomarkers in early detection of Protein Energy Malnutrition (PEM) in the heart function of children.

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Key words: NT-Pro-BNP, Hs-Troponin I, Left ventricle, Protein-energy, malnutrition.

Acknowledgments: The Division of Pediatric Cardiology, Sub-Division of Children's Health Sciences, Faculty of Medicine, Syiah Kuala University and the Metabolic Children's Nutrition Division RSUZA Hospital, Banda Aceh, Indonesia.

Contributions: HD for a conception of the research and assessment of subjects as well as drafting the manuscript with BAG. ASH, MJ, and MJ provided the ideas and perspective of the research plus statistical analysis. Particularly, BAG arranged the manuscript and was the corresponding author in the review

Conflict of interest: The authors declare no potential conflict of interest.

Funding: none.

Received for publication: 24 January 2019.
Revision received: 11 April 2019.
Accepted for publication: 11 April 2019.

Licensee PAGEPress, Italy
Pediatric Reports 2019; 11:7997
doi:10.4081/pr.2019.7997

Materials and Methods

The ethical clearance was approved by the Ethics Committee of Medicine Faculty, Syiah Kuala University No.306/KE/FK/2015.

The research was conducted in 2015-2016 by an interdisciplinary study. Sixty subjects of children with PEM were evaluated in public health centers and hospitals scattered across Banda Aceh and Aceh Besar, Indonesia. The PEM values were examined with the Kappa analysis. The echocardiography was checked in the morn-

ing and night. The analysis was based on Kappa at 0.615 (>0.6 is strong suitability).[9]

The relative size of the minimum sample in this diagnostic study was calculated using the following formula:

$$N = \frac{Z\alpha 2 \text{ sensitivity } (1 - \text{sensitivity})}{d^2 p}$$

where N= sample size; Sensitivity = expected inspection of 93%; Zα = error rate 1%, Zα = 2.576; P = Prevalence of heart function decline in PEM 81.5% [10]; d = Precision of research 10%.[10]

The weight of subjects was measured by the model 2T-120 (Tanika, Japan) and height in an upright position with a straight face and barefooted. The body length included a supine position without the use of footwear. Laboratory testing included blood tests, blood glucose levels, albumin, urea/creatinine, and blood electrolytes (Na, K, Cl). Hs-Troponin I and NT-Pro-BNP tests were conducted at the Prodia clinic laboratory. The echocardiography used was the GE Vivid E9, 5-7MHz. An echocardiographic examination was conducted to assess the left ventricular mass and left ventricular and diastolic heart function in patients in a calm state or while lying down. The results were analyzed by the 2×2 table with P<0.05, The Receiver Operating Characteristic (ROC) curve analysis was performed to obtain the area under the curve (AUC) as well as the recommended cutting off point. The following variables were calculated by using the equation: Sensitivity = a/(a+c); Specificity = d/(b+d); Positive estimation value = a/(a+b); Negative estimation value= d/(c+d); Possibility ratio positive = Sensitivity/ (1-specificity); and Possibility ratio negative=(1-sensitivity)/Specificity.[11]

The diagnosis of PEM was determined based on the reference book of the Ministry of Health of the Republic of Indonesia.[12] The nutritional status referenced the Health Standard Analysis issued by the Indonesia Ministry of Health, 2011, that evaluated the nutritional status of children based on the index of Weight/Body length or Weight/Height for children aged 0-60 months, *i.e.* the category of nutritional status was a very thin threshold (Z-Score)<-3SD and thin threshold (Z-Score)-3SD up to <-2SD. For children aged 5-18 years, the study used the IMT/U index, with these categories: nutritional status was very thin (3) threshold (Z- Score) <-3SD, borderline threshold (Z-Score) -3SD to <-2SD. The NT-pro-BNP value: (+)≥100 pg/mL and (-): <100 pg/mL and Hs-Troponin I: (+) >4 pg/mL and (-): ≤4 pg/mL. The echocardiography value: (+); EF below normal and diastolic restrictive pattern and (-): EF normal with a normal diagnostic pattern. The Hs-Troponin I was examined with the Immune-Chromatography method. Blood samples were taken from venous blood with as much as 2.5-5 mL inserted into the tube clot activator or tube LI- Heparin. The blood samples obtained were stores at 2-80°C for 48 h or at ≤600C for 4 months. The bacteria infection criterion of absolute rejection was the appearance of the thickness and bacterial contamination, but not perfect in the case of hemolysis and lipemic.[13]

The assessment of left ventricular systolic function was performed by looking at the value of the shortening fraction. The left ventricular mass profile was performed with the M-mode examination to determine the left ventricular mass. M-mode checks determined the left ventricular mass (LVM) profile with the equation: *LVM* (g) = 0.80 {+0.6}, where LVID (the left ventricular internal diastolic dimension), PWT (the left ventricular posterior wall thickness), and IVST (the thickness of the interventricular septum in the diastole).[14]

The determination of the shortening fraction (SF) and ejection fraction (EF) were determined by the SF Normal value = 28-44%, and the normal EF was 64-83%, which is also an impaired function if it was below the normal values of SF and EF. The assessment of the left ventricular diastolic function was determined by the initial peak diastolic flow rate, peak velocity during fast ventricular filling (E), and peak velocity during atrial contraction (A).[15]

Statistical analysis

The analyses of NT-Pro-BNP and Hs-Troponin I biomarkers were a bivariate, the Fisher and Mann-Whitney test, and significance (P<0.05).

Results

The total sample was 60, composed of 35 (58%) females and 25 (42%) males. Laboratory parameters such as hemoglobin, blood protein (albumin), blood sugar, sodium, potassium, and chloride had a standard (Table 1). The echocardiographic examination showed that 86.7% of PEM children had a small left ventricular mass (hypotrophy) with a median of 67.4g (standard 29.6-149.2g). The characteristics of subjects were based on echocardiography examination (Table 2).

Table 3 used the bivariate analysis with the Fisher and Mann-Whitney test on some indices of left ventricular function disorder and found significant differences in some variables such as age, NT-pro-BNP, and Hs-Troponin I levels. The results of the AUC analysis for each independent variable (Hs-Troponin I, NT-pro-BNP, or combined Hs-Troponin I and NT-pro-BNP) showed both the higher values of either NT-pro-BNP or Hs-Troponin I in line with the high proba-

Table 1. Characteristics of subjects and examination results.

Characteristics	Standard	Result
Age (month)	8-186	38
Temperature (°C)	36.5-37.5	36.95
Pulse (times/minute)	82–120	100
Systolic (mmHg)	70–85	80
Diastolic (mmHg)	35-45	40
Hemoglobin (g/dL)	10-12,2	10.6
Albumin (g/dL)	3.5-4.5	4
Glucose (mg/dL)	76-112	96
Na (mEq/L)	135-145	138
K (mEq/L)	3.5-4.5	3.95
Chloride (mEq/L)	90-110	98
NT-proBNP (pg/mL)	50-8134.4	199.35
HsTroponin I (ng/mL)	4-18.3	4.10
Group of NT-pro-BNP		
Positive ≥100 pg/mL	83.3	50
Negative <100 pg/mL	16.7	10
Group of HsTroponin I		
Positive >4 ng/mL	88.3	53
Negative ≤4 ng/mL	11.7	7

bility of impairment of the left ventricle function. These results showed the significance value for Hs-Troponin I was P=0.02 and for NT-pro-BNP, it was P=0.04 (Table 4). Figure 1 in the ROC study found the most optimal accuracy on the NT-pro-BNP result was ≥100.3 ng/mL with a sensitivity value of 85.5% and specificity of 40%. The 2x2 table showed the value of NT-pro-BNP and Troponin I biomarkers was sensitivity (NT-pro-BNP 85.5%, Hs-Troponin I 90,9% and the combination of the two markers had a sensitivity of 81.8%) (Figure 2).

Discussion

Physiologically, the left ventricle (LV) has thicker muscles than the muscles in the right ventricle (RV). Both act as a systemic pump of blood throughout the body for metabolism. In the case of PEM, there is atrophy/reduction of all striated muscles in the body including the muscles of heart/muscles in LV. Its effect to decrease the systolic and diastolic of heart function is the cause of heart failure.[16] This phenomenon can be detected by the biomarker based on how the endocrine system works in the homeostasis fluid of the body and blood pressure. The process is through the modulation of heart function that is controlled by natriuretic peptide (NP) that binds the cell surface receptor like the receptor A and NP receptor B. These receptors are expressed in the cardiovascular system, kidneys, lungs, skin, coagulation system, and central nervous system.[17] In 2005, McGrath reported the endocrine system role in the heart pump that influenced both Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP) proteins. The BNP synthesized by the heart muscles (myocardium) as the prohormone (pro-BNP), while Troponin I is released in blood circulation as the effect of necrosis of heart muscle in PEM case. Both biomarkers are appropriate for detecting heart failure.[18]

This malnutrition condition also showed that cardiac dysfunction was more associated with a systolic disorder than diastolic. The valuation of echocardiography is based on the LV systolic function by EF and FS assessments as well as LV diastolic function by assessment of E/A pattern. Table 2 shows LV value of systolic and diastolic in 52 subjects (86.7%) who experienced the heart muscles atrophy with the heart weight median of 67.38 g (29.64-149.21 g). The assessment of the left ventricular function with echocardiography with a result of decreased left ventricular function was found in children that had a

Table 2. Characteristics of subjects based on echocardiography examination.

Characteristics	Value	%
Left ventricular systolic disorder		
Yes	55	91.7
No	5	8.3
Left ventricular diastolic disorders		
Yes	51	85.0
No	9	15.0
Pattern of left ventricular diastolic disorder		
Restriction	51	85.0
Normal	9	15.0
Left ventricular systolic function		
Ejection fraction (%)	57.4	40-89
Shortening fraction (%)	29	20-58
Left ventricular diastolic function		
E (m/s)	1.1	0.62-1.89
A (m/s)	0.42	0.27-1.08
E/A	2.62	1.49-3.97
Left Ventricular Mass		
Normal	8	13.3
Hypotrophy	52	86.7
Left Ventricular Mass (g)	67.38	29.64-149.21

Table 3. Bivariate analysis of several indices against impaired left ventricular function.

Characteristic	Left ventricular disorder				P
	Yes		No		
	Results	Standard	Results	Standard	
Sex					
Male	23		2		
Female	32		3		
Age (month)	30	8-186	101	46-165	0.04[b]
Nutrition Status					
Very thin (<-3 SD)	21	100	0		
Skinny (<-2 SD)	34	87.2	5	12.8	0.15a
Pulse (times/minute)	100	82-120	104	99-106	0.18[b]
NT-pro-BNP (pg/mL)					
NT-pro-BNP	229.4	50-8134.4	100.2	50-187.7	0.04[b]
Positive	47	94	3	6	0.19[a]
Negative	8	80	2	20	
Hs-Troponin I (ng/mL)	4.2	4-18.3	4.1	4-4.1	0.02[b]
Positive	50	94.3	3	5.7	0.01[a]
Negative	5	71.4	2	28.6	

[a]The higher the value, the greater likelihood of impaired left ventricular function; [b]Positive rather than negative.

Table 4. Analysis of Under the Curve Area of each index.

Index	AUC	P	df 95 %
Hs-Troponin I[a]	0.82	0.02	(0.66 -0.97)
NT-pro-BNP[a]	0.78	0.04	(0.62 -0.94)
Group of Hs-Troponin I[b]	0.66	0.26	(0.37 -0.94)
Group of NT-pro-BNP[c]	0.63	0.35	(0.35 -0.91)
Group of Hs-Troponin I + NT-pro-BNP[d]	0.61	0.42	(0.36 -0.86)

[a]The higher value, greater than a likelihood of impaired left ventricular function; [b,c,d] are positive than negative.

systolic disorder more often than in children who had a diastolic function disorder. The diastolic disturbance pattern in the subjects was the pattern of restriction with the E/A wave ratio of 2.62 (1.49-3.97). This pattern was the same as the interference pattern when the E/A wave ratio was 2.29. The restriction pattern could return to normal with good heart functions after adequate nutrition management.[3] Furthermore, the result of the ejection fraction in the study showed values below normal by age. This result was in line with Hidayat, who found the ejection fraction in PEM I and PEM II children.[5] Furthermore, Olivares recorded a decrease in left ventricular systolic function compared with controls with the ejection fraction of 64.60±3.86% and the shortening fraction of 39.17±2.31%.[19]

Our study found the Kappa value was 0.615 (appropriated) for the indicator in the echocardiography analysis. Table 2 shows the echocardiography value of PEM is 91.7% the systolic disorder and 85% systolic disorder accompanied by an impaired restrictive diastolic function. The value of the left ventricular systolic function was found to be normal, with a median of the ejection fraction of 57.4% (standard: 40-89%) and for the shortening fraction 29% (standard: 20-58%). The observation of left ventricular diastolic function disturbance with the wave peak E, wave peak A, and E/A wave ratio were found to have the wave peak E higher than the normal value with a median 1.11 M/s. (standard 0.62-1.89 m/s). The wave peak was normal with a median 0.42 m/s (standard 0.27-1.08 m/s), and the E/A wave ratio was higher than normal with a median of 2.62 (standard 1.49-3.97).[20]

An overview of the wave peak measurements indicated the initial diastolic charge (in rapid charging) was longer than usual. Slow charging was shown by the peak of wave A (Atrium contraction) 0.42 m/s with the range (0.27-1.08 m/s). For the E/A wave ratio of values >2, this pattern illustrated the reversible restrictive pattern which could return to normal with adequate management. The E/A increase in ratio values indicated that there had been a decrease in LV adherence. Such a process may have been influenced by hypo-albuminemia that may have occurred in the subject. Hypo-albuminemia can cause interstitial edema in the myocardium. The assessment of myocytic interstitial edema should be examined histopathologically. However, hypo-albuminemia was not a category of the inclusion criteria, and all diastolic dysfunctions were a restricted pattern.[21]

Ocal (2001) investigated the decrease inside left ventricular mass was proportional to PEM child weight loss that influenced by a slow anabolic process.[22] These results were also in line with studies that mentioned the hypotrophy/decreased left ventricular mass in anorexic patients weigh 71.2±17.6 g (P<0.001), compared with a normal weight of 96.9±21.2 g.[4] Long-term effects of left ventricular mass loss (cardiac muscle atrophy) can lead to systolic and diastolic heart function impairment in the protein energy of children with malnutrition. Children with PEM are more likely to have cardiovascular disorders.[23] These effects of PEM on cardiac function caused by muscle atrophy are due to inadequate protein and cardiovascular energy or indirectly due to metabolic disorders and increased systemic demand.[24]

The NT-pro-BNP marker in cardiac excretion may characterize cardiac burden in cardiac dysfunction. The value of NT-pro-BNP remains associated with ventricular dysfunction (impaired ventricular function). In addition to echocardiography, the NT-pro-BNP is a non-specific test for detecting structural abnormalities and functions that are important. The NT-pro-BNP rate will increase as the ejection fraction decreases.[25]

Data in Table 4 explains the ROC curve with the NT-pro-BNP marker scale index. It shows that the AUC value with 95% degree of freedom has a confidence index of: 0.62-0.94 (P=0.04), and the Hs-Troponin I was 0.66-0.97 (P=0.02). Characteristics of the ROC curve of the diagnostic value of NT-pro-BNP and Hs-Troponin I were compared with the standard echocardiographic reference shown in Figure 1. The most optimal cutoff point for Hs-Troponin I accuracy ≥4.05 pg/mL, was a sensitivity of 92.7% and the specificity was 60%. For sensitivity, specificity, and accuracy, the cutoff point

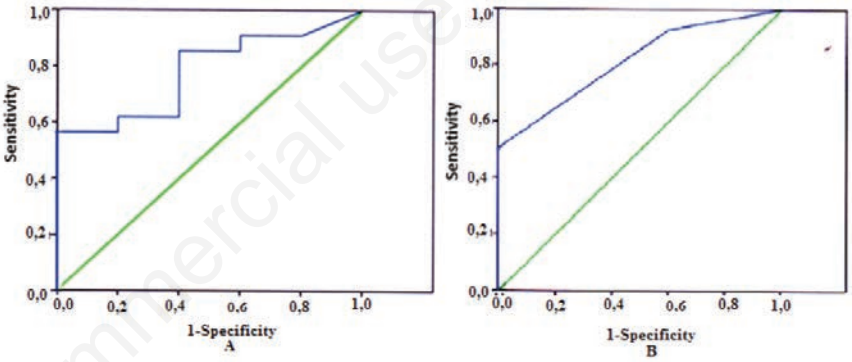

Figure 1. Diagnostic of echocardiography of AUC value (A) NT-ProBNP and (B) Hs-Troponin I. The ROC Curve is a graphical method of assessing the characteristic of a diagnostic test.

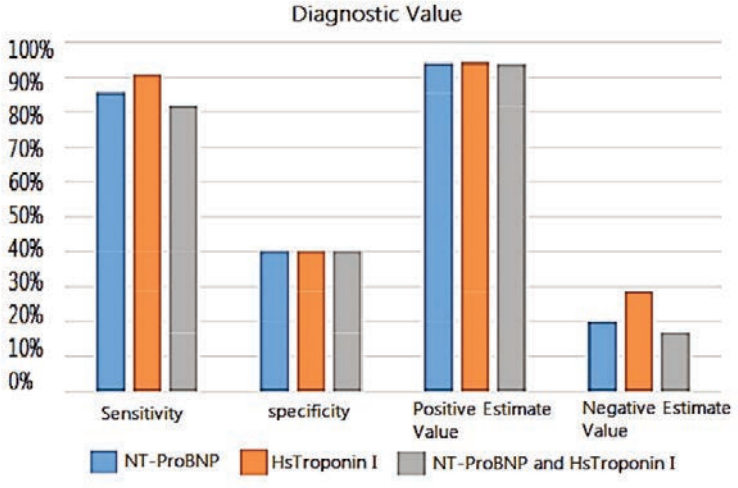

Figure 2. Diagnostic value of sensitivity and specificity of malnutrition markers.

was ≥100.3 ng/mL for NT-pro-BNP and ≥4.05 pg/mL for Hs-Troponin I. An analysis of 2×2 tables determined the diagnostic value (degree of freedom 95%).

In this study, of the number of children with impaired heart function, 94.3% had Hs-Troponin I >4 ng/mL. The median of Hs-Troponin I was 4.2 ng/mL (4-18.3). The analysis with the Fisher test showed that there was a significant difference (P=0.01) between high Hs-Troponin I and impaired heart function. Nagla reported cardiac effects that the troponin levels in children with severe malnutrition remained strongly associated with a decrease in the left ventricular mass and a decrease in the left ventricular systolic.[26] Table 4 shows the value of AUC for NT-pro-BNP is 78%, and statistically is weak, but clinically, the PEM child demonstrates the potential for falling into heart failure evaluated from ejection fraction results with the help of an echocardiography examination. The AUC value for Hs-Troponin I was 82% of these results, which indicated both statistically and clinically that a physical examination of the subjects may be appropriate at the onset of impaired heart function. There is a result of high sensitivity and positive predictive value between the two markers. In this study, only sodium, potassium, and chloride were examined, while magnesium (Mg) and calcium (Ca) were not examined because of the limited volume of blood sampling in the study subjects (Table 1). This was one of the disadvantages of this study. Additionally, one of the factors affecting the contraction heart is micronutrients such as electrolytes and minerals.[27]

In Figure 2 shown Troponin I values has the highest sensitivity (90.9%) compared with NT-proBNP (85.5%) as the biomarkers in recognizing the heart muscles damage. We have also analyzed the merge of these proteins with the 2×2 table that has a sensitivity of 81.8%, a specificity of 40%, a positive and negative guess value of 93.8% and 16.7%, respectively, a positive possibility ratio of 1.4 and a negative possibility ratio of 0.5. Kubo conducted a study to assess the Troponin I and NT-pro-BNP markers on hypertrophic cardiomyopathy with the decreased ejection of the left ventricular fraction (<50%) in the subjects whose age range from 8-9 years.[8] Weber reported the NT-pro-BNP of patients with heart failure is significance expression level in patients with non-cardiac problems (110 pg/mL) with a 90% sensitivity and 76% specificity. The NT-pro-BNP 30 pg/mL had 80% sensitivity and 87% specificity.[28] Biban (2012) gave expression to this study to include the modern protection for pediatric healthcare in the pediatric intensive care unit.[29]

Conclusions

The research has shown children who experienced PEM had hypertrophy of the heart muscles, systolic and diastolic LV dysfunction, and an increase of sensitivity and specificity for the Troponin I biomarker more than NT-pro BNP. Both biomarkers have a diagnosis value near echocardiography as the gold standard.

References

1. De Onis M, Monteiro C, Akré J, Clugston. The worldwide magnitude of protein-energy malnutrition: an overview from the WHO Global Database on Child Growth. Bull World Health Organ 1993;71:703-12.
2. Alberda C, Graf A, McCargar L. Malnutrition: etiology, consequences, and assessment of a patient at risk. Best Pract Res Clin Gastroenterol 2006;20:419-39.
3. Di Gioia G, Creta A, Fittipaldi M, et al. Effects of Malnutrition on left ventricular mass in a north-Malagasy children population. PloS One 2016;11:e 0154523.
4. Dimiati HSS, Hendarto MMA. Mass and function of left ventricle, and left of ventricle and protein malnutrition, energy type marasmus. J Kardiol Indones 2011;32:151-8.
5. Hidayat DRF. Profile of the ejection fraction on echocardiography in children Less Energy Protein at Hasan Sadikin Hospital, Bandung, Indonesia. Hospital Bull 2001;2:5-20.
6. Singh HS, Bibbins-Domingo K, Ali S, et al. N-terminal pro-B-type natriuretic peptide and inducible ischemia in the Heart and Soul Study. Clin Cardiol 2009;32:447-53.
7. El-Sayed HL, Nassar MF, Habib NM, et al. Structural and functional affection of the heart in protein energy malnutrition patients on admission and after nutritional recovery. Eur J Clin Nutr 2006;60:502-10.
8. Kubo T, Kitaoka H, Okawa M, et al. Combined measurements of cardiac troponin I and Brain Natriuretic Peptide are useful for predicting adverse outcomes in hypertrophic cardiomyopathy. Cir J 2011;75:919-26.
9. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb) 2012;22:276–82.
10. Haider M, Haider SQ. Assessment of protein-calorie malnutrition. Clin Chem 1984;30:1286-99.
11. Hajian-Tilaki K. Receiver operating characteristic (ROC) curve analysis for medical diagnostic test evaluation. Caspian J Intern Med 2013:4:627-35.
12. Indonesia Ministry of Health. Guidance of operational malnutrition energy protein in children and households. Jakarta, Health Ministry Press; 2011. pp 15-35.
13. Lee KH, Kim JY, Koh SB, et al. N-Terminal Pro-B-type Natriuretic Peptide Levels in the Korean General Population. Korean Circ J 2010;40:645-50.
14. Chengode S. Left ventricular global systolic function assessment by echocardiography. Ann Card Anaesth 2016;19:S26-34.
15. Goto T, Wakami K, Fukuta H, et al. Patients with left ventricular ejection fraction greater than 58 % have fewer incidences of future acute decompensated heart failure admission and all-cause mortality. Heart Vessels 2015;31:734-43.
16. Madu EC, Baugh DS, D'Cruz IA, et al. Left ventricular papillary muscle morphology and function in left ventricular hypertrophy and left ventricular dysfunction. Med Sci Monit 2001;7:1212-8.
17. Mair J, Hammerer-Lercher A, Puschendorf B. The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. Clin Chem Lab Med 2001;39:571-88.
18. McGrath MF, de Bold ML, de Bold AJ. The endocrine function of the heart. Trends Endocrinol Metab 2005;16:469-77.
19. Olivares JL, Vasquez M, Rodriguez G, et al. Electrocardiographic and Echocardiographic finding in Malnourished Children. J Am Coll Nutr 2005;24:38-43.
20. Mottram PM, Marwick TH. Assessment of diastolic function: what the general cardiologist needs to know. Heart 2005;91:681-95.
21. Hansen JDL, Pettifor JM. Protein energy malnutrition (PEM). In: McLaen DS, Burman D, Belton NR, Williams AF, editors. Textbook of pediatric nutrition. 6th Ed New York: Churchill Livingstone; 1991. pp. 357-90.
22. Ocal B, Unal S, Zorlu P, et al. Echocardiographic evaluation of cardiac functions and left ventricular mass in children with malnutrition. J. Paediatr Child Health 2001;37:14-7.
23. Bahera AA, Panda P, Mohaptra D, et al. Prevalence and determinants of echocardiographic left ventricular hypertrophy among hypertensive patients in a tertiary care hospital.

Pharm Clin Res. 2017;11:56-60.
24. Alaverdashvili M, Li X, Paterson PG. Protein-Energy Malnutrition Causes Deficits in Motor Function in Adult Male Rats. J Nutr 2015;145:2503-11.
25. Kotaska K, Popelova J, Tiserova M, et al. NT-proBNP and BNP values in cardiac patients with different degree of left ventricular systolic dysfunction. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2006;150:125-30.
26. Nagla HAF, Abu F, Khalid IE, et al. Myocardial dysfunction in Malnourished Children. Ann Pediatr Cardiol 2010;3:113-18.
27. Kkeveetil CV, Thomas G, Chander SJ. Role of micronutrients in congestive heart failure: A systematic review of randomized controlled trials. Tzu Chi Medical Journal 2016;28:143-50.
28. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart 2006;92:843-9.
29. Biban P, Gaffuri M, Spaggiari S, et al. Early recognition and management of septic shock in children. Pediatr Rep 2012;4:e13.