Assessment of Serum Uric Acid and Highly Sensitive C-reactive Protein in Patients with Acute Respiratory Distress Syndrome

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Abstract:

Background: Acute respiratory distress syndrome (ARDS) is characterized by the acute onset of pulmonary edema of non-cardiogenic origin, along with bilateral pulmonary infiltrates and reduction in respiratory system compliance with refractory hypoxemia that is the hallmark of the syndrome.

Objectives: This study is designed for the assessment of serum uric acid (SUA)and highly sensitive C-reactive protein (HSCRP) in patients with ARDS and for the determination of risk factors promotes the induction of ARDS.

Subjects and methods: This case control study was conducted in Al-Batool Teaching Hospital for Maternity and Children for the period from August 2017 to June 2018. 200 subjects were included, 100 patients who were admitted to neonate intensive care unit with age range 1-2 days. Another 100 age and sex matched apparently healthy infants were included as control group. A specific questionnaire form was preconstructed for this purpose. Blood samples were collected from subjects. Sera were separated and the determination of serum uric acid was carried out by (COBAS INTEGRA systems, Germany) The determination of highly sensitive C-reactive protein was measured by (COBAS INTEGRA systems, Germany) Human privacy was respected by taken patient's parents consent. Furthermore, the study was approved by the Ethical Committee in the College of Medicine.

Results: The results revealed that the mean ± SD of serum uric acid in patients was significantly higher than that of controls (328.52 ± 151.19 *versus* 264.15 ± 85.12, *t-test* = 3.71, **P = 0.001**). Similarly, the mean ± SD of highly sensitive C-reactive protein titer was significantly elevated in neonates with respiratory distress syndrome versus controls (5.19 ± 16.11 *versus* 1.3 ± 1.7, *t-test* = 2.398, P= **0.017**). The SUA was significantly higher in patients weighted less than 2.5 Kgs (*t-test* = 2.688, P= **0.008**). Furthermore, preterm patients had significantly higher SUA (*t-test* = 2.435, **P = 0.017**). The results also found that patients who required medical intervention had higher levels of SUA (*t-test* = 2.395, P = **0.024)**. Additionally, patients who were dead had significantly higher titer of SUA (*t-test* = 8.545, **P = 0.001**). While other factors including gender and age showed insignificant effect. Concerning the HSCRP, preterm patients had significantly higher titers versus term patients (*t-test* = 2.066, **P = 0.042**). However, other factors including gender, age, weight, intervention required and final outcome were failed to reach the levels of statistical significance.

Conclusion: The study concluded that the serum uric acid concentration and the highly sensitive C-reactive protein titer can be employed as diagnostic adjuncts for RDS in newly born infants, and certain patient's and mother's features were significantly associated with these markers.

Keywords: respiratory distress syndrome, Uric acid, C-reactive protein.

Introduction:

Infant respiratory distress syndrome, is a life-threatening syndrome in premature infants caused by developmental insufficiency of pulmonary surfactant production and structural immaturity in the lungs[1]. It can also be a consequence of neonatal infection[2].

The variable risk of RDS in various races/ethnicities or monozygotic/dizygotic twins through several specific mutations and surfactant protein genes polymorphisms have confirmed the genetic predisposition of RDS[3,4]. Respiratory distress syndrome affects about 1% of newborn infants and is the leading cause of death in preterm infants[5]. Systematic review and meta-analysis studies revealed that the incidence of pediatric ARDS was 3.5/ 105 person/ years and the mortality was 33.7% which was significantly associated with study location [6]. The incidence decreases with advancing gestational age, from about 50% in babies born at 26–28 weeks, to about 25% at 30–31 weeks. The syndrome is more frequent in infants of diabetic mothers and in the second born of premature twins [7].

The lungs of infants with RDS are developmentally deficient in surfactant material which helps prevent collapse of the terminal alveolar spaces throughout the normal cycle of inhalation and exhalation. Pulmonary surfactant is a complex of lipids, proteins and glycoproteins that are produced in specialized lung cells at about 26 weeks of pregnancy[8].

Therefore, the increased capillary permeability is the hallmark of RDS. Damage of the capillary endothelium and alveolar epithelium in correlation to impaired fluid remove from the alveolar space result in accumulation of protein-rich fluid inside the alveoli, producing diffuse alveolar damage, with release of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), IL-1 and IL-6 [9]. Neutrophils are recruited to the lungs by cytokines, become activated and release toxic mediators, such as reactive oxygen species and proteases, consequently the extensive free radical production overwhelms endogenous anti-oxidants and causes oxidative cell damage [10].

Uric acid acts as both pathogenic inflammatory mediator and antioxidative agent has been shown by several studies and its level correlates with the incidence, severity, and prognosis of pulmonary diseases. In this regard, Lee *et al*., (2017) [11] found that in patients with ARDS, a low serum uric acid level may be a prognostic marker of a low risk of in-hospital mortality. Moreover, it has been report that elevated uric acid levels on arrival to the medical intensive care unit in patients with sepsis are associated with poor prognosis and these patients are

at an increased risk for acute kidney injury, mortality, and ARDS [12].

C-reactive protein is an acute phase protein of hepatic origin found in blood plasma. It is a member of the pentraxin family of proteins whose levels rise in response to inflammation, infection and tissue damage **[13].** The plasma biomarkers most strongly associated with ARDS mortality, when increased, were interleukin-4, interleukin-2, angiopoietin-2, and Krebs von den Lungen-6. Decreased levels of CRP were associated with increased odds for ARDS diagnosis and mortality [14]. Furthermore, reported that antenatal maternal CRP levels were not related to neonatal outcome preterm premature rupture of membranes [15]. On the other hand, it has been reported that serum procalcitonin was more susceptible, as a diagnostic parameter of infection, to the effect of respiratory disturbance than CRP and WBC in neonates **[15].** Therefore the present study was designed for the assessment of serum uric acid and highly sensitive C-reactive protein in patients with acute respiratory distress syndrome and for the determination of risk factors exacerbating the disease.

Subjects and methods:

This case control study was conducted in Al-Batool Teaching Hospital for Maternity and Children for the period from August 2017 to June 2018. 200 subjects were included, 100 patients with ARDS who were admitted to neonate intensive care unit (NICU) with age range 1-2 days. The diagnosis of ARDS was done clinically and radiologically. They were 58 males and 42 females. The majority of them (79 %) were born by cesarean section. All patients were subjected to; detailed history from the mother; complete thoroughly physical examination, required laboratory investigation including the complete blood Count, and chest x-ray. Another 100 age and sex matched apparently healthy neonates were used as control group. A general questionnaire was preconstructed for this study to gather the necessary data that was filled by the researchers. These include neonatal, age, gender, weight, gestational age, the use of CPAP or ETT, Duration of hospitalization, and the final outcomes. The mother and demographic data include Age, educational level, type of delivery, Parity, history of chronic diseases, history of previous baby with RDS and history of maternal smoking during pregnancy.

Form each patient and control, 3 milliliters of venous blood were obtained thorough a veipuncture, 1 milliliter was placed in prelabeled EDTA tube for measuring the CBC. The remaining 2 milliliters were placed in prelabeled Eppendorf tubes, left in upright position 30 minutes at room temperature to clot, centrifuged for 5 minutes at 5000 rotation /minute for separation of sera. Sera were used for the determination of HSCRP and SUA. A quantitative determination of HSCRP and quantitative determination of the uric acid concentration in serum samples were done using the (COBAS INTEGRA systems, Germany). Human privacy was respected by taken patient's parents consent. Furthermore, the study was approved by the Ethical Committee in the College of Medicine. Statistical analyses were done using Statistical Package for Social Sciences (SPSS) version 25. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the means of variables among study groups. P value less than 0.05 was considered significant.

Results:

The results showed in table (1) that the means of serum uric acid in patient group was higher than that in control group (328.52 ± 151.19 *versus* 264.15±85.12 µmol/l) and this difference was statistically significant (*t-test* = 3.71, **P = 0.001**). Regarding the highly sensitive CRP, the results also revealed that the mean concentration (mg/l) in patient group was higher than in control group (5.19 ± 16.11 *versus* 1.3 ± 1.7 mg/l), and this difference was statistically significant (*t- test*= 2.398, **P = 0.017**).

Table (1): the distribution of mean SUA and hs-CRP among study groups.

Variable	Study Group		t- test	P- Value
	patients Mean ± SD	Control Mean ± SD		
Uric Acid	328.52 ± 151.19 µmol/l	264.15 ± 85.12 mol/l	**3.71**	**0.001**
HSCRP	5.19 ± 16.11 mg/l	1.3 ± 1.7 mg/l	**2.398**	**0.017**

It was also found that the mean ± SD of SUA concentration was insignificantly higher in females compared to males (336.55 ± 161.6 *versus* 322.716 ± 144.33, *t- test* = 0.45, **P=0.654**). The effect of the age was also insignificant, since the SUA was slightly higher in the first versus the second day (337.81 ± 139.7 *versus* 306.78 ± 138.14, *t-test* = 1.09, **P= 0.277**). Furthermore, there was significant increase in the SUA concentration in those patients weighted less than 2.5 kgs versus those weighted 2.5- 3.5 kgs (373.43 ± 168.8 *versus* 293.4 ±124.85, *t- test*= 2.688, **p= 0.008**). The gestational age was also found to had a significant effect, since preterm babies had higher SUA concentration versus those with full term (341.04 ±141.75 *versus* 299.57 ± 75.58, *t- test*= 2.435, **p= 0.017**). The results also revealed that the

SUA concentration was significantly higher in those babies who required medical intervention than those did not (337.5 ± 157.13 *versus* 268.42 ±84.41, *t-test*= 2.395, **p= 0.024**). Lastly, neonates who were dead had significantly higher serum concentration of UA compared to those babies who discharged well (497.94 ± 178.95 *versus* 272.87 ± 80.93, *t test*= 8.545, **p= 0.001**).

Regarding the HSCRP, the mean ± SD concentration in male was nearly similar to that of female with insignificantly difference (5.51 ±18.7 *versus* 5.25 ± 11.8, *t-test* = 0.033, **p = 0.974**). Furthermore, the mean concentration in the first day (6.46 ± 21.43) was higher than that in the second day (4.15 ± 7.74); However, the difference was failed to reach the levels of statistical significance (t-*test* = 0.688, **P = 0.493**). The results also revealed that babies weighted less than 2.5 Kgs had higher mean concentration of HSCRP versus those weighted between 2.5 – 3.5 Kgs, but the difference was statistically insignificant (7.74 ± 22.43 versus 3.11 ± 6.98, *t- test* = 1.41, **P = 0.161**). Additionally, the preterm newborn had higher concentration (5.97 ± 17.09) versus term babies (1.71 ± 1.58) with a statistically significant difference (t-*test* = 2.066, **P = 0.042**). Furthermore, newly born who required a medical intervention had higher mean concentration (5.64 ±17.21) compared to those did not (2.19 ± 2.57) but the difference was failed to reach the levels of statistical significance (t-*test* =1.744, **P = 0.084**). Finally, the outcome also had insignificant difference (*t-test*= 0.673, **P = 0.504**) since dead babies had higher concentration than those discharged well (7.06 ± 14.67 *versus* 4.69 ± 16.82), table (3).

Table (2): The distribution of mean SUA according to certain patient's characteristics.

Variable		Uric Acid (µmol/l)		Student t-test	P- Value
		Mean	S. D.		
Gender	**Male**	322.71	144.33	**0.45**	**0.654**
	Female	336.55	161.6		
Age (day)	**1 Day**	337.81	139.7	**1.09**	**0.277**
	2 Day	306.78	138.14		
Weight (Kg)	**< 2.5**	373.43	168.8	**2.688**	**0.008**
	2.5 – 3.5	293.4	124.85		
G.A.	**Term**	229.57	75.58	**2.435**	**0.017**
	Preterm	341.04	141.75		
Interven. required	**Yes**	337.5	157.13	**2.395**	**0.024**
	No	268.42	84.41		
Outcome	**Death**	297.94	178.95	**8.545**	**0.001**
	Discharge	272.87	80.93		

Table (3): Distribution of means of hs-SCRP by certain characteristics of patients.

Variable		hsCRP (mg/l)		Student t-test	P- Value
		Mean	S. D.		
Gender	**Male**	5.15	18.7	**0.033**	**0.974**
	Female	5.25	11.8		
Age (Days)	**1 Day**	6.46	21.98	**0.688**	**0.493**
	2 Day	4.15	7.74		
Weight (Kg)	**< 2.5**	7.74	22.43	**1.41**	**0.161**
	2.5 – 3.5	3.11	6.98		
G.A.	**Term**	1.71	1.58	**2.066**	**0.042**
	Preterm	5.97	17.09		
Inter. Required	**Yes**	5.64	17.21	**1.744**	**0.084**
	No	2.19	2.57		
Outcome	**Death**	7.06	14.67	**0.673**	**0.504**
	Discharge	4.69	16.82		

Discussion:

The present study was designed and conducted on neonates in the first two days of their live. These highly critical hours actually represent transition from maternal to paternal life. Worryingly, those neonates, they just come out to find one of life-threatening condition facing them. Therefore, no doubt, this study derived its importance from the specific ages enrolled and the fatal condition targeted. Of course beside the uniqueness, as it is the leading one in this regard at least in Iraq. In fact, upon reviewing worldwide scientific literature, the related studies are scarce. Uric acid was explored in the context of pulmonary diseases because these diseases involve the actions of reactive oxygen species and uric acid is a major

antioxidant in airway secretions and Bronchoalveolar lavage (BAL) fluid [17].

The present study showed that there is a statistically significant difference in patients with RDS compared to healthy neonates, as the means concentration of serum uric acid in RDS patients was higher than that in control group (328.52µmol/l *versus* 264.15µmol/l, **(P=0.001)**). These results are consistent with that of a study conducted in Finland 1976, which found that infants with RDS had higher serum urate concentrations during the first three days of life, and the urinary excretion of uric acid over the period of 12 to 36 hours of age was also higher than that in the normal infants. In both neonates groups, the correlation of maximal serum urate values with the urinary excretion was positive, indicating that neonatal hyperuricemia is not due to renal retention but to increase production of uric acid, and this overproduction arise from increased nucleotide breakdown associated with perinatal hypoxia **[18].** Similarly, a study conducted in Denmark in 1980 showed that daily urinary excretion of the oxypurines hypoxanthine, xanthine and uric acid during each of the first 3 days of life was determined in premature infants without hypoxia and in hypoxic premature infants (HPI) with the RDS. The loss of uric acid was statistically significantly greater in the HPI during days one, two, and three of life, and so was the loss of xanthine on days one, and two, but not on day three [19]. Even comparing to adults with RDS, the current results are consistent with that of a study conducted in Korea in 2017, in which a higher percentage of patients in the low uric acid group experienced clinical improvement from ARDS, while a higher percentage of patients with a normal to high uric acid level died from septic shock **[11].** Furthermore, it has been reported from a study conducted in 2015 in Egypt that hyperuricemia may be associated with increased mortality in patients with ARDS **[20].** Additionally, in patients with chronic obstructive pulmonary disease (COPD), a high uric acid level correlated significantly with the severity of disease or degree of hypoxemia and future exacerbation or mortality, as observed by Greek researchers in 2013 **[21].**

In another Japanese study in 2002, the authors reported that the levels of serum uric acid were increased with the severity of pulmonary embolism **[22].** Finally, a Taiwan study conducted in 2005 approved that low serum uric acid level was associated with a higher rate of intubation and fatal prognosisin patients with severe ARS **[23].**These differences might have explained by understanding the pathology of hyperuricemia, which result from hypoxia in the peripheral tissues which is known as first cause of increased uric acid in patients with pulmonary disease [11]. Moreover, another possibility of explanation of high uric acid levels is hypoxia makes more adenosine released by increased degradation of adenosine triphosphate, and this leads to the increased formation of xanthine, which is finally transformed to uric acid **[24].** Additionally, it has been reported that the purine degradation is accelerated by increased xanthine oxidase activity, which is promoted by raised right ventricular after load in patients with ARDS**[25].**

Based on the well-documented facts, the CRP is an acute phase protein that is produced in the body in response to inflammation, infection, and tissue damage **[13,26].** Therefore, qualitative or quantitative assessment of CRP in different transmissible or non-transmissible medical conditions had been intensively used **[27,28].** The high-sensitivity assays for CRP (hs-CRP) have become available in clinical laboratories and suggested the involvement of low-grade systemic inflammation in several disorders, such as cardiovascular disease and diabetes mellitus and correlate significantly with respiratory symptoms **[29,30].**

In the current study, the mean of hs-CRP among neonates with RDS was significantly higher versus that in control group (5.19 mg/l *versus* 1.3 mg/l, **P=0.017**). Actually upon reviewing the literature, studies on the association of RDS and hs-CRP levels are scarce, therefore comparing the hs-CRP changes in similar conditions may the most acceptable discussion. In a study conducted in Iran during 2011, reported that hospitalized neonates with sepsis (uncertain sepsis, clinical sepsis) had a significantly higher hs-CRP compared to those neonates without sepsis (2.22 ± 0.27 *vs* 4.80 ± 0.83, $\mathbf{P < 0.001}$) and the levels remained significant for 12-24 hours after admission **[31].** Similarly, a study in India, Prashant and co-workers (2013) **[32].** reported that hs-CRP has high specificity in detecting bacterial infection. These results were also positively correlates with a study done in India, which also suggest that serum level of hs-CRP was significantly higher in the clinically suspected sepsis group than in the control group **[33].**

American researchers stated in a study in 2013 that very low birth weight premature infants colonized with *Ureaplasma* species caused broncho-pulmonary dysplasia have an elevation of early and late hs-CRP, suggestive of a chronic low-grade systemic inflammatory response [34]. Additionally, Serum hs-CRP levels can be employed as a prognostic marker for the development of diabetes mellitus as shown by a study conducted in USA **[35].** or a prognostic marker for future cardiovascular events as shown in another study **[36].** Highly sensitive CRP is more sensitive than the conventional CRP, hs-CRP assays measures the CRP levels lower than that measured by the conventional CRP assays. When measured with a high sensitivity analytic method, CRP can be used as a diagnostic marker of neonatal infection. This is because newborns cannot produce sufficient amounts of acute phase proteins and so they respond to infection with a smaller increase in CRP compared to adults **[37].** It has also been demonstrated that hs CRP measurement below 1 mg/l

provides increased sensitivity for neonatal infection [38]. Accordingly, this study concluded that the serum uric acid concentration and the highly sensitive C-reactive protein titer can be employed as diagnostic adjuncts for RDS in newly born infants, and certain patient's and mother's features were significantly associated with these markers.

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