The Relation Between Ischemia Modified Albumin and Prognosis of Respiratory Distress Syndrome in Preterm Patients

By

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ABSTRACT

Background: Respiratory distress syndrome is a critical respiratory illness that affects premature newborns and can lead to very severe, unfavorable consequences as a result of hypoxia, **Aim:** To assess the relationship between Ischemia Modified Albumin (IMA) and the prognosis of RDS in preterm patients, **Patients and methods:** This was prospective case control study performed on 90 newborn infants in the NICU of Al-Zahra University Hospital, Faculty of Medicine for Girls, and Tala General Hospital in Menoufia governorate from November 2020 to November 2021. Patients were divided into two groups: Preterm group (n=45, GA=36 weeks) and full term group (n=45, GA>36 weeks). They followed up by clinical examination and laboratory investigational study until their outcome either discharge either death. **Results:** IMA was significantly higher among patients who needed mechanical ventilation. Duration of mechanical ventilation correlated positively with IMA levels, with statistical significance difference. Increased IMA levels were associated with an increased total hospital stay duration. Regarding outcome, IMA levels were significantly higher among patients who died, with a statistically significant difference. At a cut-off value equal to 222.8, IMA had 100% sensitivity and 98.3% specificity to predict a poor outcome for pre-term infants with respiratory distress, **Conclusion:** Ischemia-modified albumin could be used as a diagnostic modality for respiratory distress syndrome among premature neonates with high reliability and reproducibility. It could also be utilized as a predictor of disease outcome.

Key words: Ischemia Modified Albumin; Respiratory Distress Syndrome; Preterm Patients

INTRODUCTION

Respiratory distress syndrome is a critical respiratory disorder that can lead to a variety of severe adverse outcomes in premature neonates as a result of hypoxia. (varder et al;2021) Neonatal respiratory distress syndrome (NRDS) arises from physiological and structural pulmonary immaturity. The impairment of alveolar integrity induced by inadequate pulmonary surfactant levels disrupts normal gas exchange by causing acinar surface tension to be deregulated. Atelectasis induces a reduction in lung compliance due to a rise in the number of collapsed alveoli within the terminal airways. (Zhang et al;2021)

RDS leads to reduced pulmonary ventilation and perfusion, resulting in hypoxia, hypercapnia, and acidosis. Hence, early after birth, appropriate and systematic intervention should be implemented to manage infants diagnosed with RDS. Newborns with respiratory distress syndrome (RDS) can suffer from hypoxia, asphyxia, and hypoxia-ischemia, which can result in damage to many organs. These complications are major factors contributing to the higher rates of illness and death among newborns with RDS. (sweet et al;2013)

The objective of this research was to evaluate the association among Ischemia Modified Albumin and prognosis of RDS, in preterm individuals.

Ischemia-modified albumin is a novel biochemical marker utilized to promptly detect myocardial ischemia events and cerebrovascular accidents in humans. Elevated levels of IMA following seizures indicate that doing an IMA test during a seizure might potentially be valuable in predicting the diagnosis and severity of convulsions. (RUS MAGAN et al;2022)

Albumin contains 585 amino acids, and, under normal conditions, the N-terminal region of this protein forms the N-Asp-Ala-His-Lys sequence. The first three amino acids show greater metal-binding capacity and specificity. Although this region contains an inherent affinity site for cobalt (Co), it also binds tightly to copper (Cu) and nickel (Ni). (bonurono et al;2015)

IMA rapidly increases within 5–10 min after the ischemic event and remains high for 30 min. It returns to baseline 12 h after the ischemia event, but if the ischemic event persists, it continues to rise. In recent clinical studies, it has been found that IMA is a new biochemical marker for the early diagnosis of myocardial ischemic events and cerebrovascular accidents in adults.

(Ihupakula et al;2018)

PATIENTS AND METHODS

This was prospective case control study carried out on 90 newborn infants in the NICU of Al-Zahra University Hospital, Faculty of Medicine for Girls and Tala General Hospital in Menoufia governorate from November 2020 to November 2021. Cases were divided into two groups:

1st group (patients) were: 45 preterm neonates, aged less than 34 weeks and

2nd group (controls) were: 45 late preterm neonates aged 34 up to 36weeks.

Inclusion criteria: Preterm birth below 34 weeks was caused by singleton pregnancies and was diagnosed as RDS, clinically and radiologically.

Exclusion criteria: All preterm who had maternal chorioamnionitis, severe congenital cardiac disease or major congenital somatic anomalies, perinatal asphyxia, premature onset of neonatal sepsis, neonatal hypoalbuminemia (serum albumin\2.5 g/dL), maternal smoking, and placental abruption were excluded from the study.

Ethical consideration

Approval by the ethical committee of the Pediatrics department at the Faculty of Medicine at Al-Azhar University under the registration number was obtained before the study. Patients were enrolled in the study after getting informed oral and written consent from their parents. Patient data confidentiality was preserved during all study procedures. The patient and parents have the right to withdraw any time. There was no conflict of interest regarding the study or publication. There is no financial support or sponsorship

Sample size

This is a prospective cohort study. A sample size of 90 achieves 90% power to reject the null hypothesis of zero effect size when the population effect size is 0.5 and the significance level (alpha) is 0.05 using a two-sided sample z test for categorical outcomes and two-sided sample t-test for quantitative outcomes

Study Procedure

All cases were subjected to:

Full history was taken, including:-

prenatal history such as HTN&DM and Maternal fever.

Natal data as mode of delivery and risk factors such as PROM and meconium.

postnatal was obtained including gestational age, birth weight, and temperature.

Clinical examination including: -

General examination including

general examination, vital signs, Anthropometric measurements & skin, upper & lower limps.

Local – examination: inspection, palpation, & auscultation finding of air entry.

Laboratory investigations including: -

CBC (using the cell dyne ruby cell $)

RFT (serum creatine and urea) were measured using (Cobas c311 kits of Roche).

LFT(ALT&AST), Total and direct bilirubin &serum albumin were measured using (Cobas c311 kits of Roche).

CRP level was measured using turbidimetric method (biosystems; let 1920).

ABG and serum electrolytes was measured using (GEM Premier 3000).

Ischemia Modified Albumin assay by ELIZA,

Samples Collection: Blood samples were collected under complete aseptic conditions for CRP, CBC, total and direct bilirubin, serum albumin, ABG, and serum electrolytes. About 8–10 ml of blood was taken. 2 ml for CBC, 3 ml for CRP, total and direct bilirubin, serum albumin, and serum electrolytes, 2 ml for ABG, and 2–3 ml for IMA by ELISA, the Iscemic Modified Albumen (IMA) ELISA Kit (Human), and IMA by ELISA test. **(Apple et al;2005)** Serum: Utilize a serum separator tube and let samples coagulate for a duration of two hours at room temperature or overnight at a temperature of 4 degrees Celsius prior to subjecting them to centrifugation for a period of 15 minutes at a force of 1,000 x g. Dispose of the serum and perform the assay promptly, or divide the samples into smaller portions and keep them at temperatures of -20 degrees Celsius or -80 degrees Celsius. Minimize the occurrence of repetitive freeze-thaw cycles. To get optimal results, it is necessary to estimate the concentration of the target protein and choose a suitable sample dilution. This will ensure that the final concentration of the target protein is positioned in the center of the linear dynamic range of the assay. It is necessary to dilute samples that show saturation to a greater extent. Prepare diluted samples by utilizing the sample diluent. Thoroughly and carefully combine the diluted samples.

It is not advisable to pipette volumes smaller than 2 µL in order to get the highest level of accuracy in the test. Specificity: The test's ability to accurately identify individuals who do not have the condition is known as "true negatives." Increasing the level of specificity resulted in a decrease in the number of "false positives" that were included. PPV stands for positive predictive value. The prevalence of the disease among individuals with a positive diagnostic result.

I. . Radiological Evaluation:-

A chest X-ray was performed for all patients. The radiogram was assessed for radiolucency, and the

score was determined. The degree of radiolucency in both lungs was scored as follows: 0, normal

1. Cardiac and diaphragmatic margins that are still distinct despite a modest reduction in radiolucency.
2. characterized by retained cardiac and diaphragmatic margins and significantly diminished radiolucency.
3. An air bronchogram reveals significantly diminished radiolucency.
4. White Lungs. **(Perri et al;2018)**

II. ECHO Study:

ECHO study performed for all patients as Hermansen proposed that every RDS neonate should be screened for congenital heart disease especially PDA (HERMENSEN AND MAHRAJAN;2015) .

III. Follow up:

Regular monitoring of clinical parameters and IMA levels during the acute phase of RDS, at intervals determined by the severity of illness. Longitudinal follow-up visits to assess respiratory function and overall health outcomes in preterm patients, including pulmonary function tests and developmental assessments. Evaluation of the association between initial IMA levels and long-term respiratory outcomes, potentially over several years post-discharge. Comparative analysis with a control group to assess the predictive value of IMA for RDS prognosis in preterm infants.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package version 29.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results were judged at the 5% level. The used tests were Chi-square test, Fisher's Exact, Student t-test, Mann Whitney test, Receiver operating characteristic curve (ROC), Negative Predictive value (NPV) and ANCOVA test

CASE PRESENTATION

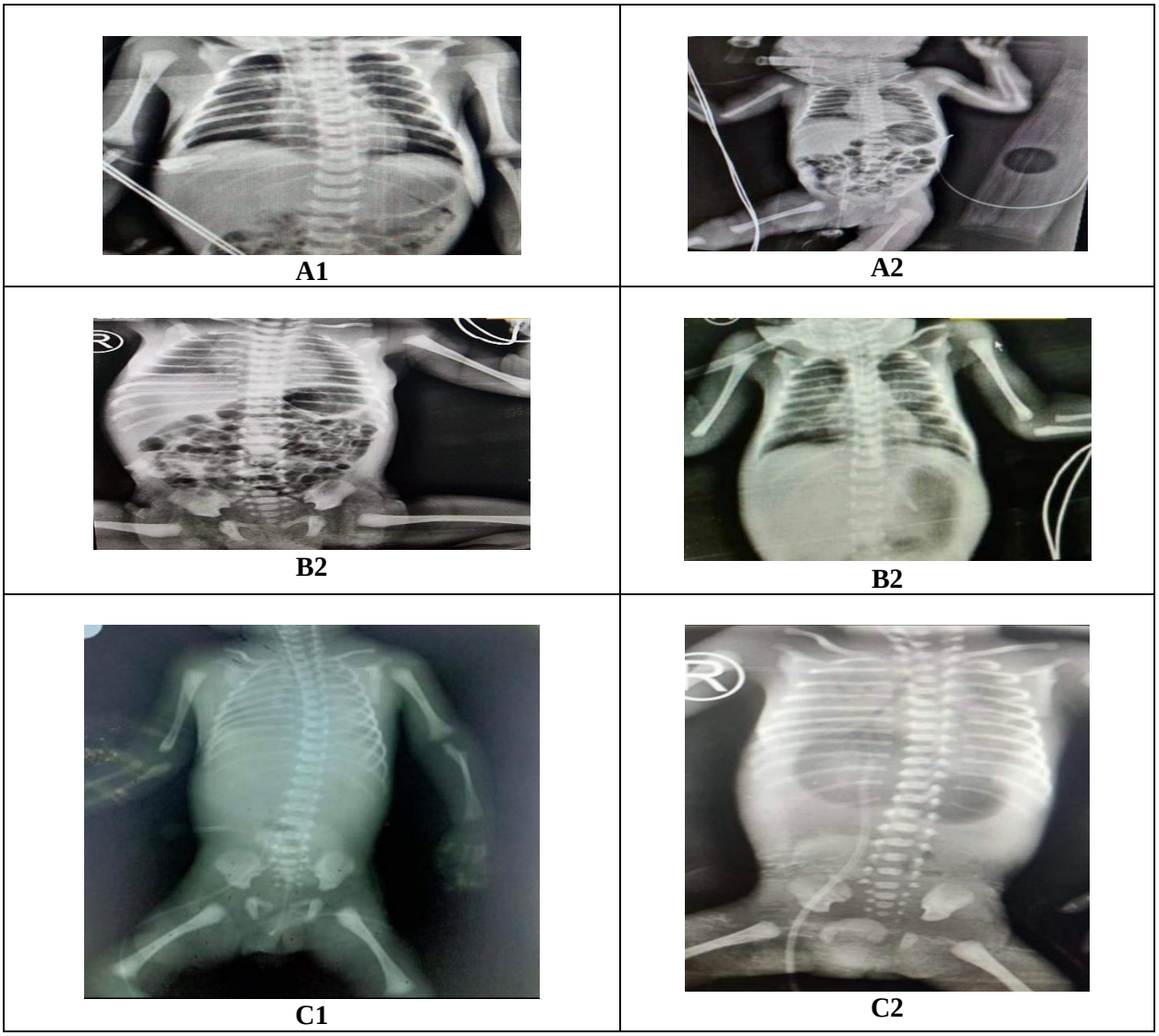

Figure (1): Shows cases of the study (a1, a2): Grade 2 radiolucency by chest x- ray, (b1, b2): Grade 3 radiolucency by chest x- ray, (c1, c2): Grade 4 radiolucency by chest x- ray

RESULTS

Table (1): Baseline and Maternal data:

	Group I (45 babies)	**Group II as a control (45 babies)**	**P value**
Gestational age (weeks) mean±SD	30.97±1.85	34.86±0.75	**0.0001***
Birth weight (K.G) mean±SD	1.4±0.23	2.08±0.46	**0.0001***

Maternal condition No. (%)			
Fever	0	0	
Meconium	4 (8.9%)	8 (17.8%)	0.215**
Hypertension	6 (13.3%)	13 (28.9%)	0.07***
Diabetes	8 (17.8%)	16 (35.6%)	0.06***
Premature rupture of membrane	39 (86.7%)	19 (42.2%)	**0.0001*** **
Mode of Delivery			
Normal	23 (51.1%)	17 (37.8%)	0.203***
Caesarean section	22 (48.9%)	28 (62.2%)	

*Student t-test**Fisher-exact test***Chi square test

This table Shows that: Gestational age in study group was lower than control group with statistically significant difference (p value: 0.0001). Study group patients had lower birth weight than control group with statistically significant difference (p value: 0.0001). There was no statistically significant difference between both groups regarding maternal conditions except PROM which had more frequency among the study group (p value: 0.0001).

Table (2): Clinical data of studied cases.

	Study group (45 babies)	Control group (45 babies)	P value*
Chest examination			
Respiratory rate (breath/min) mean±SD	66.66±3.2	46.22±4.8	**<0.001**
Tachypnea	45 (100%)	0	**<0.001**
Grunting	34 (75.6%)	0	**<0.001**
Chest retraction	45 (100%)	0	**<0.001**
Cyanosis	9 (20%)	0	**0.002**
Cardiac examination			
Heart rate (beat/min) mean±SD	140.2±7.1	133.73±8.04	**<0.001**
Murmur	2 (4.4%)	1 (2.2%)	0.557
CNS examination			
Lethargy	9 (20%)	0	**<0.001**
Suckling reflex			
Good	16 (35.6%)	16 (35.6%)	1
Weak	29 (64.4%)	29 (64.4%)	
Motor reflex			
Good	36 (80%)	45 (100%)	**0.002**
Weak	9 (20%)	0	

Muscle tone			
Good	32 (71.1%)	45 (100%)	**<0.001**
Weak	13 (28.9%)	0	

*Student t-test; Level of significance<0.05

This table Shows that: There was significant variation amongst both groups concerning respiratory symptoms, which was worse among the study group. Both groups were comparable regarding the strength of the suckling reflex; however, there was a significant distinction among both groups regarding the incidence of lethargy (p<0.001), motor reflex (p = 0.002), and muscle tone (p<0.001).

Table (3): Laboratory finding.

	Study group (45 babies)	Control group (45 babies)	P value*
White blood cells (/10^3/mm^3) mean±SD	14.07±0.7	15.17±0.7	0.45
Hemoglobin (g/dL) mean±SD	17.2±1.5	17.07±1.2	0.65
Platelets (/10^3/mm^3) mean±SD	206.032±49.9	215.8±50.5	0.358
CRP mean±SD	8.1±3.36	7.8±4.056	0.268
Total bilirubin mean±SD	5.09±0.8	5.09±0.079	0.899
Direct bilirubin mean±SD	0.2±0.08	0.25±0.42	0.431
Albumin mean±SD	3.07±0.35	3.44±0.4	**<0.001**
pCO2 (mmHg) mean±SD	34.28±11.5	37.05±3.3	0.124
pO2 (mmHg) mean±SD	80.9±24.7	90.8±7.1	0.011
HCO3 (mEq/L) mean±SD	18.3±5.7	17.4±2.5	0.3
Sodium (mEq/L) mean±SD	138.9±5.7	139.3±3.9	0.672
Potassium (mEq/L) mean±SD	4.9±0.9	4.4±0.68	0.16
Total calcium (mg/dL) mean±SD	8.4±0.46	8.5±0.4	0.09
Ionized calcium (mg/dL) mean±SD	4.8±0.3	4.8±0.2	0.663
Ischemia modified albumin () mean±SD	155.08±54.37	36.4±11.09	**<0.001**

*Student t-test; Level of significance<0.05

This table Shows that: Both groups were comparable regarding CBC criteria and CRP levels. Serum albumin was lower significantly among the study group (p<0.001). PO2 was higher significantly among control group (p= 0.002).Ischemia modified albumin levels were higher significantly among the study group (p<0.001).

Table (4): Correlation between IMA and radiologic findings

	IMA mean±SD	Test of significance	P value*
Respiratory distress degree			
II	30.68±6.04	34.6	**<0.001**
III	40.23±14.22		
IV	139.58±37.5		
Chest x- ray grades of radiolucency			
II	140 ± 10.3	34.7	**<0.001**
III	133 ± 6.7		
IV	246 ± 12.08		
ECHO finding			
PDA	130.16±35.4	7.52	**<0.001**
PFO	138.98±29.4		
ASD	132.4±41		
TR	128.47±13		
Combined	233.8±66.27		

*Analysis of variance (ANOVA) test; Level of significance<0.05

This table Shows that: IMA levels were correlated with the degree of respiratory distress, and patients with grade IV respiratory distress had higher levels of IMA with a statistically significant difference ($p<0.001$). There were statistically significant distinctions among different chest x-ray radiolucency grades and IMA levels, with much higher levels among grade IV cases ($p< 0.001$). (Table 4)

Table (5): Correlation between IMA and management, hospital stay and outcome

	IMA mean±SD	Correlation co-efficient (r)	P value
Mechanical ventilation			
Yes	212.95±61.9	0.532*	**<0.001**
No	134.04±32.17		
Mechanical ventilation duration		0.766#	**<0.001**
Hospital stay		0.519#	**<0.001**
Outcome			
Improved	138.63±34.66	0.3*	**<0.001**
Died	262.005±32.5		

*Point- biserial correlation; #Spearman correlation; Level of significance<0.05

This table Shows that: IMA was significantly higher among patients who needed mechanical ventilation (r = 0.532). Duration of mechanical ventilation correlated positively with IMA levels, with statistical significance (r = 0.766). Increased IMA levels were related to increased total hospital stay duration (r = 0.519). Regarding outcome, IMA levels were significantly higher among cases who died with significant variance (r = 0.3).

Table (6): Multiple regression analysis for significant factors correlated with IMA levels

	B coefficient	95% CI Lower	95% CI Upper	P value
Gestational age	-3.6	-0.7113	0.2775	**<0.001**
Birth weight	-1.3	-0.6309	-0.1371	0.09
Serum albumin	-2.9	-0.57	-0.043	**0.005**
Respiratory distress grades	2.2	0.0364	1.1369	**<0.001**
ECHO findings	-0.003	0.6975	0.8961	0.56
Mechanical ventilation	1.97	0.28	0.71	0.056
Mechanical ventilation duration	0.98	0.6095	0.8650	0.6
Hospital stay duration	0.32	0.2660	0.7051	0.38
Outcome (death)	2.36	0.0007	0.5455	**<0.001**

Multiple regression analysis; Level of significance <0.05

This table Shows that: Nine factors that correlated significantly with IMA were entered into the multiple regression analysis. Out of them, four factors maintained their statistical significance when adjusted to all significant factors. These factors included gestational age, serum albumin, respiratory distress grade, and death as an outcome.

Table (7): Accuracy of IMA in predicting outcome.

	AUC	Cut-off value	Sensitivity	Specificity	95% CI (lower)	95% CI (upper)	P value
IMA	0.989	222.8	100%	98%	0.61	1	**<0.001***

*Receiver operator analysis

This table Shows that: At a cut-off value equal to 222.8, IMA had 100% sensitivity and 98.3% specificity to predict a poor outcome for pre-term infants with respiratory distress.

Table (8): Accuracy of IMA in diagnosis of respiratory distress

	AUC	Cut-off value	Sensitivity	Specificity	95% CI (lower)	95% CI (upper)	P value*
IMA	0.986	72.37	97.8%	100%	0.98	1.036	**<0.001**

*Receiver operator analysis; Level of significance<0.05

This table Shows that At a cut-off value equal to 72.37, IMA has a sensitivity of 97.8% and a specificity of 100% in the diagnosis of respiratory distress in pre-term babies.

DISCUSSION

In our study, the main presentation of neonates with RDS was tachycardia, tachypnea, grunting (75%), chest retraction (100%), and cynaosis. CNS manifestations were present in some patients as leathergy (20%), weak motor reflex (20%), and weak muscle tone (28.9%). These findings were reported by **Hermansen and Lorah. (Hermansen and Lorah;2007)**

Luo et al., reported that RDS manifestations are similar to acute respiratory distress syndrome (ARDS), and the difference may be that ARDS occur in the late pre-term with a lower need for surfactant. **(Luo and Chen et al;2019)**

Parkash et al., reported all newborns (100%) had signs and symptoms of a respiratory rate above 60 breaths per minute. Of them, 60.9% (125 neonates) experienced grunting, 100% (205 neonates) showed subcostal retractions, nasal flaring was observed in all 205 neonates (100%), and 39.5% (81 neonates) displayed cyanosis. **(Parkash** et al;2015)

In the current study, there was no statistically significant difference between the patient and control groups regarding sodium, potassium, and calcium (either total or ionized). Contrary to the current study, **Nickavar et al.,** proposed association between RDS and low serum calcium. Also, he considered hypocalcemia a predictor of poor prognosis. **(crickaavan** et al;2018) Also, **Iqbal et al.,** reported that presence of hypocalcemia among RDS patients increases the need for mechanical ventilation. **(Iqbal et al;2015)**

Hypocalcemia among RDS patients was shown by different authors in other studies. **(Yokoyama** et al;2010) &(Mohamed Hegazi et al;2012)

In the current study, non-invasive ventilation was used in 73.3% of the patients, and mechanical ventilation was used in 26.7% of the patients. Similarly, it was reported in the USA that the need

for NIMV increased from 69.9% to 74.3%, and this was related to a decreased need for invasive mechanical ventilation (60.4% to 56.6%) **Donda et al.,** However, the percent of populations on mechanical ventilation was higher than what has been reported in the current study. The difference may be due to the larger sample size. **(Donda et al;2012)**

In the current study, the length of the hospital stay was longer, with a statistically significant difference among the study group and the control group (17.86±6.4: 7.24±2.1; p<0.001). **Kahevic et al.,** reported a similar finding regarding the difference between both groups; however, in his study, RDS patients stayed for a longer duration than RDS patients in our study. **(Kahveci et al;2016)**

In our study, the RDS patients spent a mean duration of 3.5±1.6 days on nasal masks, a mean duration of 9.2±2.3 days on CPAP, and a mean duration of 8.5±4.4 days on mechanical ventilation. This duration was lower than the duration reported in a study by **Kahveci et al. (Kahveci et al;2016)**

In another study by **Dani et al.,** The length of hospital stay was 15.3± 6.5 days, which was similar to our results. However, duration on CPAP (3.5±1.5 days) and duration on mechanical ventilation (2.3±1.2 days) were shorter than what was reported in this study. **(Dani et al;2018)**

Thus, IMA was measured in both groups, and it was significantly higher in RDS patients than in the control group (155.08±54.37: 36.4±11.09; p<0.001). At a cut-off value equal to 72.37, IMA has a sensitivity of 100%and a specificity of 98.3% in the diagnosis of respiratory distress in pre-term babies.

It was reported that a cut-off value for IMA was established at 0.72 ABSU. The sensitivity of IMA was 91.8%, the specificity was 78.6 percent, the positive predictive value was 79.1 percent, and the negative predictive value was 91.7%. The area under the curve (AUC) was 0.93, with a 95% confidence interval of 0.88 to 0.98. **(Kahveci et al;2016)**

In our research, IMA levels correlated inversely with gestational age and birth weight, and this comes in accordance with the inverse correlation between the incidence of RDS and gestational age and birth weight. While there was no significant correlation between IMA levels and maternal conditions, In **Kahveci et al.,** there was no correlation among gestational age, birth weight, maternal conditions, or IMA levels. **Kaheveci et al.,** did not report a significant association among age, birth weight, and incidence of RDS. **(Kahveci et al;2016)** In our study, there was no significant association between IMA and white blood cells, hemoglobin, CRP, or bilirubin. On the other hand, there was a statistically significant negative correlation with serum albumin (r = -0.3; p = 0.026).

In contrary to these results, **Yerlikaya et al.,** reported a statistically significant correlation between IMA and white blood cells, hemoglobin, CRP, or bilirubin; however, he conducted his study on neonatal sepsis patients, not RDS. **(Yerlikaya et al;2014)**

Also, **Erdem et al.,** found a statistically significant correlation between IMA levels and serum bilirubin in neonates, contrary to what was reported in our study. **(Erdem et al;2011)**

Yakut et al., reported statistically significant correlation between CRP and IMA levels among necrotizing enterocolitis neonates**. (Yakut et al;2014)**

IMA also showed a statistically significant positive correlation with the need for mechanical ventilation, MV duration, and hospital stay duration. This goes hand in hand **with Dursun et al.,** who evaluated the effect of mechanical ventilation or CPAP on levels of IMA among 16 neonates who needed assisted ventilation for any reason, and he found a statistically significant positive correlation between IMA and the duration of CPAP or mechanical ventilation. **(Dursun et al;2018)** These findings could reflect that CPAP and MV activated oxidative stress and, hence, increased IMA levels. The same findings were reported in other studies. **(Chiang et al;2012)**

Regarding outcome, IMA was elevated significantly among RDS neonates with poor outcomes (non-survivors), and at a cut-off value equal to 222.8, IMA had 100% sensitivity and 98.3% specificity to predict poor outcomes for preterm infants with respiratory distress. On the other hand, grade of radiotranslucency did not affect the outcome, with no statistically significant differences between improved and deceased patients regarding x-ray radiotranslucency grade. Likely, **King et al.,** reported that chest x-ray translucency had mild to moderate accuracy in predicting the outcome of RDS in neonates, and he suggested searching for more accurate tools. **(King et al;2020)**

In the multiple regression analysis to predict elevated levels of IMA among RDS neonates in our study, gestational age, serum albumin, respiratory distress grade, and death as an outcome were the main significant predictors. This came in hand with **Hekimoglu et al.,** who reported that Albumin is the primary component that significantly impacts the reliability of serum IMA levels observed in sepsis. **(Hekimoglu et al;2017)**

CONCLUSION

Ischemia-modified albumin could be utilized as a diagnostic modality for respiratory distress syndrome among premature neonates with high reliability and reproducibility. It could also be used as a predictor of disease outcome. chest x-ray grades of translucency failed to predict the disease outcome accurately.

RECOMMENDATIONS

We recommend further longitudinal studies to assess the dynamic changes in ischemia modified albumin (IMA) levels over time in preterm infants with respiratory distress syndrome (RDS). We recommend further studies to investigate the role of oxidative stress, inflammation, and ischemia-reperfusion injury in modulating IMA levels and their impact on pulmonary function and lung injury severity. We recommend further studies to assess the sensitivity, specificity, and predictive value of IMA measurements in identifying infants at high risk of adverse outcomes and guiding clinical decision-making.

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