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ORIGINAL ARTICLE

Assessment of Pentraxin 3 Level as a Novel Reliable Biomarker for Early Diagnosis of Pulmonary Arterial Hypertension in Neonates

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ABSTRACT

Background: Newborn pulmonary arterial hypertension (PAH) is a serious neonatal disease that even with modern mechanical ventilation modes has a high mortality rate. Pentraxin 3 (PTX_3) is a novel biomarker release from endothelial vascular cells and macrophages with a crucial role in cell proliferation and angiogenesis regulation. However, in all neonatal intensive care units (NICU) echocardiography may not always be readily available. So, our work aimed to assess serum level of PTX_3 in PAH newborns.

Methods: This is a case-control study performed on 36 neonates divided into 3 groups; including healthy neonates (group I), congenital heart disease (CHD) without PAH (group II), and with PAH (group III). This study was carried out at NICU of pediatric department, Faculty of Medicine, Zagazig University. All neonates were subjected to full clinical examination. Systemic diagnosis of CHD and PAH was made using echocardiography machine. All participants were referred for measurement of PTX_3 Level.

Results: There was no significant difference among the 3 groups with respect to demographic characteristics; age (P = 0.292), and birth weight (P = 0.345). PTX_3 levels in PAH group were significantly higher than CHD-without PH and healthy groups (8.08 ± 0.69 vs. 5.47 ± 0.98 and 2.71 ± 0.48 ng/mL, P = 0.001, respectively). No significant correlation was found between PTX_3 concentrations and cardiac ejection fractions (EF) between PAH and CHD-without PAH (r = 0.232, P = 0.173). However, a significant positive correlation was detected between PTX_3 concentrations and heart rate (r = 0.444, P = 0.007) or respiratory rate (r = 0.658, P = 0.0001) among these two groups.

Conclusions: Serum PTX_3 level is significantly higher in PH neonates, hence it may be regarded as a new adjuvant diagnostic tool for the early assessment of PH in neonates.

Keywords: Pentraxin 3; Pulmonary Hypertension; Congenital Heart Disease; Neonate.

INTRODUCTION

Neonatal pulmonary arterial hypertension (PAH) is a serious illness during the neonatal era and regarded to be one of the major reasons for respiratory impairment in neonates. In more than 10% of newborns with respiratory impairment, PAH may constitute a serious cause of morbidity and death in this population [1]. Data suggested that PAH happens in 1-2 infants / 1000 live births [2]. Recent research in Egypt revealed that 5% of the investigated population had PAH [3].

PAH may be primary or secondary to several causes during neonatal periods, including meconium aspiration, congenital heart disease, and bronchopulmonary dysplasia [4]. Due to its association with adverse cardiorespiratory outcomes, early detection of PAH is critical. [5].

Cardiac catheterization is the gold standard for PAH diagnosis, but it is invasive and seldom used as the initial technique for diagnosis. As a result, echocardiography is the primary screening technique for detecting PAH in the neonatal population. Nevertheless, echocardiography in all

neonatal ICU might not always be accessible. Therefore, it can be useful to measure special biomarkers when testing neonates with PAH [6].

The novel biomarker Pentraxin 3 (PTX_3), which was demonstrated to be beneficial in the assessment of PAH in adult patients [7]. C-reactive protein (CRP) is a short pentraxin originated from liver in response to systemic inflammatory cytokines, whereas PTX_3 is a subclass of long pentraxins that is highly expressed in the heart and synthesized by local vascular cells, such as smooth muscle cells, endothelial cells, and fibroblasts, as well as innate immunity cells. At sites of inflammation, PTX3 plays a well-known role in the innate immune response to infection [7, 8]. It is crucial in the regulation of cell proliferation and angiogenesis. [9].

The CRP serum levels mediate inflammation, whereas a PTX_3 serum level is related to infectious disease severity and may be utilized for bacteremia and fatal infection, as an independent predictive biomarker [10]. PTX_3 is a commonly utilized biomarker in clinical contexts, according to numerous studies [10, 11]. Also, recently PTX3 was involved in patients with heart disease as a predictor of adverse clinical results [12]. As a result, PTX_3 has noteworthy attention in cardiovascular medicine as a more effective and rapid inflammatory marker. It has been demonstrated that PTX_3 levels are higher in congestive heart failure and acute myocardial infarction. [12]. Recently, the role of PTX_3 as a particular biomarker for PAH diagnosis was also established. [13].

The majority of cardiovascular disease research associated with PTX_3 is limited to adult patients [14, 15, 16]; just a few clinical uses of PTX_3 as a neonatal marker investigation have been performed in neonatal diseases [6, 13]. To the best of our knowledge, has still not been thoroughly studied in newborn infants with PAH. The purpose of this current study is therefore aimed to evaluate plasma PTX_3 levels in early diagnosis of newborns who complain of PH and compare them with those who have other CHD without PAH and healthier neonates.

METHODS

This is a case control study was conducted in NICU in Zagazig University Hospitals and Zagazig Public Hospital, Zagazig City, Sharika Governorate, Egypt, for a period of eight months from January to August 2019. The procedures of this research were conducted following the Helsinki Declaration and were authorized by the Research Ethical Committee, and according to the obtained consent from the Institutional Review Board (IRB); (IRB Number: ZU-IRB#4975#11-11-2018) Faculty of Medicine, Zagazig University.

Thirty-six newborn babies of > 34 weeks of gestation were involved in the studied population and divided into 3 groups: twelve apparently healthy neonates without any obstetrical problem included 6 male and 6 females, (group I), twelve congenital heart disease without PAH included 5 male and 7 female (group II, CHD), and twelve CHD with PAH included 6 male and 6 female (group III, CHD-PAH).

Before the beginning of the study, the suggested protocols were declared to all parents, who accepted and thier neonates met the inclusion criteria that mentioned below. Full prenatal history taking of maternal infection, diseases and antibiotic or drug administrated to mother. Natal history: which include sex, gestational age, birth weight, invasive procedure (as blood transfusion, endotracheal intubation and mechanical ventilation). Complete clinical examination included general reflexes, vital signs (normal HR is 100 to 165 beats per minute and normal RR is 30 to 55 breaths per minute) Fleming et al [17], systemic examination including neurological, respiratory, cardiovascular, abdominal …etc.

Specific Investigations: echocardiography

According to echocardiographic findings by pediatric cardiologist, a transthoracic 2D echocardiography and tissue Doppler imaging device (GE-Vivid 3, General Electric, Milwaukee, WI, USA) with 2.5 and 3.5 MHz transducers on outpatient basis at baseline was performed for measurement of pulmonary arterial pressure (PAP) in neonates using standard techniques. PAP was calculated by measuring the peak regurgitant tricuspid Doppler velocity and converting it to a right ventricular, to right atrial gradient using the modified Bernoulli equation ($4v^2$), [where: v is the maximum velocity of the tricuspid valve regurgitant jet]. Right atrial pressure (RAP) was estimated from the degree of collapse of the inferior vena cava (i.e., variation in the diameter) with inspiration. Right ventricular systolic pressure (RVSP) was calculated by adding the trans tricuspid pressure gradient to the RAP estimated.

Inclusion criteria were: Neonates from first day to 28 days old, both male and female, congenital heart disease and > 34 weeks of gestation, while exclusion criteria were: Severe sepsis suspected or

proved by high c-reactive protein (CRP >10 mg/dLand/or positive blood culture), Severe hypoxic respiratory failure, diffused intravascular coagulation (PaO2 b 50 mm Hg despite sufficient invasive mechanical ventilation), low Apgar, non-congenital cardiac disorders (e.g. endocarditis), or chorioamnionitis maternal history.

Methodology

After exclusion of non-respondents' parents or neonates with the above-mentioned exclusion criteria, all study participants provided signed informed consent from their parents, then all neonates were referred for measurement of pentraxin 3 Level.

Evaluation of Pentraxin 3 plasma levels (PTX_3)

According to the manufacturer's instructions, an enzyme-linked immunosorbent assay (ELISA) was applied to detect PTX_3 level.

Sample Collection

Five ml of venous blood were withdrawn from every neonate in each group under full aseptic condition after fasting overnight. Blood was transferred to an Eppendorf tube at 37 °C for 30 minutes to clot and centrifuged at 4000 rpm for a further 10 min using (Heraeus Biofuge Primo, Thermo Scientific, Waltham, MA). The obtained serum was put in aliquots, stored at -80 ° C till the time of analysis for determination of marker serum level using ELISA.

Test principle

Human PTX_3 is an enzyme immunoassay technique that may be stated in three stages as reported early by Farhadi et al., 2017 [6].

Inject samples

Test wells: The serum sample was diluted by serum diluent (supplied within kit box) then 40 µl was mixed with 10 µl of PTX_3 conjugate and 50 µl Streptavidin-HRP, then seal the sealing membrane, and gently shaking. The wells were incubated for 60 min at 37 ° C then washed 30 × times with washing solution. Aliquot of 100 µl of chromogenic substrate was added and the mixture was incubated for 10 min at 37 ° C away from light then 100 µl of stop solution was added. An assay was performed by measuring the OD using ELISA reader set to 450 nm. A reference concentration of PTX_3 was used to prepare assay calibration curve. *Blank well:* aliquot of tetramethylbenzidine (TMB), a chromogenic substrate only, *Standard wells:* aliquot of 50 µl standard (supplied within kit box) was mixed with 50 µl Streptavidin-HRP, were subjected to the same procedure. PTX_3 level was calculated with reference to stander calibration curve of PTX_3. The optical density (OD) for every well was estimated spectrophotometrically with an ELISA reader (Stat fax 303 plus) at 450 nm. The reaction mixture's color intensity is proportional to the PTX_3 concentration of the test specimens, standards, and controls the mean OD of each triplicate was calculated.

Statistical analysis:

Gathered data during the history, laboratory examinations, basic clinical investigation, and result evaluations were coded and analyzed with Microsoft Excel software. For analysis, data were then entered into the SPSS version 20.0 (Statistics Package Social Science, SPSS Inc., Chicago, IL), USA. Chi square test (X^2) was applied to estimate qualitative variable difference and association, whereas ANOVA or Kruskal Wallis was used to calculate the differences between quantitative independent multiple groups. Paired nonparametric t-test was used to calculate P value in each group (It was thought that $P < 0.05$ was significant).

RESULTS

Demographic characteristics of 36 neonates (50 % were females) including 12 healthy controls, 12 CHD without PAH and 12 CHD with PAH, are presented in **(Table 1).** The average age of all neonates involved in our current study was 11.75 ± 8.65, 10.75 ± 8.65 and 16.08 ± 9.18 days, respectively. **(Table 1)** demonstrated that there is no statistically significant difference regarding age ($P = 0.292$), gestational age in week ($p = 0.241$), and birth weight in kg ($p = 0.345$) among the 3 groups of the current research. Additionally, there was non-significant difference with respect to CRP among all studied group (I, II and II), $P = 0.75$, with a highly significant difference within group II and III concerning cyanosis and grunting, compared with healthy group (I), ($p < 0.05$), as presented in **(Table 1)**.

Also, the result of our study revealed that healthy control group (I) was significantly associated with no ECHO finding. The commonest heart defects in our patients were atrial septal defect (ASD) followed by PFO in both CHD, CHD with PAH groups, as represented in **(Table 2)**.

As represented in **(Table 3),** serum PTX_3 in CHD-PAH (group III) (8.08 ± 0.69 ng/mL) was substantially greater than the CHD (groups II) and control healthy (group I) (5.47 ± 0.98 and 2.71 ± 0.48 ng/mL, respectively, $p \leq 0.001$). The mean

PTX_3 of the CHD (group II) was also significantly higher in comparison to control (group I).

In newborns with PAH, EF ratio was not significantly differentiated from CHD neonates without PAH (75.58 ± 8.42% versus 73.5± 6.05, respectively, P = 0.19). The serum PTX_3 and all other variables have been calculated for multiple correlations. They demonstrated that non-significant correlations were found between PTX_3 and EF (negatively correlated, r = 0.232, P = 0.173), whereas the PTX_3 concentration and RR (r = 0.658, P = 0.0001) and with the HR (r = 0.444, P = 0.007) were significantly correlative, as illustrated in **(Table 3).**

Multiple regression analyses of the participant's characters and serum PTX_3 related to PAH showed that AUC of PTX_3 was 0.83 (95%CI: 0.75 - 0.89) and 0.91 (95 %CI: 0.87 – 0.99) for CHD (group II) and CHD-PAH, P < 0.001, respectively. The best diagnostic cut-off point (threshold concentration) was PTX_3 = 3.98 ng/ml that maximized true +ve and false -ve outcomes (with 94.8 % sensitivity and specificity of 88.8 %), for CHD (group II) P < 0.001. Additionally, the best diagnostic cut-off point of CHD-PAH (group III) was PTX_3 = 6.88 ng/ml, (with 96.3 % sensitivity and specificity of 98.3 %), P < 0.001, as shown in **(Table 4)** and shown in Receiver operating characteristic (ROC) curve of CHD (group II) **(Figure 1)** and CHD-PAH (group III) **(Figure 2).**

Table 1: Baseline characteristics of neonates, cyanosis and grunting distribution among studied groups.

	Group I (N = 12) Healthy		Group II (N = 12) CHD		Group III (N = 12) CHD-PH		Total		Test	P-value
	Number	%	Number	%	Number	%	Number	%		
Age (Day) Range	11.75 ± 8.65 1 - 25		10.66 ± 8.9 1 – 27		16.08 ± 9.18 3 – 28				1.277#	0.292
GA (weak)	37.66 ± 1.15		37.08 ± 0.79		37.66 ± 0.88				F= 1.485	0.241
CRP (mg/dl))										
-Ve	11	91.7%	11	91.7%	10	83.3%	32	88.8%	0.56 ‡	0.75
+Ve	1	8.3 %	1	8.3 %	2	16.7 %	4	11.2%		
Cyanosis										
-Ve	12	100 %	7	85.4 %	4	33.3%	23	63.8%	8.7 ‡	0.01*
+Ve	0	0.0%	5	41.6%	8	41.7%	13	36.2%		
Grunting										
-Ve	12	0.0%	4	33.3%	4	33.3%	20	55.6%	11.4 ‡	0.003*
+Ve	0	0.0%	8	66.7 %	8	66.7 %	16	44.4 %		

GA = Gestational age; CRP = C-reactive protein; # = Kruskal Walis; ‡ = X^2

Table 2: ECHO finding comparison among studied groups

	Group I (N = 12)		Group II (N = 12)		Group III (N = 12)		Total		Test (X^2)	P-value
	Number	%	Number	%	Number	%	Number	%		
Normal	12	100 %	0	0.0 %	0	0.0 %	12	33.3%	45.38	0.00**
ASD	0	0.0 %	4	33.3 %	3	25.0 %	7	19.4%		
AV CANAL	0	0.0 %	0	0.0 %	1	8.3%	1	2.8%		
COR_PULMONAL	0	0.0 %	0	0.0%	1	8.3%	1	2.8%		
PDA	0	0.0 %	0	0.0 %	2	16.7%	2	5.6%		
PDA & ASD	0	0.0 %	1	8.3 %	0	0.0 %	1	2.8 %		
PDA & VSD	0	0.0 %	1	8.3 %	0	0.0 %	1	2.8 %		
PFO	0	0.0 %	5	41.7 %	4	33.3 %	9	25.0%		
VSD	0	0.0 %	1	8.3 %	1	8.3 %	2	5.6%		

ASD = Atrial Septal Defects; AV CANAL = Atrioventricular Canal; PDA = patent Ductus arteriosus; VSD = Ventricular septal Defect; PFO = Patent Foramen Ovale

Table 3: Pentraxin3 level distribution among studied groups and its correlation with other parameters

	Group I	Group II	Group III	F	P-value
Pentraxin 3	2.71 ± 0.48	5.47 ± 0.98	8.08 ± 0.69	153.944	0.001**
EF	70.16±6.93	75.58±8.42	73.5±6.05	1.72	0.19
RR	60.41±11.59	75.16±11.06	80.5±5.01	13.809	0.001**
HR	123.5±4.73	126.41±5.83	131.5±6.06	6.321	0.005*
Correlation of Pentraxin3 with other parameters					
		Age	**GA**	**HC**	**RR**	**HR**	**EF**
Pentraxin 3	R	0.190	0.031	-0.093	0.658	0.444	0.232
	P	0.268	0.860	0.590	0.0001**	0.007**	0.173

GA = Gestational Age; HC = head circumference; RR = Respiratory Rate; HR= Heart Rate; EF = Ejection fraction.

Table 4: Multiple logistic regression interpretation of pentraxin 3 regarding congenital heart disease (CHD) with or without pulmonary hypertension (PH)

	AUC	95% Confidence Interval		Sensitivity %	Specificity %	Cut-off Values	p-value (Sig.)
		Lower Bound	Upper Bound				
CHD	0.83	0.75	0.98	94.8%	88.8%	> 3.98	< 0.001**
CHD-PH	0.91	0.87	0.99	96.3%	98.3%	> 6.88	0.00**

AUC = Area under the curve.

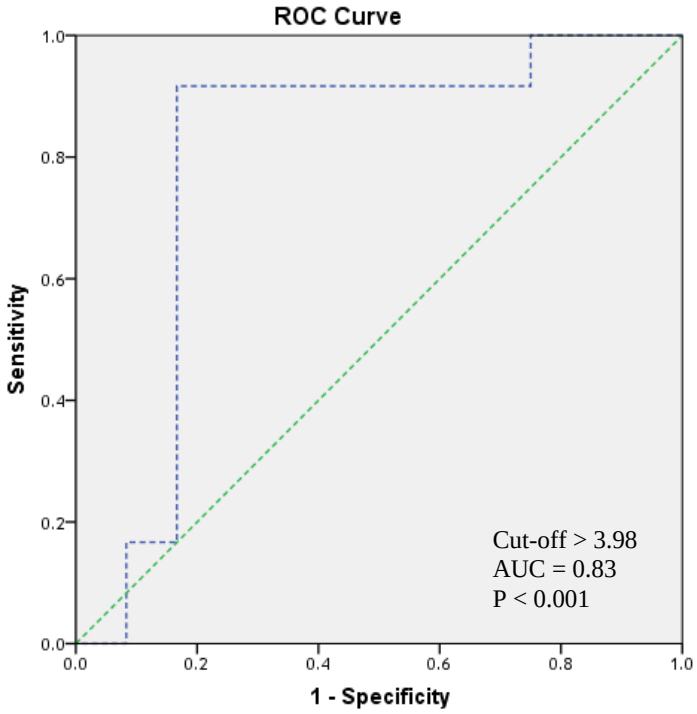

Figure 1: Receiver operating characteristic (ROC) curve for detection of Pentraxin 3 cutoff regarding CHD (group II).

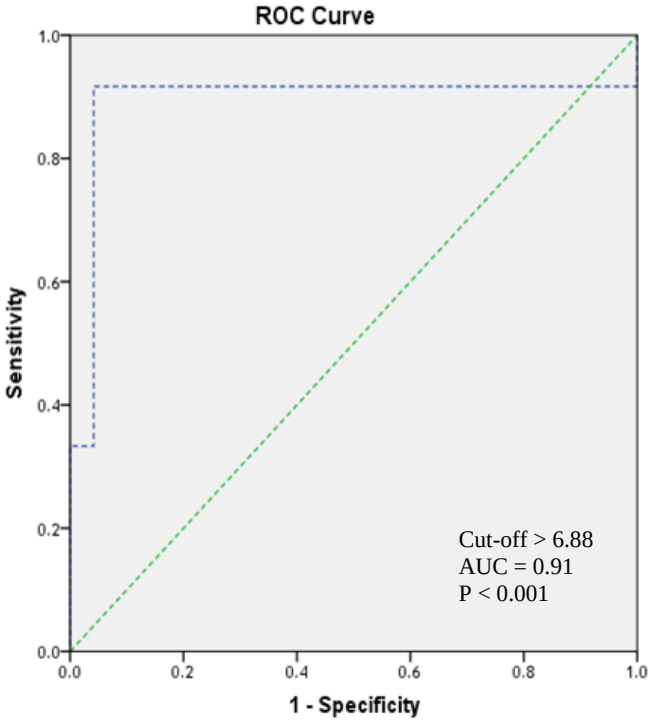

Figure 2: Receiver operating characteristic (ROC) curve for detection of Pentraxin 3 cutoff regarding Pulmonary Arterial Hypertension (group III).

DISCUSSION

PAH is one of the most severe neonatal diseases that might be idiopathic, linked with CHD, lung illness or postoperative. In the clinical management of PAH, early diagnosis, risk investigation, and disease progress follow-up are critical components. Treatment decisions are currently based on evaluations of the severity of the illness based on the symptoms and exercise capacity. Unfortunately, these assessments show considerable subjectivity and inaccuracy. Consequently, the interest and research to identify effective biomarkers in PH have increased. A biomarker is defined generically by the US Food and Drug Administration (FDA) as a "characteristic that is measured and analyzed objectively as an indication of biological processes, pathogenic processes or pharmacological response to a treatment".

PTX_3 is a member of an evolutionarily conserved proteins family that comprise CRP and serum amyloid P. In innate immunity and inflammation, PTX_3 performs a crucial part, in which in response to inflammatory signals, PTX_3 is produced by innate immune and vascular cells via Toll-like receptor (TLR) recruitment [6]. In response to inflammation, PTX_3 is produced by different vascular and immune cells [8]. As a result, the existence of PTX_3 might indicate infection and inflammation.

Some published research articles have shown the vital role of high PTX_3 levels in adult people with cardiovascular comorbidities such as acute myocardial infarction [14], unstable angina [15] and congestive heart failure [16]. These findings suggest plasma PTX_3's potential role as a novel predictive inflammatory biomarker for neonatal pulmonary hypertension.

The present study is one of the earliest experimental trials on the utility of the local vascular inflammatory biomarker PTX_3, as a diagnostic means for early diagnosis of PAH in neonates. Only two earlier trials indicated the usefulness of PTX_3 in newborn children as a cardiovascular biomarker [6, 18]. In the current study, thirty-six neonates were involved; 12 with CHD without PAH and 12 complain of PAH, compared to 12 health neonates.

In our research, we observed no significant difference among the study groups concerning the demographic characteristics (age, gestational age, and birth weight) and CRP, which is agreed with the reported results of Farhadi et al, [6] and Tamura et al, [7]. While the cyanosis and grunting were significantly higher in cases of group II and III.

Interestingly, the mean serum PTX_3 was shown to be considerably greater in PAH neonates in comparison to healthy group and CHD neonates without PAH. Furthermore, the average PTX_3 of CHD without PAH was considerably greater compared to healthy neonates' group (I). The results of many investigations were in line with our current finding and demonstrating that the mean PTX_3 serum was substantially higher in neonates who complain of PAH than that of healthy or CHD neonates with normal PAH, Farhadi et al, [6] and El Wakeel et al, [13].

Numerous associations between serum PTX_3 and all other variables were calculated to elucidate our outcomes. It has demonstrated a positive correlation between RR and HR with serum PTX_3, which could be attributed to the role of PTX_3 in vascular disorders and angiogenesis. In inflammatory sites, PTX_3 is not only released by endothelial cells, but by macrophages and monocytes also, which infiltrates the inflammation sites in pulmonary hypertension [19]. There was no association between serum PTX_3 and EF, which are in line accordance with findings reported by Farhadi et al, [6].

Our results are consistent with early studies, which confirmed the critical role of assessment of PTX_3 level elevation in early diagnosis of patient with cardiovascular disorder [6, 13].

El Wakeel et al., 2019 assessed PTX_3 serum levels in 3 groups of neonates, with thirty cases per group. The 1st group of PH, the 2nd group of CHD without PH, and the 3rd group of healthy newborns. They showed a considerable elevation of average serum PTX_3 for neonates with PH than healthy and CHD newborns ($p \leq 0.001$, $p = 0.02$ respectively). Furthermore, the average PTX_3 of CHD neonates was considerably higher compared to the healthy group ($p = 0.06$). Because PTX_3 is not a liver-dependent biomarker, the authors suggest that measurement of PTX_3 levels in newborns could be beneficial as a predictor of pulmonary hypertension in neonates than other acute-phase proteins [13].

Also, in line accordance with Farhadi et al., 2017 results, who investigated the plasma PTX_3 level in seventy-two newborns [21 in PH (group I), 19 in CHD-PH (group II), and 32 in healthy neonates (group III)] and noted that the level of PTX_3 in PH neonates was significantly higher compared to CHD-PH and healthy neonates (2.12 ± 2.32 vs. 0.58 ± 0.57 and 1.03 ± 1.38 ng/ml, P=0.008, respectively). There was non-significant association between cardiac EF and PTX_3 concentrations among group 1 and 2, ($r = 0.009$, $P = 0.97$). Nevertheless, between PTX_3 concentrations and pulmonary pressure, there was considerable positive association among the two groups, ($r=0.499$, $P = 0.001$). They found that PTX_3 might be regarded as an innovative additional diagnostic technique for assessing pulmonary hypertension in conjunction with echocardiography or as a diagnostic tool where echocardiography isn't readily available for verification of elevated pulmonary pressure [6].

Other earlier studies of the serum PTX_3 assessment that showed contrary findings, Sciacca et al, who evaluated the relationship of blood PTX_3 to the seriousness of respiratory impairment and several echocardiographic variables in the late pre-term neonates with hypoxic respiratory failure. Nevertheless, they observed that PTX_3 to be greater in patients with severe hypoxic respiratory distress, contrary to our finding, they reported a substantial reversal association among ejection fraction and serum PTX_3 levels [20]. One of the explanations for the unusual conclusion to our study may be that neonates involved in our research merely identified with PAH or CHD without severe hypoxic respiratory distress or heart failure.

Concerning the ROC curve, we suggested that PTX_3 regarding CHD group II [AUC with threshold concentration > 3.98 ng/ml (with sensitivity of 95.5% and specificity 88.8%)] and PAH group III [cutoff > 6.88 ng/ml (with sensitivity 96.3% and specificity 98.3%)], Figure (1 and 2, respectively), indicated that serum PTX_3 elevation was correlated with the presence of PAH which is in sound accordance with previous results reported by Farhadi et al., 2017 (AUC = 0.683, sensitivity 90.5% and specificity 33.3%) [6], and Tamura et al., 2012 revealed that PTX_3 (AUC_{ROC} 0.866; with cutoff of 2.84 ng/ml, sensitivity 74 %, specificity 84 %) was more precisely predictor than either CRP or brain natriuretic peptide (BNP) in the presence of PAH [7].

CONCLUSION

The result of our study revealed that PTX_3 levels were increased in newborn infants with PH compared to those without PAH and healthy neonates. Plasma PTX_3 might be regarded as an innovative additional potential reliable biomarker in the early diagnosis of neonatal PAH in conjunction with echocardiography or as a beneficial initial assessment tool when

echocardiography isn't readily accessible for elevated pulmonary pressure verification.

REFERENCES

[1]. **Robin H, and Steinhorn**. Neonatal pulmonary hypertension. Pediatr. Crit. Care Med. 2010; 11 (2): 79 - 84.

[2]. **Abman SH.** Recent advances in the pathogenesis and treatment of persistent pulmonary hypertension of the newborn. Neonatol. 2007; 91:283-90.

[3]. **Mohsen AH, Amin AS**. Risk factors and outcomes of persistent pulmonary hypertension of the newborn in neonatal intensive care unit of Al-Minya University Hospital in Egypt. J Clin Neonatol. 2013; 2 (2):78-82.

[4]. **Aktas YS, Diniz G, Ortaç R, Aktas EO**, Pulmonary hypertension grading in the neonate: pediatric autopsy series compared with etiology of lung disease. Aegean Pathol. J. 2004; 1: 76 - 80.

[5]. **Cuna A, Kandasamy J, Fineberg N, Sims B**. B-type natriuretic peptide is a biomarker for pulmonary hypertension in preterm infants with bronchopulmonary dysplasia, Res. Rep. Neonatol. 2013; 3: 33 - 36.

[6]. **Farhadi R, Rafiei A, Hamdamian S, Zamani H, Yazdani J.** Pentraxin 3 in neonates with and without diagnosis of pulmonary hypertension. Clin Biochem. 2017; 50 (4-5): 223 - 227.

[7]. **Tamura Y, Ono T, Kuwana M, Inoue K, Takei M, Yamamoto T, et al.** Human pentraxin 3 as a novel biomarker for the diagnosis of pulmonary arterial hypertension. PLoS One 2012; 7 (9): e45834.

[8]. **Doni A, Peri G, Chieppa M, Allavena P, Pasqualini F, Vago L, et al.** Production of the soluble pattern recognition receptor ptx3 by myeloid, but not plasmacytoid, dendritic cells. Eur J Immunol. 2003; 33: 2886 - 2893.

[9]. **Garlanda C, Bottazzi B, Bastone A, Mantovani A.** Pentraxins at the crossroads between innate immunity, inflammation, matrix deposition, and female fertility. Annu Rev Immunol. 2005; 23: 337- 366.

[10]. **Huttunen R, Hurme M, Aittoniemi J, Huhtala H, Vuento R, Laine J, et al.** High plasma level of long pentraxin 3 (PTX3) is associated with fatal disease in bacteremic patients: a prospective cohort study. PLoS One 2011; 6 (3); e17653.

[11]. **Inoue K, Kodama T, Daida H.** Pentraxin 3: a novel biomarker for inflammatory cardiovascular disease, Int. J. Vasc. Med. 2012; 2012: 657025.

[12]. **Duran S, Duran I, Kaptanagasi FA, Nartop F, Ciftci H, Korkmaz GG.** The role of pentraxin 3 as diagnostic value in classification of patients with heart failure. Clin Biochem. 2013; 46: 983 – 987.

[13]. **El Wakeel MA, Sabry RN, El-kassas GM, Abd El-Gaffar SA, El batal WH, Galal EM, et al.** Pentraxin 3: A Potential Novel Predictor for Neonatal Pulmonary Hypertension. Open Access Maced J Med Sci. 2019; 7 (15): 2424 - 2427.

[14]. **Peri G, Introna M, Corradi D, Iacuitti G, Signorini S, Avanzini F, et al.** PTX3, a prototypical long pentraxin, is an early indicator of acute myocardial infarction in humans. Circ. 2000; 102: 636 – 641.

[15]. **Inoue K, Sugiyama A, Reid PC, Ito Y, Miyauchi K, Mukai S, et al.** Establishment of a high sensitivity plasma assay for human pentraxin3 as a marker for unstable angina pectoris. Arterioscler Thromb Vasc Biol. 2007; 27: 161–167.

[16]. **Suzuki S, Takeishi Y, Niizeki T, Koyama Y, Kitahara T, Sasaki T, et al.** Pentraxin 3, a new marker for vascular inflammation, predicts adverse clinical outcomes in patients with heart failure. Am Heart J. 2008; 155: 75 – 81.

[17]. **Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I, et al.** Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet. 2011; 377 (9770) : 1011- 1018.

[18]. **Akin T, Gunes D, Coban MT, Kurtoglu S.** Pentraxin 3 concentrations of the mothers with preterm premature rupture of membranes and their neonates, and early neonatal outcome, J. Matern. Fetal Neonatal Med. 2014; 14: 1–6.

[19]. **Vergadi E, Chang MS, Lee C, Liang OD, Liu X, Fernandez-Gonzalez A, et al.** Early macrophage recruitment and alternative activation are critical for the later development of hypoxia-induced pulmonary hypertension. Circ. 2011; 123: 1986 - 1995.

[20]. **Sciacca P, Betta C, Mattia G, Li Volti G, Frigiola A, Curreri S, et al.** Pentraxin-3 in late-preterm newborns with hypoxic respiratory failure, Front. Biosci. (Elite Ed.). 2010; 2: 805–809.

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