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# Platelet indices as a predictive marker in neonates with respiratory distress

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## Abstract

**Background** The neonatal intensive care unit (NICU) frequently gets admissions due to respiratory distress (RD). Platelet indices are a beneficial biomarker in order to gauge the severity of neonatal RD. We aimed to assess platelet indices as a potential predictor in neonates with RD.

**Methods** This prospective research involved 120 neonates who had been admitted to the NICU with evidence of RD. On admission and after respiratory support was reduced; a complete blood count (CBC) was performed to determine platelet count (PC), mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), platelet mass index (PMI), and platelet large cell ratio (PLCR).

**Results** MPV and PDW were significantly higher after respiratory support reduction. PC and PMI were significantly higher in neonates exhibiting moderate and severe distress. PC of  $276.5 \times 10^9/L$  had the highest degree of predictability of RD severity (area under curve (AUC) 0.762, sensitivity 81.5%, specificity 64.3%), 95% confidence interval (0.7–0.9), while PMI of 2473.5 fL/nL was the best cut-off point to predict severity of RD (AUC 0.663, sensitivity 63%, specificity 57.1%) 95% confidence interval (0.6–0.8). There was a significant difference in the average PC between different oxygen modes.

**Conclusion** Higher PMI and PC are associated with moderate and severe RD and can be used to predict the severity of neonatal RD.

**Keywords** Neonates, Platelet indices, Respiratory distress

## Background

In both term and preterm newborns, respiratory illnesses are the most prevalent causes of entrance to the neonatal intensive care unit (NICU) [1]. One of the most frequent neonatal conditions is respiratory distress (RD) which can affect as many as 7% of all term infants and is on the rise among prematures [2].

According to research conducted by Cairo University on newborn mortality in the intensive care unit of a children's hospital in Egypt, neonatal mortality from RD

accounts for 26.7% of all neonatal fatalities and the primary reason for all NICU admissions [3].

Lungs and platelets (PLTs) have an intimate relationship. Megakaryocytes are found in mammalian lungs which is considered a site of thrombopoiesis. In the recuperation process of the lungs, PLTs presumably perform specific functions. In pulmonary defenses and integrity, platelets play a fundamental role [4]. Maintaining endothelial integrity and barrier function requires the presence of PLTs [5].

Platelet (PLT) indices are used to assess their function. Plateletcrit (PCT) is a measure of the quantity of PLTs and their proportion in whole blood [6,7]. The average PLT size is quantified by mean platelet volume (MPV), while the variation of PLT size is demonstrated by platelet distribution width (PDW). Typically, the PLT count has an inverse relationship with MPV and PDW [8].

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### Laboratory investigations

All participants' blood samples were drawn for a complete blood count (CBC); platelet indices were examined upon entrance to the NICU, and subsequently verified after reduction of respiratory support.

Applying the following equation, PMI was calculated:  $(PMI = [\text{Platelet counts}] \times [\text{mean platelet volume}/103])$  (fL/nL) [13].

### Sample collection

Venipuncture was performed to obtain 2 ml of venous blood, which was then placed in tubes containing tripotassium-ethylenediaminetetraacetic acid (EDTA) to avoid coagulation. Within 30 min of being collected, samples were swiftly shipped to the lab for processing. The automated cell counter (Sysmex KX-21N) was used to analyze the obtained EDTA samples in order to get all PLT indices: MPV expressed in femtolitre (fl), PCT expressed in percentage (%), platelet count (PC) calculated in cubic millimeter ( $\times 1000/\text{mm}^3$ ), PDW and PLCR measured in percentage (%).

### Statistical methods

Version 28 of SPSS' statistical software program was used to examine the data. Utilizing the Kolmogorov-Smirnov single-sample test, the data's normalization was evaluated. Numbers and percentages are used to represent qualitative data. Mean and standard deviation were used to depict quantitative parameters. The comparison between results before applying respiratory support and after elimination was done using Wilcoxon test. The Mann-Whitney test was used to contrast the two sets of numerical data, and the Kruskal-Wallis test by post hoc test will be employed for pairwise comparison when considering more than two participants. Spearman correlation was used to correlate continuous data. To identify the ideal cut-off value, receiver operator characteristic (ROC) curves were applied. Significance was defined as ( $p \leq 0.05$ ).

### Results

There were 120 participants in our research, with 55.8% males and 44.2% females. Participants' average ages were  $6 \pm 4.7$  days and weights were  $2.7 \pm 0.6$  kg on average. The mean GA of the patients was  $36.5 \pm 1.8$  weeks, 73% of them were delivered via cesarean section. Twenty-nine (24.1%) patients were diagnosed as respiratory distress syndrome (RDS) and 91 (75.8%) were diagnosed as transient tachypnea of newborn (TTN). Half of the participants used nasal CPAP, 31.7 % of the patients were mechanically ventilated, and 18.3 % received low flow nasal oxygen. The average duration of hospitalization was

$4.8 \pm 2.1$  days, while the average time to reduce respiratory support was  $2.7 \pm 1.1$  days. Consanguinity and family history were evident in 6.7% and 5% respectively. Approximately 76.6% of the subjects had RD grades III and IV (Table 1).

After receiving oxygen treatment, there was a statistically significant increase in the average MPV ( $8.9 \pm 1.1$  versus  $8.7 \pm 1.2$ ,  $p$ -value=0.016) as well as the mean PDW ( $15.5 \pm 2.6$  versus  $14.9 \pm 2.5$ ,  $p$ -value=0.010); nevertheless, there was statistically insignificant change regarding the results of PC, PCT, PMI, and PLCR before and following treatment (Table 2).

Neonates presented with moderate and severe distress had significantly higher PC than those with mild distress ( $317.9 \pm 76.6$  versus  $264.2 \pm 37.9$ ,  $p$ -value 0.001), and these patients also had a higher average PMI ( $p$ -value.009) as shown in Table 3.

The best cut-off points for PC on the ROC curve analysis to anticipate the severity of RD were  $276.5$  ( $\times 1000/\text{mm}^3$ ); the area under the curve (AUC) was 0.762; the 95% confidence interval (CI) was (0.7–0.9); and the sensitivity and specificity were 81.5% and 64.3%, respectively (Fig. 2). With a sensitivity of 63% and specificity of 57.1%,

**Table 1** Sociodemographic characteristics of the participants

Characteristics	Total number (n=120)
<b>Gender</b>	
Female	53 (44.2%)
Male	67 (55.8%)
<b>Age (days)</b>	$6 \pm 4.7$
<b>Weight (kg)</b>	$2.7 \pm 0.6$
<b>Mode of delivery</b>	
Normal delivery	32 (26.7%)
Cesarian section	88 (73.3%)
<b>Gestational age (weeks)</b>	$36.5 \pm 1.8$
<b>Mode of respiratory support</b>	
Low-flow nasal oxygen	22 (18.3%)
Mechanical ventilation	38 (31.7%)
Nasal CPAP	60 (50%)
<b>Duration for removal from respiratory support (days)</b>	$2.7 \pm 1.1$
<b>Length of stay in hospital (days)</b>	$4.8 \pm 2.1$
<b>Consanguinity</b>	
Negative	112 (93.3%)
Positive	8 (6.7%)
<b>Family history</b>	
Negative	114 (95%)
Positive	6 (5%)
<b>Respiratory distress</b>	
I&II	28 (23.3%)
III&IV	92 (76.7%)

**Table 2** Comparison of platelets indices before and after respiratory support reduction

Platelet indices	Evident RD	Improved RD	p-value
<b>PC</b> (*1000/mm <sup>3</sup> ) Mean ± SD	305.4±73.1	306.7±77.2	0.687
<b>MPV</b> Mean ± SD	8.7±1.2	8.9±1.1	<b>0.016</b>
<b>PCT</b> Mean ± SD	0.27±.1	0.28±.1	0.396
<b>PDW</b> Mean ± SD	14.9±2.5	15.5±2.6	<b>0.010</b>
<b>PMI</b> Mean ± SD	2670.4±718.0	2713.5±826.9	0.845
<b>PLCR</b> Mean ± SD	16.6±3	16.7±3.9	0.569

PC Platelet count, MPV Mean platelet volume, PCT Plateletcrit, PDW Platelet distribution width, PMI Platelet mass index, PLCR Platelet large cell ratio

**Table 3** Relation between platelet indices and respiratory distress

Platelet indices	Mild distress (n= 28)	Moderate and severe distress (n= 92)	p-value
<b>PC</b> (*1000/mm <sup>3</sup> ) Mean ± SD	264.2± 37.9	317.9± 76.6	<0.001
<b>MPV</b> Mean ± SD	8.9±1.2	8.7±1.1	0.256
<b>PCT</b> Mean ± SD	0.26±0.09	0.28±.1	0.265
<b>PDW</b> Mean ± SD	15.6±3.2	14.7± 2.3	0.475
<b>PMI</b> Mean ± SD	2374.1± 482.1	2760.5± 754.9	0.009
<b>PLCR</b> Mean ± SD	15.8±2.9	16.8± 3.04	0.057

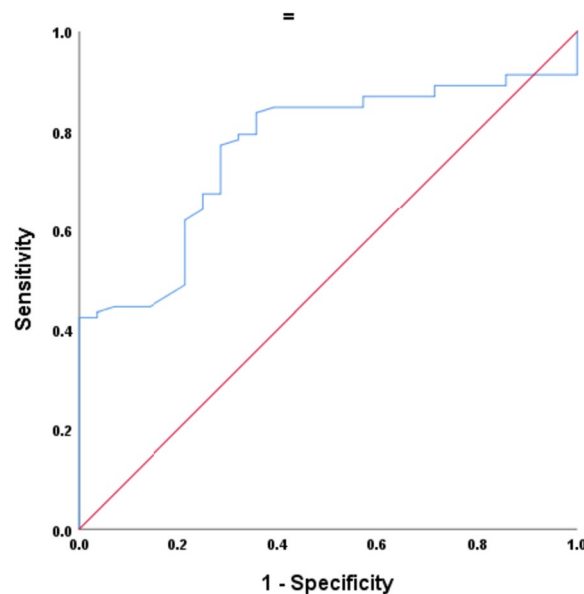
PC Platelet count, MPV Mean platelet volume, PCT Plateletcrit, PDW Platelet distribution width, PMI Platelet mass index, PLCR Platelet large cell ratio

the best cut-off point for PMI was 2473.5 fL/nL, with an AUC of 0.663 and a 95% CI (0.6–0.8) (Fig. 3, Table 4).

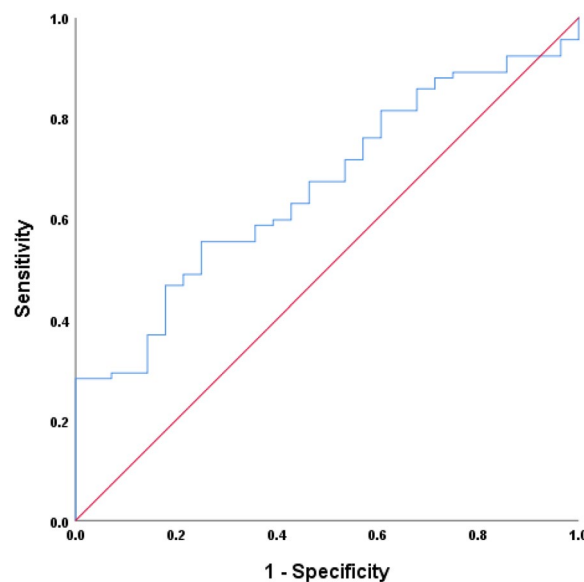
There was a significant difference in the average PC between different oxygen modes after doing a pairwise comparison, the significant difference between nasal CPAP and low-flow nasal oxygen (adjusted *p*-value 0.007), and mechanical ventilation and low-low nasal oxygen (adjusted *p*-value < 0.001) (Table 5).

Table 6 shows multivariate analysis of factors associated with respiratory distress and revealed that platelet number was the factor independently affecting depression; neonates with platelet ≥276.5 had a 7.9 odds ratio to get severe respiratory distress.

As a consequence of our research, the period of respiratory support and PCT were shown to be statistically



**Fig. 2** ROC curve to assess the diagnostic accuracy of platelets in predicting the severity of reparatory distress



**Fig. 3** ROC curve to assess the diagnostic accuracy of PMI in predicting the severity of reparatory distress

significantly positively correlated. It was also shown that PDW and the duration of respiratory support had insignificant negative correlation. It was statistically significant that PCT, PDW, and PLCR all had a negative correlation with GA.

**Table 4** The diagnostic accuracy of platelet and PMI, and in predicting the severity of respiratory distress

Platelet indices	Cut off point	AUC	95% CI	Sensitivity	Specificity	<i>p</i> -value
PC (*1000/mm <sup>3</sup> )	276.5	0.762	0.7–0.9	81.5	64.3	<0.001
PMI	2473.5	0.663	0.6–0.8	63	57.1	0.009

PC Platelet count, PMI Platelet mass index, AUC Area under the curve, CI Confidence interval

**Table 5** Relation between platelet indices and oxygen mode

Platelet indices	Low flow nasal cannula ( <i>n</i> = 22)	Nasal CPAP ( <i>n</i> =60)	Mechanical ventilation ( <i>n</i> = 38)	<i>p</i> -value
PC (*1000/mm <sup>3</sup> ) Mean ± SD	261.6± 38.3	312.7± 83.7	319.2± 61.2	<0.001
MPV Mean ± SD	9.3±1.1	8.6±1.3	8.5±1.1	0.071
PCT Mean ± SD	0.26±1	0.27±1	0.29±.09	0.359
PDW Mean ± SD	15.9±3.5	14.7±2.5	14.5±1.8	0.230
PMI Mean ± SD	2426.5± 490.0	2746.1± 876.0	2691.9± 503.0	<b>0.202</b>
PLCR Mean ± SD	16.4±2.9	16.5±3.4	16.9±2.3	0.216

CPAP continuous positive airway pressure, PC platelet count, MPV mean platelet volume, PCT plateletcrit, PDW platelet distribution width, PMI platelet mass index, PLCR platelet large cell ratio

**Table 6** Multivariate analysis of factors associated with respiratory distress

	<i>p</i> -value	OR	95% CI for OR	
			Lower	Upper
Platelet (≥276.5 vs. 276.5)	<0.001	7.9	3.1	20.2

The factor independently affecting depression was platelet number; neonates with platelet ≥276.5 had a 7.9 odds ratio to get severe respiratory distress

OR Odds ratio, CI Confidence interval

## Discussion

Involved in the biogenesis of PLTs, the lungs could generate 10 million PLTs every hour, or around 50% of all PLTs [14]. Human lungs operate as PLT reservoirs, releasing them in reaction to specific triggers [4].

In our investigation, we discovered that, with the exception of MPV and PDW, which exhibited a significant increase, all PLT indices (PC, PCT, PMI, PLCR) showed an insignificant increase in mean value after acquiring respiratory support. This is consistent with findings of El Mashad et al. [15] and Sweet et al. [16], who reported that there was a non-significant difference regarding platelet and that MPV was significantly higher in preterms with respiratory distress syndrome (RDS). In a study conducted by Mishra et al. [17], it was discovered that the levels of platelet indices (MPV and

PCT) were significantly higher in the group of those who diagnosed as RD (*p*-value 0.003). MPV was considered to be a measure of platelet generation and consumption, and it can also be correlated with the severity of various disorders [16]. In a study conducted by Go et al. [18], the bronchopulmonary dysplasia (BPD) group did not show an increase in the PC and PCT with increasing age and remained at a low level. BPD microvascular dysplasia and halted pulmonary development can both interfere with the process of biosynthesis and discharge of PLTs, since the pulmonary capillary bed is contracted or morphologically modified which disturbs the pulmonary megakaryocyte fragmentation or spatial arrangement [19]. Such outcomes may suggest that the improvement of lung disease and lung development have an impact on PLT manufacture. A future study including assessment of PLT indices with longer-term follow-up could help clarify the risk of development of BPD in neonates with RD especially premature infants.

PC and PMI were significantly higher in neonates presented with moderate and severe distress compared with those presented with mild distress (*p*-value < 0.001 and 0.009 respectively). This is consistent with a study done by Franciuc et al. [20] who compared RDS group and non-RDS group and found that PC (320.16 ± 115.89 versus 358.50 ± 283.47, *p*-value 0.696) and PMI (3701.90 ± 1240.91 versus 3862.45 ± 3142.11, *p*-value 0.881)

showed higher levels in RDS group. PLTs participate in maintaining the barrier function of the endothelium: the discharge of soluble compounds that preserve the barrier sturdiness via endothelial cell signals; physical blocking of endothelial barrier gaps; preservation of vital endothelial cell structure necessary for barrier integrity; promoting or expediting endothelial cell proliferation [21]. There's substantial confirmation that PLTs can improve function of endothelium and lower its permeability, and that adequate levels of circulated PLTs could be crucial in maintaining the integrity of the alveolar capillaries' barrier and other capillary beds [22]. When compared to platelet count alone, platelet mass provides a more accurate reflection of platelet function [23]. Mangalpally et al. [24] and Gerday et al. [13] stated that due to bigger platelets' higher enzymatic activity compared to smaller platelets, PMI is correlated with platelet functionality. Recent research showed that platelet mass index, rather than PC, should be employed as a marker for platelet transfusion [25]. Gerday et al. [13] revealed that employing platelet mass lessens the necessity for platelet transfusions.

We observed a significant difference in the average PC between different oxygen modes. PC was significantly higher in patients that require mechanical ventilation ( $p$ -value < 0.001). Increased demand for oxygen and mechanical ventilation drives inflammatory cells to gather in pulmonary tissue [26]. As a major inflammatory cells, PLTs have functions which encompass the immunological continuum [27]. Lung defense is strengthened by the inflammatory functions of platelets [28].

Our study's strength is that platelet function is determined by platelet indices such as MPV, PCT, PDW, and PLCR, which can be promptly and readily measured by a routine CBC. These standards are affordable and accessible to all institutions, including developing countries.

Since we investigated treatment results that emerged in the early stage, our study had certain limitations. Longer follow-up periods are recommended; our advice is to expand the term of monitoring to include the entire neonates' whole hospital experience and to detect BPD cases and its relationship with changes in PLT parameters.

## Conclusion

Higher PMI and PC are associated with moderate and severe respiratory distress which may allow clinicians to predict the severity of neonatal respiratory distress. PC is significantly higher in mechanically ventilated patients.

## Abbreviations

AUC	Area under curve
BPD	Bronchopulmonary dysplasia
CBC	Complete blood count
CI	Confidence interval
CPAP	Continuous positive airway pressure

EDTA	Ethylenediaminetetraacetic acid
GA	Gestational age
PC	Platelet count
PCT	Plateletcrit
PDW	Platelet distribution width
PMI	Platelet mass index
PLCR	Platelet large cell ratio
PLT	Platelet
PLTs	Platelets
PVI	Platelet volume indices
MPV	Mean platelet volume
NICU	Neonatal intensive care unit
RD	Respiratory distress
RDS	Respiratory distress syndrome
ROC	Receiver operating characteristic

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## Availability of data and material

The datasets analyzed in this study are available from the corresponding author upon reasonable request.

## Authors' contributions

Manar Aref and Sarah Abdelrashid were involved with study concept and design. Manar Aref was involved with patients' inclusion and data collection. Sarah Abdelrashid analyzed the data and performed data interpretation and tables' design. Sarah Abdelrashid wrote the manuscript. Manar Aref revised the manuscript. All authors reviewed and took full responsibility for the final version of the manuscript.

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## Declarations

### Ethics approval and consent to participate

This study was approved by research ethical committee October 6 University (REC-O6U), Egypt. Prior to enrolment, patients' guardians granted informed consent after being apprised of the study's purpose.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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