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The Effect of Hemodynamically Significant Patent Ductus Arteriosus on Necrotizing Enterocolitis and Cerebral Changes in Preterm Infants

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ABSTRACT

Background: Hemodynamically significant patent ductus arteriosus (HSPDA) is associated with increased mortality and several significant morbidities including necrotizing enterocolitis (NEC), cerebral ischemia, intraventricular hemorrhage, pulmonary hemorrhage, or bronchopulmonary dysplasia.

Objectives: The aim of the current work was to assess the cerebral hemodynamic changes and NEC in preterm infants diagnosed with HSPDA and to investigate the role of Human Epithelial derived neutrophil chemoattractant-78/ C-X-C Motif Chemokine Ligand 5 (ENA-78/CXCL5) as a diagnostic tool for NEC in HS PDA.

Patients and Methods: This prospective case-control research was carried out on preterm infants (GA < 34 weeks) admitted at the Neonatal Intensive Care Unit, Benha University Hospitals, over one year from June 2021 till June 2022. Within 72 hours of birth, an echocardiographic examination was performed to check for a PDA. The included neonates were divided into three groups. 1st group was diagnosed with HSPDA, the second with non HSPDA, and the third with no PDA as control group. All newborns were exposed to full history taking, general and local examination, chest and abdominal radiographs, cranial ultrasound, and lab investigations in the form of CBC, electrolytes, and human (ENA-78/CXCL5) assay.

Results: There was an increased incidence of cerebral ischemia, abnormal retrograde cerebral blood flow in anterior cerebral artery, intracranial hemorrhage, and periventricular leukomalacia (p-value <0.001, <0.001, <0.001, and 0.03 respectively) in hemodynamically significant PDA more than non-significant PDA and control group**.** Univariate logistic regression analysis showed that the left atria to aortic ratio and retrograde flow in descending aorta are significant and independent factors associated with cerebral ischemia, intracranial hemorrhage and hypotension**.** No variation in the incidence of NEC or mortality between the studied groups.

Conclusion: It could be concluded that HSPDA is associated with higher incidence of cerebral complications. Human (ENA-78/CXCL5) had a role in the diagnosis of NEC in HS PDA.

Keywords: Hemodynamically, Patent Ductus Arteriosus, Necrotizing Enterocolitis, Cerebral, Preterm Infants.

INTRODUCTION

Preterm newborns frequently have patent ductus arteriosus (PDA), which is a common finding. When a HSPDA is present, substantial systemic to pulmonary shunting causes systemic hypo perfusion and pulmonary hyper perfusion **(1)**.

The "ductal steal" percentage of aortic blood flow that is redirected into the pulmonary circulation rises when pulmonary vascular resistance decreases after birth. This causes the lungs to get an excessive amount of blood flow, which increases the risk of developing pulmonary congestion, pulmonary edema, and progressive respiratory failure. The perfusion of important organs, such as the bowel, kidneys, and brain, may be affected due to the systemic circulation's blood flow being switched **(2)**. Newborns with HSPDA exhibit pulmonary edema, systolic murmur, broad pulse pressure, bounding pulses, hyperactive precordium, and elevated oxygen demand **(3).**

A number of echocardiographic indices can be used to assess an HSPDA. These indicators can be divided into four groups: the size of the PDA shunt, the volume overload's extent, the level of pulmonary overflow, and the magnitude of systemic hypo perfusion **(4)**. Blood flow in the descending aorta, cerebral or renal arteries may reverse during diastole when there is significant ductal shunting with a significant increase in the ratio of the dimensions of the left atrium to the aortic root of ≥1.5:1, a ductal width of ≥1.5 mm, and left ventricular volume and pressure loading **(5).**

Among newborns with a hemodynamically significant PDA, complications of prematurity like pulmonary edema, bronchopulmonary dysplasia, NEC, heart failure, intraventricular hemorrhage, and a protracted requirement for ventilator and/or oxygen support are more likely **(6, 7).**

The best way to manage a HSPDA continues to be highly contested. Options for treatment include surgical ligation, medicinal closure, and conservative measures. The prophylactic technique seeks to treat the PDA during the first 24 hours post-delivery, usually without echocardiographic examination and irrespective of its hemodynamic effect. Preterm children with a tiny or non-hemodynamically significant PDA do not have to worry about probable side effects of COX inhibitors such as acute kidney injury, thanks to the "early targeted" strategy which suggests treatment only of PDA with hemodynamic significance. However, trials comparing the early focused strategy to conservative care failed to show improvements in significant newborn outcomes, such as IVH, NEC, or premature retinopathy **(8).**

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ENA 78 is a CXC chemokine that promotes leukocyte activation and recruitment in inflammatory disorders. A premature infant's inflammatory bowel necrosis known as NEC is characterized by an infiltration of many macrophages, a small number of neutrophils, and few lymphocytes. The chemokine CXCL5 attracts macrophages to the swollen gut mucosa in murine newborn enterocolitis [(9)].

This study was aimed to evaluate the cerebral hemodynamic alterations (IVH and cerebral ischemia) and necrotizing enterocolitis in preterm neonates with HS PDA. We also sought to examine the significance of Human (ENA-78/CXCL5) as a diagnostic tool for NEC in HS PDA.

PATIENTS AND METHODS

This prospective case control study included a total of 30 preterm infants (GA 34 weeks) with PDA and 24 preterm infants with no PDA served as control, referred to the Neonatal Intensive Care Unit, Benha University Hospitals. This study was conducted over one year from June 2021 till June 2022.

Exclusion criteria: GA > 34 weeks, patients with congenital heart disease (other than PDA), persistent pulmonary hypertension of newborn, congenital cerebral malformations, congenital GIT malformations, congenital infection, and any other associated anomalies, death, or transfer before 72 hours of birth, refusal to sign informed written consent.

After applying strict inclusion and exclusion criteria, the remaining preterm infants had a PDA echocardiogram screening done during the first 72 hours after birth.

They were divided into three groups: 1st group diagnosed with HS PDA by echocardiographic criteria, the second with non-HSPDA, and the third with no PDA as control group.

All newborns were exposed to the following:

Full history taking stressing on age of the mother at conception. parental consanguinity, the mother's health and pregnancy history, detailed antenatal history, cause of preterm delivery, incidence of hypoxia or any complication at delivery, congenital heart disease in the family, and maternal history (hypertension, anemia, diabetes mellitus, infection with rubella, maternal epilepsy and maternal exposure to alcohol or teratogenic drug).

Clinical examination stressing on:

General examination: Vital signs, signs of hyperdynamic circulation, cyanosis and anthropometric measurements.

Heart examination: Assessment of pulsations, heart sounds, murmurs, clicks, or irregular beats.

The chest examination: signs of respiratory distress.

Abdomen examination: Abdominal girth, abdominal tenderness or rigidity, constipation, or bloody stools.

Application of Bell staging for degree of NEC

Neurological examination: Head circumference, consciousness level, signs of lateralization.

Radiology: Plain chest X-ray and Plain X-ray of abdomen in orthostasis.

Transthoracic echocardiography:

1. A pediatric cardiologist used a Vivid-I ultrasound scanner (GE Healthcare, UK) with a transducer 6Hz to do echocardiography. Based on the PDA flow velocity, the range of the color Doppler mapping scale was modified. To enhance the color image inside the duct and get rid of any peripheral color interference, the range for the color increase percentage was adjusted between 70 and 90.
2. PDA size is taken at its narrowest point, which is typically at the pulmonary end either on 2D image or color Doppler after optimizing gain settings, measured in two views: high parasternal view and suprasternal view. PDA diameter > 1.5 mm is a criterion for HS PDA **[(10)].**
3. Evaluation of PDA shunt direction using Doppler application and color flow.
4. Using either pulsed or continuous wave Doppler in the ductus arteriosus permits the determination of shunt velocity across the PDA throughout the cardiac cycle. Measurements can be made of the peak velocity during systole and diastole. **Non-restrictive shunts exhibit low peak diastolic velocities and a gradient of systolic to end-diastolic velocities > 2 [(10)].**
5. By placing the cursor perpendicular to the aorta at the level of the aortic valve or the septum at the tip of the mitral valve leaflets, respectively, one can calculate the LA/Ao ratio and Left ventricular end diastolic diameter (LVEDD) from the parasternal long axis view in M-mode. **Significant levels are defined as those with LA/Ao ratios above 1.40 and LVEDD z scores above 2 [(1)].**
6. With the pulsed wave, Doppler sample gate placed distal to the ductus arteriosus origin, a suprasternal or high parasternal view (ductal ampulla) can capture flow patterns from the descending aorta. **To satisfy the HS PDA requirements, diastolic blood flow in the descending aorta must be retrograde or nonexistent [(11)].**
   - In addition to a PDA diameter at its narrowest point ≥1.5 mm, we considered PDA to be hemodynamically significant when at least one of the following conditions was satisfied: Left atrial-to-aortic root ratio ≥1.5; unrestrictive pulsatile transductal flow, absence of diastolic flow in the descending aorta; and abnormal diastolic flow in the anterior cerebral artery **[(2)].**

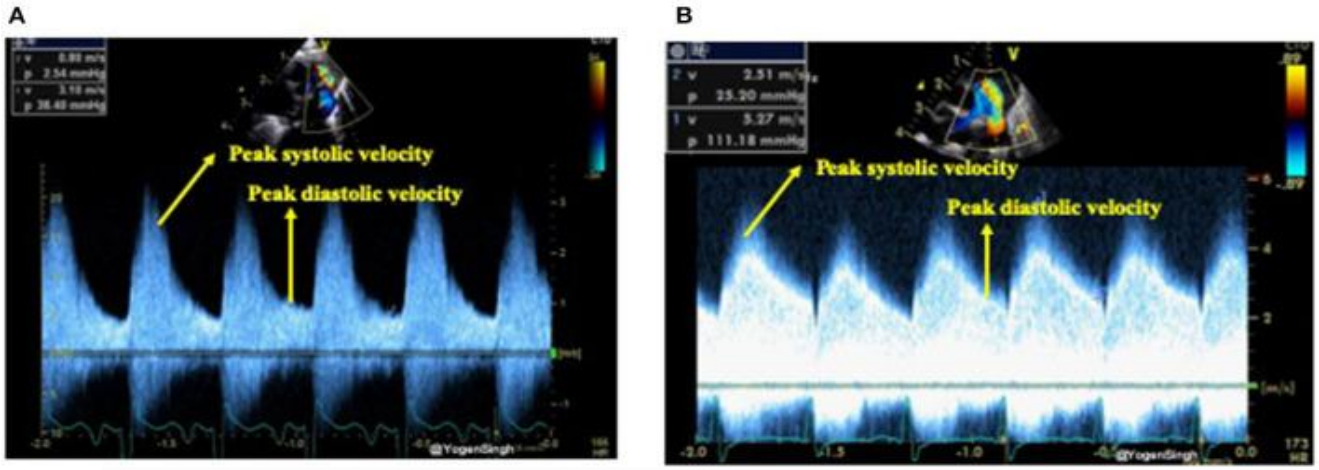

Fig. (1): Evaluation of restrictive and nonrestrictive (pulsatile) flow patterns during Doppler assessment of PDA [(10)].

Cranial Ultrasound and Doppler:

The cerebral Doppler sonography was carried out using a transducer of 7.0 MHz. on newborns who were either asleep, sedated or in a peaceful waking state.

1. Color duplex Doppler module was used to record the blood flow velocity in the brain. The transducer measured the anterior cerebral arteries (ACA) via the anterior fontanelle in the midsagittal and coronal planes with the necessary angle compensation for velocity measurement [(12)].
2. We measured peak systolic velocity, end-diastolic velocity, and resistive index. (peak systolic velocity - end-diastolic velocity) / peak systolic velocity is the formula for resistive index [(13)].
3. Evaluation of morphology to detect cerebral ischemia, intracranial hemorrhage, and periventricular leukomalacia, and to rule out any additional malformations.

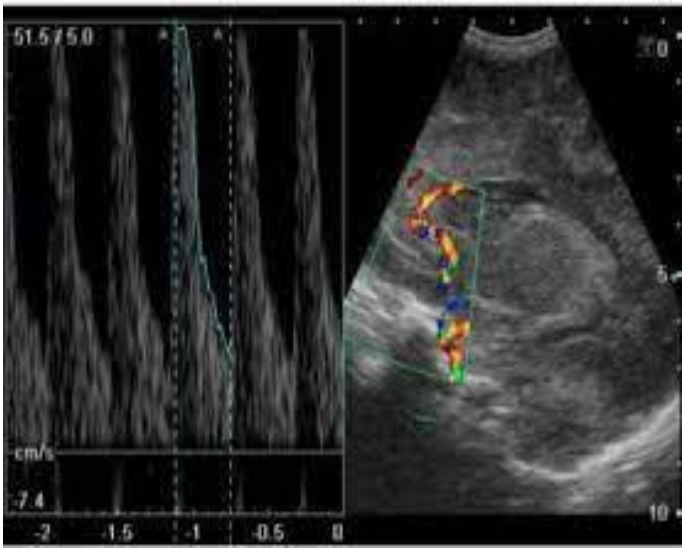

Fig. (2): Trans Cranial Doppler Ultrasonography in PDA.

Laboratory investigations:

1. CBC, renal function tests (creatinine and urea), electrolytes (Na ,K, Cl) and arterial blood gases, and occult blood in stool.
2. ENA-78 level determination was performed using ENA-78. Human ELISA kits provided by SunRed, China, 201 – 12 – 0132; sensitivity was 0.906pg/ml; assay range was 1pg/ml to 300pg/ml.

Outcomes:

We regarded the rate of neonates having a minimum of one of the following morbidities to be the primary outcome: intracranial hemorrhage (IVH) stage2, periventricular leukomalacia, NEC Bell-Stage 2, GIT perforation, or hypotension. We evaluated mortality as a secondary outcome.

Ethical Consideration:

The study protocol had been submitted for approval by Institutional Review Board, Benha University. Approval of the Committee on Ethics of Benha Faculty of Medicine was taken. Obtaining informed written consent from the parents who were fully informed about all study procedures and gave their permission before the children enrollment in the study. Confidentiality and personal privacy had been respected in all levels of the study. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

The gathered data were recorded, displayed, and statistically analyzed using SPSS 28.0 for Windows (SPSS Inc., Chicago, IL, USA) as follows: (1) Coding and editing. (2) Data entry in a computer. (3) The data were compiled and displayed in tables and graphs. (4) The Kolmogorov-Smirnov test is accustomed to examining the variables' normality of distribution.

The gathered information was condensed into mean and SD for parametric data, median and IQR for nonparametric data, and qualitative data as a number and a percentage. To compare qualitative data, the Chi-square test was employed. To compare parametric quantitative data between the various study groups, one-way ANOVA was performed. and the post hoc

Bonferroni test was used to identify differences within groups. Mann-Whitney test and Kruskall-Wallis were applied to compare two groups' non-parametric quantitative data.

Intragroup differences were found using the posthoc test. (5) Sensitivity, specificity values, and Area under the curve (AUC) of Human (ENA-78/CXCL5) marker predictability of unrestrictive PDA were calculated using the ROC Curve (Receiver Operating Characteristic). (6) Every test had two sides. In this study, $p < 0.05$ was considered the acceptable threshold of significance, $p \leq 0.001$ was deemed highly statistically significant (HS), and $p > 0.05$ was deemed non-statistically significant (NS).

RESULTS

We considered 120 preterm infants for the study. We excluded 66 newborns for having congenital defects, congenital infections, congenital cardiac conditions other than PDA, early hospital transfers, or deaths that occurred during the first 72 hours of life. Thus, we included 54 infants, 19 with HSPDA, 11 with non HSPDA and 24 as control group.

Table (1) demonstrates that there were no significant differences between research groups regarding gestational age, weight, and sex. However, cesarean section was significantly more common among infants with HSPDA with p-value of 0.02.

Table (1): Comparison of the three groups regarding demographic data

Variable		HSPDA (n=19) N. %		Non HSPDA (n=11) N. %		Control (n=24) N. %		Test of significance	p-value
GA (weeks) (median & IQR)		30	29-31	31	29-31	31	29-32	Kruskall Wallis= 1.285	.526
Weight (g) (median & IQR)		1412.26	269.19	1385.36	373.60	1435.58	335.63	ANOVA= .095	.909
Sex	Male	11	57.9%	4	36.4%	12	50%	Chi-square= 1.292	.524
	Female	8	42.1%	7	63.6%	12	50%		
Mode of delivery	Vaginal	2	10.5%	6	54.5%	5	20.8%	Chi-square= 7.634	**.02(S)**
	CS	17	89.5%	5	45.5%	19	79.2%		

GA: Gestational Age, PDA :Patent ductus arteriosus .

Regarding Echo findings Table (2) shows that PDA Diameter, Left atrium/aorta ratio , Absent or reverse flow Descending aorta flow and LVEDDz score were significantly higher among HSPDA ($p<0.001$).

Table (2): Comparison between the three groups regarding Echo findings

Variable		HSPDA (n=19)		Non HSPDA (n=11)		Control (n=24)		Test of sig.	p-value
PDA Diameter (mm) (mean&SD)		2.6	2-2.9	1.25	1.15-1.40	-	-	Z Mann-Whitney= 4.375	**<.001(HS)**
Left atrium/aorta ratio * (mean&SD)		1.61	0.302	1.19	0.083	0.95	0.16	One Way ANOVA= 51.4	**<.001(HS)**
Descending aorta flow (N. & %)	Absent or reverse flow	17	89.5%	0	0.0%	0	0%	Chi-square= 45.7	**<.001(HS)**
	normal flow	2	10.5%	11	100%	24	100%		
LVEDD : * Z score (median &IQR)		2	2-2.5	0.7	0.5-1.7	0.35	0.2-0.69	KruskallWallis = 34.58	**<.001(HS)**
PDA flow (N. &%)	Non restrictive flow	19	100.0%	0	0%	-	-	Chi-square= 108	**<.001(HS)**
	Restrictive flow)	0	0%	11	100%	-	-		

PDA: Patent ductus arteriosus , LVEDD : Left ventricular end diastolic dimension .

* Control Vs restrictive p<.01(S) ** Control vs restrictive p<0.001 (HS). Control Vs unrestrictive p<.001(HS) Control Vs unrestrictive p<.001(HS). Restrictive Vs unrestrictive p<.001(HS) Restrictive vs unrestrictive p<.001 (HS)

Table (3) shows increased incidence of cerebral ischemia, abnormal retrograde cerebral blood flow in MCA, intracranial hemorrhage, and periventricular leukomalacia (p-value <0.001, <0.001, <0.001 and 0.03 respectively) in hemodynamically significant PDA more than non-significant PDA more than control group. Resistive index is significantly higher in HSPDA than non HSPDA than control group with p value <0.001. The incidence of NEC is more in neonates with HS PDA, but with no statistical significance. No difference in mortality between the three groups

Table (3): Comparison between the three groups regarding morbidity and mortality

Variable		**HSPDA (n=19) N. %**		**Non HSPDA (n=11) N. %**		**Control (n=24) N. %**		**Chi-square test**	**p-value**
NEC	Yes	8	42.1%	3	27.3%	3	12.5%	4.853	.08
	No	11	57.9%	8	72.7%	21	87.5%		
Cerebral Ischaemia	Yes	12	63.2%	2	18.2%	0	0.0%	64.192	**<.001 (HS)**
	No	7	36.8%	9	81.8%	0	0.0%		
Resistive index on cerebral blood flow (Median &IQR)		0.91	0.85-0.93	0.84	0.82-0.85	0.72	0.71-0.74	42.410	<.001 (HS)
Cerebral blood flow in ACA	Absent or retrograde	14	73.7%	1	9%	1	4.2%	81.35	<.001 (HS)
	Normal	5	26.3%	10	91%	23	95.8%		
ICH	Yes	11	57.9%	3	27.3%	0	0.0%	58.725	**<.001(HS)**
	No	8	42.1%	8	72.7%	0	0.0%		
PVL	Yes	4	21.1%	3	27.3%	0	0.0%	6.673	**.036(S)**
	No	15	78.9%	8	72.7%	24	100%		
Mortality	Survival	17	89.5%	10	91%	22	91.7%	.061	**.970**
	Death	2	10.5%	1	9%	2	8.3%		

(NEC: necrotizing enterocolitis, ICH: intracranial hemorrhage, PVL: periventricular leukomalacia)

In a sensitivity univariate logistic regression analysis, Left atria to aortic ratio and retrograde flow in descending aorta were significant and independent factors associated with cerebral ischemia, intraventricular haemorrhage and hypotension (Table 4).

Table (4): Univariate logistic regression analysis

Predictor / Dependent	**GA**	**Gender**	**Body weight**	**Maternal pre-eclampsia**	**PDA diameter**	**Left atria to aortic ratio**	**Flow in descending aorta**
NEC OR (95% C.I)	1.239 (0.878-1.75)	0.679 (0.199-2.315)	1.001 (0.999-1.003)	1.206 (0.35-4.11)	.299 (.08-1.04)	.240 (.046-1.26)	**.333 (0.09-1.185)**
Cerebral ischemia OR (95% C.I)	1.065 (0.758-1.49)	1.00 (0.29-3.37)	1.00 (0.998-1.002)	8.11 (1.6-41.13)	* **.230 (.065-.810)**	** **.027 (.003-0.225)**	** **0.04 (.01-.225)**
ICH OR (95% C.I)	.884 (.629-1.243)	.455 (.129-1.6)	.999 (0.997-1.001)	.123 (.024-.623)	3.196 (0.981-10.4)	** **48.25 (5.22 -445.6)**	** **20.77 4.43-97.27**
Hypotension OR (95% C.I)	** **2.07 (1.35-3.17)**	0.568 (0.286-2.55)	** **1.003 (1.001-1.005)**	* **3.39 (1.05-10.95)**	0.574 (0.196-1.68)	* **0.114 (0.02-0.635)**	* **0.202 (0.05-0.69)**
Mortality OR (95% C.I)	1.48 (0.87-2.52)	4.52 (0.47-43.4)	1.001 (0.998-1.004)	000 (.000-.000)	.336 (.047-2.82)	.538 (.049-5.85)	**0.662 (.10-4.37)**

*P<.05 (S). **P<.001(HS)

Table (5) shows that Human (ENA-78/CXCL5) was statistically significant higher among Unrestrictive ductal flow (41.77±9.58) then Restrictive ductal flow (35.87±5.04) then control group (27.48±1.33) (p<0.001).

Table (5): Comparison of study groups regarding Human (ENA-78/CXCL5):

Characteristics	HSPDA (n=19)		Non HSPDA (n=11)		Control (n=24)		Test of sig.	p-value
Human (ENA-78/CXCL5) / pg / ml (mean ± SD)	41.77	9.58	35.87	5.04	27.48	1.33	27.7	<0.001*
Post hoc test			P1=0.04*		P1<0.001* P2=0.005*			

P1 from Unrestrictive ductal flow, P2 from Restrictive ductal flow.
ENA-78/CXCL5: Epithalial neutrophil activating peptide 78 ELISA Kit.

Table (6): Receiver Operating Characteristic (ROC) curve analysis of the cut-off values of Human (ENA-78/CXCL5) for prediction of NEC

Variable (baseline)	Cutoff value	AUC	95% CI	Sensitivity	Specificity
Human (ENA-78/CXCL5)	>34.7	0.84	0.72 - 0.95	87.5	75

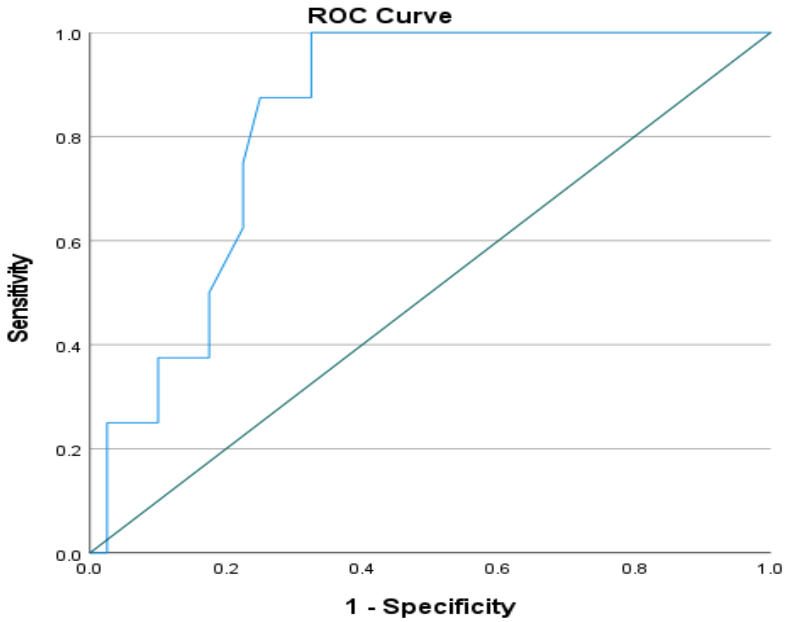

Figure (3): Receiver Operating Characteristic (ROC) curve analysis of the cut-off values of Human (ENA-78/CXCL5) for prediction of NEC.

DISCUSSION

This study demonstrated that the presence of HSPDA in preterm infants is linked to significant morbidities and adverse outcomes. The hemodynamic significance of PDA is diagnosed clinically or by certain echocardiographic indices. Trans cranial ultrasound is a valuable and noninvasive tool to assess cerebral hemodynamic changes in the form of cerebral circulation, velocity, direction of flow, and resistive index. Also, morphological changes can be detected in the form of intraventricular hemorrhage or periventricular leukomalacia. GIT complications, mainly NEC, are assessed by clinical examination and application of modified Bells staging.

The present study showed no significant difference between study groups regarding gestational age, weight, and sex with p value (0.5, 0.9, and 0.55 respectively). Similar to our study, **Jim *et al.*** [14] and **Van der Laan *et al.*** [1] demonstrated that there were no significant changes in gestational age, birth weight, or gender between HSPDA group and control group. This delineates that most of the outcomes are more related to

the hemodynamic significance of the PDA, rather than body weight or gestational age.

Maternal preeclampsia was significantly higher among infants with HSPDA (88.9% than non HSPDA (66.7%) the control group (20.8%) [15-16]. However, between groups, there was no statistically significant difference. regarding the age of mother and diabetes mellitus with p value of 0.7 and 0.5 respectively [17-19].

Our results suggest that mean systolic BP and diastolic BP were statistically significantly lower in neonates with HSPDA (p<0.001). However, no statistically significant difference existed between the groups regarding respiratory rate, heart rate, and temperature. These clinical outcomes rely on the extent of left-to-right shunting, also known as stealing phenomenon [20], which can impair circulation to key organs like the bowel, kidney, and brain [21].

Similar to our study, **Han *et al.*** [22] **and Kim *et al.*** [23] showed that when comparing the PDA group to the control group, the mean systolic and diastolic blood pressures were considerably lower in the PDA group.

In contrary to our results, **Jim *et al.*** [14] results revealed substantial variations in heart rate and mean arterial pressure (MAP) between those HSPDA group and control group. This may be supported by **Gillam-Krakauer *et al.*** [24] study which reported that the "steal" from the aorta during diastole necessitates an increase in cardiac output. Extremely preterm newborns are unable to raise their stroke volume and must thus increase their heart rate in order to enhance their cardiac output.

Regarding Echo in the present study, PDA diameter left atrium/aorta ratio, absent or reverse flow descending aorta flow and LVEDD score were statistically significantly higher among HSPDA (p<0.001).

The most accurate bedside test to identify PDA is an echocardiogram. Furthermore, it can help in assessing the systemic hypoperfusion caused by shunt volume and the hemodynamic effects of pulmonary overcirculation. This might be performed by methodically examining (a) ductal features, (b) pulmonary overcirculation parameters, and (c) indicators of systemic hypoperfusion [4, 25].

These results were comparable to **Arlettaz** [26] study which viewed that the primary HSPDA echocardiographic criteria are an enlarged left atrium with a left atrium to aortic valve (LA:Ao) ratio of ≥1.5, absence or retrograde diastolic flow in the descending aorta, absence or retrograde diastolic flow in the mesenteric superior artery and/or in the anterior cerebral artery, a moderate to large PDA diameter, with a narrowest point of ≥1.5 mm, and an open pulsatile transductal flow.

In agreement with our study, **Smith *et al.*** [27] study revealed that duct size and ratio variations were seen between the large PDA group, the no PDA group, and the small PDA group. While for systolic flow velocity, the no PDA group as well as the large and small PDA groups had variances. Between the large PDA group and the small PDA group, there was a discernible difference in the diastolic flow velocity.

In disagreement with our study, **Hanna *et al.*** [28] concluded that left atrium Z-score appeared to be a significant early parameter (at 48-72 hours of age); and left pulmonary artery Z-score was a useful parameter associated with hemodynamic instability. Left heart parameters including LV diameter, Ao VTI, and Desc Ao were later markers (96 hours of age onwards).

The incidence of NEC was higher among HSPDA (42.1%) than non HSPDA (27.3%), and both more than control group (12.5 %) but with no statistical significance (p=0.08). Superior mesenteric artery and abdominal aorta diastolic blood stealing, together with subsequent intestine hypoperfusion, contribute to predisposition to NEC in premature infants with PDA [29].

Similar to our study, PDA and NEC were not found to be significantly associated with one another in **Ognean *et al.*** [30]. Likewise, NEC did not differ significantly between patients with and without PDA in **Chen *et al.*** [31], this lack of significance may be attributed to small number of NEC cases.

In an argument with our results, the study done by **Dollberg *et al.*** [32] found that infants who were given indomethacin medication and those who were not that the development of NEC was independently correlated with the existence of patent ductus arteriosus (odds ratio: 1.53, 1.85 respectively). NEC risk was not elevated by indomethacin therapy in the absence of PDA (odds ratio, 0.72).

This study shows increased incidence of cerebral ischemia, abnormal retrograde cerebral blood flow in anterior cerebral artery (ACA), intracranial hemorrhage, and periventricular leukomalacia with statistical significance in hemodynamically significant PDA more than non-significant PDA more than control group (p value <0.001, <0.001, <0.001 and 0.03 respectively). Also, the resistive index for blood flow in ACA was higher in HSPDA (0.91) than non HSPDA (0.84) and both more than control group (0.72) with significant value (p value <0.001).

Higher risks of intraventricular hemorrhage (IVH), cerebral white matter damage, and decreased cerebral perfusion are also present in preterm neonates with HSPDA. These infants may be more vulnerable to harm because of variations in cerebral perfusion pressure both during and after ductal shunting. Maintaining cerebral blood flow despite variations in cerebral perfusion pressure requires intact cerebral autoregulatory function, however, preterm infants are more vulnerable to compromised cerebral autoregulation [33]. Changes in the positioning of the probe have no impact on the resistive index value because they have a similar impact on the values of peak systolic velocity and end-diastolic velocity.

It was found by **Jim *et al.*** [14] study that IVH was more common overall in the PDA group than in the

control group (p=0.006). However, the degree or grade of IVH did not differ statistically between the two groups. In **Ognean *et al.* [30]** study, PDA was also linked to a considerably higher rate of IVH in the PDA group compared to Group 2 which did not have PDA ($p < 0.0001$). However, **Van der Laan *et al.* [1]** suggested that HSDA and retrograde diastolic blood flow in the Dao do not compromise cerebral and renal oxygen delivery. Also, **Kim *et al.* [23]** revealed that the size of the PDA had no effect on the velocity of cerebral blood flow throughout the cardiac cycle. This might be a result of sustained cerebral autoregulatory function (at least during systole). **Ecury-Goossen *et al.* [13]** showed that resistive index in all cerebral arteries was lower in neonates without patent ductus arteriosus, but with no statistical significance.

In a sensitivity univariate logistic regression analysis, left atria to aortic ratio and retrograde flow in descending aorta were significant and independent factors associated with cerebral ischemia, intracranial hemorrhage and hypotension.

To our knowledge, our study is the first to compare human (ENA-78/CXCL5) as regard ductal flow groups. We found that Human (ENA-78/CXCL5) was statistically significantly higher among unrestrictive ductal flow (44 pg/ml) than restrictive ductal flow (32.6 pg/ml) than control group. (27.5 pg/ml) with p value <0.001.

Human (ENA-78/CXCL5) was statistically significantly higher among patients with NEC than patient without NEC with cut-off value of 34.7 ng/mL with 87.5% sensitivity and 75% specificity. A good example of a chemokine is ENA-78, also known as CXCL-5, which has been shown to be positively and repeatedly correlating with the quantity of recruited neutrophils in the lung fluids of infants with respiratory distress syndrome, necrotic enterocolitis, and cerebral hemorrhage **[34].**

CONCLUSION

Preterm newborns with hemodynamically significant PDA have a greater likelihood of incidence of cerebral complications in the form of abnormal cerebral blood flow and higher resistive index.

Left atrium to aortic ratio and retrograde flow in descending aorta are independent predictors for development of cerebral ischemia, intracranial hemorrhage and hypotension. No significant variation in incidence of NEC and mortality between the studied groups.

Human (ENA-78/CXCL5) had a role in the diagnosis of NEC. Also, we found a higher level of Human (ENA-78/CXCL5 in HSPDA. We recommend a further study to reveal the pathophysiology of this role.

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