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THE VALUE OF MEAN PLATELET VOLUME AND RED CELL DISTRIBUTION WIDTH AS PROGNOSTIC MARKERS OF COMMUNITY ACQUIRED PNEUMONIA IN CHILDREN

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ABSTRACT

Background: Community acquired pneumonia(CAP) is one of the significant causes of morbidity and mortality in children, and the value of measuring red cell distribution width(RDW)and mean platelet volume(MPV) inpredicting progression of disease in patients with CAP is unclear. **Objective:** The aim of this study was to examine the prognostic value of certain complete blood count parameters including RDW and MPV in children with definitive diagnosis of CAP. **Materials and Methods:** An Analytical Prospective Prognostic Study was conducted in children with a proven diagnosis of CAP aged 2 months up to 13years, who were admitted to department of pediatric, Tishreen University Hospital in Lattakia-Syria between April 2021 and April 2022. On admission serum RDW and MPV levels were determined. **Results:** A total of 122 children, 71 males (58.2%) and 51 females (41.8%) with median age 3 years were included in the study. A statistically significant increase in RDW, MPV, and CRP were seen in children with duration of hospitalization longer than 7 days and in presence of complications compared to other children($p<0.05$). Frequency of lobar pneumonia was higher in complicated patients and with longer duration of hospitalization compared to other children; (86.4% versus 47%) and (85% versus 39%) respectively, p:0.0001. In patients with longer duration of hospitalization compared to other children, there was an increasing in duration of fever (5.22±4.2 versus 2.08±0.8, p:0.0001), need for oxygen therapy (37.5% versus 28%, p:0.2), admission to ICU (10% versus 1.2%, p:0.02), and rate of complications (47.5%versus 4.8%, p:0.001). In complicated patients compared to other children, there were an increasing in duration of fever (5.54±3.2 versus 2.58±2.5, p:0.0001), hospitalization (11.5±4.6 versus 5.91±2.9, p:0.0001), need for oxygen therapy (40.9% versus 29%, p:0.2), admission to ICU (18.2% versus 1%, p:0.0001). Using Pearson's correlation coefficient, duration of fever and hospitalization were found to increase significantly with increase in RDW;(r:0.2, p:0.02) and (r:0.31, p:0.001) respectively. In addition to, positive correlation was found between MPV and levels of WBC (r:0.31, p:0.002), duration of fever (r:0.36, p:0.01), and hospitalization (r:0.41, p:0.001). When the peak RDW reached 16.2, progressive of disease could be predicted with an area under the ROC curve of 0.87(95% CI:0.68-0.96) with sensitivity 83% and specificity 74.2%. In addition to, the best cutoff value of MPV that can be used to predict progressive of pneumonia was 11.2 with sensitivity 82% and specificity 80%. **Conclusion:** The current study demonstrated that high levels of MPV andRDW are associated with severity of pneumonia.

KEYWORDS: Pneumonia, prognostic, MPV, RDW.

INTRODUCTION

Community acquired pneumonia (CAP) is defined as an acute infection of pulmonary parenchyma in individual who acquired infection in the community.[1] It is classified according to the etiologic pathogens into two types: typical CAP that results from S pneumonia, H influenza, and M catarrhalis, and atypical CAP which results from mycoplasma pneumoniae, chlamydia, and respiratory viruses.[2] CAP is considered one of the most common condition encountered in the clinical practice and potentially serious infection disease with public health burden.[3] The incidence of CAP among children younger than 5 years varies geographically, which estimated to be 3.3 per 1000 in resource countries and

approximately 231 per 1000 in resource limited countries.[4] Diagnosis of CAP can be made depending on clinical manifestations, physical examination, with confirmation diagnosis by radiographic findings, although it is not necessary in mild cases that will be treated as outpatients.[5] Complications involving respiratory tract are more likely to develop in bacterial pneumonia than viral type, which include: pleural effusion, empyema, lung abscess, and pneumatocele.[6]

Complete blood count(CBC) is considered quick, inexpensive, and easy accessibility test that used in routine evaluation of infection. It includes a widerange of parameters that related to red blood cell(RBC), white blood cells(WBC), platelets(PLT) and their indices.[7] Platelets is defined as circulating anucleate disc shaped cells, which play an important role beyond hemostasis and thrombosis in regulation of the inflammatory and immune responses. Mean platelet volume(MPV) is an indicator of platelet function and activation, and it has been considered as an inflammation marker in some chronic inflammatory disorders.[8] Red cell Distribution Width(RDW) refers to size variability of erythrocytes, and it has been reported that increased levels of RDW is associated with inflammation.[9]

Many biomarkers have been used to assist in prognostication of patients with CAP, such as MPV and RDW. We conducted this study owing to the high frequency of morbidity and mortality that associated with CAP and absence of local studied that investigate the prognostic value of MPV and RDW in children with CAP. Therefore, the objectives of the study were to: 1- explore the prognostic role of RDW and MPV in CAP patients. 2- determine the optimal cut-off value of RDW and MPV with regards to important clinical outcomes among CAP patients.

Study Population

After approval by local research ethics committee, an Analytical Prospective Prognostic study was conducted in 122 patients with a diagnosis of CAP seen at Pediatric Department, Tishreen University Hospital over a period of one yearfrom April 2021 to April 2022.

Inclusion Criteria were as follows: Children of both sexes aged 2 months and older with a diagnosis of CAP clinically according to World Health Organization(WHO) criteria and radiologic depending on the findings of chest X-ray(CXR).[10]

Non – Inclusion Criteria: Patients with one of the following: hematologic diseases, congenital and acquired cardiologic diseases, presence of concomitant inflammation. The history, review of systems, and physical examination were performed in all patients on admission. Vital signs including: temperature (C°), heart rate (HR: beats per minute), oxygen saturation (SpO2 %), and respiratory rate (RR: breaths per minute) were measured. Blood samples were collected for measurement of complete blood count(CBC), neutrophil (NEUT), lymphocyte(LYM), C-reactive protein(CRP), hemoglobin(Hb), red cell distribution width(RDW), platelet count(PLT), and mean platelet volume(MPV). Pneumonia was classified according to the findings of CXR into: interstitial pneumonia in 56 cases (45.9%), and lobar pneumonia in 66 cases (54.1%). Patients were classified depending on duration of hospitalization as follow: ≤7 days in 82 cases (67.2%) and >7 days in 40 cases (32.8%). Outcome of the study population was recorded which included: requirement to oxygen therapy, complications, and admission to intensive care unit(ICU).

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version20. Basic Descriptive statistics included means, standard deviations(SD), median, Frequency and percentages. Chi-square test or Fisher exact test was used to study the relation between categorical variables. Independent t student test or Mann Whitney was used to compare 2 independent groups. The receiver operating characteristics(ROC) curves were constructed, and the area under curve(AUC) was established to assess the ability of peak RDW and MPV in predicting progressive of disease. Pearson's correlation coefficient was used to measure the association between quantitative variables. P value <0.05 was considered as statistically significant.

RESULTS

The study included a group of 122 patients with a proven diagnosis of CAP. The baseline characteristics of patients were as shown in Table (1). Age ranged from 2 months to 13 years, with a median age of 3 years. Males represented 58.2% of the study sample and females 41.8% with male to female ratio was.

1.3:1. Depending on radiological findings, pneumonia is classified into two types as interstitial pneumonia in 56 cases (45.9%) and lobar pneumonia in 66 cases (54.1%). The mean length of stay of patients was 6.9±3.9 days (range:1-26 days), and 67.2% of the patients were with duration less than or equal 7 days.

Table 1: Demographic characteristics of CAP patients.

Variable	Result
Age(years)	2 month-13 years (Median: 3 years)
Sex (n %)	
Male	71(58.2%)
Female	51(41.8%)
Radiological pattern (n%)	
Interstitial pneumonia	56(45.9%)
Lobar pneumonia	66(54.1%)
Length of stay in hospital (n %)	
≤7	82(67.2%)
>7	40(32.8%)

Patients were classified according to the duration of hospitalization as follow; group I included 82 patients with duration≤7 days and group II included 40 patients with duration>7 days. No significant difference was found between the groups in terms of age, gender, number of previous hospitalizations, and vital signs (p>0.05). In group I, a mean age was 3.70±2.8 years, males represented 58.5% and females 41.5% of the patients. 74.4% of the patients had no previous episode of hospitalization, 23.2% had one episode, and 2.4% had two episodes. The mean values of HR, SpO2, temperature and RR were130.36±17.2, 94.41±7.6, 38.48±0.9 C°, and 43.63±10.2 respectively.

In group II, a mean age was 4.33±4.3 years, males represented 57.5% and females 42.5% of the patients. 72.5% of the patients had no previous episode of hospitalization, 20% had one episode, and 7.5% had two episodes. The mean values of HR, SpO2, temperature and RR were 128.65±23.26, 93.31±14.14, 38.37±0.8 C°, and 45.85±14.6 respectively.

Table 2: Demographic characteristics of the study population according tolength of hospital stay.

Variable	Duration of hospitalization		P value
	Group I ≤7 days	Group II >7 days	
Sex			
Male	48(58.5%)	23(57.5%)	0.9
Female	34(41.5%)	17(42.5%)	
Age(years)	3.70±2.8	4.33±4.3	0.3
Number of previous hospitalizations			
0	61(74.4%)	29(72.5%)	
1	19(23.2%)	8(20%)	0.4
2	2(2.4%)	3(7.5%)	
Vital signs on admission			
Heart rate (HR: beats per minute)	130.36±17.2	128.65±23.26	0.6
Oxygen saturation (SpO2 %)	94.41±7.6	93.31±14.14	0.5
Temperature(C°)	38.48±0.9	38.37±0.8	0.5
Respiratory rate (RR: breaths per minute)	43.63±10.2	45.85±14.6	0.3

There were no significant differences between two groups regarding laboratory investigations except of CRP, RDW, and MPV which were significantly higherin group II; (89.45±56.1 versus 49.80±39.1), (16.35±2.5 versus 13.68±2.6), and (12.20±1.4 versus 10.12±0.4), p:0.0001. Interstitial pneumonia was more frequent in group I (61% versus 15%), whereas lobar type was observed more frequently in group II (85% versus 39%),p;0.0001.

Table 3: Laboratory and radiological investigations of the study population according to length of hospital stay.

Variable	Duration of hospitalization		P value
	Group I ≤7 days	Group II >7 days	
Laboratory investigations			
WBC(10^3/µL)	12.86±5.1	14.73±7.1	0.1
Neu (10^3/µL)	64.84±19.2	65.62±21.2	0.8
L(10^3/µL)	26.96±17.6	27.33±19.7	0.9
CRP(mg/L)	49.80±39.1	89.45±56.1	0.0001
Hb(g/dl)	11.04±0.8	11.08±1.2	0.8
RDW (%)	13.68±2.6	16.35±2.5	0.0001
PLT(10^3/µL)	344.02±121.1	367.97±148.5	0.3
MPV(FL)	10.12±0.4	12.20±1.4	0.0001
Radiologic findings			
Interstitial pneumonia	50(61%)	6(15%)	0.0001
Lobar pneumonia	32(39%)	34(85%)	

As shown in table (4), duration of fever was significantly longer with increasing the duration of hospitalization; 5.22±4.2 in group II versus 2.08±0.8 in group I, p:0.0001. Using oxygen therapy for pneumonia treatment was higher in patients with longer duration of hospitalization without presence of significant difference (37.5% versus 28%, p:0.2). Complications were observedmore frequently in group II than group I; pleural effusion (40% versus 2.4%, p:0.0001) and lung abscess (7.5% versus 1.2%, p:0.04). one patient (1.2%) was admitted to ICU in group I versus 4 patients (10%) in group II, p:0.02.

Table 4: Outcome of the study population according to length of hospital stay.

Variable	Duration of hospitalization		P value
	Group I ≤7 days	Group II >7 days	
Clinical course			
Duration of fever(days)	2.08±0.8	5.22±4.2	0.0001
Need for oxygen therapy	23(28%)	15(37.5%)	0.2
Complications			
Pleural effusion	2(2.4%)	16(40%)	0.0001
Lung abscess	1(1.2%)	3(7.5%)	0.04
Admission to ICU	1(1.2%)	4(10%)	0.02

Patients who were experienced of complications were older (5.30±4.6 versus 3.60±3, p: 0.03). There were no significant differences between patients according to presence of complications in terms of gender, number of previous hospitalizations, and vital signs (p>0.05). In complicated patients group, males represented 63.6% and females 36.4% of the patients. 68.2% of the patients had no previous episode of hospitalization, 22.7% had one episode, and 9.1% had two episodes. The mean values of HR, SpO2, temperature and RR were 126.90±22.1, 91.61±18.8, 38.55±0.8 C°, and 46.77±16.9 respectively. In uncomplicated patients group, males represented 57% and females 43% of thepatients. 75% of the patients had no previous episode of hospitalization, 22% had one episode, and 3% had two episodes. The mean values of HR, SpO2, temperature and RR were 130.44±18.7, 94.59±7.09, 38.42±0.9 C°, and43.83±10.4 respectively.

Table 5: Demographic characteristics of the study population according topresence of complications.

Variable	Complications		P value
	Present	Absent	
Sex			
Male	14(63.6%)	57(57%)	0.5
Female	8(36.4%)	43(43%)	
Age(years)	5.30±4.6	3.60±3	0.03
Number of previous hospitalizations			
0	15(68.2%)	75(75%)	
1	5(22.7%)	22(22%)	0.4
2	2(9.1%)	3(3%)	
Vital signs on admission			
Pulse rate	126.90±22.1	130.44±18.7	0.4
Oxygen saturation	91.61±18.8	94.59±7.09	0.2

SpO2	38.55±0.8	38.42±0.9	0.5
Temperature Respiratory rate	46.77±16.9	43.83±10.4	0.2

There were no significant differences regarding to laboratory investigations according to presence of complications except of CRP, RDW, and MPV which were significantly higher in complicated patients; (98.89±54.4 versus 56.04±44.91, p;0.0001), (17.89±2.2 versus 15.91±2.6, p:0.02), and (12.34±1.3 versus 10.18±0.6, :0.01). Interstitial pneumonia was observed more frequently in uncomplicated patients (53% versus 13.6%) whereas lobar type was more frequent in complicated patients (86.4% versus 47%),p;0.001.

Table 6: Laboratory and radiological investigations of the study population according to presence of complications.

Variable	Complications		P value
	Present	Absent	
Laboratory investigations			
WBC(10^3/µL)	15.25±8.2	13.08±5.2	0.1
Neu (10^3/µL)	73.54±16.7	63.24±20.05	0.2
L(10^3/µL)	20.18±14.7	28.60±18.7	0.05
CRP(mg/L)	98.89±54.4	56.04±44.91	0.0001
Hb(g/dl)	10.98±1.2	11.06±0.9	0.7
RDW (%)	17.89±2.2	15.91±2.6	0.02
PLT(10^3/µL)	370±177.5	347.89±118.5	0.4
MPV(FL)	12.34±1.3	10.18±0.6	0.01
Radiologic findings			
Interstitial pneumonia	3(13.6%)	53(53%)	0.001
Lobar pneumonia	19(86.4%)	47(47%)	

As shown in table (7), duration of fever was significantly longer in complicatedpatients; 5.54±3.2 versus 2.58±2.5, p:0.0001. Using of oxygen therapy was higher in complicated patients without significant difference(40.9% versus 29%, p:0.2). Duration of hospitalization was significantly longer in complicated patients (11.5±4.6 versus 5.91±2.9, p:0.0001). In addition to, 4 cases (18.2%) were admitted to ICU in complicated patients versus 1 case (1%)in uncomplicated patients, p:0.0001.

Table 7: Outcome of the study population according to presence ofcomplications.

Variable	Complications		P value
	Present	Absent	
Clinical course			
Duration of fever(days)	5.54±3.2	2.58±2.5	0.0001
Need for oxygen therapy	9(40.9%)	29(29%)	0.2
Duration of hospitalization	11.5±4.6	5.91±2.9	0.0001
Admission to ICU	4(18.2%)	1(1%)	0.0001

We studied the relationship between RDW and the variables of study, we found that with increasing RDW, there was a significant increasing in fever duration (r: 0.2, p: 0.02), and duration of hospitalization (r:0.31, p:0.001).

Table 8: Correlation between RDW levels and study variables.

Variable	RDW	
	r	P-value
Age	-0.03	0.7
WBC	0.01	0.8
Neu	0.03	0.6
L	0.002	0.9
Hb	-0.05	0.5
PLT	0.1	0.1
CRP	0.01	0.8
Pulse rate	0.04	0.5
Oxygen saturation SpO2	-0.01	0.8
Temperature	0.04	0.6

Respiratory rate	0.08	0.3
Duration of fever(days)	0.20	0.02
Duration of hospitalization	0.31	0.001

We studied the relationship between MPV and the variables of study, we found that with increasing MPV, there was a significant increasing in duration of fever (r: 0.36, p: 0.01), hospitalization (r:0.41, p:0.001), and levels of WBC (r:0.31, p:0.002).

Table 9: Correlation between MPV levels and study variables.

Variable	MPV	
	r	P-value
Age	0.04	0.6
WBC	0.31	0.002
Neu	0.002	0.9
L	-0.05	0.5
Hb	0.02	0.7
PLT	-0.03	0.7
CRP	-0.07	0.4
Pulse rate	0.04	0.6
Oxygen saturation SpO2	-0.1	0.08
Temperature	-0.09	0.3
Respiratory rate	0.01	0.8
Duration of fever(days)	0.36	0.01
Duration of hospitalization	0.41	0.001

Analysis of the ROC curve illustrated an 0.87 area under the curve (AUC) for RDW levels as a predictor of complications (95% CI:0.68-0.96). The AUC of this biomarker indicated a high diagnostic value for outcome with the optimal threshold value being 16.2 with a sensitivity of 83% and specificity of 74.2%(figure 1).

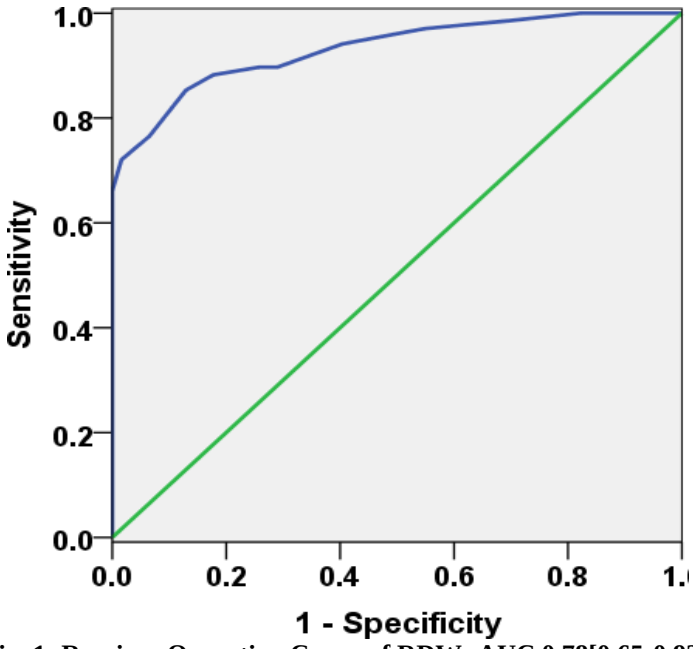

Fig. 1: Receiver Operating Curve of RDW: AUC 0.78[0.65-0.92].

Analysis of the ROC curve illustrated an 0.83 area under the curve (AUC) for MPV levels as a predictor of complications (95% CI:0.71-0.90). The AUC of this biomarker indicated a high diagnostic value for outcome with the optimal threshold value being 11.2 with a sensitivity of 82% and specificity of 80.8%(figure 2).

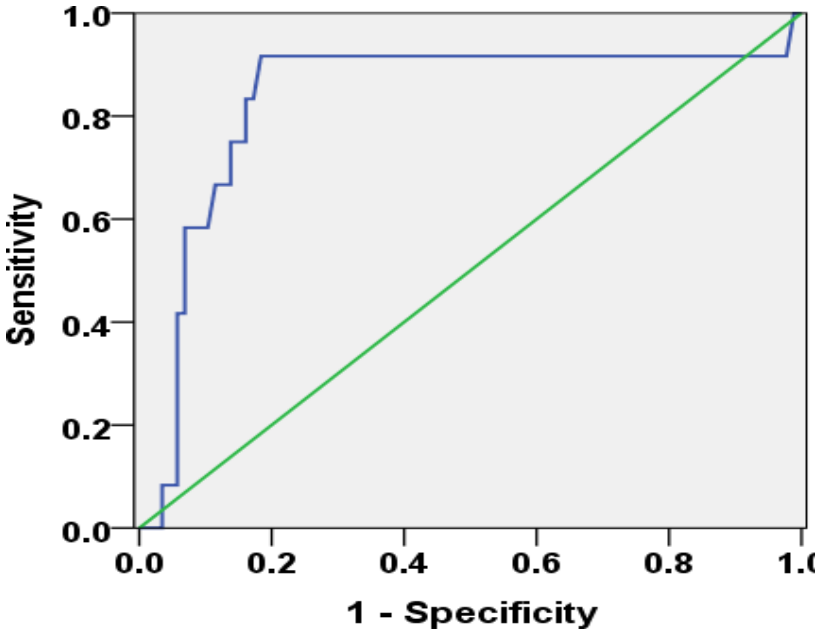

Fig. 2: Receiver Operating Curve of MPV: AUC 0.78[0.65-0.92].

DISCUSSION

This Prospective, single-center study investigated the prognostic impact ofadmission levels of RDW and MPV in hospitalized children with CAP.

The present study demonstrated the main findings. First, levels of RDW, MPV, and CRP were significantly higher in patients with longer duration of hospitalization and in presence of complications, and lobar pneumonia was the most frequent type on CXR in those patients. Second, duration of fever, need for oxygen therapy, admission to ICU, and occurrence of complications (pleural effusion and lung abscess) were significantly higher in complicated patients and in patients with longer duration of stay in hospital. Third, positive correlation was found between RDW and both duration of fever and hospitalization. In addition to, positive correlation was found between MPV and the following variables: levels of WBC, duration of fever and hospitalization. Finally, it is also demonstrated that RDW and MPV levels carry an important prognostic information in pneumonia patients regarding duration of fever and hospitalization in which the cutoff value of RDW and MPV 16.2 and 11.2 were significant independent predictors for progression the disease. The exact mechanisms that might explain these changes are not completely understood, which include: increasing in platelet production resulting from overconsumption in state of inflammation and occurrence of changes in MPV values due to increased platelet activity. In addition to, increased levels of RDW may result from inflammatory state and oxidative stress in infection. The results of current study are comparable with the previous studies that conducted in children with CAP and evaluated prognosticvalue of MPV.

Oncel et al (2013) found in case- control study conducted in 100 healthy and 196 patients with a diagnosis of CAP that MPV values were significantly higher in hospitalized CAP patients compared to outpatients (7.32±0.71 versus 6.83±0.5, p:0.01). MPV cut-off for making a diagnosis of CAP was 8.1 with sensitivity of 91% and specificity of 51%.[11]

Sahin et al (2017) demonstrated in case- control study conducted in 71 healthy, and 190 patients with a diagnosis of CAP that MPV values were significantly lower in CAP patients (7.78 ± 0.89 versus 8.38 ± 0.93, p:0.001) without any effect on duration of hospitalization.[12]

Hamed et al (2022) demonstrated in case-control study conducted in 100 children (50 healthy and 50 with diagnosis of CAP) who aged 1 month- 3 years presence of positive correlation between levels of MPV and severity of disease(p:0.0001). AUC of MPV in pneumonia cases was 0.98 with sensitivity of 100% and specificity of 88%.[13]

Mohammed et al (2022) found in a study performed in 60 children with a diagnosis of CAP that mean value of MPV was significantly higher in severe cases of pneumonia compared with other patients (10.7±0.89 versus 9.81±0.97,p:0.0001). AUC of MPV in mild cases of pneumonia was 0.91 with sensitivity of 86.7% and specificity of 83.3%, while AUC of MPV in severe cases was 0.78 with sensitivity of 83.3% and specificity of 70%.[14]

There are limited studies that evaluated predicting value of RDW in children with diagnosis of CAP. Warawut et al (2021) found in a study conducted in 100 children with a proven diagnosis of CAP that patients with higher levels of RDW had a significant elevated clinical respiratory score than children with normal RDW.[15]

Lee et al (2022) demonstrated in a study conducted in

1459 children with a diagnosis of CAP that higher levels of RDW on admission was associated with an increased risk of severe CAP.[16]

In summary, monitoring levels of MPV and RDW on admission might beuseful prognostic markers for CAP.

Declarations Competing of Interests
All the authors do not have any possible conflicts of interest.

Ethical consideration
After discussing the study with the parents, all of them gave a complete and clear informed consent to participate in the study. This study was performed in accordance with the Declaration of Helsinki.

Availability of data and materials
Most of the data was in the article, and other data can be asked from thecorresponding author.

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Author contributions
All authors performed the measurements and wrote the article. Literature review was done by Dr. Batoul salameh, and all authors performed analytic calculations and performed the numerical simulations.

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