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Neutrophils-to-Lymphocytes Ratio in Children with Acute Heart Failure

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ABSTRACT

Background: Heart failure is a common cause of morbidity and mortality in pediatric patients in the third world. Heart failure in children occurs due to heart lesions that cause volume overload as in large ventricular septal defect or due to lesions that causes obstruction to flow as in aortic stenosis.

Objective: This study aimed to evaluate the neutrophils to lymphocytes ratio in children with heart failure & to investigate if this ratio is helpful in predicting mortality and adverse outcome in those patients.

Patients and methods: Our study was performed over a number of 80 children 40 of them were having CHD with acute heart failure, 20 of them were congenital heart disease (CHD) without failure and 20 of them were normal. The was conducted in Pediatric Cardiology Unit and Pediatric ICU, Zagazig University Children Hospitals during the period from February 2017 till May 2018.

Results: Our present work showed that neutrophils, CRP and NLR were statistically higher in the Heart failure group compared to cardiac group and control group. While lymphocytes and oxygen saturation (SO_2) were statistically lower in the heart failure group. The echocardiographic findings showed that compared to cardiac group, the heart failure group was significantly higher regarding PAP and LVEDD but significantly lower regarding EF and FS.

Conclusion: Elevated NLR seems to be a predictor of short-term mortality in patients with acute heart failure.

Keywords: Neutrophils-to-lymphocytes ratio, Children, Acute heart failure.

INTRODUCTION

Heart failure is a clinical entity where the heart does not function to its best level as it does in its healthy state. Compared with adult patients, where heart failure resulted from an insult to the myocardium, heart failure in children occurs due to heart lesions that cause volume overload as in large ventricular septal defect or due to lesions that causes obstruction to flow as in aortic stenosis [(1)]. Acute heart failure in children in the developed communities is often due to cardiomyopathic causes or palliated congenital heart disease as opposed to developing countries where unoperated congenital heart disease and acquired heart disease are the 2 that are more prevalent**.**

Acute heart failure (AHF) is the term used to describe the rapid onset of or change in symptoms and signs of heart failure (HF) [(3)]**.** The prevalence of the syndrome is increasing. In addition, AHF is associated with high mortality and morbidity [(4)]**.** Therefore, the early identification of patients at high risk of AHF is important. Many prognostic factors have been found to be related to AHF in past studies. Several of these factors are associated with inflammation [(3)]**.**

The neutrophil-to-lymphocyte ratio (NLR) in the peripheral blood is reported to be an easily assessable factor. An increased neutrophil count might reflect inflammation, and lymphopenia is an indicator of physiologic stress. Data on the ability of the NLR to predict cardiovascular risk in different patient groups have been reported. However, the relationship between the NLR and in-hospital mortality in AHF patients has not been assessed [(5)]**.**

NLR reflects the balance of the neutrophilia of inflammation and the relative lymphopenia of cortisol-induced stress response. NLR has been proposed as a prognostic marker predicting worse clinical outcomes in cardiovascular diseases including acute heart failure, and acute myocardial infarction [(5)]**.**

The aim of this study was to evaluate the neutrophils to lymphocytes ratio in children with heart failure & to investigate if this ratio is helpful in predicting mortality and adverse outcome in those patients.

SUBJECT AND METHODS

The current study was a case-control study that was conducted in Pediatric Cardiology Unit and Pediatric ICU, Zagazig University Children Hospitals during the period from February 2017 until May 2018.

Ethical approval: The study protocol was approved by Ethics Committee, Faculty of Medicine, Zagazig University.

An informed consent from parents was provided after explanation of the nature and the purpose of the investigations to the parents prior to participation in the study.

This study was conducted on 60 infants and children (33 males & 27 females) with congenital heart disease attending to the Pediatric Cardiology Unit and the Pediatric ICU, Zagazig University

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Hospitals. Their ages ranged from 2 months to 2 years. Twenty healthy children of sex & age matched to the patients were taken as control group.

Inclusion Criteria:

Age group ranged from 2 months to 2 years, patients with CHD: All patients' cardiac diagnoses were made based on clinical examinations and investigations including electrocardiography, and echocardiography. These were confirmed by cardiac catheterization and multi-slice CT when needed and children with clinical acute heart failure.

Exclusion Criteria:

Hematological disorders or neoplastic metastasis to B.M., sepsis, chronic inflammatory conditions, acute pericarditis, glucocorticoid therapy or history of use 3 months before admission, children with chronic heart failure.

The studied children were divided into the following groups:

- **Group I (Heart failure group):** 40 patients having clinical evidence of acute heart failure (23 males and 17 females) their mean age was 12.91 ± 2.71 months.
- **Group II (Cardiac group**): 20 patients having congenital heart diseases (10 males and 10 females) with no clinical signs of HF. Their mean age was 13.05 ± 5.01 months.
- **Group III (Control group**): 20 normal children (11 males and 9 females) their mean age was 12.7±4.21 months.

All the studied groups were subjected to detailed history, full clinical examination, anthropometric measures including weight, height, BMI, head circumference (HC) and mid arm circumference, imaging technique (echocardiography) for diagnosis for patients, and serum NLR was assessed in all patients and controls.

Statistical Analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures were coded then entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. Qualitative data were represented as number and percentage. Quantitative data were represented by mean ± SD.

The following tests were used to test differences for significance. Difference and association of qualitative variable by Chi square test (X^2). Differences between quantitative independent groups by t test, multiple by ANOVA, predictors by logistic regression. P value was set at ≤ 0.05 for significant results & ≤ 0.001 for high significant result.

RESULTS

Table (1): Demographic data & anthropometric measures among studied groups

			CHD with HF group	CHD group	Control group	F/ X^2	P
			Mean ± SD	Mean ± SD	Mean ± SD		
Age (month)			12.91 ± 2.71	13.05±5.01	12.7±4.21	1.240	0.341
HT (cm)			63.65±11.77*	78.95±9.34	84.65±6.25	34.086	0.00**
WT (kg)			6.51±2.12	9.4±2.08	12.29±1.75	45.675	0.00**
HC (cm)			41.45±4.23*	47.55±1.84	46.55±1.9	29.493	0.00**
BMI [Wt /Ht (m^2)]			15.48±2.06	15.32±1.71	17.09±1.25*	6.515	0.002*
Sex	**Female**	**N**	17	10	9	0.303	0.85
		%	42.5%	50.0%	45.0%		
	Male	**N**	23	10	11		
		%	57.5%	50.0%	55.0%		
Total		**N**	40	20	20		
		%	100.0%	100.0%	100.0%		

Height, weight and BMI were significantly lower in heart failure group compared to the other 2 groups. H.C. was significantly lower in heart failure group.

Table (2): Post Hoc test of demographic data & anthropometric measures

Dependent Variable	Group	Group	P
Age (month)	Control	CHD group	.436
		CHD with HF group	.100
	CHD group	CHD with HF group	.300
HT (cm)	Control	CHD group	.077
		CHD with HF group	.000
	CHD group	CHD with HF group	.000
WT (kg)	Control	CHD group	.000
		CHD with HF group	.000
	CHD group	CHD with HF group	.000
HC (cm)	Control	CHD group	.339
		CHD with HF group	.000
	CHD group	CHD with HF group	.000
BMI [Wt /Ht (m^2)]	Control	CHD group	.002
		CHD with HF group	.002
	CHD group	CHD with HF group	.725

Height, weight and H.C were significantly lower in the heart failure group than the other two groups. Weight and BMI were significantly lower in the cardiac group than the control group. No significant difference in age was found between any of the studied groups.

Table (3): Clinical picture of diseased patients

	Group				Total		X^2	P
	CHD with HF group		CHD disease group					
	N	%	N	%	N	%		
Dyspnea	38	95%	2	10%	40	66.7%	41.0	0.00**
Cough	39	97.5%	2	10.0%	41	68.3%	46.9	0.00**
Tachycardia	25	62.5%	8	40.0%	33	55.0%	2.72	0.099
Sweating	28	70.0%	10	50.0%	38	63.3%	2.29	0.13
Recurrent chest infection	26	65.0%	13	65.0%	39	65.0%	0.00	1.0
Hepatomegaly	10	25.0%	2	10.0%	12	20.0%	1.82	0.17
Delayed social & language development	19	47.5%	6	30.0%	25	41.7%	1.68	0.19
Delayed motor development	20	50.0%	6	30.0%	26	43.3%	2.17	0.14
Feeding difficulties	38	95.0%	11	55.0%	51	85.0%	41.0	0.099

Dyspnea and Cough were significantly associated with heart failure.

Table (4): Laboratory investigations among studied groups

	CHD with HF group	CHD group	Control	F	P
HB (gm./dl)	12.25±1.13	11.95±1.25	12.03±0.78	1.526	0.214
HCT%	41.12±1.8	39.3±4.8	41.05±2.08	2.165	0.068
TLC	6.23±1.24	7.12±1.14	6.23±0.69	1.124	0.302
Platelets	279±53	211±25	240±91	1.916	0.253
Neutrophils%	70.42±3.8*	56.85±6.47	52.95±8.36	70.925	0.001
Lymphocytes %	16.57±3.17*	31.9±8.13	34.15±8.19	81.680	0.002
NLR	4.41±1.05*	1.92±0.55	1.58±0.22	100.914	0.003
SO_2%	82.85±2.27	91.65±4.12	98.15±0.58	241.554	0.001
CRP (mg/l)	16.25±1.15	6.15±1.02	2.14±1.35	1.987	0.009

There were significant differences between the three groups as regards neutrophils, lymphocytes, NLR, SO_2% and CRP.

Table (5): Post Hoc tests of laboratory findings

Dependent Variable	Group	Group	P
Neutrophils	Control	CHD group	.061
		CHD with HF group	.000
	CHD group	CHD with HF group	.000
Lymphocytes	Control	CHD group	.054
		CHD with HF group	.000
	CHD group	CHD with HF group	.000
NLR	Control	CHD group	.201
		CHD with HF group	.000
	CHD group	CHD with HF group	.000
SO_2	Control	CHD group	.000
		CHD with HF group	.000
	CHD group	CHD with HF group	.000
CRP	Control	CHD group	.055
		CHD with HF group	.000
	CHD group	CHD with HF group	.000

Neutrophils, CRP and NLR were significantly higher in heart failure group compared to the other groups. Lymphocytes were significantly lower in heart failure group compared to the other groups. SO_2 was significantly higher in control group than the other two groups.

Table (6): X ray findings in CHD groups

	Group				Total		X^2	P
	CHD with HF group		CHD group					
	N	%	N	%	N	%		
Prominent vascular marking	28	70.0%	10	50.0%	38	63.3%	2.29	0.13
Cardiomegaly	21	52.5%	9	45.0%	30	50.0%	0.3	0.58
Chest infection	18	45.05%	5	25.0%	23	38.33%	1.23	0.09

No significant difference in X-ray findings between the CHD with HF & CHD without HF.

Table (7): Echocardiographic findings in diseased groups

	CHD with HF group	CHD group	t	P
Systolic PAP (mmHg)	39.1±4.7	29.05±4.2	8.073	0.00**
EF %	53% ±3%	71% ±3.5%	-20.635	0.00**
FS %	27% ± 2%	41% ± 2 %	-17.047	0.00**
LVESD (mm)	16.7±1.87	17.45±2.3	-1.354	0.181
LVEDD (mm)	29.65±2.05	27.25±1.51	4.618	0.00**

Heart failure group has significantly higher systolic PAP and LVEDD and significantly lower regard EF and FS as compared to the CHD children without HF.

DISCUSSION

Our study showed that males are more likely to have acute heart failure (57.5%) than females. This agrees with **Mehta and Cowie** [6] who found that the incidence and prevalence of heart failure is lower in females than in males at all ages. However, in CHD group; males and females were equal to have congenital heart diseases. This did not agree with **Amel-Shahbaz *et al.*** [7] who found that the frequency of CHDs in female was more than male and VSD, PDA, ASD, PS, and TOF were most common in CHDs, respectively. This may be due to the few number of collected patients in our study (60) compared to (3714) in their study.

In our study height and head circumference were significantly lower among cases with HF than in the other two groups with no significant difference between other two groups. Weight, Height and BMI were significantly different among groups; higher in control followed by CHD group then the heart failure group. This agrees with **Daymont *et al.*** [8] who found that children with congenital heart disease experience early, simultaneous decreases in growth velocity across weight, length, and head circumference. The

simultaneous decrease suggests a role for altered growth regulation in children with CHD.

The study showed that heart failure patients are more frequent to suffer from cough, dyspnea, tachycardia, sweating and recurrent chest infection. **Satou *et al.*** [9] found that regardless of the etiology, the first manifestation of congestive heart failure is usually tachycardia.

Our study also showed that unlike normal children the heart failure and cardiac patients are more frequent to have delayed social and motor development. **Mari *et al.*** [10] found that children with congenital heart disease are likely to have a developmental delay with significant difference between children who have undergone surgery and those awaiting surgery under clinical follow-up.

Bjarnason *et al.* [11] showed that Often, cardiac disease means a restriction of the affected child's perceptual and motor experience. Complex and severe heart defects may, at least temporarily, cause limited exercise tolerance and therefore require a certain amount of rest. Times of inpatient examinations or corrective operations are always periods of more or less strict immobilization. Depending on their duration and the child's age and mental stability, cardiac diseases can lead to developmental stagnation or regression. Anxiety and worries about the ill child often cause parents to adopt overprotective behavior. Great uncertainty exists, especially with regard to the danger to which one might expose children by allowing them to engage in physical activity. This is often unnecessarily with children whose physical capacities are grossly normal.

Our study showed that VSD followed by PDA were the most common congenital heart disease among cardiac group and the heart failure group. This agrees with **Amel-Shahbaz *et al.*** [7] who found that ventricular septal defect (VSD) was found to be the most frequent of CHDs (27%). Patent ductus arteriosus (PDA) (16.8%), atrial septal defect (ASD) (15.8%), pulmonary stenosis (PS) (11%) and Tetralogy of Fallot (TOF) (8.9%) were more prevalent in CHDs after VSD.

Our study showed that neutrophils and NLR were significantly higher among heart failure group than in the other two groups and lymphocytes were significantly lower among heart failure group than the other two groups. This is the core of our study because we suppose that nutrophilia, high NLR ratio and lymphopenia are indicators of bad prognosis in children with acute heart failure.

Inflammatory reactions play a pivotal role in the development of HF [12]**.** White blood cells and their subtypes are remarkable inflammatory markers in HF. As a result of inflammatory stimulus, leukocytes release many inflammatory cytokines, such as TNF-α, IL-6, and CRP, as well as some proteolytic enzymes. These pro-inflammatory cytokines have destructive effects on the myocardium, resulting in decreased LV function and HF [13].

The main role of neutrophils in cardiac patients may be explained by secretion of various inflammatory mediators such as elastase, myeloperoxidase and O_2 free radicals, which cause tissue damage [14]**.**

Lymphopenia is seen to be more common in stressful conditions such as HF due to the activation of the hypothalamic-pituitary-adrenal axis. The activation of this axis leads to cortisol secretion, and increased cortisol levels result in a decrease in the relative concentration of lymphocytes**.** Lymphopenia is an independent prognostic factor and is also associated with decreased survival in patients with HF [15]**.**

Previous studies illustrated that NLR could be a potential surrogate marker of systemic inflammation in its ability to predict CRP levels [16]**.**

Our study found that CRP was positive in (57.5%) of the heart failure group while it was positive in (40%) of the CHD group. It also showed that there was positive correlation between NLR and CRP in the heart failure group. This agrees with **Anand *et al.*** [17] who found that a direct relationship between elevated plasma CRP and the progression of HF. Higher plasma CRP is associated with a worse hemodynamic and neurohormonal profile and a poorer quality of life. CRP is a predictor of adverse clinical outcomes.

Our study showed that oxygen saturation (SO_2) was significantly lower in the heart failure group than CHD group. This agrees with **Ioana *et al.*** [18] who found that patients with mild to moderate acute heart failure might show modest reductions in oxygen saturation, whereas patients with severe heart failure may have severe oxygen desaturation, even at rest. Pulse oximetry is also useful for monitoring the patient's response to supplemental oxygen and other therapies.

Heart failure group was significantly higher PAP and LVEDD but significantly lower EF and FS.

The mean pulmonary artery pressure (PAP) was higher in the heart failure group. This agreed with **Barst *et al.*** [19] who found that the estimated prevalence of CHD is approximately six to 10 per 1,000 live births and 4–15% of patients with CHD will go on to develop PAH**.** In the French National Registry of PAH, PAH-CHD was the second most commonly associated form of PAH (after connective tissue disease-associated PAH) [20]. The prevalence of PAH in patients with CHD varies according to the size and location of the cardiac defect [21]**.** In the Dutch CONCOR registry, which included patients with both corrected and uncorrected defects, PAH prevalence rates varied from 3% in patients with patent ductus arteriosus to 100% in patients with an aortopulmonary window [22]**.**

CONCLUSION

Elevated NLR seems to be a predictor of short-term mortality in patients with acute heart failure. The NLR is an easily derived and routinely available measure. Therefore, NLR might assist in identifying patients at increased risk of mortality.

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