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ORIGINAL ARTICLE

Comparative Study between Modified Ross Score and Pediatric Heart Failure Index using pro-BNP in Quantifying Severity of Heart Failure in Pediatrics.

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ABSTRACT

Background: Pediatric Heart Failure Index (PHFI) and Modified Ross Score are a validated rating measures for evaluating pediatric heart failure that are useful because they can promote the assessment of treatment and analysis of outcomes. The present work aimed to evaluate the specificity and sensitivity of Modified Ross and Paediatric Heart Failure Index for quantifying severity of heart failure using pro-B-type Natriuretic peptide.

Methods: A comparative study was conducted on 48 patients (26 males and 22 females) with congestive heart failure whose ages ranged from 4 months till 2 years, all cases have the Congestive Heart Failure (CHF) inclusion criteria. They were submitted to complete history taking, physical examination, X- ray chest and heart, ECG, echocardiography, classification of CHF severity according to PHFI Score, Modified Ross Score and laboratory investigations. The laboratory investigations were a routine such as: CBC and a special investigation as NT-pro-BNP serum level using NT-pro-BNP ELISA kit

Results: our study showed a statistically significant positive correlation between M-ROSS scale and pro-BNP levels. There was a high statistically significant positive correlation between PHFI diagnostic scale and pro-BNP level and HR among studied patients. There is a positive correlation between PHFI score and modified Ross score According to modified Ross score. BOTH scores showed high ability to detect severe cases, as PHFI accuracy reaching up to 94.5% and, while accuracy of M-Ross was 90.5%.

Conclusion: The study revealed that PHFI was more significant correlation with NT-proBNP than M-ROSS, so PHFI seems more accurate and sensitive to severe cases than M-ROSS.

Keywords: Modified Ross Score, Pediatric Heart Failure Index, PHFI, pro-BNP, Heart Failure.

INTRODUCTION

Heart failure is a complicated clinical syndrome arising from various primary and secondary causes, and common mechanisms of disease progression, that correlate significantly with morbidity, mortality and cost. Children heart failure is commonly imputed to congenital heart disease (CHD) and Cardiomyopathy coexisting , with diverse risks based on the particular type of malformation**. [1]** It results in characteristic clinical manifestations like growth retardation, difficulties in feeding, respiratory distress, intolerance and fatigue exercises and is associated with circulatory, neurohormonal and molecular abnormalities. **[2]**

Percent of Children with heart failure is 10 to 33 of all cardiac admissions. Although the rate of heart failure in children with congenital heart disease was only 6 to 24 percent, A little more than half of the pediatric heart failure cases reported were due to congenital heart disease. This illustrates the fact that the common cause of heart failure is congenital heart disease. **[3]**

Evolution of an exact classification for children heart failure has been considered a daunting quest for many years. Based on functional limitation, the New York Heart Association (NYHA) classification has limited value for babies and children. **[4]**

The NYHA grading system was adapted to infants and children by **Ross et al**. 3 continuous scales were developed to overcome the problem of several grading systems, which were limited to different populations. **[5]**

Based on the physiologic variable The Ross scale was developed in 1992 these variables were greatest predictive of the heart failure grade in babies less than 6 months of age **[6].** The Ross score was subsequently modified by Reithman et al. and Laer et al. using both case history and criteria of physical examination regardless of age. **[7] [8]**.

PHFI was described by Connolly et al. that was designed to score the severity of children heart failure, regardless the causes and age. In addition to assessing signs and symptoms, the PHFI puts the current used medications in consideration also tends to be an instrument which is reliable and convenient for assessing the severity of children heart failure. **[9]**

Natriuretic peptides (NPs) are polypeptide hormones that are different in genetic bases but have the same amino acid ring and related structures. They have characteristic natural actions which antagonize the mechanism of rennin-angiotensin-aldosterone system and have a strong effect on the regulation of blood pressure and extracellular fluid balance and influence the physiology of the body through their activities of sympathetic inhibition, complex collaboration with cytokines and vasopressin, natriuresis , diuresis and vasodilation. **[10]**

The level of Brain natriuretic peptide (BNP) is correlated with patient clinical condition and imaging techniques to prove a diagnosis of CHF. BNP is a strong predictor of clinical severity and deteriorating systolic function in children with heart failure**. [11]**

There was a characterized correlations between heart failure clinical classifications and diagnostic workup. PHFI seems better correlated with biologic, radiologic, echocardiographic and electrocardiographic valuation of children heart failure. NT-proBNP was correlated with Clinical severity but not with troponin 1. **[12]**

Our study aimed to evaluate the specificity and sensitivity of Modified Ross and Paediatric Heart Failure Index for quantifying severity of heart failure using pro-B-type Natriuretic peptide (pro BNP).

METHODS

A comparative study was done in Pediatric Cardiology Unit and Pediatric intensive care unit of pediatric department, Zagazig University Hospitals, in the period from April 2018 till April 2019.

SUBJECT

Study included 48 patients with congestive heart failure whose ages ranged from 4 months till 2 years, they were devided into 2 groups: **Group (1) was** Thirty patients with congenital heart disease (CHD) and **Group (2)** was Eighteen patients with dilated cardiomyopathy (DCM).

Inclusion criteria:

Any case of heart failure due to cardiac disease (CHD,DCM) included in pediatric age (4 months-2 years).

Exclusion criteria:

Patients outside the age group, Patient with heart failure due to non cardiac causes as lung disease and Endocrinal or metabolic diseases or Patients with end-stage renal disease (ESRD) on dialysis were excluded from study cases.

Methods:

All cases were submitted to complete history taking, physical examination, laboratory investigations and classification of CHF severity according to PHFI Score and Modified Ross Score. The laboratory investigations were a routine such as: CBC and a special investigation which is serum level of NT-proBNP using NT-proBNP ELISA kit.

X- ray chest and heart were performed and its finding included pulmonary edema, cardiomegaly and pleural effusion .also ECG,Echo-cardiographic examination included left ventricular end-diastolic (LVED) , left ventricular end-systolic (LVES), posterior wall (PW),lnterventriculare septum (IVS) dimentions , ejection fraction (EF) of the left ventricle and fractional shortening (FS) were measured to all patients.

Ethical considerations:

This study was ethically approved from, Institutional Reviewer Board (IRB) in Faculty of Medicine, Zagazig University Hospital. Well-informed verbal and written parental consent from every case or their caregivers that participates in this research was taken. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were analyzed using IBM SPSS 23.0 for windows (SPSS Inc., Chicago, IL, USA) and NCSS 11 for windows (NCSS LCC., Kaysville, UT, USA). Quantitative data were expressed as mean ± standard deviation (SD), while non parametric data were expressed as median. Qualitative data were expressed as frequency and percentage. Quantitative data were tested for normality using Kolomogrov Smirnove test, assuming normality at P>0.05. Analysis of variance (ANOVA) F test used to compare

between more than two means that normally distributed. Krusskal-wallis test used to compare between more than two means that was not normally distributed.Pearson`s correlation test performedto find type of relation between two quantitative variables. Receiver operating characteristic (ROC) curve analysis was used to identify optimal cut-off values. Area Under Curve (AUC) was also calculated.

RESULTS

Total sample size included 48 congestive heart failure patients of unlike severities, 30 congenital heart disease patients and 18 dilated cardiomyopathy patients. The age of the studied group ranged from 4 months to 2 years with mean 15.7 and weight ranged from 2.1- 12kg and while Height ranged from 50-95 cm. The commonest gender incidence of congestive heart failure was in males (54.2%), consanguinity recorded 6 (12.5%) cases. The most of the studied cases (62.5%) had CHD.

all studied cases complained of dyspnea and 91.7% of them had hepatomegaly on examination, while only 16.7% suffered of cyanosis and 3.6% failed to thrive Table (1). 68.8% of the studied population showed cardiomegaly on x-ray, while 31.3% gave the picture of pulmonary edema. Table (2)

the LVEDD diameter of the studied group ranged from 14 to 60 with mean 40.9, while at systole it was ranged from 8 to 51 with mean 31.57. PW ranged from 0.6 to 11 with mean 5.5. Regarding ejection fraction ranged from 36 to 83% with mean of 45.3 %. Table (3)

PHFI and M-Ross scale showed statistically highly significant difference between three classes of heart disease severity. Also, there was an almost perfect agreement between the two scoring systems. Table (4)

Our study showed a high statistically significant difference in pro-BNP levels regarding severity of heart failure, as its levels was higher among severe cases, ranged from 5800 up to 10300 with mean 6300. Table (5)

There was a statistically significant positive correlation between M-Ross scale and pro-BNP levels, also positive correlation with PHFI scale but not reach significant level, while there was a negative correlation between M-Ross with FS and EF of studied patients but not reach significant level. Table (6)

There was a high statistically significant positive correlation between PHFI diagnostic scale and pro-BNP level and HR among studied patients, also there was statistically significant negative correlation with FS and EF. Table (7)

Receiver Operating curve (ROC) was performed for assessment of predictive values for PHFI, M-Ross and pro-BNP levels fig(1)

There was a high accuracy of PHFI, reaching up to 94.5% with ability to detect severe cases of heart failure up to 92.5% and specifically exclude 90.9% of not severe cases, while accuracy of M-Ross was 90.5% with ability to detect severe cases of heart failure up to 90.8% and specifically exclude 88.3% of not severe cases, as regard to pro-BNP ROC predict very high accuracy reaching up to 97.2% with ability to detect severe cases of heart failure up to 95.9% and specifically exclude 91.3% of not severe cases. Table (8).

Table (1): Clinical data among the studied population:

Variable	Cases (n=48)	
	N	%
Cyanosis	9	16.7
Dyspnea	48	100
Hepatomegaly	44	91.7
Diaphoresis	10	20.8
Failure to thrive	3	6.3

Table (2): X-ray findings among the studied population:

Variable	Cases (n=48)	
	N	%
Cardiomegally on x-ray:	33	68.8
LV enlargement	12	36.4
RV enlargement	10	20.8
BV enlargement	11	22.9
Pulmonary edema on x-ray:	15	31.3

Table (3): Echo-cardiographic findings of the study population:

Characteristics	(n=48)
LVEDD(mm):	
Mean ± SD	40.9 ± 13.06
Range **(median)**	14 – 60 (32.4)
***LVESD*(mm):**	
Mean ± SD	31.57 ± 12.4
Range ***(median)***	8 – 51 (26.1)
***PW*(mm):**	
Mean ± SD	5.5 ± 2.74
Range **(median)**	0.6 – 11 (6.1)
***IVS*(mm):**	
Mean ± SD	6.5 ± 3.17
Range **(median)**	0.52 – 14 (6.3)
FS(%):	
Mean ± SD	20.5 ± 5.89
Range **(median)**	21 – 43 (28.2)
EF (%):	
Mean ± SD	45.3 ± 10.1
Range **(median)**	36 – 83 (40.5)

EF = Ejection fraction
FS = Fractional shortening
LVEDD= Left ventricular end diastolic dimensions
LVESD = Left ventricular end systolic dimensions

Table (4): Difference in scoring system (M-Ross and PHFI) as regard failure severity among the studied group.

Variables	Mild HF N=12	Moderate HF N=14	Severe HF N=22	F Test	P-value
PHFI					
Mean ±SD	**10.3 ± 1.24**	**17.4 ± 1.36**	**23.2 ± 2.3**	**194.1**	**<0.001****
Range	**9 – 11**	**13 – 19**	**20 – 27**		
	Mild HF N=6	**Moderate HF N=20**	**Severe HF N=22**		
M-Ross					
Mean ±SD	**4.33 ± 1.21**	**8.3 ± 0.85**	**11.1 ± 1.11**	**114.1**	**<0.001****
Rang	**3 – 6**	**7 - 9**	**10 - 12**		

*P-value<0.05 is siginificant **P-value<0.001 is highly significant

Table (5): Difference in pro-BNP levels as regard heart failure severity of PHFI scoring among the studied group.

Variables	Mild HF N=12	Moderate HF N=14	Severe HF N=22	KW* Test	P-value
Pro-BNP					
Median	**2100**	**5100**	**6300**	**9.15**	**<0.001****
Range	**580 – 4200**	**4800 – 5500**	**5800 – 10300**		

**P-value<0.001 is highly significant *Krusskal-wallis test of non-parametric data

Table (6): Pearson's correlation between M-Ross scale and clinical data of heart failure among studied cases.

Variables	M-Ross	
	r	P
Pro-BNP	**0.914**	**0.001 (HS)**
PHFI	0.187	0.112 (NS)
FS	-0.231	0.165 (NS)
EF	-0.213	0.823 (NS)
HR	0.284	0.05 (NS)

EF = Ejection fraction FS = Fractional shortening
HR: Heart rate

Table (7): Pearson's correlation between PHFI scale and clinical data of heart failure among studied cases.

Variables	PHFI	
	R	P
Pro-BNP	**0.643**	**0.000 (HS)**
HR	**0.671**	**0.000 (HS)**
FS	**-0.456**	**0.02 (S)**
EF	**-0.624**	**0.001 (S)**

Table (8): Reliability data of PHFI, M-Ross and pro-BNP levels as a predictor for severe cases of heart failure.

Variables	Cut off	AUC	P-value	PPV	NPV	sensitivity	specificity	Accuracy
PHFI	**18.5**	**0.943**	**<0.001**	**92.1%**	**96.7%**	**92.5%**	**90.9%**	**94.5%**
M-ROSS	**9.5**	**0.936**	**<0.001**	**89.1%**	**89.7%**	**90.8%**	**88.3%**	**90.5%**
Pro-BNP	**2100**	**0.926**	**<0.001**	**95.7%**	**97.7%**	**95.9%**	**91.3%**	**97.2%**

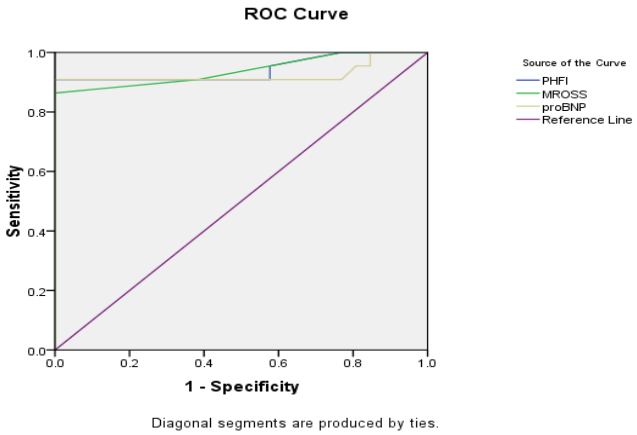

Figure (1): Receiver Operating curve (ROC) for PHFI, M-Ross and pro-BNP levels as a predictors for severity of heart failure.

DISCUSSION

Heart failure was defined as a advanced clinical and pathophysiological syndrome that happens due to cardiovascular and non-cardiovascular anomalies. These anomalies cause characteristic clinical manifestation as poor growth, respiratory distress, edema, and exercise intolerance, associated with circulatory, neurohormonal and molecular turbulences. The most common causes are congenital heart disease and Cardiomyopathies that lead to acute and chronic heart failure, consecutively. **[13]**

This study aimed to compare the M-Ross score and PHFI in quantifying severity of life-threatening heart failure in pediatric age group, and their relation to biochemical marker brain natriuretic peptide (BNP).

In our study the commonest gender incidence of congestive heart failure was in males (54.2%). This

result detected that, the prevalence of CHF higher in males than females**.**

In the study of **zhao et** for determination the prevalence of congenital heart disease at live birth, he found that the predominance of Female in mild CHD , and predominance of male in severe CHD**.[14]**

In our study Consanguinity recorded 6 (12.5%) cases, **Fazeriandy et al** case-control study, they recorded 14 patients (14%) with CHD were born of consanguineous marriages. **[15]**

In our study the most of the studied cases (62.5%) had CHD, while 37.5% of them had cardiomyopathy, and this was consistent with a systematic review by **Hinton and ware** that the incidence of children with CHD estimated at 8 per 1000 live births and the incidence of children with cardiomyopathy was 1.13 cases per 100,000 children**. [1]**

Dyspnea and hepatomegaly were the most common presentations in our study. Dyspnea presented in all (100%), hepatomegaly presented in 44 cases (91.7%). while Cyanosis, diaphoresis and failed to thrive were the least common manifestations. Cyanosis presented in 9 cases (16.7 %), diaphoresis presented in 10 cases (20.8%) and failed to thrive presented in 3 cases (6.3%).

Dyspnea was recorded as being the most prevalent symptom in **Elwan et al** study, it accounted for 47.6 percent of cases, and failed to thrive was 26.20 percent of cases.

Regarding chest X ray findings 33 (68.8%) patient suffered from cardiomegaly while 31.3% gave the picture of pulmonary edema, while there were no cases with Pleural effusion. The same result in **Elwan et al** study who found that 29 cases (69%of cases) in chest X-ray were appeared with cardiomegaly, increasing pulmonary vasculature represented in 97.6% of cases. **[16]**

Regarding echocardiographic parameters in our study, there was a high statistical increase in LVESD, and LVEDD. Also, there was statistically highly decrease in FS, and highly significant decrease in EF.

parallel to our study **Abou al fotouh et al** study that by comparing left ventricular EF, FS and mitral valve E/A ratio of the control group to the three groups of cases it was reported a high statistical significant decrease in the three groups of cases, while LVESD and LVEDD reported high statistical significant increase in groups of cases compared to the control group. [17]

As regard to PHFI and M-ROSS scale the difference between three classes of heart disease severity was statistically highly significant. There was an almost perfect agreement between both ROSS and PHFI scoring systems.

according to modified Ross score the ratio of Mild CHF represented 12.5% (6 cases) with mean 4.33 ± 1.21, Moderate CHF represented 41.7% (20cases) with mean 8.3 ± 0.85, and Severe CHF represented 45.8% (22 cases) with mean 11.1 ± 1.11..1023

While according to PHFI scoring systems, Mild CHF represented 25% (12cases) with mean 10.3 ± 1.24, Moderate CHF represented 29.2% (14cases) with mean 17.4 ± 1.36, and Severe CHF represented 45.8% (22 cases) with mean 23.2 ± 2.3.

Our study showed highly statistically significant difference in the grades of clinical severity according to Modified Ross Score as pro-BNP levels was higher among severe cases, ranged from 5800 up to 10800 and also for PHFI scoring.

Pro-BNP levels were statistically highly significant different that was higher among severe cases, ranged from 5800 up to 10800 with mean 6300. So, our study revealed that the level of NT-proBNP was higher in the more severity of CHF based on Modified Ross and also for PHFI Classification.

In our study there was a statistically significant positive correlation between M-ROSS scale and pro-BNP levels with p-value **0.001**, also positive correlation with PHFI scale but not reach significant level with p-value0.112, while there was a negative correlation between M-ROSS with FS and EF of studied patients but not reach significant level.

But as regarding PHFI diagnostic scale there was a high statistically significant positive correlation between PHFI diagnostic scale and pro-BNP level and HR among studied patients with p-value **0.000**, also there was statistically significant negative correlation with FS and EF.

These results were in agreement with **WU et al study** who found that PHFI score was correlated positively with modified Ross score, in different severities of children heart failure PHFI score differed significantly **[18]**. Also agreed with **Zhang et al study** that reporeted A significantly positive correlation between M-Ross score and NT-proBNP, and between PHFI score and NT-proBNP. The correlation between PHFI and NT-proBNP was superior to that between modified Ross score and NT-proBNP **[19].**

The diagnostic test validity is measured against a gold standard by Specificity and Sensitivity for dichotomous outcomes. ROC curve or Receiver operating characteristic curve is the plot that illustrate the trade-off between (1-specificity) and sensitivity through a sequence of cut-off points when the diagnostic test is on ordinal scale or continuous**. [20]**

ROC curve was performed for evaluation of predictive values for PHFI, M-ROSS and pro-BNP levels as a predictors for severity of heart disease and the result was

high accuracy of PHFI reaching up to 94.5% with ability to detect severe cases of heart disease up to 92.5% and specifically exclude 90.9% of not severe cases, while accuracy of M-Ross was 90.5% with ability to detect severe cases of heart disease up to 90.8% and specifically exclude 88.3% of not severe cases, as regard to pro-BNP ROC predict very high accuracy reaching up to 97.2% with ability to detect severe cases of heart disease up to 95.9% and specifically exclude 91.3% of not severe cases.

The result of WU study Showed that the area under the ROC curve of PHFI diagnosing HF was 0.964, and the totality of specificity and sensitivity was favorite when > or = 8 was set as the cut-off point. it showed a high sensitivity but low specificity If was set > 2 as cut-off point. The sensitivity of PHFI was 100% > was set 2 as cut-point for heart failure diagnosing, but the specificity reported 4.5%.[18]

PHFI, modified Ross and NYHA classifications, were compared by **Tissieres et al** using 20 children with HF from rheumatic heart disease. Three systems correlated with the cardiothoracic index on chest X-ray, but PHFI was better on end-systolic wall stress, left ventricle (LV) mass, left atrium/aortic ratio, also NT-proBNP. [12]

Zhang et al reported that PHFI could be used as a reference criteria of heart failure different severities. as it was highly valuable for diagnosing chronic children heart failure that 0 - 6 scores is being without heart failure, while mild degree is 7 - 10 scores, moderate degree is 11 - 13 scores and severe degree of heart failure is 14 - 30 scores .19] As a result of ROC values, we can say that PHFI score system is more accurate and sensitive than Modified Ross scoring system, while proBNP marker has the highest sensitivity and accuracy.

Limitation of study:

the sample size was relatively small so we weren't able to study the specificity of each score in different age groups.

CONCLUSION

The study revealed that PHFI is more accurate and sensitive to severe cases than M-Ross.

RECOMMENDATIONS

Through the results of our study we recommend using of PHFI score for classification of severity of heart failure. Also, Future study according to age-based classification to detect accuracy of both score in different age even in neonates.

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