The Republic of Iraq
Ministry of Higher Education
and Scientific Research
University of Diyala
College of Medicine

ASSESSMENT OF SERUM URIC ACID AND HIGHLY SENSTIVE C-REACTIVE PROTEIN WITH ACUTE NEONATAL RESPIRATORY DISTRESS SYNDROME

A Thesis

Submitted to the Council of theCollege of Medicine / University of Diyala in a PartialFulfilment of the requirements for the Degree of Master of medicine in Pediatrics

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ACKNOWLEDGMENTS

Thanks to **God** who enabled me to complete this work

My deepest gratitude goes to my Supervisors, **prof. Dr. Abdul Razak Shafiq Hassan** and **prof**. **Dr. Dawood Salman Hameed AL-Azzawi** for suggesting the subject and their scientific guidance throughout the study

I offer personal expression of gratitude to my family and friends for their help and support

I would like to thank the deanery of Medical College /Diyala University /Pediatric Department

Deep thanks and appreciation are to all the medical and paramedical staff who helped me to do this study

I offer personal expression of gratitude to all staff of the neonatal care unit specially Dr.Sura Qias C.A.B.P. Pediatrician-chief of NICU At Al-Batool teaching Hospital - and Laboratory staff in Al-Batool Teaching Hospital for their kind help in Collection of sample

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Dedication

This study is whole heartedly dedicated to my beloved family who has been my source of inspiration and gave me strength

Declaration

I hereby declare that this thesis is my original work except for the question and citation which have been only dulyaknowlgement.
I also do have that it has not been previously, and not currently submitted for any others degree at university of Diyala or other institutions.

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SUMMARY

Acute respiratory distress syndrome is a disease of acute onset characterized by hypoxemia .It infiltrates on chest radiographs.Among preterm infants; it is typically due to a quantitative deficiency of pulmonary surfactant. Aside from the degree of prematurity, diverse environmental and genetic factors can affect the development of respiratory distress syndrom.In premature infants, Respiratory distress syndrom develops because of impaired surfactant synthesis and secretion leading to atelectasis, ventilation-perfusion inequality, and hypoventilation with resultant hypoxemia and hypercarbia. Thus, clinically presents as tachypnea, nasal flaring, retractions, and grunting and may progress to respiratory failure. Mortality rates range from 30% to 75%, and most deaths are a consequence of multiorgan failure.

Uric acid acts as both pathogenic inflammatory mediator and an ant oxidative agent correlates with the incidence, severity, and prognosis of pulmonary diseases. C-reactive protein , on the other hand, is an acute-phase protein of hepatic origin and found in blood plasma, whose levels rise in response to inflammation, infection and tissue damage. The association between serum uric acid and C-reactive protein levels and Acute respiratory distress syndrom has only been marginally studied.

This is a cross-sectional study conducted at Al-Batool Teaching Hospital for Maternity and Children for the period from August 2017 to June 2018, aiming at determination of the levels of serum uric acid and highly sensitive C-reactive protein titer among newly born with Acute respiratory distress syndrom. Two hundred subjects were included, 100 patients who were admitted to Neonatal care unit with age range 1-2 days. They were 58(58%) males and 42(42%) females. The majority of them (79 %) were born by cesarean section. The control group was age and sex matched apparently healthy infants. A specific questionnaire form was preconstructed for this purpose to ascertain the role of socio-demographic and maternal factors.

Blood samples were collected. Sera were separated and kept frozen at -20 °C till use. Determination of Serum uric acid was carried out by uric acid integration; the determination of highly sensitive C-reactive protien was measured byC-Reactive protein (Latex) high sensitive. Human privacy was respected by taking patient's parents verbal' consent. Furthermore, the study was approved by the Ethical Committee of the College of Medicine- Diyala university.

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 protien titer was significantly elevated in Respiratory distress syndrom patients compared to controls (5.19 ± 16.11*versus*1.3 ± 1.7, *t-test* = 2.398, P= **0.017**).

In the patient group, the statistical analyses showed that the Serum uric acid was significantly higher in patients weighted less than 2.5 Kgs compare to those weighted 2.5-3.5 Kgs (373.43±168.8 *versus* 293.4±124.85, *t-test* = 2.688, P= **0.008**). Regarding the gestational age, preterm patients had significantly higher Serum uric acid compared to term patients (341.04 ±141.75 versus 229.57 ± 75.58, *t-test* = 2.435, **P = 0.017**). The results also showed that patients who required medical intervention had higher levels of serum uric acid than those who didn't (337.5± 157.13*versus*157.13± 84.41, *t-test* = 2.395, P = **0.024)**.Furthermore, It was found that patients who were dead had significantly higher titer of Serum uric acid compared to those who were discharged well (297.94 ± 178.95 *versus* 272.87 ± 80.93, *t-test* = 8.545, **P = 0.001**). It is worthy to mention that the majority of patients (88%) were discharged well. However, other factors including gender and age showed insignificant effect (**P = 0.654** and **P =0.277**) respectively.

Concerning the highly sensitive C-reactive protien titer levels, the results found that preterm patients had significantly higher titer compared to term patients (5.97 ± 17.09 *versus* 1.71± 1.58, *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 (**P =0.974**, **P =0.493**, **P =0.161**, **P =0.084** and **P =0.504**) respectively.

The results were also showed that maternal factors namely, history of previous baby with Respiratory distress syndrom and using steroid medication before delivery had neither effect on the mean concentration of Serum uric acid (**P =0.618 and P=0.8**)respectively**,** nor the mean titer of highly sensitive C-reactive protien (**P =0.963 and P = 0.951**) respectively.

The present study concluded that the serum uric acid concentration and the highly sensitive C-reactive protein titer can be employed as diagnostic predictor for respiratory distress syndrome in newly born infants, and certain patient's and mother's features are significantly associated with these markers.

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List of Abbreviations

AECC	American-European Consensus Conference
ALI	Acute Lung Injury
ARDS	Acute Respiratory Distress Syndrome
ATP	Adenosine Triphosphate
BAL	Broncho Alveolar Lavage
BNP	Brain Natriuretic Peptide
BPD	Bronchopulmonary Dysplasia
CIPNM	Critical Illness Polyneuropathy and Myopathy
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CRP	C-Reactive Protein
CXR	Chest-X-Ray
DAD	Diffuse Alveolar Damage
DPG	Diphosphoglycerate
DPPC	Dipalmitoylphosphatidylcholin
ECMO	Extracorporeal Membrane Oxygenation
EDTA	Ethylenediaminetetraacetic acid
FBM	Fetal Breathing Movements
FLF	Fetal Lung Fluid
FRC	Functional Residual Capacity
GA	Gestational Age
HbA	Hemoglobin-A
HFOV	High Frequency Oscillatory Ventilation
HPI	Hypoxic Premature Infants
HPV	Hypoxic Pulmonary Vasoconstriction
HSA	Human Serum Albumin
HSCRP	High Sensitive C-Reactive Protein
ICU	Intensive Care Unit

iNO	Inhaled Nitric Oxide
IRDS	InfantRespiratory Distress Syndrome
IVH	Intraventricular Hemorrhage
L/S	lecithin/sphingomyelin Ratio
MAPSS	Multi Angle Polarized Scatter Separation
MODS	Multiple Organ Dysfunction Syndrome
MV	Mechanical Ventilation
NICU	Neonatal Intensive Care Unit
NO-cGMP	Nitric Oxide-cyclic Guanosine Monophosphate
NOS	Nitric Oxide Synthase
NRDS	Neonatal Respiratory Distress Syndrome
OI	Oxygenation Index
OR	Odd's Ratio
OSA	Obstructive Sleep Apnea
OSI	Oxygen Saturation Index
WHO	World Health Organization
PALICC	Pediatric Acute Lung Injury Consensus Conference
PAP	Positive Airway Pressure
PARDS	Pediatric Acute Respiratory Distress Syndrome
PC	Phosphatidylcholine
PCT	Serum Procalcitonin
PDA	Patent DuctusArteriosus
PEEP	Positive End Expiratory Pressure
PG	Phosphatide Glycerol
PROM	Premature Rupture Of Membranes
PVR	Pulmonary Vascular Resistance
RDS	Respiratory Distress Syndrome
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
SD	Standard Deviation
SP	Surfactant proteins
SPSS	Statistical Package for Social Sciences
SR	Single Read
TTN	Transient Tachypnea of Newborn

TV	Tidal Volume
V/Q	Ventilation / Perfusion Ratio
VILI	Ventilator Induced Lung Injury

CHAPTER ONE
INTRODUCTION

INTRODUCTION

1.1 Background

Respiratory Distress Syndrome (RDS) is a life threatening pulmonary disease primarily of the premature infant caused by surfactant deficiency; pulmonary surfactant is a surface-active lipoprotein complex (phospholipoprotein) formed by type II alveolar cells. The proteins and lipids that make up the surfactant have both hydrophilic and hydrophobic regions. By adsorbing to the air-water interface of alveoli, with hydrophilic head groups in the water and the hydrophobic tails facing towards the air, the main lipid component of surfactant, dipalmitoyl phosphatidyl choline (DPPC), reduces surface tension. As a medication, pulmonary surfactant is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system (19^{th} WHO Model List of Essential Medicines, 2015).

Pediatric acute respiratory distress syndrome is one of the most challenging disease entities in the pediatric intensive care unit (ICU). PARDS was recently defined by the Pediatric Acute Lung Injury Consensus Conference (PALICC) group as acute-onset hypoxic respiratory failure with new infiltrate(s) on chest radiography not fully explained by cardiac failure or fluid overload (Khemani *et al*, 2015).About 1 in 20,000-30,000 newborn US infants will have RDS. Approximately half of neonates born at gestation age of 26-28 weeks will develop RDS, while about 30% of 30-31 gestation week neonates will develop it (Hintz *et al*., 2007). Although prematurity is the primary risk factor, there are several other risk factors including maternal diabetes, cesarean section, asphyxia, rapid labor, and complications that reduce blood flow to the fetus. Internationally, RDS occurs less frequently than in the US but overall, it is more common in white premature infants (Qiu *et al*., 2008).

Pathophysiology of RDS is characterized by increased vascular permeability, increased lung weight and loss of aerated tissue within the seven days of insult. Hypoxemia, bilateral opacities on the chest x-ray, decreased lung compliance and increased physiological dead space are telltale clinical signs. Diffuse alveolar damage characterized by edema, inflammation, hyaline membrane formation or pulmonary hemorrhage are the pathological hallmark (Ranieri *et al*., 2012). Symptoms observed in infants with RDS are indicative of difficulty with breathing. They typically present shortly after birth, at times hours afterwards, and include: cyanosis, tachypnea, nasal flaring, subcostal and intercostal retractions, expiratory grunting and apnea, several of the complications of RDS are reduced with adequate treatment (Schwab *et al*., 2013). In certain cases, a combination of the disease and its treatment result in the complications of patent ductusarteriosus (PDA), pulmonary hemorrhage, pneumothorax, bronchopulmonary dysplasia (BPD), septicemia, hypertension, failure to thrive and intraventricular hemorrhage (IVH)(Purohit and Corden, 2016).

Urgent delivery of care to infants with hyaline membrane disease is very important. Resuscitation is the primary treatment required so as to minimize sequelae of the disease. It entails administration of warm, moist oxygen and assisted ventilation. The oxygen is critically important but it can also cause damage to the lungs via generation of radical ions. As such, great care is taken to ensure that the patients are receiving the smallest possible amount of oxygen required (Gillies and Wells, 2005). Continuous positive airway pressure (CPAP) is often used to promote ventilation, by keeping the alveoli open at the end of expiration thereby reducing the chances of atelectasis (Murray and Stewart, 2008).

Surfactant replacement therapy has reduced the mortality rate from respiratory distress syndrome by about half. The surfactant protects the immature lung from inflammation and it also partially restores the surface tension that helps keep alveoli from collapsing. It is typically administered shortly after birth (Doyle *et al*.,

2007). Corticosteroids are another group of medications used in the management of infants at risk for hyaline membrane disease. In this case, mothers at an increased risk of having children with hyaline membrane disease are given steroid either betamethason with 2doses of 12mg 24hours apart or dexamethasone with dose of 6 mg given 4 doses every 12 hours apart . Typically, the symptoms worsen a few days after birth but slowly improve afterwards. The goal is to support the infant while the lungs begin producing surfactant (Fremont *et al*., 2010).There are many previous studies investigated the biological markers of acute lung diseases, including ARDS, in both the plasma or serum as well as bronchoalveolar lavage fluid and biochemical panel with the hope to better elucidate pathophysiological mechanism of ARDS and to identify the potential markers of severity and outcome (Pediatric Acute Lung Injury Consensus Conference, 2015).

Despite the body of literature connecting C-reactive protein (CRP) with prognosis in other diseases, little is known about the characteristics of CRP levels in patients with ARDS and acute lung injury (ALI). With the advent of C-reactive protein , there is a detectable systemic inflammatory marker available with the ability to detect even lower levels using high sensitivity CRP , which has ability to identify a systemic inflammatory marker if present in very low birth weight premature infants with respiratory distress. So using serum hs-CRP as a biomarker looking for systemic inflammatory response if present (Tsimikas *et al*., 2006).High sensitivity testing has been used to predict cardiovascular outcomes, endocrine disorders, cancer mortality, and inflammatory asthma phenotypes, the role of hs-CRP in premature infants is less well established. In newborns, IL-6 and CRP are known to rise within hours after birth even in term infants, and then quickly return to normal levels (Ko *et al*., 2012). It appears to play an important role in neutrophil chemotaxis, asneutrophils are known to accumulate in the lungs of patients with ARDS and are thought to play a pivotal role in lung injury. Studies showed that it can stimulated chemotaxis at lower concentrations but inhibits it, along with other characteristic neutrophil functions, at higher concentrations (Sabatine *et al*., 2007).

Among various categories of predictive and influential factors reported for assessment of pediatric acute respiratory distress syndrome is Uric acid estimation, Uric acid is the final end product of metabolic degradation of purine nucleotides. Hypoxia, as occurs in the ARDS and heart failure, results in depletion of adenosine triphosphate (ATP) and purine nucleotide metabolism activation, which leads into uric acid accumulation and hyperuricemia (Shimizu *et al*., 2002). Uric acid has antioxidant property and is responsible for 60% of the plasma antioxidant capacity. In addition, it has proinflammatory role in high levels (Maiuolo *et al*., 2016). The infants with ARDS 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 in the normal infants. In both groups of neonates, the correlation of maximal serum urate values with the urinary excretion was positive, which indicates that neonatal hyperuricemia is not due to renal retention but to increased production of uric acid. It is postulated that this overproduction results from increased nucleotide breakdown associated with perinatal hypoxia (Raivi, 1976).

1.2 Aims of the study

The present study was designed to achieve the following goals:

1.Exploring of importance of serum hs-CRPand the concentration of serum uric acid as a prognostic markers in the diagnosis of newborn RDS.

2.Invistigating the association of certain sociodemografic,maternal,and patients factors on the prognostic values of these markers.