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Hyperglycemia and Red Cell Distribution Width for Prediction of Mortality in Preschool Children with Community Acquired Pneumonia (CAP)

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Abstract

Background

Community acquired pneumonia (CAP) is a major infectious cause of mortality in preschool children especially in developing countries. Red Cell Distribution Width (RDW) has been associated with poor outcomes of CAP. We aimed to determine whether admission stress hyperglycemia and RDW can predict mortality in preschool children with CAP for early identification of patients at risk of mortality.

Materials and Methods

This is a prospective cohort analysis of a single-center study conducted in the pediatric department and Pediatric Intensive Care Unit (PICU) of Minia Children's University hospital, El-Minia, Egypt during the period from September 2016 to February 2017. The patients were 1-59 months old children, with community acquired pneumonia. Measurement of admission serum glucose and RDW in addition to complete blood picture was done to all participating children. Assessment of the severity of CAP was done using Pediatric Respiratory Severity Score.

Results: The male gender consumes a high percentage in the Non survivors group (72.7%). The hyperglycemias patients had a statistically significant risk of developing septic shock and respiratory failure than the other groups (23.8%, p<0.001 for both). The RDW was significantly associated with in hospital mortality (Odds ratio 7.245, 95%CI: 3.078-17.055, p<0.001). Also, Admission serum glucose was significantly associated with in hospital mortality (Odds ratio: 1.033, 95%CI: 1.021-1.047, p <0.001). RDW was the most accurate factor for prediction of mortality at the cutoff point >17.4, sensitivity 90.9% and specificity 92.1%, followed by admission serum glucose at cutoff point >110 mg/dl, sensitivity 90.9%, and specificity 78.95 %.

Conclusion

According to the results**,** elevated RDW and admission hyperglycemia are reliable predictors of mortality in preschool children with community acquired pneumonia.

Key Words: Children, Mortality, Prediction models, Red Cell Distribution Width.

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1- INTRODUCTION

Pneumonia is a killer of 1 million children under the age of 5 every year and is responsible for 15% of preschool deaths (1); the most of this percentage occurring in the developing countries (2). In Egypt, pneumonia and other acute respiratory infections are responsible for 10% of preschool deaths (3). Hyperglycemia may be an adaptive response to stress, providing the glucose dependent organs, such as the brain with energy (4). There is an association between stress hyperglycemia and poor outcome in adults and children who are critically ill (5). The Red cell distribution width (RDW) is an easy and cheap tool as it is a part of the routine blood picture. It reflects the variation in size of red blood cells. Many studies demonstrate a significant association between elevated RDW levels and mortalities of patients caused by different diseases as coronary disease, heart failure (6), pulmonary hypertension, acute pulmonary embolism and cardiac arrest (7). The objective of our study was to investigate the role of admission hyperglycemia and RDW as prognostic markers of preschool deaths caused by community acquired pneumonia (CAP).

2- MATERIALS AND METHODS

2-1. Study design and setting

This prospective study was conducted at Minia University Children's hospital, Al-Minia, Egypt during the period from September 2016 -February 2017. Written informed consents were taken from parents of all enrolled children after clarifying the aim and all steps of the study to them.

2-2. Selection of participating patients

A total of 174 preschool children were enrolled in the study. Children were eligible if fulfilling the following criteria, their age between 1-59 months, admitted to the respiratory in-patient unit or Pediatric intensive care unit (PICU) with CAP which is defined as presence of the clinical picture of an acute infection of the pulmonary parenchyma in a person who take the infection in the community, as differentiated from hospital-acquired (nosocomial) pneumonia (8). Children were excluded if they had nosocomial pneumonia, diabetes mellitus, suspected/confirmed inborn errors of metabolism, and a dextrose infusion 2 hours prior to admission, received steroids within 72 hours of admission, or long-lasting pulmonary disease (cystic fibrosis, bronchiectasis), history of aspiration pneumonia, chronic debilitating neurologic disease, or immune deficiency. Participating children were divided into two groups: Group 1 survivors, their number was 152 children who survive and improved and Group 2 Non survivors; their number was 22 children who died from community acquired pneumonia.

2-3. Data collection

Data were collected from the parents or legal guardians to obtain demographic data as (age, sex), comorbidities (including heart failure, hepatic, renal, and central nervous system diseases), clinical data and examination of the patients with evaluation of the severity of CAP by using The Pediatric Respiratory Severity Score (PRESS). The PRESS assessed tachypnea, wheezing, retraction (accessory muscle use), Partial Oxygen Saturation (SpO2), and feeding difficulties, with each component given a score of 0 or 1, and total scores were classified as mild (0–1), moderate (2–3), or severe (4–5) (9), and assessment of the outcomes, including the main outcome which is the mortality in addition to the length of stay in the hospital, complications which develop either on admission or during stay in the hospital, including, pleural effusion, empyema, lung abscess, pneumothorax, respiratory failure or signs of severe sepsis or septic shock according to international pediatric sepsis consensus conference

criteria, 2005 (10). Chest X-ray was done for every child with CAP. Hyperglycemia and hypoglycemia were defined as blood glucose greater than 8.3mmol/L (150 mg/dL), and less than 2.5mmol/L (45mg/dL), respectively (11, 12).

2-4. Laboratory data

Complete blood count (CBC) including: RDW and serum glucose were done to all participating children in the first 24 hours of admission.

2-5. Blood sampling

Three ml of venous blood was withdrawn by well trained personnel during first 24 hours after admission before starting antibiotic therapy under aseptic condition from all participating patients. Two ml of blood put into an EDTA tube for the determination of CBC ' including RDW". The remaining one ml put into a sodium floured tube for assay of admission blood glucose.

2-6. Methods

Complete blood picture was done using an automated blood counter (Sysmex KX-21N). Admission blood glucose was measured using fully automated clinical chemistry, auto-analyzer system Flexor (Selectra) Junior/E/XL, (ELITech, France).

2-7. Data analysis

All data were coded, tabulated, and statistically analyzed using SPSS software version 25.0 (Statistical Package for Social Sciences). Descriptive statistics were done for non-parametric quantitative data by mean, standard deviation (SD) and minimum and maximum of the range, and median, while they were done for categorical data by number and percentage. Analyses were done for non-parametric quantitative data using Mann Whitney test between the two groups. Analyses were done for qualitative data using the Chi square test (if number per cell > 5), and Fisher exact test (if number per cell < 5). Simple binary logistic regression analysis was done to explore the risk factors and for prediction of mortality. The Receiver Operating Characteristic (ROC) curve analysis of the Pediatric Respiratory Severity Score (PRESS), Red Cell Distribution Width (RDW), and admission blood glucose was done to determine Area under the curve (AUC), optimal cutoff, sensitivity, specificity and accuracy predicting the mortality. Significance was defined as $p<0.05$.

2-8. Ethical approval

The study was designed to respect the expected ethical aspects. It was performed according to the Declaration of Helsinki 1975, as revised in 2008 and approved by the Institutional Review Board and Medical Ethics Committee of Minia University.

3- RESULTS

This prospective cohort study done in Minia University Children Hospital, Al-Minia (Egypt), during the period from September 2016 to February 2017; 174 preschool children with community acquired pneumonia (CAP) who admitted to the respiratory in-patient unit or pediatric intensive care unit (PICU) participating in this study; and 22 children died during the hospital stay (12.6%). As regards baseline and clinical features of both survivors and non- survivors groups in **Table.1** there was no statistically significant difference in the mean age between both groups (**Figure.1**). The majority of deaths were in boys (72.7%, n= 16). There are two main complications in the non- survivors group respiratory failure in 14 cases (63.6%), and septic shock in 8 cases (36.4%). The values of RDW were significantly lower in survivors than the other group (15.5 vs. 18, respectively). Higher concentrations of admission glucose (AdmGlc) were reported in the non- survivors group than survivors group and by stratification of the

patients, according to the values of AdmGlc, we found that in the non-survivors group, 14 cases (72.7%) were hyperglycemic and 6 cases (27.3%) lie in the range between 61 and 150 mg/dl; while in the survivors group a great proportion of patients 78.8% between 61 and 150 mg/dl. The clinical outcomes and severity risk factors were grouped according to AdmGlc levels in **Table.2.**

Length of stay **(**LOS) (complete words) was greatest about 10 days in 42 cases who lie in the hyperglycemic group and less about 6.6 days in 126 cases who lie in the AdmGlc II with a range of 61 to 150 mg/dl and the mean of LOS was 4.3 days in 6 cases who lie in AdmGlc I group with Admission blood glucose <60. The patients who lie in the hyperglycemic AdmGlc III group had a statistically significant risk of developing septic shock and respiratory failure than the other groups (23.8%, p <0.001 for both**)**. Also, 22 of hyperglycemic cases (52.4%) needed to be admitted to PICU; while only12 cases (9.5%) of AdmGlc II needed to be admitted to the PICU. Further analysis of the relations of the studied predictors and mortality using simple logistic regression analysis was done. The RDW is significantly associated with in hospital mortality (odds ratio [OR]: 7.2, 95%CI: 3.1-17.1 and p <0.001) then PRESS the second factor that significantly associated with the in-hospital mortality (OR: 3.5, 95% CI: 3.5 and p <0.001). Also, AdmGlc was significantly associated with in hospital mortality (OR: 1.033, 95%CI: 1.0-1.0 and p <0.001) **(Table.3)**.

The ROC analysis was done to determine the prognostic accuracy of RDW, AdmGlc and PRESS for prediction of mortality in preschool children with CAP (**Figure.2**). RDW was the most accurate factor for prediction of mortality at the cutoff point >17.4, sensitivity 90.9% and specificity 92.1%, followed by AdmGlc at cutoff point >110 mg/dl, sensitivity 90.9% and specificity78.95 % and lastly PRESS at the cutoff point > 3, sensitivity 81.8% and specificity 64.5% (**Table.4).**

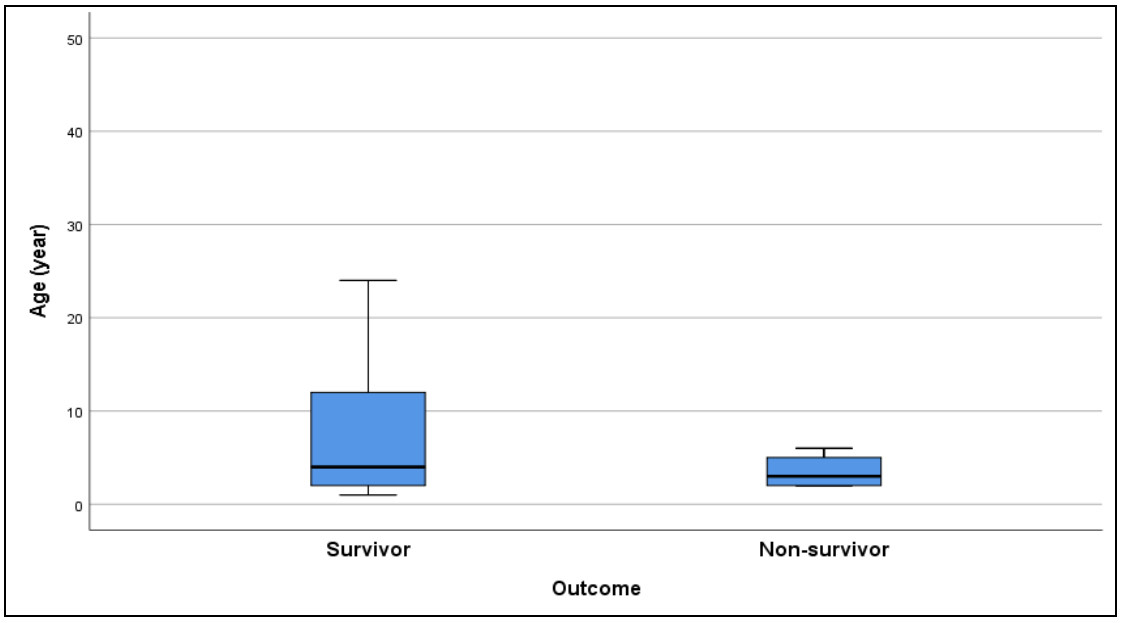

Fig.1: Outcome and age distribution in survivors and Non-survivors groups.

Table-1: The comparison between survivors and non survivors groups as regard demographic and baseline data.

Demographic and baseline data		Survivors (n=152)	Non-survivors (n=22)	P- value
Age ¶	Range	(1-48)	(2-6)	
In months	Mean ± SD	10.3±12.5	3.5±1.5	0.104
	Median	4	3	
Sex β	Male	84(55.3%)	16(72.7%)	0.121
	Female	68(44.7%)	6(27.3%)	
Weight ¶	Range	(3-22)	(2-5)	
In Kg.	Mean ± SD	7.2±3.9	4.3±1	<0.001
	Median	6	5	
PRESS ¶	Range	(2-5)	(3-5)	
	Mean ± SD	3.1±0.9	4.1±0.7	<0.001
	Median	3	4	
Complications $	No	140(92.1%)	0(0%)	
	Septic shock	4(2.6%)	8(36.4%)	
	Pneumothorax	2(1.3%)	0(0%)	<0.001
	Respiratory failure	4(2.6%)	14(63.6%)	
	Effusion	2(1.3%)	0(0%)	
PICU admission ¶	No	140(92.1%)	0(0%)	<0.001
	Yes	12(7.9%)	22(100%)	
RDW ¶	Range	(14.2-18.3)	(16.2-18.7)	
	Mean ± SD	15.5±1.2	18±0.7	<0.001
	Median	15	18.2	
AdmGlc ¶	Range	(54-210)	(105-291)	
mg/dl	Mean ± SD	101±34.2	171.4±54.5	<0.001
	Median	90	160	
AdmGlc $	<60	6(3.9%)	0(0%)	
mg/dl	61-149	120(78.9%)	6(27.3%)	<0.001
	>150	26(17.1%)	14(72.7%)	
LOS ¶	Range	(3-18)	(2-18)	
In days	Mean ± SD	6.9±3.3	10.1±4.6	0.001
	Median	6	9	

¶: Mann Whitney test for non-parametric quantitative data; B: Fisher exact test for qualitative data; $: Chi square test for qualitative data; PRESS: Pediatric Respiratory Severity Score; PICU: Pediatric Intensive Care Admission; RDW: Red Cell Distribution Width; AdmGlc: Admission glucose; LOS: Length of Stay; SD: Standard deviation.

Table-2: The clinical outcomes and severity grouped by admission glucose level.

Clinical Outcomes	AdmGlc			P- value		
	AdmGlc I < 60	AdmGlc II 61-150	AdmGlc III >150	I vs II	I vs III	II vs III
	n=6	n=126	n=42			
LOS ¶						
Range	(4-5)	(2-18)	(4-18)	0.030	0.001	<0.001
Mean ± SD	4.3±0.5	6.6±3.1	10±4			
Median	4	6	10			
Complications $						
No	6(100%)	112(88.9%)	22(52.4%)			
Septic shock	0(0%)	2(1.6%)	10(23.8%)	1	0.082	<0.001
Pneumothorax	0(0%)	2(1.6%)	0(0%)			
Resp. failure	0(0%)	8(6.3%)	10(23.8%)			
Effusion	0(0%)	2(1.6%)	0(0%)			

PICU $						
No	6(100%)	114(90.5%)	20(47.6%)	1	0.025	<0.001
Yes	0(0%)	12(9.5%)	22(52.4%)			
PRESS ¶						
Range	(2-2)	(2-5)	(2-5)	0.001	0.001	<0.001
Mean ± SD	2±0	3.1±0.9	3.7±1			
Median	2	3	4			

¶: Mann Whitney test for non-parametric quantitative data; $: Chi- square test for qualitative data; B: Fisher exact test for qualitative data; LOS: Length of Stay; PICU: Pediatric Intensive Care; PRESS: Pediatric Respiratory Severity Score; SD: Standard deviation.

Table-3: Association between prognostic factors and mortality by Simple logistic regression analysis.

Prognostic factors	Odds ratio	95% CI	P- value
Weight	0.449	0.292-0.691	<0.001
LOS	1.224	1.095-1.368	<0.001
PRESS	3.491	1.911-6.376	<0.001
RDW	7.245	3.078-17.055	<0.001
AdmGlc	1.033	1.021-1.047	<0.001

PRESS: Pediatric Respiratory Severity Score; LOS: Length of Stay; RDW: Red Cell Distribution Width; AdmGlc: Admission glucose; CI: confidence interval.

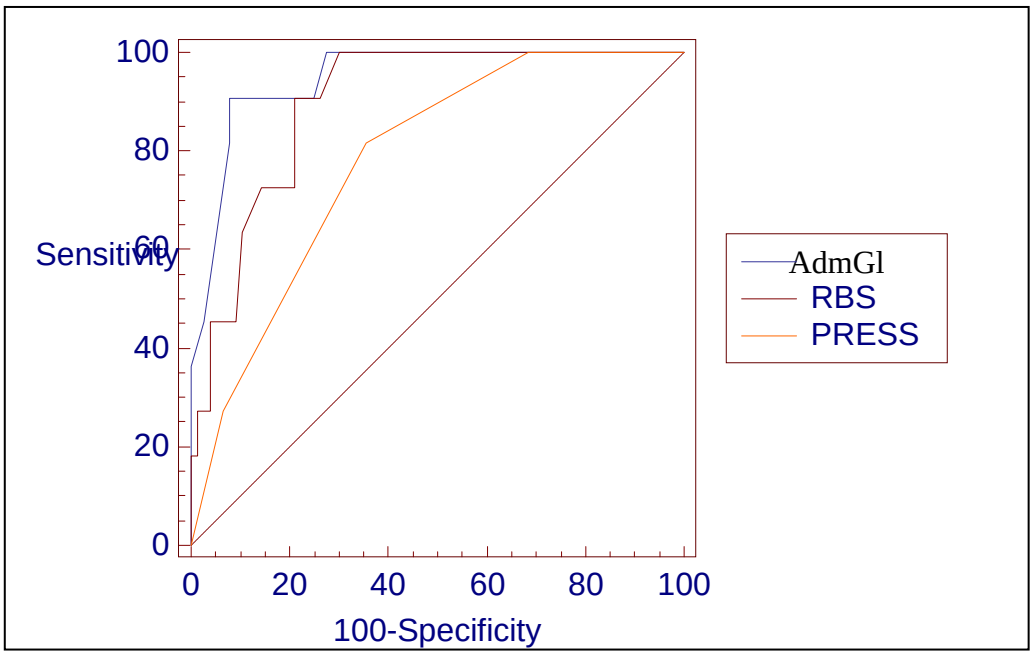

Fig.2: ROC curve analysis for prediction of mortality between the studied groups.

Table-4: ROC curve analysis for prediction of mortality between the studied groups.

ROC analysis	PRESS	RDW	AdmGlc
cutoff point	>3	>17.4	>110
AUC	0.782	0.949	0.898
AUC 95% CI	0.713-0.841	0.904-0.976	0.844-0.939
P- value	<0.001	<0.001	<0.001
Sensitivity	81.8	90.9	90.9
Specificity	64.5	92.1	78.95
PPV	25	62.5	38.5
NPV	96.1	98.6	98.4
Accuracy	67.7	92	79.5

ROC area: Receiver-Operator Characteristic area under the curve; PPV: Positive Predictive Values; NPV: Negative Predictive Values; PRESS: Pediatric Respiratory Severity Score; RDW: Red Cell Distribution Width; AdmGlc: Admision glucose.

4- DISCUSSION

Community acquired pneumonia (CAP) in preschool children exert a great burden in developing countries and still associated with a higher incidence and mortality rates (13). We hypothesized that readily available clinical parameters can be used to assess the risk of morbidity and mortality in preschool children with community acquired pneumonia. Our results support this hypothesis in as much as the RDW, AdmGlc, and the PRESS had significant predictive characteristics and warrants further investigation. Comparison between non- survivors and survivors groups as regard baseline and clinical data showing that the mean age in both groups is young (3.5 months and 10.3 months, respectively) signifying that poor outcome of CAP increase in this younger age group which is considered as a risk factor for mortality from CAP. Many studies found a strong association between young age and poor outcome which can be explained by that in this young age group, these children have narrower airways and immature defense mechanisms of the airways (14). In our study, we found the in-hospital mortality rate 12.6%; this percentage similar to many studies done in Africa and found that the overall mortality rates in preschool children from CAP ranged from 8% to 15.3%, respectively (15). Prominence of the male gender in the non-surviving group (72.2%) indicating that the male gender has a more severe course and poor outcome of the CAP than females in the preschool age group so we consider male gender as a predictive risk factor for mortality in children with CAP. In accordance with our results, Muenchhoff and Goulder, who found the similar results (16). This sex difference could be explained by multifactorial mechanisms firstly Steroid sex hormones exert several functions during the enhancement of the immune system. Estrogens at normal levels, enhancing both cellular and humoral immunity, whereas androgens have an anti-inflammatory effect (17). Second, the peripheral airways are disproportionately narrower in early life in males. These narrowing precipitate respiratory tract infections (RTIs) (18). In our study we found a significant association between elevated RDW and mortality in preschool children with CAP evidenced by significant higher levels of RDW in Non survivors group than in survivors group ($p < 0.001$). In addition elevated RDW was found to be significantly associated with in-hospital mortality (OR: 7.2, 95%CI: 3.1-17.1 and $p < 0.001$), and by ROC analysis for prediction of mortality it was found that elevated RDW is the most accurate predictor biomarker for mortality

at cutoff point >17.4, sensitivity 90.9% and specificity 92.1%. Similarly to our finding Miranda 2017 (19) who found a significant correlation between elevated RDW and mortality in children with CAP. The elevated levels of RDW in pneumonic children is caused by hypoxia leading to pulsatile secretion of erythropoietin (EPO) which enhance the secretion of immature reticulocytes leading to variations in the size of red blood cells and an elevated RDW (20). The elevated RDW may be a sign of cytomembrane instablity which may lead to multiple organ dysfunctions contributing to the poor outcome and the increase in the mortality (21).

3-1. The relationship between high blood sugar and mortality

In our study, we found that 72.7% of patients in the non- survivors group were hyperglycemic which means that hyperglycemic patients associated with increasing risk of mortality. Also, 27.3% of the Non survivors group have admission blood glucose (AdmGlc) lying between 61and 150mg/dl. By logistic regression analysis, AdmGlc is significantly associated with in-hospital mortality (OR: 1.0, 95%CI: 1.0-1.1 and p <0.001), and by ROC analysis for prediction of mortality, we found that the admission AdmGlc is a useful marker for mortality at the cutoff point >110 mg/dl, sensitivity 90.9% and specificity78. 95 %. Similar results by Banna Zadeh et al. (22) who studies the impact of hyperglycemia in NICU and found that the deaths were higher in patients with hyperglycemia; also, Patki and Chougule (23) found similar results. The relation between hyperglycemia and disease severity or mortality can be explained by that the stress hyperglycemia is a commonly encountered problem in many critical diseases as pneumonia. It appears to be a normal body response to face a stressful condition which helps the body to survive. Hyperglycemia itself isn't a direct cause of death, but reflects the critical illness (24). Endogenous and exogenous factors are responsible for Stress-hyperglycemia. Critical illness increases the release of cortisol which enhance the generation of glucose. In addition other hormones like glucagon and growth hormones suppress glucose utilization and enhance insulin resistance thus aggravate hyperglycemia (25). Stress hyperglycemia increase the oxidative stress damage, mitochondrial dysfunction, cell death leading to organ failure (26). By grouping the participating patients according to their admission AdmGlc levels we find that LOS increase by increasing the levels of AdmGlc being the highest in the hyperglycemic group. In concordance to us Hirshberg et al. (27) who found a significant correlation between hyperglycemia and mortality, length of hospital stay and risk of nosocomial infections.

As every day increase in the length of stay increase the risk of mortality the relation between the LOS and hyperglycemia indirectly affirm the association between hyperglycemia and mortality. We find that hyperglycemic patients have a significant risk for developing respiratory failure and septic shock. Also, many studies reported an association between high glucose levels during hospital or ICU stay and sepsis (28, 29). Several mechanisms could explain the relation between hyperglycemia and sepsis, including the direct effect of hyperglycemia on innate immunity, particularly on neutrophils (30). Hyperglycemia inhibits all protective functions of neutrophils. Hyperglycemia also has important effects on microvasculature which could result disturbances between inflammatory and anti-inflammatory cytokines (30). In the present study, 52.4% of hyperglycemic patients admitted to PICU indicating that hyperglycemic patients have a more severe course than others so hyperglycemia is a

good indicator of disease severity. The Pediatric Respiratory Severity Score (PRESS) was found to be significantly associated with the in-hospital mortality (OR: 3.5, 95% CI: 3.5 and p <0.001), and by ROC analysis for prediction of mortality in preschool children with community acquired pneumonia (CAP) PRESS is a good predictor for mortality at the cutoff point >3, sensitivity 81.8%, and specificity 64.5% so PRESS is an easily applicable reliable score for initial assessment of the disease severity.

4-1. Limitations of the study

Limitation of the study measurement of blood sugar on admission only may obscure the true incidence of hyperglycemia with CAP as values of blood sugar in the 1st 24 hours may exceed the admission value. This study was done in a single hospital. Iron, folate and vitamin B12 were not included in our study and they affect RDW.

5- CONCLUSION

Elevated RDW values on admission can be used to predict cases at high risk of mortality for early management and to decrease preschool deaths from community acquired pneumonia. Admission hyperglycemia is significantly associated with mortality, complications and disease severity so this hyperglycemia should not be ignored and doesn't neglect glycemic control even in patients who not admitted to the PICU as such control may decrease complications, severity and risk of mortality. PRESS is a simple and trustable score for initial evaluation of children in the emergency department.

6- ABBREVIATIONS

RDW: Red Cell Distribution Width; RBS: random blood sugar; CAP: Community Acquired Pneumonia; PRESS: Pediatric Respiratory; Severity Score; PICU: Pediatric Intensive Care Unit; RTIs: Respiratory Tract Infections; AdmGlc: Admissiom glucose.

7- AUTHORS' CONTRIBUTIONS

ANM participated in the study design, data collection, analysis and manuscript writing. HMM did the lab work and participated in manuscript writing. All authors read and approved the final manuscript.

8- CONFLICT OF INTEREST: None.

9- ACKNOWLEDGMENTS

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