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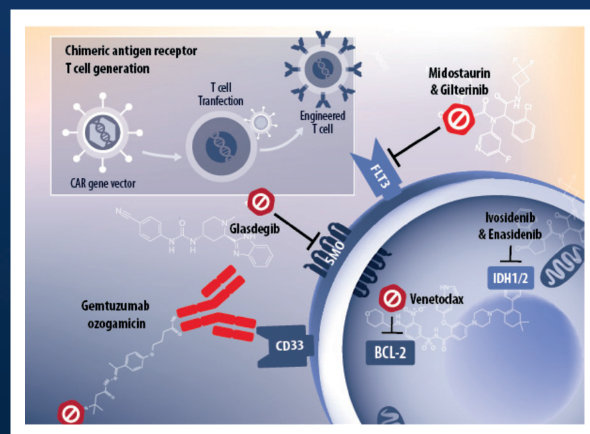

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Correlation between Heart Failure with N-Terminal-Pro-B Type Natriuretic Peptide and Cardiothoracic Ratio from Chest Radiograph in Pediatric Heart Disease

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ABSTRACT

Objective: The aim of this study is to determine the correlation between the symptom of heart failure and basic investigations; N-Terminal-Pro-B Type Natriuretic Peptide (NT-proBNP) and cardiothoracic (CT) ratio from chest radiograph in pediatric heart disease.
Methods: One-hundred-eighty children (aged 1-15 years) with underlying heart disease were enrolled in this prospective cross-sectional study. The heart failures were categorized based on the Ross classification into 2 groups, non-heart failure (Ross classification I) and heart failure (Ross classification II-IV). The NT-proBNP level was determined and chest radiograph was done in posteroanterior upright position for CT ratio.
Results: The mean NT-proBNP level was 223.1 pg/ml (±180.3) and a mean CT ratio was 53.6% (±5.6) in the non-heart failure group. The mean NT-proBNP level was 1,054 pg/ml (±1,840.3) and a mean CT ratio was 58.6% (±6.1) in heart failure group. There was a significantly positive correlation between heart failure symptoms and the level of NT-proBNP and CT ratio. In this study, the cut-off value of NT-proBNP for heart failure was more than 400 pg/ml (OR 6.97, ROC 0.694, sensitivity 52.6%, specificity 86.3%) and CT ratio more than 55% (OR 3.57, ROC 0.654, sensitivity 68%, specificity 62.8%).
Conclusion: In pediatric heart diseases, there are strong positive correlations between heart failure with both NT-proBNP and CT ratio. These correlations help in the diagnosis of heart failure. NT-proBNP level more than 400 pg/ml and CT ratio more than 55% are indicative of heart failure in our population. Both investigations are inexpensive, readily available and do not require specialist experts.

Keywords: NT-proBNP; cardiothoracic ratio; heart failure (Siriraj Med J 2019; 71: 356-363)

INTRODUCTION

Pediatric heart diseases are more often than not congenital and less frequently acquired disease. Heart failure is one of the most important problems in pediatric cardiology clinic. The etiologies of heart failure from congenital heart diseases are mainly from volume over load and/or pressure over load. A normally-structured heart in which the disease left ventricle function in opposite to its normal function is most common cause of heart failure.[1] The clinical signs of heart failure in children include poor feeding, respiratory distress, poor weight gain, edema and exercise intolerance. There are

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standard guidelines for diagnosis and treatment of heart failure for adult in worldwide practice.[2-4] In children, the practice guidelines reviewed by many studies showed no uniformed recommendation for diagnosis and treatment of heart failure due to variant pathophysiology in pediatric heart failure and small studies subjects.[5-7] These studies suggested that we should combine symptoms, physical examinations, investigations for diagnosis and treatment and reliant on the pathophysiology of heart failures in individual children.

In out-patient department, the investigations which most readily available in every hospital and useful for diagnosis of heart failures in children are chest radiography, electrocardiogram, blood test for neuro-hormonal activation; brain natriuretic peptide (BNP) and N-Terminal-Pro-B Type Natriuretic Peptide (NT-proBNP). NT-proBNP and cardiothoracic ratio from chest radiograph are widely used with a standard cut-off value for heart failure in adult, but there is no consensus for children. Contributing factors are the various types of ventricular impairment, underlying cardiac morphology, age, gender, and assay method for NT-proBNP affecting the reference values for both markers. For chest radiograph one usually calculates the CT ratio for determination of cardiomegaly in the diagnosis of heart failure. The aim of this study was to determine the correlation between symptoms and signs of heart failure with basic investigations; NT-proBNP and CT ratio from chest radiograph in pediatric heart diseases.

MATERIALS AND METHODS

We performed a prospective cross-sectional study on 180 children (aged 1-15 years) with underlying heart diseases with diagnosis and follow-ups at the cardiology clinic of Department of Pediatric, Faculty of Medicine, Naresuan University, Thailand from September 2015 to May 2018. The study was approved by the Ethics Committee of Naresuan University (COA No. 208/2015). Heart failure was categorized by a pediatric cardiologist based on Ross classification[8] during follow up in cardiology clinic. The patients were categorized into 2 groups: non-heart failure (Ross classification I) and heart failure (Ross classification II-IV). The baseline characteristics: age, gender, underlying heart diseases, current medication and body mass index (BMI) were recorded.

The NT-ProBNP level was assayed with 3 ml of heparinized blood and immunoassay by Roche cobas h 232 instruments (Roche Diagnostics Ltd. CH-6343, Rotkreuz, Switzerland). The normal adult range of this assay is 0-300 pg/ml, and a value of more than 450 pg/ml is suggestive of heart failure in adult with age below 50 years.[3,4] Presently, there are no clear standards and there is no consensus of normal range for children.

The chest radiograph was done in posteroanterior upright position for CT ratio. Patients who could not have chest radiographs done in upright position were excluded from the study. The CT ratio is the ratio of maximal horizontal cardiac diameter to maximal horizontal thoracic diameter (inner edge of ribs) in chest radiography.

Prior to performing the procedures, all patients and their parents (or families) were briefed on the risks and benefits of the procedure. Only upon consent from the patients and their families were the procedure carried out.

Sample size

The proportion of NT–pro-BNP in patients with heart failure in Evelyn Lechner et al showed the NT–pro-BNP in patients with heart failure to be 0.39 and patients without heart failure was 0.6; 2, Alpha of 0.05; 3 and Beta of 0.2 for testing two independent proportions (two-tailed test).[9] The total sample size of 176 patients.

Statistical analysis

Continuous data with normal distribution were shown as mean and standard deviation (SD) and those with non-normal distribution as median and minimum: maximum. Categorical data was shown as frequency and percentage. The odds ratio and 95% confidence interval (95%CI) were used to compare the association between NT–pro-BNP and CT ratio presence of heart failure. A receiver operating characteristic (ROC) analysis was used to determine the diagnostic utility of NT-proBNP and CT ratio for heart failure. A p-value of less than 0.05 was regarded statistically significant.

RESULTS

The study consisted of 180 patients, 91 males (50.6%) and 89 females (49.4%) patients. In all the subjects, the mean age was 6.3 years (±4.3 years), the mean weight was 21.7 kg (±12 kg), the mean height was 112.9 cm (±26.7 cm) and the mean BMI was 15.6 (±2.9). The diagnosis of heart disease was categorized into 3 major hemodynamics groups; ventricular volume load (62.2%), ventricular pressure load (22.2%) and combine ventricular load (15.6%). The diagnosis in ventricular volume load group was (1) left to right shunt lesion: ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA) (2) valvular regurgitation: mitral valve regurgitation (MR), aortic valve regurgitation (AR), Ebstein's anomaly with tricuspid valve regurgitation

(TR), rheumatic heart disease with valvular regurgitation (3) postoperative total correction of tetralogy of Fallot (TOF) with pulmonary valve regurgitation (PR). The diagnosis in ventricular pressure load group was (1) valvular stenosis: pulmonary valve stenosis (PS), aortic valve stenosis (AS), corrected translocation of great artery (TGA) with severe PS, VSD with severe PS (2) TOF with moderate to severe PS (3) pulmonary hypertension (PHT) or Eisenmenger's complex: complete atrioventricular canal defect (CAVD) with PHT, Double Outlet Right Ventricle (DORV) with PHT (4) coarctation of aorta (COA). The diagnosis in combine ventricular load group was single ventricle (SV) with postoperative Glenn's operation, SV with postoperative aortopulmonary shunt or pulmonary artery banding, pulmonary atresia (PA) with VSD postoperative aortopulmonary shunt. For all patients, the mean NT-proBNP was 583.1 pg/ml (±1,282.9) with median of 225 pg/ml (19:9,000) and a mean of CT ratio was 55.7% (±6.3) with median of 56% (40.3:84) (Table 1). The Fig 1 and 2 are the distribution of NT-proBNP level and CT ratio of all patients in each Ross classification group.

TABLE 1. Clinical characteristics, NT-proBNP and CT ratio of patients in heart failure and non-heart failure group.

Characteristic	All patients (n=180)		heart failure (n=78)		Non-heart failure (n=102)		P-value
	n	%	n	%	n	%	
Sex (male)	91	50.6	35	44.9	56	54.9	0.182
Age (year)							0.199
1-5	94	52.2	45	57.7	49	48.0	
6-15	86	47.8	33	42.3	53	52.0	
Mean (±S.D.)	6.3	(±4.3)	5.9	(±4.5)	6.6	(±4.1)	
Weight (kg)							0.074
Mean (±S.D.)	21.7	(±12)	19.9	(±12)	23.1	(±11.8)	
Height (cm)							0.006
Mean (±S.D.)	112.9	(±26.7)	106.7	(±27.8)	117.7	(±24.9)	
BMI (kg/m²)							0.963
Mean (±S.D.)	15.6	(±2.9)	15.6	(±3.3)	15.6	(±2.6)	
Diagnosis							<0.001
Ventricular volume load	112	62.2	33	42.3	79	77.5	
Ventricular pressure load	40	22.2	17	21.8	23	22.5	
Combine ventricular load	28	15.6	28	35.9	0	0.0	
NT-proBNP (pg/ml)							
Mean (±S.D.)	583.1	(±1282.9)	1054	(±1840.3)	223.1	(±180.3)	
Median (min : max)	225	(19 : 9000)	406.5	(19 : 9000)	171	(44 : 1080)	
CT ratio							
Mean (±S.D.)	55.7	(±6.3)	58.6	(±6.1)	53.6	(±5.6)	
Median (min : max)	56	(40.3 : 84)	57.9	(40.3 : 84)	53.9	(42.3 : 68.8)	

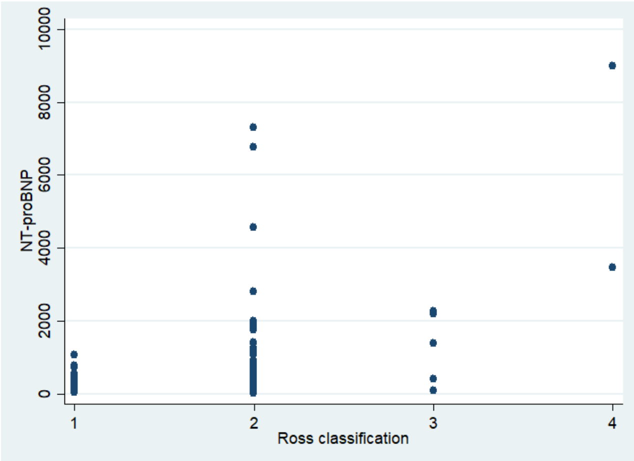

Fig 1. Scatter plot of NT-proBNP level grouped by Ross classification in all patients.

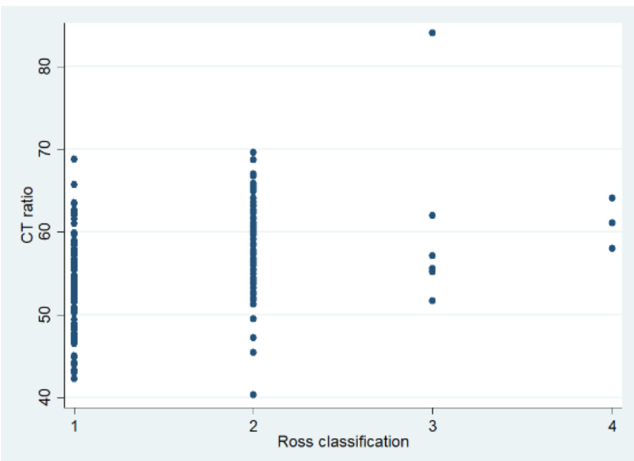

Fig 2. Scatter plot of CT ratio grouped by Ross classification in all patients.

Non-heart failure group

The non-heart failure group (n=102, 56.7%), defined as asymptomatic patients with Ross classification class I, included 56 males (54.9%) and 46 females (45.1%). The mean age was 6.6 years (±4.1 years), the mean weight was 23.1 kg (±11.8 kg), the mean height was 117.7 cm (±24.9 cm) and the mean BMI was15.6 (±2.6). The diagnosis in this group revealed that the patients had mainly acyanotic heart disease (99%) which consisted of 77.5% of ventricular volume load 22.5% of ventricular pressure load and no diagnosis of combine ventricular load. The mean NT-proBNP was 223.1 pg/ml (±180.3) with median of 171 pg/ml (44:1080) and a mean of CT ratio was 53.6% (±5.6) with median of 53.9% (43.3:68.8) (Table 1).

Heart failure group

The heart failure group (n=78, 43.3%), defined as symptomatic patients with Ross classification class II-IV, included 35 males (44.9%) and 43 females (55.1%). The majority of Ross classification in this group was class II (88%) The mean age was 5.9 years (±4.5 years), the mean weight was 19.9 kg (±12 kg), the mean height was 106.7 cm (±27.8 cm) and the mean BMI was 15.6 (±3.3). The diagnosis in this group was acyanotic heart disease in 49%, which consisted of 42.3% of ventricular volume load, 21.8% of ventricular pressure load and 35.9% of combine ventricular load. The mean NT-proBNP was 1,054 pg/ml (±1,840.3) with median of 406.5 pg/ml (19:9,000) and a mean CT ratio was 58.6% (±6.1) with median of 57.9% (40.3:84) (Table 1). There were significant differences between heart failure and non-heart failure group in both NT-proBNP level and CT ratio ($p<0.05$) (Figs 3-4).

The NT-proBNP level base on hemodynamic groups

The mean NT-proBNP in ventricular volume load group was 920.9 pg/ml (±1,772.7) in the heart failure group and 213.6 pg/ml (±182) in the non-heart failure

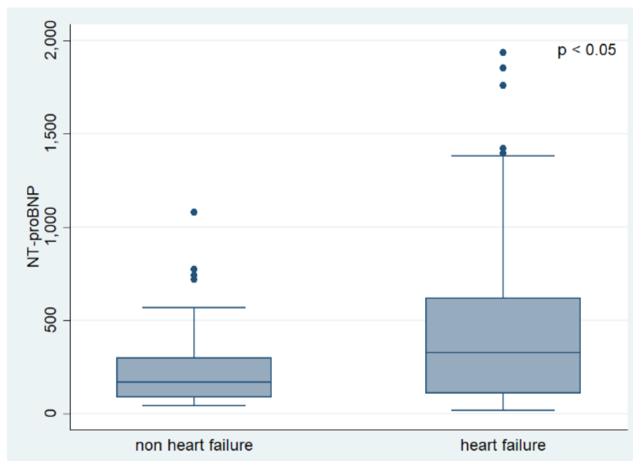

Fig 3. The box-plot of NT-proBNP level in patients with clinical heart failure and non-heart failure.

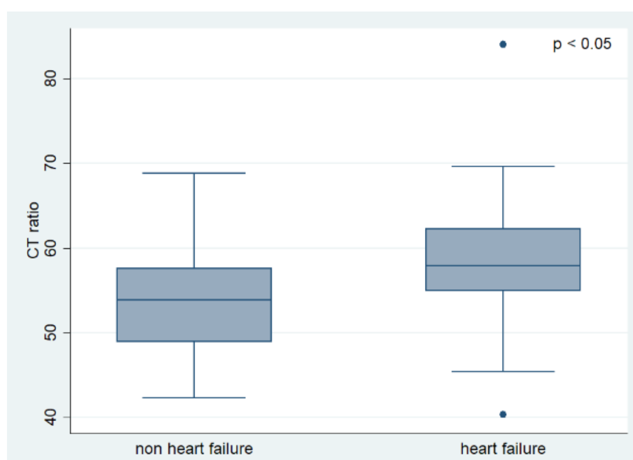

Fig 4. The box-plot of CT ratio in patients with clinical heart failure and non-heart failure.

group. The mean of NT-proBNP in ventricular pressure load group was 1381 pg/ml (±2656.3) in heart failure group and 255.6 pg/ml (±174.3) in non-heart failure group. The mean NT-proBNP in combine ventricular load group was 1012.3 pg/ml (±1,289.3) in heart failure group (Table 2).

Correlation between Heart failure and NT-proBNP

The correlation of NT-proBNP between the 2 subgroups of symptom (non-heart failure and heart failure group) showed a significant positive correlation with area under the curve (AUC) of receiver operative characteristic (ROC) curve of 0.697 (Fig 5). The level of NT-proBNP showed an increase correlation with a higher level indicating greater possibilities for heart failure. The cut-off value of NT-proBNP from our study for diagnosis of heart failure in pediatric heart disease population was more than 400 pg/ml with sensitivity at 52.6%, specificity at 86.3% (Table 3).

Correlation between Heart failure and CT ratio

The correlation of CT ratio with 2 subgroups of symptom (non-heart failure and heart failure group) showed a significant positive correlation with AUC of ROC curve 0.728 (Fig 5). The CT ratio showed increase correlation when higher level of CT ratio indicated higher odd for heart failure. The appropriate cut-off value from our study for diagnosis heart failure in pediatric heart disease was a CT ratio more than 55% with sensitivity at 68%, specificity at 62.8% (Table 4).

DISCUSSION

The brain natriuretic peptide (BNP) and NT-proBNP are synthesized by ventricular myocytes in response to the pressure load, the volume load or an increase in myocardial wall stress. Both hormones are the most well studied biomarker for diagnosis of heart failure in adult and children. In this study, we found a significant and strong positive correlation between NT-proBNP

TABLE 2. The NT-proBNP level in hemodynamic subgroup.

Diagnosis	All patients (n=180) NT-proBNP (pg/ml)		Heart failure (n=78) NT-proBNP (pg/ml)		Non-heart failure (n=102) NT-proBNP (pg/ml)	
	Mean	(±S.D.)	Mean	(±S.D.)	Mean	(±S.D.)
Ventricular volume load	422	1016.9	920.9	1772.7	213.6	182
Ventricular pressure load	733.9	1797	1381	2656.3	255.6	174.3
Combine ventricular load	1012.3	1289.3	1012.3	1289.3	NA*	NA*

*no patient in this subgroup

TABLE 3. The correlation of clinical of patients with NT-proBNP.

Outcome	NT-proBNP (pg/ml)		
	>300	>350	>400
Odds ratio (95% CI)	4.43 (2.34 to 8.38)	6.14 (3.09 to 12.20)	6.97 (3.40 to 14.28)
ROC	0.672	0.692	0.694
Sensitivity (%)	59.0	55.1	52.6
Specificity (%)	75.5	83.3	86.3

TABLE 4. The correlation of clinical of patients with CT ratio.

Outcome	CT ratio (%)		
	>50	>55	>60
Odds ratio (95% CI)	8.46 (2.84 to 25.14)	3.57 (1.92 to 6.65)	4.87 (2.18 to 10.86)
ROC	0.631	0.654	0.624
Sensitivity (%)	94.9	68.0	34.6
Specificity (%)	31.4	62.8	90.2

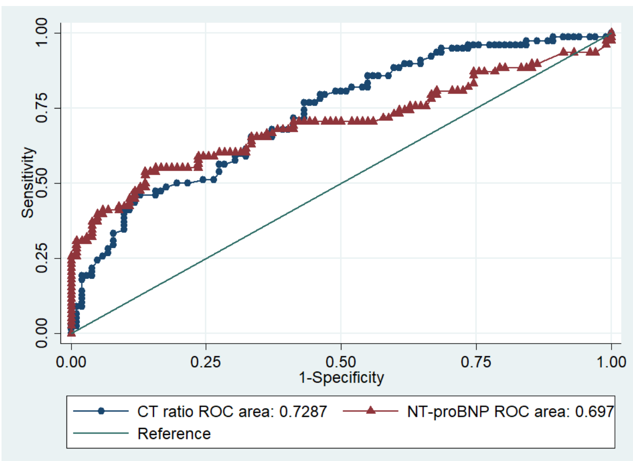

Fig 5. The ROC curves of NT-proBNP and CT ratio for the diagnosis of heart failure in pediatric heart disease population.

and CT ratio with clinical of heart failure in children with underlying heart disease. These results are similar to the previous studies showing a correlation between NT-proBNP and symptoms and signs of pediatric heart failure defined with New York Heart Association (NYHA), Ross and modified Ross classification scores.[9-11]

In non-heart failure group, the mean NT-proBNP level (mean 223.1±180.3 pg/ml, median 171 pg/ml) in this study was almost within the normal range in healthy children, when matched with age and sex in A CALIPER pilot study. The reference value of immunoassay for NT-proBNP level using the same kit as ours from A CALIPER pilot study showed the level in boys and girls age 1 to 5 years to be 12.5-308.4 pg/ml and those aged 5 to 15 years to be 7.9-177.9 pg/ml.[12] Another study by A Nir, et al which studied the reference value of NT-proBNP using a similar method in 58 normal children (4 months to 15 years) showed normal 5-391 pg/ml, median 90 pg/ml.[13] In this study, in hemodynamic asymptomatic children, there was no different in the mean of NT-proBNP as compare to the previous normal reference value. This result suggested that even with underlying heart disease, the NT-proBNP would exhibit similar level. These children had minimal ventricular load and wall stress. Our result was different from A Uner and colleagues study on NT-proBNP level in symptomatic, asymptomatic heart disease and control normal children. It showed significant different level of NT-proBNP among the 3 groups.[14] This observation may be due to the larger sample size of pediatric heart disease in ours study.

Similar to the previous studies, in heart failure group, the mean NT-proBNP was significantly higher than asymptomatic patient. The previous studies showed higher NT-proBNP level in children with heart failure compared to normal children.[10,13-14] F-J Zhou, et al found that the children with congenital heart disease admitted to hospital with pneumonia and heart failure had higher NT-proBNP level than those with pneumonia alone.[15] We also observed that ventricular wall stress might be higher in the pressure load group than volume load or combined ventricular load based on NT-proBNP level (Table 2). The combined ventricular load group consisted mainly of patients with cyanotic complex congenital heart disease with all subjects having symptomatic heart failure with elevation of NT-proBNP values and higher than symptomatic ventricular volume load group. The systematic review in usefulness of brain natriuretic peptide in complex congenital heart disease by Jannet A Eindhoven, et al showed result to be the same as our study.[16] Evelyn Lechner, et al were studied in single ventricle heart disease and the results showed that the RV morphology yielded a higher NT-proBNP than the LV morphology. It is thus concluded that the morphologic right ventricle might be more stressed as a systemic ventricle than the morphologic left ventricle.[9]

The cut-off value of NT-proBNP for diagnosis of heart failure in children was not well established. The NT-proBNP cut off value in acute heart failure for adult aged below 50 years yielded a figure of more than 450 pg/ml with sensitivity at 98% and specificity at 76% form PRIDE study.[17] In children, a previous study by Masaya Sugimoto, et al showed cut-off value in symptomatic heart failure for patients with heart disease aged below 3 years of more than 438 pg/ml with sensitivity at 88.7%, specificity at 91.8%. In patient aged more than 3 years, it was more than 295.2 pg/ml with sensitivity at 94.7%, specificity at 95.9%.[18] The other study by Murat Sahin showed that the cut-off value for diagnosis ventricular dysfunction in children between 4 months to 17 years old was more than 514 pg/ml with sensitivity at 95%, specificity at 80%.[11] In our study done with the same analysis of NT-proBNP showed a nearly cut off value as Masaya Sugimoto study in which NT-proBNP of more than 400 pg/ml had sensitivity at 52.6% and specificity at 86.3% for diagnosis of heart failure in children aged more than 1 year old.

The other commonly used investigation for diagnosis heart failure is chest radiograph. Although echocardiogram, cardiac catheterization, cardiac MRI and multi-detector CT are now commonly used imaging techniques to investigate cardiac disease, the chest radiograph is still necessary for first step of investigation. To evaluate of cardiac enlargement, the CT ratio from chest radiograph has long been accepted as the method of choice.[19] The accepted upper limit of normal CT ratio is 50% in children and adult and 60% in infant.[20] The diagnostic accuracy from CT ratio for evaluation of function both LV and RV from many studies showed low accuracy.[21-22] In LV systolic function showed no significant association with CT ratio in patients with preserved left ventricular ejection fraction who had undergone computed tomography coronary angiography. But the CT ratio correlated with LV size and LV ejection fraction (LVEF) in patients with depressed LVEF.[21] In another study, The CT ratio reflected atrial dilatation rather than ventricular dilatation.[22] Our study showed a significant positive correlation of CT ratio with symptomatic heart failure in pediatric heart disease. The appropriate cut-off value of CT ratio was more than 55% (OR 3.57; 1.92-6.65, ROC 0.654, sensitivity at 68%, specificity at 62.8%) for the diagnosis of heart failure in pediatric heart disease. This result was similar to the study of Konstantinos Dimopoulos, et al, in which cardiomegaly was present in both simple and complex adult with congenital heart disease and CT ratio more than 55% corrected with the patients' symptom and predicted an 8-fold increased risk of death.[23]

CONCLUSION

The NT-proBNP level and CT ratio are helped in the diagnosis of heart failure in pediatric heart disease. NT-proBNP level more than 400 pg/ml and CT ratio more than 55% were predictive of heart failure in our population. Both investigations are inexpensive, readily available and do not require specialist experts for interpretation.

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