

## Early Predictors of Transient Tachypnea of Newborn

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### Abstract

**Background:** Early diagnosis of transient tachypnea of newborn (TTN) is important for early treatment and good prognosis, but it is misdiagnosed with some diseases that occur in neonates like neonatal sepsis.

**Aim:** The study aims at investigating lactate, lactate dehydrogenase (LDH) and cystatin-C (Cys-C) as markers for early diagnosis of TTN.

**Patients and methods:** Blood samples taken within 1 hour after birth from 40 neonates who later developed TTN and from 40 neonates who did not develop TTN as a control group. Eighty neonates who were admitted to the NICU at Tanta University Hospital with gestational age above 37 weeks during the period 12 months (from December 2011 to May 2012), were included in this study. Neonates with RD during the first 24 hours of life constituted the patient group (n=40; 28 male: 12 female) and neonates without respiratory problems constituted the control group (n=40; 20 male; 20 female), written informed consent was obtained from all parents.

**Results:** Babies with TTN showed significantly higher levels of lactate, lactate dehydrogenase activity (LDH) and cystatin-C (Cys-C) level ( $P < 0.05$ ) in their serum than babies without TTN who act as a control group. When using the value of 2.2 pg/ml for serum lactate as a cutoff value the sensitivity was 92%, the specificity was 85%, the +PV% was 87% and the -PV% was 81% and the accuracy was 88. When using the value of 920 IU/L for serum LDH as a cutoff value the sensitivity was 94%, the specificity was 87%, the +PV% was 89% and the -PV% was 82% and the accuracy was 90. When using the value of 1.73 mg/L for Cys-C as a cutoff value the sensitivity was 96%, the specificity was 90%, the +PV% was 94% and the -PV% was 87% and the accuracy was 92%.

**Conclusion:** Serum lactate level, LDH activity and Cys-C level increased in babies with TTN if compared with babies without TTN. Hence lactate, LDH and Cys-C can be used for early diagnosis of TTN and early treatment with better prognosis.

**Keywords:** Transient tachypnea of newborn; Lactate; Lactate dehydrogenase; Cystatin-C

### Introduction

Transient tachypnea of the newborn (TTN) is a neonatal lung disease which has a picture of lung edema due to delayed resorption of lung fluids [1]. TTN is an important cause of respiratory distress in the neonates [2]. Most of the cases are benign, self-limited, but there are rare incidences of developing severe respiratory distress which denotes that the neonate had malignant TTN [3].

The mechanism of clearing alveolar fluid in the fetus is mainly occur through and after labor. During late pregnancy, as a result of increased secretion of epinephrines and other hormones, the neonatal mature lung switches from secreting fluid into the air spaces to starting reabsorbing it [4,5].

The resorption of neonatal lung liquid also occurs after birth because of changes of the oncotic pressure between alveoli, interstitial tissue and small blood vessels.

Delayed resorption of lung fluid in the fetus is considered the main cause of TTN where the fluid fills the air spaces and moves into the interstitial tissue, perivascular tissues and interlobar fissures until it is drained by the lymphatics or capillaries. The excess lung fluid in TTN results in decreased lung functions. Tachypnea will occur to compensate for decrease gas exchange associated with increased lung fluid [6-8].

Some markers which result from hypoxia-ischaemia induced cell damage in affected organs can be used for early prediction of TTN. Lactate dehydrogenase (LDH), lactate and also cystatin-C (Cys-C) are good predictors of hypoxia-ischaemia of the affected organs [9]. LDH is an enzyme found in the cells of several body tissues, including the heart, liver, kidneys, lung, brain, red blood cells and muscle. It is responsible for changing muscle lactic acid into pyruvic acid, which is an important step in producing energy in the cells [10]. Lactic acidosis occurs when the production of lactate exceeds lactate

clearance. The increase in production of lactate is usually caused by tissue hypoxia, either from decreased oxygen supply or a defect in oxygen metabolism because of depression of the mitochondrial pyruvate dehydrogenase complex, which ultimately lead to increased anaerobic metabolism [11].

Cystatin C is a non-glycosylated low molecular weight protein manufactured by nucleated cells at a constant rate, easily filtered by the glomeruli, and destructed in the tubuli [12]. Cystatin C serum concentration is independent of gender or muscle mass and not affected by jaundice or most of neonatal diseases [13,14]. Also, very low individual variation of cystatin C in controls [15].

The study aims at investigating lactate, LDH and Cys-C as markers for early diagnosis of TTN.

### Aim of the Study

The present study aims at investigating lactate, LDH and Cys-C as markers for early diagnosis of TTN.

### Patients and Methods

Eighty neonates who were admitted to the NICU at Tanta University Hospital with gestational age above 37 weeks during the period 12 months (from December 2011 to May 2012), were

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included in this study. Neonates with RD during the first 24 hours of life constituted the patient group (n=40; 28 male; 12 female) and neonates without respiratory problems constituted the control group (n=40; 20 male; 20 female), written informed consent was obtained from all parents. The classic TTN was defined in the study according to the following inclusion criteria adopted from the literature [16-21]. The following infants were excluded from the study: infants with an antenatal history suggestive of chorioamnionitis or maternal infection, significant congenital malformation, infants with a history of meconium at delivery who required intubation and endotracheal suctioning, a low enough Apgar score to require advanced resuscitation, chest X-ray finding denoting of pneumonia, which is not the same with the radiological features of TTN, infants who required mechanical ventilation, and those who showed signs of early neonatal septicemia. All infants in the study received an initial blood gas, complete blood count, C-reactive protein (CRP), blood culture and chest X-ray at four hours of age if respiratory signs persisted (Table 1).

### Chemicals

Chemicals used unless otherwise described were purchased from Sigma (Sigma, St Louis, USA) and were of high analytical grade.

### Blood sampling

Blood samples were collected from the patients and controls in the first hour after birth on sterile non-treated tubes. The collected blood centrifuged for 10 minutes at 3000 rpm at 4°C for serum separation which was further aliquoted and stored at -80°C till analysis.

### Biochemical assay

**Assesment of serum LDH activity:** LDH activity was estimated according to the method of Babson and Babson [22]. It catalyzes the conversion pyruvate to lactate, NADH is oxidized to NAD in the process. The rate of decrease in NADH at wave length 340 nm is directly proportional to the LDH activity and determined spectrophotometrically [22].

**Assesment of serum lactate level:** Lactate was measured according to a method previously described by Brandt et al. 1980. Briefly, serum was added to an NAD<sup>+</sup> -glycine-hydrazine solution to form pyruvate hydrazone coupled with the reduction of NAD<sup>+</sup> to NADH at a pH<9.0. NADH was measured spectrophotometrically at 340 nm [23].

**Assesment of serum Cys-C level:** Enzyme linked immunosorbent assay (ELISA) was used to detect serum levels of Cys-C (Quantikine, R and D Systems Inc., Catalog Number DSCTC0) according to manufacturers' instructions and read on microplate reader (Stat Fax\*2100, Fisher Bioblock Scientific, France), at 450 nm with correction wavelength set at 570 nm.

### Statistical analysis

It was performed by using SPSS for Windows, version 17. Data were expressed as range and mean ± standard deviation (SD)/ or numbers and percentages. Differences between groups in continuous variables were tested for significance with paired t-test while univariate analysis was done with the *Chi-square* test. For all statistical tests done, *P* value <0.05 was considered significant. Linear correlation coefficient was used to assess different correlations. Receiver operating characteristics (ROC) analysis was used to identify the optimal threshold values of the studied parameters.

### Results

Table 2 shows the characteristics of the study group.

Table 3 shows that serum lactate are higher in TTN babies in comparison with controls.

Table 4 shows that serum LDH are higher in TTN babies in comparison with controls.

Table 5 shows that serum Cys-C are higher in TTN babies in comparison with controls.

Table 6 shows significant positive correlation between seum levels of lactate, LDH and Cys-C in TTN patients.

Table 7 shows data of ROC (receiver operating characteristic)curve for serum lactate between the two studied groups. When using the value of 2.2 pg/ml as a cutoff value the sensitivity was 92%, the specificity was 85%, the +PV% was 87% and the -PV% was 81% and the accuracy was 88%.

Table 8 shows data of ROC curve for serum LDH between the two studied groups. When using the value of 920 IU/L as a cutoff value the sensitivity was 94%, the specificity was 87%, the +PV% was 89% and the -PV% was 82% and the accuracy was 90.

Table 9 show data of ROC curve for serum Cyst-C between the two studied groups. When using the value of 1.73 mg/ L as a cutoff value the sensitivity was 96%, the specificity was 90%, the +PV% was 94% and the -PV% was 87% and the accuracy was 92%.

### Discussion

Transient tachypnea of the newborn is an important cause of respiratory distress in neonates. Delayed resorption of lung fluid after delivery is considered the main etiology in TTN [1].

<b>Antenatal history</b>	Absence of PROM, chorioaminitis, maternal infection, meconium Risk factors: CS, IDM, earlier sibling with TTN
<b>Clinical signs</b>	No advanced resuscitation Tachypnea shortly after birth Persistent beyond 4 h of age Rate up to 120 breath per minute Mild increase in work of breath ±grunting Needs ≤40% FIO <sub>2</sub> nasal canula Neurologically and hemodynamically: normal PCO <sub>2</sub> : not more than 60 mmHg
<b>Radiological Signs</b>	Normal or increased lung volume ± mild cardiomegaly Prominent lung markings Fluid in interlobar fissure Mild pulmonary edema No consolidations
<b>Normal CBCand CRP</b>	

PROM=Premature rupture of membrane, CS=Caesarean section, IDM=Infant of diabetic mother, CBC=complete blood count

Table 1: Criteria of classic TTN [16-21].

Character	Patient group (n=40)	Control group (n=40)
Gender (M/F)	28/12	20/20
Weight (gm)	2914 ± 326	2916 ± 221
Gestational age (wks)	38.1 ± 1.9	38.3 ± 1.6
Mode of delivery (NVD, CS)	Apr-36	20/20

Table 2: Characteristics of the study group as regard gender, weight, gestational age and mode of delivery.

Groups	Lactate					T-test	
	Range	Mean	±	SD	T	P-value	
Controls	1.8 - 2.2	1.95	±	0.35	7.552	0.001*	
Patients	2.2 - 2.6	2.42	±	0.18			

\*p value <0.05 is significant

**Table 3:** Comparison of serum lactate level (mmol/L) of patient and control group (each of 40 neonates).

Groups	LDH					T-test	
	Range	Mean	±	SD	t	P-value	
Controls	750 - 920	836	±	140	5.831	0.001*	
Patients	920 - 1190	1025	±	150			

\*P value < 0.05 is significant

**Table 4:** Comparison of serum LDH level (IU/L) of patient and control group (each of 40 neonates).

Groups	Cystatin-C					T-test	
	Range	Mean	±	SD	t	P-value	
Controls	1.3 - 1.7	1.5	±	0.2	10.213	0.001*	
Patients	1.72 - 2.05	1.9	±	0.15			

\*p value < 0.05 is significant

**Table 5:** Comparison of serum Cystatin-c level (mg/ L) of patient and control group (each of 40 neonates).

	Cystatin-C		Lactate	
	r.	p	r.	p
Lactate	0.542	0.001*		
LDH	0.651	0.001*	0.529	0.001*

**Table 6:** Correlation between Lactate(mmol/L), LDH level (IU/L) and Cystatin-c level (mg/ L).

ROC curve between patients and control as regard lactate					
Cutoff	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
> 2.2	92%	85%	87%	81%	88%

**Table 7:** ROC curve between patient and control group as regard lactate.

Cutoff	Sens	Spec.	PPV	NPV	Accuracy
> 920	94%	87%	89%	82%	90%

**Table 8:** ROC curve between patient and control group as regard LDH.

Cutoff	Sens	Spec.	PPV	NPV	Accuracy
> 1.73	96%	90%	94%	87%	92%

**Table 9:** ROC curve between patient and control group as regard Cyst-C.

The TTN has been reported to occur more frequently in full-term or near-term infants, cesarean delivery, maternal sedation, perinatal asphyxia and male infant [24].

In our study, we observed a high incidence of TTN neonates who were delivered by CS which is one of the most important risk factor of TTN and this results were in agreement with many other studies which also stated that most of the cases of TTN are born by CS [24-28].

In our study we observed a positive correlation between the levels of lactate and LDH levels and the occurrence of TTN and this results were in agreement with the studies which demonstrated a positive correlation with perinatal asphyxia with increased levels of lactate and LDH and the occurrence of TTN [25].

In our study we observed a significant increase in the lactate and LDH levels in neonates with TTN in comparison with the neonates in the control group and this in agreement with studies done on

another marker which is N-terminal pro-B-type natriuretic peptide in predicting the severity of TTN [26].

In our study, we observed a significant increase in the levels of lactate and LDH levels in neonates with TTN which is predisposed by perinatal hypoxia in comparison with the neonates in the control group and this in agreement with studies done on Lactate dehydrogenase in predicting hypoxic ischemic encephalopathy in newborn infants [27,9].

There are several risk factors that aggravate TTN symptoms such as male sex, Cesarean section delivery, low Apgar score, perinatal hypoxia. Lactate and Lactate dehydrogenase have also been implicated in a few studies [28].

The Cys C level is especially useful in neonates, and unlike serum Cr, it is unaffected by gestational age or maternal GFR [29].

In our study we observed a significant increase in the Cyst-C levels in neonates with TTN in comparison with the neonates in the control group and this in agreement with studies done serum Cys C which showed significant correlations with TTN symptom duration, which suggests an association between renal function and TTN symptom duration. We conclude that lactate, LDH and Cyst-C might be useful for early detection of TTN patient with early treatment and better prognosis

## Conclusion

In conclusion serum lactate level, LDH activity and Cys-C level increased in babies with TTN if compared with babies without TTN. Hence lactate,LDH and Cys-C can be used for early diagnosis of TTN and early treatment with better prognosis and also to differentiate between TTN ptients and other neonatal diseases with different lines of treatment.

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