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ORIGINAL ARTICLE

Lactate dehydrogenase as a predictor of bronchiolitis severity in children in teaching hospitals in Egypt

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ABSTRACT

Abstract: Background: Bronchiolitis is the most common lower respiratory tract
Infection in infants <1 year of age, Lactate Dehydrogenase (LDH) may be a useful biomarker to assist the clinician in the decision to hospitalize a child with bronchiolitis
Aim of current study was to study the efficacy of LDH in both nasal secretions (NW-LDH) and serum (S-LDH) as a useful biochemical indicator of bronchiolitis severity and to help recognition of patients with bronchiolitis who should be hospitalized using LDH level or possible pediatric intensive care unit admission (PICU)
Subject and Methods: The present study was conducted on 96 patients with bronchiolitis (< 24 months old) presenting to pediatric department of Al ahrar and Ahmed Maher Teaching Hospital during the period from November 2018 to April 2019. Patients were subjected to history taking, anthropometry, detailed clinical examination general and systemic. Investigations included blood gases & C-reactive protein (CRP), chest X –ray if necessary, total LDH activity in both nasal secretions and serum.
Results: In bronchiolitis, percentage of male was higher than female (65.6%, 34.4 %), with a mean ±SD of age 8.25±2.61 months, percentagof mild , moderate and severe cases were 36 (37.5%) , 44(45.8 %) ,16 (16.7%) respectively. No significant difference in serum LDH(S-LDH) between mild cases " not require admission " moderate "require hospital admission " or severe cases "require PICU admission (P: 0.167) while there was significant difference in nasal wash LDH (NW-LDH) among different grades of severity(P:0.001) .The significant predictors for severity of bronchiolitis were NW-LDH , younger age.
Conclusion: **NW**-LDH is a biochemical Predictor of bronchiolitis severity, hospital, PICU admission than S-LDH if demographic variable and viral etiology are taken in consideration
Keywords: Lactate dehydrogenase , nasal wash, intravenous fluid, bronchiolitis

INTRODUCTION

Acute bronchiolitis is a diagnostic term used to describe the clinical picture produced by several different viral lower respiratory tract infections in infants and very young children [1]. The commonest cause is respiratory syncytial virus (RSV) accounts for about 76%, rhinovirus for 18%, influenza virus for 10%, coronavirus for 2%, and human meta-pneumovirus for 3%, and 1% had parainfluenza.[2]. It begins as an upper respiratory tract infection, which then spreads to the lower respiratory tract in 1 to 3 days. RSV infection occurs in almost all infants by 3 years of age, but only a minority develops bronchiolitis. This observation has led to the

hypothesis that host and possibly environmental factors play a role in disease pathogenesis [3]. It is a leading cause of hospitalization in young children and accounts for 2.4 ,3.1% of hospital admission among infancy <1year in in UK and USA respectively [4 ,5] . It account for 18 % of pediatric hospital admission less than 1 year age in developed countries [6] In accounts for around 13% of PICU admissions in the UK [7] thus being a significant burden on PICU beds with a "winter surge" in activity predictably from November to February [8]. Unfortunately , no available about acute epidemiology of bronchiolitis in Egypt. LDH is an enzyme implicated in the conversion of lactate to pyruvate in the cells of most body tissues. When found extra-cellular or in the bloodstream, it indicates cell damage and inflammation [8]. LDH levels in young children with bronchiolitis varied according to viral etiology and disease severity. High LDH values in nasal washes were associated with a reduced risk of hospitalization, possibly due to a robust antiviral and inflammatory response in the upper airways, the primary site of viral replication [9]. On other hand Mehta et al. found that NW-LDH, is a predictive of bronchiolitis severity and can help distinguish children requiring PICU level care from those admitted to the general floor, or discharged home from the emergency center Biomarkers such as NW-LDH and NW-caspase 3/7 reflect a complex pathway for control of respiratory viral infections and bronchiolitis disease severity [10]. Because of possible role of LDH nasal or serum in assessing severity of acute bronchiolitis and distinguishing cases possibly not need hospitalization and can be treated at home and cases needs hospitalization or PICU admission we assessed NW-LDH and serum LDH in children acute bronchiolitis

PATIENTS AND METHODS

Patients group:

The study included 96 patients with bronchiolitis below 24 months old presented to pediatric department of Al ahrar , Ahmed Maher Teaching Hospitals , Patients were subjected to *detailed history* including age ,sex,: prenatal ,natal ,postnatal , nutritional developmental ,immunization history. Infants less than 24 months with symptoms of upper respiratory tract viral infection (running stuffy nose , cough , non-reversible wheezing and respiratory difficulty not explained by other causes were included in the study [11]. Family history of asthma, antenatal maternal smoking, pregnancy complications Questionnaire about previous history of wheezes, various allergies i.e. allergic rhinitis ,conjunctivitis, atopic dermatitis ,family history of asthma and atopy Those with preterm labor , LBW, previous admission in NICU , allergies , suspected immunodeficiency anatomical or congenital causes of wheezing or severe malnutrition, anemia , recurrent wheezing , pneumonia , focal bacterial infection respiratory distress unrelated to viral URI , were *excluded* from study . Also, *Detailed clinical examination* including heart rate, respiratory rate, temperature. weight , height and their percentiles. Heart, abdominal , detailed chest examination. Assessment of severity of respiratory distress were done. O2 saturation was checked for cases with respiratory distress Patients were *classified* as *a-mild cases*: showed normal amount of feeding , no sign of breathing difficulty , respiratory rate (R.R.) >60/min in<2 months old , >50 in ≥ 2mo old , no grunting, mild retraction , wheezing, O2 saturation >92% and generally look normal *b-Moderate cases* : feeding amount less than usual but still > half of normal amount , sign of breathing difficulty , respiratory rate (R.R.) >60/min , no grunting , moderate retraction , wheezing, O2 saturation 88-92% and generally look irritable c- Severe cases : as moderate cases + grunting , severe retraction , O2 saturation <88% , feeding decreased to less than half amount , generally look lethargic [12]

Laboratory investigations:

Complete blood count CBC , blood film, CRP. chest –x ray, C.T. scan were done to exclude anatomical and congenital causes of wheezing were done , arterial blood gases LDH nasopharyngeal and serum was estimated .Nasal wash and sera specimens were diluted in 1:1 and 1:1.2 in phosphate buffer saline respectively and assayed in duplicate following protocol instruction (cytotoxic

detection kit. Roc Applied Science LDH (Roche. Applied. Science) was used to calculate absolute values to be used to construct a standard curve. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.Written consent have been taken from parents of all children in this study , The study also was approved from research ethics committee in general organization for teaching hospital and institutes in Cairo.

Statistical Analysis:

The data were entered, coded and processed on computer using Statistical Packaged for Social Science ***(SPSS version 20).*** The level P = 0.05 was considered the cut-off value for significance. Description of quantitative variables as median and range and of qualitative variables as number and percentage. Non parametric test(Mann-Whitney for two **and Kruskal-Wallis for more)**were used to assess statistical significance between median and rang of two or more population.

Chi-Square test was used to compare qualitative variables between groups,

The correlation coefficient method was used to correlate different parameter.

Regression Model was used to find out the most significant independent predictors affecting outcome. P value > 0.05 = statistically insignificant , P ≤ 0.05* = statistically significant, P < 0.01**= highly significant.

RESULTS

Out of 96 patents, 63 (65.6%) were male and 33 (34.4%) were female . The mean ± SD of age (months), weight(Kg) , height (cm) were 8.25±2.61 ,8.02±1.61,72.41±7.51 respectively. Descriptive statistic using crosstabs revealed significant increase in cases with family history of asthma and previous wheezing beyond one year old (Phi ,P : 0.389 , 0.00 & 0.42 ,0.00 respectively) "Table 2". Also ,it showed significant increase in O2 supplement from mild to moderate to severe cases (Phi 0.679 P: 0.001) "Table 3"

The percentage of mild cases (mild distress not need hospitalization) was 36 (37.5%) , moderate cases with moderate distress required hospitalization no PICU admission was 44(45.8 %) "Table 4" .Severe casas needed PICU admission was 16 (16.7%) . Most cases admitted to PICU had tachypnea >70/min, grunting, marked retraction .Ten cases had respiratory acidosis or 2 has respiratory alkalosis

The abnormal Chest x-ray findings (broncho-vascular markings and bilateral hyperinflation) were found in 34 of cases in comparison to 62 of cases had normal chest x-ray findings. Most severe cases admitted in PICU showed abnormal x -ray finding, most mild cases showed normal x-ray .Those cases with abnormal finding when can be possible cause of wheeze other than bronchiolitis were excluded from the study. . Also cases with laboratory evidence of anemia or abnormal CBC and cases with evidences of focal bacterial infection or pneumonia based on CBC, CRP or Chest x-ray were excluded from the study.

Nebulization with β agonist, inhaled steroids was given to most cases admitted in PICU , cases with recurrent attacks and cases with family history of asthma. No significant correlation was found between both S-LDH and NW-LDH (r 0.089 p 0.387) " data not shown"

Table (4) shows that there was no significant statistical difference in serum LDH regarding age , sex, previous similar attacks and family history of asthma . However there was a significant statistical difference in nasopharyngeal LDH regarding the age (in favor of age ≥12 months). No significant difference in NW-LDH regarding gender, family history of bronchial asthma or recurrent attacks in cases with bronchiolitis.

Table (5) shows relation of both S-LDH and NW-LDH to treatment options of bronchiolitis which reflect severity and severity grades S-LDH did not show significant differences in cases required hospitalization , O2 supplement , or nebulization compared to cases which required the same lines of management . Also , it showed no significant difference between cases with hospital stay more

than 3 days compared to those which stays 3 days. However cases required hospitalization, O2 supplement, showed lower values of NW-

LDH compared with cases which did not require same line of management No significant difference in NW-LDH between cases which received nebulization and cases did not receive same line of management. Also cases which stay in hospital more than 3 days showed lower values of NW-LDH compared to cases which stays 3 days or less.

Multivariable analysis showed significant differences in NW-LDH among different grades of severity of acute bronchiolitis (mild cases not require hospitalization , moderate and sever cases require hospitalization and PICU admission).

Multiple Linear Regression Models (table 6) were constructed to evaluate the demographic and clinical variables impacting for both Serum and NWLDH showing that age , hospital stay bronchiolitis severity are not significant predictors for S-LDH while they are significant predictors for NW-LDH .Weight is not significant predictor for both serum and NW LDH

(table 6) Also , Multinomial Logistic Regression Models, were constructed to evaluate predictor of severity of bronchiolitis (table7, figure 1) Significant predictors are younger age , lower NW-LDH value . Hospital stay length ,S-LDH ,and weight are not predictors for severity of bronchiolitis

Table (1) Demographic Data of Patients Group

Age "months" (mean ± SD)	**8.25±2.61**
Weight "kg" (mean ± SD)	8.02±1.61
Height "cm" mean ± SD	72.41±7.51
Sex	Male :63 (65.6 %) &Female 33(34.4 %)

Table (2) Family History of Asthma, Previous Wheezing in Bronchiolitis Below and Above 1 Year Age (Chi square Test)

		< 12 mo (83)	**≥ 12 m(13}**	**Chi square Test**	
				Phi	P
Family History of Asthma	+ve	16	9	0.369	0.00
	-ve	67	4		
Previous Wheezing	+ve	14	9	0.42	0.00
	-ve	69	4		

Table (3) Severity of Bronchiolitis : Relation to O_2 Supplement (Chi square Test)

	O_2) Supplement	**No O_2 Supplement**	**Chi square Test**	
			Phi	P
Mild Cases(36)	32	4	0.697	0.00
Moderate Cases(44	11	33		
Severe Cases(16)	0	16		

Table (4) : Comparison of serum and nasopharyngeal LDH with different parameters using Mann-Whitney test

Parameter		Serum LDH			Nasopharyngeal LDH		
		Median	Range	P value	Median	Range	P value
Age	< 12 mo (83)	500	40-2501	P 0.906 (Z- 0.118)	202	40-989	0.01 Z 3.443
	≥ 12 m(13}	920	30-1200		523	321-752	
Sex	Female (33)	450	30-2020	P 0.597 Z 0.529)	352	40-750	0.062 Z 1.867
	Male (63)	542	40-2501		201	45-989	
Prev. attacks	No (73)	500	40-2020	P 0.6 Z 0.524	250	42-989	P 0.171 Z 1.369
	Yes (23)	600	30-2501		152	40-752	
Family history of B. A.	No {71)	500	40-2501	P 950 Z 0.063	230	42-898	P 0.947 0.0947
	Yes {25}	600	30-1200		425	40-752	

Table (5) : Serum and nasopharyngeal LDH relation to treatment options

Parameter		Serum LDH			Nasopharyngeal LDH		
		Median	Range	P value	Median	Range	P value
Hospitalization(Mann-Whitney Test)	No (36)	900	30-1600	P 0.059 Z -1.889	641	70-989	P 0.001* Z -6.649
	Yes (60)	405	40-2501		146	40-605	
O_2 supplment (Mann-hitney Test)	≤ 24 (43)	800	30-2501	P 0.258 Z -1.131	532	55-989	P<0.001** Z -5.663
	> 24 (53)	410	40-2020		125	40-742	
Nebulization (Mann-Whitney Test)	No (64}	502	40-2501	9	230	40-898	0.99
	Yes (32}	505	30-1700	P 0.963 Z -0.047	285	42-752	0. P P P 0.585 Z -0.544
Hospital stay lengths (Mann-Whitney Test)	≤ 3 days (44)	665	30-2020	P 0.442 Z 0.759	541	85-989	P 0.001** Z -7.126
	> 3 days (52)	405	40-2501		122	40-750	
Severity of disease **(Kruskal-Wallis Test)**	I(36)	900	30-600	P 0.167	641	70-989	P 0.001
	II(44)	435	40-2501	Chi-Square 3.579	201	40-605	Chi-Square 53.534
	III(16)	362	220-1255	2	64	42-250	

Table (6) : Multiple Linear Regression Models for Nasopharyngeal & Serum-LDH

Predictors	Serum LDH				Nasopharyngeal LDH			
	ß coefficients	P value	95% Confidence Interval		ß coefficien	P value	95% Confidence Interval	
			Lower Bound	Upper Bound	Upper Bound		Lower	Lower Bound
Age	-0.17	0.431	-108.025	64.51	0.274	0.031	2.475	50.148
Weight	0.043	0.825	-101.12	1212126.52	-0.153-	0.18	-59.994-	11.232
Hospital stay length	0.098	0.421	-65.3	140.137 1 7	-0.425-	0.001	- 118.107 -	-54.922-
Severity classification	-0.332	0.074	-463.662	21.674	-0.372-	0.001	- 208.621 -	-59.897

Table (7) : Multinomial Logistic Regression Models for Predictors of Bronchiolitis severity

Predictors	Chi-Square	P value
Age	6.810	0.033
Weight	2.202	0.333
Hospital stay length	5.78	0.056
NW-LDH	12.919	0.002
Serum LDH	5.745	0.057

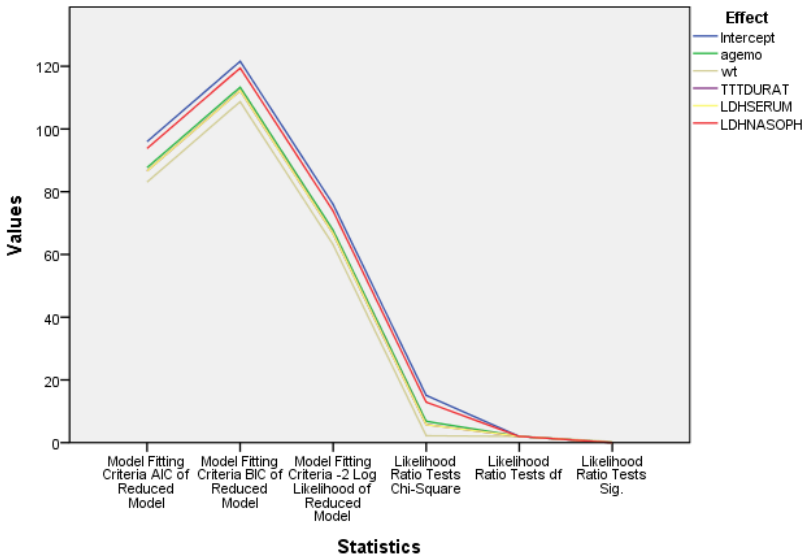

Figure 1 : Multinomial Logistic Regression For Age , Weight , Treatment Duration Versus Bronchiolitis Severity

DISCUSSION

One of the primary challenges in bronchiolitis management is the highly heterogeneous disease presentations, ranging in severity from mild disease not require intervention or hospitalization to severe disease requires intensive care admission and mechanical ventilation. Despite different risk factor are present, they fail to stratify the disease severity [13, 14] .

Different clinical biomarkers were used to accurately predict disease severity in bronchiolitis and enhanced decision-making , therapeutic intervention, and follow-up [15]. In this study we measured LDH both serum and nasal wash to evaluate their role and value as predictors of severity and management of children with bronchiolitis. In this study the percentage of male 63 (65.6%) was higher than female 33(34.4%) . This is in agreement with Bria et al [16] who stated that bronchiolitis is more common in male. Our age range was from to 4-13 months with mean age 8.25±2.61 months (Table 1)This finding in agreement with previous reports about age prevalence of bronchiolitis [17, 18, 19] . Significant increase in recurrent cases and family history of asthma after 12 month age was observed in this study (Table 2) . The explanation may be that bronchiolitis in infancy is a possible risk factor of subsequent recurrent wheezing and asthma in life later [20 , 21]. S-LDH did not show any relation to age , sex, weight, family history of bronchial asthma or children with previous attacks(table 4) of bronchiolitis, hospitalization or severity of disease .Little studies were done about S-LDH in in respiratory infection . Our finding in agreement with Laham et al[9] This lack of association of S-LDH as a marker with respiratory infection or severity of bronchiolitis possibly due to non-specificity of its source in the blood stream , possibly it comes from different tissues other than the respiratory system , so the respiratory component in the serum did not cause significant changes in its serum level [22]. Possibly little leak occurred from damaged alveolar cell into blood stream. Lack of correlation between both SLDH and NW-LDH supported this explanation . NW-LDH did not show any relation to sex , recurrence of bronchiolitis or family history of bronchial asthma. However cases more than 1 year age showed higher level of NW-LDH than those with less than 1 year. Mehta et al [10] found that children aged 4-12 months admitted in acute care unit had lower NW-LDH compared to those aged >12 months and did not required hospitalization. In our study hospitalized cases showed lower values of NW-LDH than non-hospitalized case (table 5). In agreement with our finding, Laham FR et al [9] who found that lower NW-LDH can be a predictor of hospital admission .The same finding was reported by Mansbach t al [22] who found that higher NW LDH was associated with reduced risk of hospitalization >24 hours .

Multivariable analysis showed significant difference between mild , moderate and severe cases in NW-LDH . Regression analysis model showed that age, hospital stay length and severity of bronchiolitis negatively impacting NW-LDH(table 6) In agreement to this results , Lahman et al [9] found that need for O2 supplement, age less than 3 months is predictor for severe bronchiolitis . In our study multiple linear regression revealed that lower NW-LDH, younger age , longer hospital stay are significant predictor for severe bronchiolitis . Similar results was found recently by Barak et al [23]. They found that children with bronchiolitis who has fever and required O2 thereby had lower NW-LDH than those without fever and did not required O2 thereby. Also they found negative correlation between NW LDH and hospital stay length, bronchiolitis severity. Because LDH is an enzyme released in cell damage and inflammation , intuitively, one would expect higher levels in nasal washes in more severe disease, as the enzyme is released extra-cellularity upon tissue injury. Evidences suggest that innate immune responses during respiratory virus infections are mainly protective and that the degree of the inflammatory response is inversely related to disease severity [24,25] The main source of

LDH in nasal wash was found to be from polymorph leucocytes and alveolar macrophage [9] . Also , LDH correlated with inflammatory mediators and cytokines in bronchiolitis and children with otitis media [9,26]. Children died of overwhelming viral infection did not show cytokine storm but showed a paucity of lymphocytes and natural killer cells, unchecked viral replication, and apoptotic crisis [27] .It is expected that children with high NW-LDH developed high inflammatory response which resulted in clearance of the infection while those with low level were unable to develop enough protective response. Contrary to our study Mehta et al [10] found positive correlation between bronchiolitis severity and NW-LDH. The difference from our study may be due to difference in demography of patients , epidemiology and viral etiology of the disease . They found racial differences in the NW-LDH . Also they found that children exposed to cigarette smoking had higher values of NW LDH. Most of their viral pathogen were RSV which had the highest NW-LDH value compared to other viruses [9,10] . Similar results of such positive correlation to bronchiolitis severity in RSV bronchiolitis was described by Mohammed S [28]. We did not make viral study or screening to assess relation of viral etiology to NW-LDH level . Demographic, epidemiological and seasonal differences possibly contribute to validity of LDH as a marker of severity of the disease. Also, Ide et al [26] found high NW-LDH in children with viral upper respiratory tract infection was associated with increased risk of otitis media as subsequent complication .Contrarily to our study they suspected that high marker of NW-LDH is associated with more tissue damage and increase risk for developing otitis media, so high values in their study is a marker of increased risk of complication rather than being protective. Also their study included older age group with expected high level of production of LDH No relation found of NW LDH or SLDH to cases received nebulization, however cases received supplemental O2 showed lower values of NW LDH . Most cases received O_2 were severe and expected to show lower values of the marker (table 5). In agreement with this finding , Laham et al [9] and Barak et al [23] who found that cases required O2 supplements and has hospital stay length > 24 hours had lower NW-LDH compared to those did not required O2 supplement and needed hospital stay < 24 hours . Most cases received O_2 in our study were severe and expected to show lower values of this marker.The only limitation in our study that we did not make viral study to evaluate viral etiology in relation to LDH level .The study has clinical implication. LDH determination is cheep, available in most laboratories can help to differentiate between mild moderate or severe cases of bronchiolitis and their line of management whether at home or hospital .Also help to predict prognosis of cases.

Further studies are required to investigate the exact value of both serum and NW LDH as a predictors of severity of acute bronchiolitis in children and evaluate the role of different variables as viral etiology, demography as age, race ,sex and other possible factors.

CONCLUSION

NW-LDH is useful marker to predict severity of viral bronchiolitis in children and can help to differentiate between cases treated at home and cases require hospital or PICU admission but it is important to keep in consideration demographic variables such as race ,age, locality. Also we must keep viral etiology in consideration

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