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High-sensitivity troponin T in preterm infants with a hemodynamically significant patent ductus arteriosus

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Abstract---Background: The incidence of patent ductus arteriosus (PDA) is inversely related to gestational age. Cardiac troponin T (cTnT) is a specific marker for myocardial ischemic injury. The aim of this work was to investigate if a hemodynamically significant patent ductus arteriosus leads to elevated high- sensitivity troponin T (hsTnT) levels in serum.Methods: This prospective observational research included 60 preterm infants <34 weeks' gestation, weighing <1500 g with PDA. Patients were classified into two groups according to the ECHO findings: Group A: preterm infants who hadhs.PDA (PDA >1.5 mm and LA: Ao >1.2 and group B: preterm infants without hs.PDA. All cases were subjected to clinical examination, echocardiogram and hsTnT assay.Results: Serum hsTnT levels was significantly elevated in patients with hs PDA compared to patients without hs PDA. High sensitive T-troponin can significantly detect hsPDA with AUC of 0.986, P value <0.001. At cut off >100 pg/ml, it's a significant detector with sensitivity of 93.33%, specificity of 90%, PPV of 90.3, NPV of 93.1 and diagnostic accuracy of 91.5%. PDA had a significant positive correlation with hsTnT (r=0.803, P<0.001), Conclusions: HsTnT can significantly detect hemodynamically significant PDA in preterm infants with high sensitivity and specificity.

Keywords---high-sensitivity troponin T, preterm infants, A hemodynamically, patent ductusarteriosus.

Introduction

The prevalence of patent ductus arteriosus (PDA) is inversely related to gestational age (GA). Because of improving survival of premature infants, there was increased in the prevalence of PDA (~30%) [1]. The left to right shunt across PDA rises as pulmonary vascular resistance decreases, causing volume overload on the left side of the heart and stretching of the left atrial myocardium. Myocardial stretching can increase oxygen need of cardiac myocytes [2] . The diastolic steal phenomenon that happens throughout left to right shunting might also result in decreasing coronary blood flow and decreasing oxygen supply [3]. Cardiac troponin T (cTnT) is a particular indicator of myocardial ischemia [4]. Therefore, the American College of Cardiology and the European Society of Cardiology have advised evaluating cTnT (>99th percentile interpreted as myocardial ischemia) levels to diagnose of acute coronary syndromes and acute myocardial infarction in the adult people [5]. Within the newborn population, elevated cTnT levels are also found in infants with birth asphyxia, respiratory distress, and fetal placental insufficiency [6].

Within the adult population, high sensitive troponin T (hsTnT) analyses are more sensitive (4–10 times) than conventional cardiac troponin (cTn) levels with added sensitivity for cardiac myocyte necrosis [7]. The possible benefit of hsTnT as more fast diagnosis in acute coronary syndrome, population assessment for the presence of cardiac dysfunction in asymptomatic cases, prognostic information in stable cases with coronary artery disease, and congestive heart failure. Its prognostic value is also being evaluated in cases with heart failure, coronaryartery disease, diabetes mellitus, pulmonary embolism, and pulmonary artery hypertension [8]. Despite the prevalence and clinical relevance of cardiac dysfunction in preterm children with PDA, the role of biomarkers and myocardial function has not been thoroughly investigated. There is a deficiency of a true gold average for assessment of a hemodynamically significant patent ductus arteriosus (hsPDA). The information, that are accessible for troponins, are incompatible, with one study of troponin T in 80 preterm infants with PDA indicating that It may provide as a good indicator of ductal importance and therapeutic efficacy [9] yet another investigation found no connection between troponin T and PDA in 23 preterm infants with respiratory distress syndrome (RDS) and PDA [10].The aim of this work was to investigate if a hsPDA leads to elevated hsTnT levels in serum.

Patients and Methods

This prospective observational research was performed at neonatal intensive care unit (NICU), pediatric department, Faculty of Medicine, Benha University from May 2021 to May 2022. The study included 60 preterm infants <34 weeks' gestation, weighing <1500 g with PDA. Infants with structural congenital heart defects (except patent foramenovale or small atrial septal defect/small ventricular septal defect) and known congenital or chromosomal anomalies were excluded.

An informed written consent was obtained from parents of the patients. The Ethics Committee of Faculty of Medicine approved the study, Benha university. Patients were classified into two equal groups according to the ECHO findings:

- Group A: preterm infants who had hs.PDA (PDA >1.5 mm and LA: Ao >1.2
- Group B: preterm infants without hs.PDA (PDA diameter < 1.5 mm LA: Ao <1.2 according to Jainan and Shah PS. JAMA Pediatr. 2015 [11]

Each preterm infant was subjected to: Full history, infant data (APGAR scores, RDS, use of surfactant, bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC), full clinical examination (Chest, heart, abdominal), radiological examination, echocardiogram and laboratory investigations (C reactive protein (CRP), Complete blood count (CBC), and high sensitive troponin T (hsTNT)).

Radiological investigation

Chest X ray can detect cardiomegaly (left atrial and left ventricular enlargement if not complicated). There may be evidence of aortopulmonary window occlusion, pulmonary edoema, and lung congestion.

Echocardiogram

The ECHO was performed by a Philips Ultrasound model iE33 (Philips, Bothell, WA, USA) by two recorded pediatric cardiac sonographers. Standard neonatal apical, parasternal, subcostal, and high parasternal windows. Ejection fraction determined by any echo mode, such as 2D, M-mode, and 3-D mode, that could explain LV endomyocardial lining at end-systole and diastole. The suggested technique to determine EF is the Simpson's or modified Simpson's method utilizing apical four- chamber and two-chamber views. Fraction shortening and EF could be determined by M-mode in PLAX or PSAX views or Simpson's biplane technique. FS determined by calculating LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD): Fraction shortening (FS)=LVEDD−LVESDLVEDD×100%.

High sensitive troponin T measurements

Blood sample (umbilical arterial line/peripheral) was collected in gel separator tube within 30 min of ECHO. The collection of blood samples was carried out by venipuncture. 3ml of blood was drawing under complete aseptic condition then divided into 2 parts.: 1ml was put in EDTA vacutainer tube for CBC measurement, mixed thoroughly and transported to the laboratory where it was immediately analyzed. 2ml of blood was put in gel separator tubes for measurement CRP and hsTNT. Gel separator tube was put 30 min for clotting then centrifuged for obtaining serum. The detached serum was kept at -20 c till assay. The hsTnT assay was done using Roche Elecsys hsTnT quantitative assay kits provided by Roche Diagnostics group, Indianapolis, in USA. The hsTnT assessments were determined by Cobas E411 equipment provided by Roche diagnostics group.

Test principle

The hsTnT assay, an electro chemiluminescent sandwich enzyme-linked immunosorbent assay, has a lower limit of detection of 0.01 pg/l, with minimal cross reactivity with cardiac troponin I (0.002%) and skeletal troponin T (0.001%). This third-generation assay is unaffected by bilirubin levels, hemolysis, or renal insufficiency, and it has a repeatability coefficient for a paired sample of 10% with a variability coefficient for precision analysis of 6.4%. The high-sensitivity cardiac troponin test is the latest generation of the cardiac enzyme testing that allows for detection of very low levels of troponin T. Hs-troponin [12].

Limits of detection and quantitation of hsTNT
Normal range: 1-14 pg/ml
Equivocal: (level of detection) :14-99 pg/ml
Abnormal: >100 pg/ml

Steps: All of the assay steps were done automatically using the instrument: The sample was put in the wells including alkaline phosphatase-labeled anti cardiac troponin antibodies (conjugate). The conjugate mixture was rotated in and out of the SPR® numerous times. Unbound components are removed in washing stages. During each step, the substrate (4-Methylumbelliferyl phosphate) circulated in and out of the SPR®. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone). The intensity of the fluorescence is proportional to the concentration of antigen found in the sample. the results were automatically assessed by the instrument in relation to two calibration curves stored in memory. A fluorescence threshold value establishes the calibration curve to be applied for each sample.

Statistical analysis

Statistical analysis was performed using SPSS v27 (IBM©, Chicago, IL, USA). Shapiro-Wilks test and histograms were utilized for evaluating the normality of the distribution of data. Numerical parametric variables were represented as mean and standard deviation (SD) and were examined by unpaired student t-test. Numerical non-parametric variables were represented as the median and interquartile range (IQR) and were examined by Mann Whitney-test. Categorical data were represented as frequency and percent and examined by the Chi-square test. A two-tailed P value < 0.05 was considered statistically significant. Linear Correlation coefficient (r) used for recognition of correlation between two numerical variables in one group. The overall diagnostic performance of each test was evaluated by ROC curve analysis.

Results

There was insignificantly different between two groups as regard neonatal demographic data, maternal history and anthropometric data however, APGAR score was significantly higher after 5 minutes compared to 1 minute in both groups. Table 1 Pericardial pulsation, respiratory rate and the incidence of murmur were significantly increased in the cases had hsPDA than those had not hsPDA (P =0.024, 0.047, 0.007 respectively). Heart rate was insignificantly

different between two groups. O2 saturation, systolic and diastolic BP were significantly decreased in cases had hsPDA than those had not hsPDA (P =0.006, 0.001, <0.001 respectively) while pulse pressure was significantly increased in cases had hsPDA than cases had not hsPDA (P =0.002). Laboratory investigations represented in Hb, WBCs, RBCs, PLT and CRP showed insignificantly different between two groups. PDA and LA:AO were significantly increased in cases had hsPDA than cases had not hsPDA (P <0.001) but EF and SF were significantly decreased in cases had hsPDA than others (P <0.001). High sensitive T-troponin was significantly increased in cases had hsPDA than cases had not hsPDA. Table 2

By comparing between pre and post treatment in patients with hsPDA, high sensitive T- troponin, PDA and LA:AO were significantly decreased post-treatment while EF and SF weresignificantly increased post-treatment than pre-treatment (P values<0.001). Table 3 There was insignificantly different between both groups regarding neonatal complications. The need for oxygen support was significantly increased in cases had hsPDA than cases had not hsPDA (P =0.001), therefore, the duration of oxygen support and hospital stay was significantly extended in cases had hsPDA than cases had not hsPDA (P =0.013, 0.001). Inotropes and fluid intake were insignificantly different between both groups. Out of 30 patients with hsPDA, 12 patients died which were significantly increased than the group without hsPDA in which 5 patients had died (P value=0.045). Table 4

PDA had a significant positive correlation with respiratory rate (r=0.408, P=0.001), O2 saturation (r=0.866, P<0.001), high sensitive T-troponin (r=0.803, P<0.001), SF (r=0.597, P<0.001), length of O2 saturation (r=0.512, P<0.001) and hospital stay (r=0.408, P=0.001) but had a significant negative correlation with LA:AO (r=-0.744, P<0.001) and EF (r=-0.777, P<0.001). There was insignificant correlation between PDA and heart rate. Table 5 High sensitive T-troponin can significantly detect hsPDA with AUC of 0.986, P value <0.001. At cut off >100 pg/mL, it's a significant detector with sensitivity of 93.33%, specificity of 90%, PPV of 90.3, NPV of 93.1 and diagnostic accuracy of 91.5%. Figure 1

Discussion

PDA is the most prevalent cardiac disease among newborns [13]. The GA is inversely associated to the occurrence of PDA. It remains open at 4 days of age in 10% of neonates born between 30 and 37 weeks, 80% of those born between 25 and 28 weeks, and 90% of those born 24 weeks gestation [10]. The hemodynamic consequences of the PDA are determined by the pressure gradient between the aorta and PA as well as by the size and resistance of the DA [14]. In this study regarding the clinical presentation, pericardial pulsation, respiratory rate and the incidence of murmur were significantly increased in cases had hsPDA than cases had not hsPDA (P value=0.024, 0.047, 0.007 respectively). Heart rate was insignificantly different between two groups. O2 saturation, systolic and diastolic BP were significantly decreased in cases had hsPDA than cases had not hsPDA, while pulse pressure was significantly increased in cases had hsPDA than cases had not hsPDA (P value=0.002).

In the same line with our findings, Vaisbourd et al., compared coronary flows among premature infants had hs PDA, had not hsPDA and no PDA. Compared to newborns without PDA, infants with hsPDA had significantly higher myocardial oxygen demand, BPD, and length of mechanical ventilation (days) (overall $p<0.05$). O2 saturation was significantly lower in infants with hsPDA, heart rate was comparable in two groups. However, regarding systolic and diastolic blood pressure, they observed insignificantly different between two groups. As their study was pilot study with a smaller sample size, they were unable to detect tiny differences across factors, which may explain the inconsistency with our findings [15].

In the current work, hs-cTnT was significantly increased in cases had hsPDA than cases had not hsPDA (P value<0.001). We may hypothesize that the difference in hs cTnT levels is a result of the higher oxygen need of stressed and stretched myocytes caused by hsPDA. Our results are supported by, Asrani et al., who documented that the mean of hs cTnT amounts were significantly increased in cases had hsPDA than cases had not hsPDA($p = 0.01$) [16]. In the same context, the association between hs cTnT levels and respiratory failure in new- borns was studied by Tüfekci et al., 113 healthy new-borns and 93 new-borns with non-cardiac respiratory failure, were assessed. Hs cTnT was determined in the umbilical cord and 24-96 h after birth in infants. Umbilical cord, 99th percentile and postnatal day 2-4 median hs cTnT were significantly higher in new-borns with non-cardiac respiratory failure compared to healthy group [17].

In the present study, PDA and LA:AO were significantly higher in cases had hsPDA than cases had not hsPDA (P values<0.001) but EF and SF were significantly lower in cases had hsPDA than others (P values<0.001). In the same line with our findings, Vaisbourd et al., documented that PDA, PDA diameter/birth weight (mm/ kg) and aortic valve (cm) were significantly increased in cases had hsPDA than cases had not hsPDA [15]. Contrary to our findings, Asrani et al., established that EF and SF were insignificantly different between hsPDA and patients without hsPDA. Smaller number of hsPDA patients as they included only 17 infants with hsPDA whereas we enrolled 30 infants with hsPDA may adequately explain this variation between the two studies [16].

In the current study, by comparing between pre and post treatment in patients with hsPDA, hs- cTnT, PDA and LA:AO were significantly decreased post-treatment while EF and SF were significantly increased post-treatment compared to pre-treatment (P values<0.001). Our results are compatible with Asrani et al., who reported that average PDA diameter in infants was higher in infants with hsPDA in the pre- treatment than with the diameter in the post- treatment ($p = 0.0007$). The average LA:AO ratio was higher in infants with hsPDA in the pre-treatment than with the post-treatment group ($p = 0.06$) [16]. In the present study, the need for oxygen support was significantly increased in cases had hsPDA than cases had not hsPDA (P value=0.001), the duration of oxygen support and hospital stay was significantly longer in patients with hsPDA than patients without hsPDA (P value=0.013, 0.001). Inotropes and fluid intake were insignificantly different between both groups. Out of 30 patients with hsPDA, 12 patients died which were significantly higher than the group without hsPDA in which 5 patients died (P value=0.045).

In the same line with our findings, Asrani et al., documented that inotropes and fluid intake were insignificantly different between hsPDA patents and those without hsPDA [16]. In the current study, hs-cTnT can significantly detect hsPDA with AUC of 0.986, P value <0.001. At cut off >100 pg/ml, it had sensitivity of 93.33%, specificity of 90%, PPV of 90.3, NPV of 93.1 and diagnostic accuracy of 91.5%. Our results came in line with, Asrani et al., who reported that hs cTnT at cut-off value 170 pg/ml, showed 70% sensitivity and 55% specificity. The ROC curve for hs cTnT showed AUC of 0.718 depicting it to be a good PDA diagnostic test [16].

Conclusions

Serum high- sensitivity troponin T levels was significantly elevated in cases with hs PDA than cases without hs PDA. High- sensitivity troponin T can significantly detect hemodynamically significant PDA with AUC of 0.986, p value <0.001. At cut off >100 pg/mL, it had high sensitivity 93.33%, specificity 90%, PPV 90.3, NPV 93.1 and diagnostic accuracy of 91.5%.

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Table 1
Neonatal demographic data, maternal history, anthropometric data in thestudied groups

		Pt with hsPDA (n=30)	Pt without hsPDA (n=30)	P value
Sex	Male	15 (50%)	15 (50%)	1.00
	Female	15 (50%)	15 (50%)	
Postnatal age (days)		3.03 ± 1.07	2.9 ± 1.12	0.639
Gestational age (weeks)		32.3 ± 1.42	32.2 ± 1.65	0.802
APGAR at 1 minute		6.07 ± 1.2	6.37 ± 0.93	0.284

APGAR at 5 minutes		8.4 ± 0.67	8.57 ± 0.5	0.283
P between 1&5 minutes		<0.001*	<0.001*	
Maternal history				
Maternal age (years)		28.63 ± 3.71	27.5 ± 4.07	0.265
Mode ofdelivery	N.V. D	3 (10%)	7 (23.33%)	0.299
	C.S	27 (90%)	23 (76.67%)	
PROM		10 (33.33%)	11 (36.67%)	0.787
Chorioamnionitis		2 (6.67%)	6 (20%)	0.129
DM		5 (16.67%)	6 (20%)	0.739
HTN		4 (13.33%)	8 (26.67%)	0.197
Pre-eclampsia		7 (23.33%)	6 (20%)	0.754
Antenatal steroids		16 (53.33%)	15 (50%)	0.796
Antenatal $MgSO_4$		4 (13.33%)	3 (10%)	0.688
Anthropometric data				
HC (cm)		31.43 ± 1.14	31.2 ± 1.49	0.499
Length (cm)		43.57 ± 2.11	43.43 ± 2.24	0.813
Weight (kg)		1.33 ± 0.14	1.33 ± 0.15	0.972

Data are presented as mean ± SD or frequency (%). hsPDA: hemodynamically significant patent ductus arteriosus, APGAR: Appearance, Pulse, Grimace, Activity, and Respiration, PROM: Premature rupture of membranes, DM: diabetes mellitus, HTN: hypertension, HC: head circumference, *: significant as P value ≤ 0.05

Table 2
Clinical evaluation, laboratory investigations, high sensitive T-troponin andECHO findings of the studied groups

		Pt with hsPDA (n=30)	Pt without hsPDA (n=30)	P value
Pericardial pulsation		13 (43.33%)	5 (16.67%)	0.024*
Murmur	Harsh murmur	5 (16.67%)	0 (0%)	0.047*
	Soft murmur	11 (36.67%)	10 (33.33%)	
	Negative	14 (46.67%)	20 (66.67%)	
Heart rate (beats/min)		154.07 ± 10.97	150.97 ± 12.92	0.321
Respiratory rate (breaths/min)		63.8 ± 8.03	57.27 ± 9.81	0.007*
Oxygen saturation (%)		93.67 ± 2.59	95.67 ± 2.87	0.006*
Systolic Blood pressure (mmHg)		50.23 ± 3.07	52.73 ± 2.73	0.001*
Diastolic Blood pressure (mmHg)		31.07 ± 3.66	35.5 ± 2.36	<0.001*
Pulse pressure (mmHg)		19.5 ± 3.12	17.23 ± 2.37	0.002*
Laboratory investigations				
Hb (g/dL)		16.58 ± 1.97	16.6 ± 1.89	0.955
WBCs (*10^3cells/mL)		11.4 ± 3.55	13.02 ± 5.7	0.192
RBCs (*10^3cells/mL)		5.46 ± 1.16	4.91 ± 1.01	0.054
PLT (*10^3cells/mL)		221.7 ± 77.76	193.03 ± 75.8	0.813
CRP		3 (10%)	8 (26.67%)	0.181
High sensitive T-troponin (pg/mL)		182.7 ± 59.62	67.23 ± 25.96	<0.001*
ECHO findings				

PDA (mm)	3.8 ± 0.99	1.31 ± 0.1	<0.001*
LA:AO	1.48 ± 0.12	1.15 ± 0.07	<0.001*
EF (%)	0.58 ± 0.07	0.66 ± 0.03	<0.001*
SF (%)	0.28 ± 0.04	0.34 ± 0.03	<0.001*

Data are presented as mean ± SD or frequency (%), hsPDA: hemodynamically significant patent ductus arteriosus, Hb: haemoglobin, WBCs: white blood cells, RBCs: red blood cells, PLT: platelet, CRP: c-reactive protein, LA:AO: Left Atrial to Aortic root ratio, EF: ejection fraction, SF: Shortening Fraction *: significant as P value ≤0.05

Table 3
High sensitive T-troponin and ECHO findings pre and post treatment in patients with hsPDA

	Pre-treatment	Post-treatment	P value
High sensitive T-troponin (Pg/mL)	182.7 ± 59.62	134.4 ± 46.55	<0.001*
PDA (mm)	3.8 ± 0.99	2.96 ± 0.78	<0.001*
LA:AO	1.48 ± 0.12	1.29 ± 0.11	<0.001*
EF (%)	0.58 ± 0.07	0.65 ± 0.04	<0.001*
SF (%)	0.28 ± 0.04	0.32 ± 0.02	<0.001*

Data are presented as mean ± SD, hsPDA: hemodynamically significant patent ductus arteriosus, LA:AO: Left Atrial to Aortic root ratio, EF: ejection fraction, SF: Shortening Fraction, *: significant as P value ≤ 0.05

Table 4
Neonatal complications of the studied groups, Comparison between the studied groups regarding type and duration of O2 support, treatment received, length of hospitalstay and mortality

		Pt with hsPDA (n=30)	Pt without hsPDA (n=30)	P value
RDS		6 (20%)	7 (23.33%)	1
NEC		3 (10%)	3 (10%)	1
BPD		9 (30%)	5 (16.67%)	0.222
ROP		10 (33.33%)	4 (13.33%)	0.067
IVH		4 (13.33%)	2 (6.67%)	0.671
IDM		4 (13.33%)	6 (20%)	0.731
Comparison between the studied groups				
O2 support	N.C	6 (20%)	8 (26.67%)	0.001*
	CPAP	16 (53.33%)	5 (16.67%)	
	MV	6 (20%)	6 (20%)	
	OFF	0 (0%)	10 (33.33%)	
Inotropes		14 (46.67%)	7 (23.33%)	0.103
Fluid intake (>120 ml/kg/d)		18 (60%)	11 (36.67%)	0.12
Length of Oxygen support (days)	Median	13.5	6.5	0.013*
	IQR	10 – 22.75	5 – 14.25	

Length of hospital stay (days)	Median	30	14	0.001*
	IQR	23.5 - 35	12 - 28	
Mortality		12 (40%)	5 (16.67%)	0.045*

Data are presented as frequency (%), hsPDA: hemodynamically significant patent ductus arteriosus, RDS: Respiratory distress syndrome, NEC: NEC, BPD: Bronchopulmonary dysplasia, ROP: Retinopathy of prematurity, IVH: Intraventricular haemorrhage, IDM: Infants of diabetic mothers.

Table 5
Correlation between PDA and different parameters of the studied patients

	PDA (mm)	
	r	P
Respiratory rate (breaths/min)	0.408	0.001*
Heart rate (beats/min)	0.217	0.096
oxygen saturation (%)	0.866	<0.001*
ısitive T-troponin(pg/mL)	0.803	<0.001*
LA:AO	-0.744	<0.001*
EF (%)	-0.777	<0.001*
SF (%)	0.597	<0.001*
length of oxygen support (days)	0.512	<0.001*
Hospital stay (days)	0.408	0.001*

PDA: Patent ductus arteriosus, LA:AO: Left Atrial to Aortic root ratio, EF: ejection fraction, SF: Shortening Fraction, *: significant as P value ≤ 0.05, r: correlation coefficient.

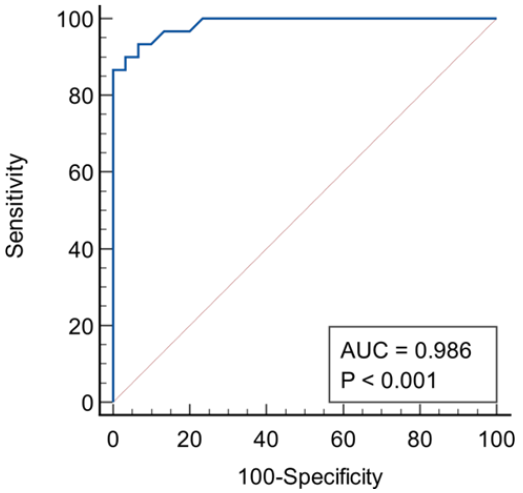

Figure 1. ROC curve of high sensitive T-troponin for early diagnosis of hsPDA