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ROLE OF PLATELET MASS INDEX IN PREDICTION OF SEVERITY OF TRANSIENT TACHYPNEA OF THE NEWBORN

By

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ABSTRACT

Background: Transient tachypnea of the newborn (TTN) is a benign, self-limited condition that can present in full-term or late preterm infants. TTN is caused by delay in clearance of fetal lung fluid after birth.

Objective: To evaluate the role of platelet mass index (PMI) in predicting the severity of transient tachypnea of newborn (TTN).

Patient and methods: This was a case control study followed by follow up of cases till remission of TTN. It was carried out on 100 term and near-term neonates with TTN. Platelet mass index (PMI) test was done by CBC which included platelet count, as well as platelets indices such as mean platelets (MPV) in neonatal intensive care unit at Damietta, Al-Azhar University Hospital. PMI was calculated using the following formula: PMI = platelet count x mean platelet volume /103 (fl/nl).

Results: Decreased platelet count and PMI were significantly associated with TTN when compared to control group. Increased duration of oxygen therapy was significantly associated with decreasing platelet count and PMI. MPV did not differ significantly between cases and controls as well as according to duration of oxygen therapy. Platelet count and PMI showed significant increase after remission. PMI showed significant positive correlations with platelet count, and significant negative correlations with duration of oxygen therapy. No significant correlations were found regarding of PMI with other parameters among studied TTN cases.

Conclusion: Lower PMI and platelet count were associated with longer duration of oxygen therapy in patient with TTN, which could be used in prediction of severity of TTN.

Key words: TTN, Platelets, MPV, PMI.

INTRODUCTION

Transient tachypnea of the newborn (TTN) is a common respiratory problem that develops shortly after birth in term and late preterm infants, but resolves in ≤2–5 days without significant morbidity. Preterm birth, cesarean delivery, male gender, low birth weight, macrosomia,

perinatal asphyxia, maternal sedation, maternal diabetes, and asthma are the risk factors associated with the occurrence of TTN *(Jha et al., 2021)*. Failure of the newborn to effectively clear the fetal lung fluid soon after birth can lead to respiratory distress. Tachypnea is the most common clinical feature. In most cases, TTN is self-limited and resolves without the need for medical intervention *(Gunes et al., 2022)*. Tachypnea is the most prominent feature. Infants typically have cyanosis and increased work of breathing, mild intercostal and subcostal retractions, and expiratory grunting. The anterior-posterior diameter of the chest may be increased *(Moresco et al., 2020)*.

Infants with mild to moderate TTN are symptomatic for 12 to 24 hours which may persist for 72 hours in severe cases. Infants rarely require a supplemental oxygen concentration greater than 40 percent to achieve adequate oxygenation. TTN signs include mild to moderate hypoxemia and mild hypercapnia, resulting in respiratory acidosis. Complete blood count and differential are normal *(Dutcher, 2020* and *Salamaet al., 2020)*. Chest X ray findings include, alveolar effusion signs, interstitial effusion signs, increased thickened, and blurred lung markings radiating from the hilum of the lung, and extending outward *(Liu et al., 2018)*. Thickening or fuzziness of the pleural line, partial or complete disappearance of A-lines, and appearance of B-lines are signs of lung ultrasonography *(Liu et al., 2018, Sharma and Farahbakh, 2019)*.

TTN is a self-limited condition. Supportive care is the mainstay of treatment *(Dehdashtian et al., 2018)*. Routine NICU care including continuous cardiopulmonary monitoring, maintenance of neutral thermal environment, securing intravenous (IV) access, blood glucose checks, and observation for sepsis should be provided *(Johnson, 2020)*. Oxygen support may be required if pulse oximetry or ABG suggest hypoxemia *(Hagen et al., 2017)*. Endotracheal intubation and requirement of ECMO support is usually uncommon but should always be considered in patients with declining respiratory status *(Moresco et al., 2020)*.

Platelet volume indices (PVI) are a group of parameters which are inexpensive and derived from routine blood counts. The mean platelet volume (MPV) and platelet distribution width (PDW) are the most validated and prominent. Variations in PVI are indicative of changes in platelet function. Platelet size, measured by these parameters, correlates with platelet activity *(Leader et al., 2012)*. MPV is a simple and accurate marker of the functional status of platelets as larger platelets are more reactive *(Slavka et al., 2011)*.

The lungs are an ideal bioreactor to produce mature platelets from megakaryocytes *(Lefrancais et al., 2017)*. Platelets contribute to the basal barrier integrity of the alveolar capillaries, which selectively restricts the transfer of water, proteins, and red blood cells out of the vessels. Platelets reduce lung fluid accumulation and lung edema due to an unknown mechanism, bolster pulmonary vascular repair, and contribute to hemostatic and inflammatory defense of the healthy lung *(Weyrich and Zimmerman, 2013)*. Platelet mass index

(PMI) is related to platelet functionality because larger platelets are enzymatically more active than smaller platelets *(Ilhan and Bor, 2019)*.

PATIENTS AND METHODS

This study was a descriptive and prospective study, followed by follow up of cases till remission of TTN. It was carried out on 100 term and near-term neonates with TTN in neonatal intensive care unit at Damietta Al-Azhar University Hospital. Regarding TTN neonates, their mean gestational age was 37 weeks. They were 68% males and 32% females. In addition, 100 healthy control neonates were selected to be matched in age and gender. Patients were subdivided into three subgroups according to the duration of oxygen therapy (≤24 h, 24 to 48 h and >48 h). It was conducted from Oct 2020 until December 2021; Ethics committee was obtained by Damietta Al-Azhar University Council. Written informed consents were obtained from their parents.

Inclusion Criteria: Term and near-term neonates with TTN, gestational age > 36 weeks, birth weight > 2200 g, and both genders (birth weight > 10th percentile).

Exclusion criteria: Infants with other respiratory disorders, congenital cardiac diseases, asphyxia and non-respiratory disorders that may lead to tachypnea, infants who had causes of early onset thrombocytopenia, and infants who were small for gestational age (birth weight <10 percentile).

Criteria used to confirm a diagnosis of TTN: Onset of tachypnea <6 hr after birth and persistence of tachypnea >12hr, patients needed oxygen requirement, and X- ray findings. All newborn in the study was subjected to full history taking and full examination.

Treatment: The mainstay of treatment of TTN was supportive care. The degree of respiratory support should be guided by the degree of illness. Pulse oximetry was used, and supplemental oxygen was provided to keep saturation above 95% oxygen via nasal canulla or oxygen hood. The oxygen saturation was constantly monitored, and the response to oxygen suplementation was evaluated.

Noninvasive continuous positive airway pressure (CPAP) support was reserved for these neonates who had severe distress, or those who required higher concentrations of oxygen (>40%) to maintain their saturation which was evaluated with pulse oxymetry. When the clinical signs of respiratory distress disappeared (Silverman score = 0), arterial oxygen saturation was >95% without oxygen therapy, as measured on pulse oximetry, and respiratory rate was < 60 breath per minute, TTN was resolved.

Laboratory analyses: Blood samples were collected carefully from peripheral vein in the first 6hr of life before any medication, and I.V infusion, and after remission of TTN. The blood samples for complete blood count (CBC) were placed in tubes containing K3-EDTA. Platelet count and MPV were assessed ≤1 h after collection. PMI was calculated from the CBC by using the following formula: PMI = platelet count × mean platelet volume / 103 (fl/nl).

Data acquisition: Birthweight, gestational age, mode of delivery, 1 and 5 min Apgar scores, maternal pregnancy disease, respiratory support (kind of respiratory support, oxygen saturation and

duration of oxygen supplementation), CBC ≤ 2 h after birth and after remission of TTN, and complication data were recorded.

Statistical Analysis:

Student t-test and one way analysis of variance (ANOVA) were used to assess the statistical significance of the difference between two or more study group means respectively. Mann Whitney test was used to assess the statistical significance of the difference of a non-parametric variable between two or more study groups respectively. ANOVA was used to assess difference between more than two groups, followed by post hoc Tukey test. Chi-Square and Fisher's exact tests were used to compare qualitative data. Paired sample t-test was used to assess changes in parameters over time. Normally distributed variables are presented as mean ± SD, whereas nonparametric continuous variables are presented as median. Categorical variables are presented as n (%). Correlation analysis was used to assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables. The ROC Curve (receiver operating characteristic) provided a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups. A p value was considered significant if <0.05 at confidence interval 95%. Statistical package for the Social Sciences (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) was used for analysis.

RESULTS

TTN cases were significantly associated with higher frequency of CS, lower APGAR score at 5 minutes lower hemoglobin and hematocrit, longer length when compared to healthy control group. No significant differences were found between TTN cases and healthy control groups regarding gravidity, parity, abortion, living children, associated maternal diseases and NICU admission of previous babies. TTN cases showed significantly lower platelet count, (PMI), while WBCs and MPV did not differ significantly between both groups **(Table 1)**.

Table (1): Comparison of infant and maternal characteristics among studied groups

Parameter		Group	TTN n=100	Control n=100	*P*
Gestational age (weeks)		**mean±SD**	37±0.8	37.4±2	0.123
Birth weight (kg)		**mean±SD**	3±0.4	3±0.3	1
Gender	**Male**	**N (%)**	68	58	0.143
	Female	**N (%)**	32	42	
Length (cm)		**mean±SD**	48.2±4.8	49.2±1.3	0.046
HC (cm)		**mean±SD**	34.3±1.4	34.1±3.3	>0.05
AC (cm)		**mean±SD**	31.8±1.4	31.7±1.6	>0.05
Mode of delivery	**CS**	**N (%)**	98	88	**0.006**
	NVD	**N (%)**	2	12	
APGAR at 5 minutes		**mean±SD**	7.9±1	9.6±0.6	**<0.001**
Obstetric history	**Gravidity**	**median (range)**	2(1-6)	2(1-7)	0.830
	Parity	**median (range)**	2(1-6)	2(1-5)	0.478
	Abortion	**median (range)**	0(0-3)	0(0-4)	0.537
	Living children	**median (range)**	2(1-6)	2(1-5)	0.468
maternal diseases	**No**	**N (%)**	68	61	0.135
	Anemia	**N (%)**	26	24	
	resolved UTI	**N (%)**	3	1	
	Rheumatoid arthritis	**N (%)**	1	0	
	Hypothyroidism	**N (%)**	0	3	
	Infertility	**N (%)**	0	3	
	history of preterm labor	**N (%)**	0	3	
	Bronchial asthma	**N (%)**	0	1	
	Anemia+ resolved UTI	**N (%)**	2	3	
	Anemia+ hypothyroidism	**N (%)**	0	1	
NICU admission of previous babies		**N (%)**	10	7	0.447
Hemoglobin (g/dL)		**mean±SD**	14.7±1.1	15.7±1.6	**<0.001**
Hematocrit (%)		**mean±SD**	47.1±4.1	50.3±5	**<0.001**
WBCs X10^9/L		**mean±SD**	14.6±2.8	15.7±2.3	0.003
platelet X10^9/L		**mean±SD**	214.6±29.9	299±26.3	**<0.001**
MPV (fL)		**mean±SD**	8.9±0.5	8.6±0.5	>0.05
PMI (fL/nL)		**mean±SD**	1.9±0.3	2.6±0.2	**<0.001**
Positive CRP		**N (%)**	0	0	1

Numerical data were expressed as mean and SD, compared by t test or median and range, compared by Mann-Whitney test. Categorical data were expressed as number and percentage; compared by Chi square test.

Median duration of oxygen therapy was 28 hours, ranged from 12 to 72 hours, 36% required oxygen therapy <24 hours, 42% required oxygen therapy 24-48 hours and 22% required oxygen therapy >48 hours. Increased duration of oxygen therapy was significantly associated with decreasing platelet count and PMI, while MPV did not differ significantly according to duration of oxygen therapy. After remission, platelet count, MPV and PMI did not differ significantly in between different TTN groups according to duration of oxygen therapy **(Table 2)**.

Table (2): Comparison of platelet indices according to duration of oxygen therapy

Parameter \ Duration of oxygen therapy			<24 hours	24 – 48 hours	> 48 hours	p^1	p^2	p^3	p^4
			n=36	n=42	n=22				
Before treatment	**platelet $X10^9$/L**	**mean±SD**	246.2±19.7	204.9±13.9	181.3±10.7	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	MPV (fL)	**mean±SD**	8.8±0.5	8.9±0.4	9.1±0.5	0.483	0.260	0.895	0.402
	PMI (fL/nL)	**mean±SD**	2.2±0.2	1.8±0.1	1.6±0.1	**<0.001**	**<0.001**	**<0.001**	**<0.001**
After remission	**platelet $X10^9$/L**	**mean±SD**	317.1±22.7	314.1±25.7	304.9±17.8	0.142	0.566	0.152	0.131
	MPV (fL)	**mean±SD**	8.9±0.5	9.2±0.4	9.3±0.5	0.002	0.028	0.076	0.331
	PMI (fL/nL)	**mean±SD**	2.8±0.2	2.9±0.2	2.8±0.1	0.309	0.166	0.965	0.249

P^1, comparison between <24, 24-48 hours and >48 hours subgroups.
P^2, comparison between <24, 24-48 hours subgroups.
P^3, comparison between <24, and >48 hours subgroups.
P^4, comparison between 24-48 hours and >48 hours subgroups.

Among all studied TTN cases, after remission, platelet count and PMI showed significant increase. While MPV did not differ significantly when compared to baseline parameters. Similar results were found after stratifying patients according to duration of oxygen therapy **(Table 3)**.

Table (3): Comparison of platelet indices before and after remission among all studied cases

Parameter	All studied cases		oxygen therapy <24 hours		oxygen therapy 24-48 hours		oxygen therapy >48 hours	
	At admission	After remission	At admission	After remission	At admission	After remission	At admission	After remission
platelet X109/L	214.6±29.9	313.2±23.3	246.2±19.7	317.1±22.7	204.9±13.9	314.1±25.7	181.3±10.7	304.9±17.8
P	**<0.001**		**<0.001**		**<0.001**		**<0.001**	
MPV (fL)	8.9±0.5	9.1±0.5	8.8±0.5	8.9±0.5	8.9±0.4	9.2±0.4	9.1±0.5	9.3±0.5
P	0.460		0.384		0.102		0.211	
PMI (fL/nL)	1.9±0.3	2.8±0.2	2.2±0.2	2.8±0.2	1.8±0.1	2.9±0.2	1.6±0.1	2.8±0.1
P	**<0.001**		**<0.001**		**<0.001**		**<0.001**	

SD, standard deviation; paired sample t test was used.

Receiver operating characteristic (ROC) curve of PMI was conducted for discrimination between TTN cases and control groups. PMI showed high accuracy AUC (AUC=0.984). At best cut off value (<2.37 fL/nL), sensitivity was 96%, specificity was 92%, PPV was 92.3%, NPV was 95.8%, and accuracy was 94%. Moreover, ROC curve of PMI was conducted for discrimination between TTN cases whose required oxygen less than and more than 48 hours. PMI showed high accuracy AUC (AUC=0.903). At best cut off value (<1.75 fL/nL), sensitivity was 95.5%, specificity was 80.8%, PPV was 58.4%, NPV was 98.5%, and accuracy was 84% **(Figure 1)**.

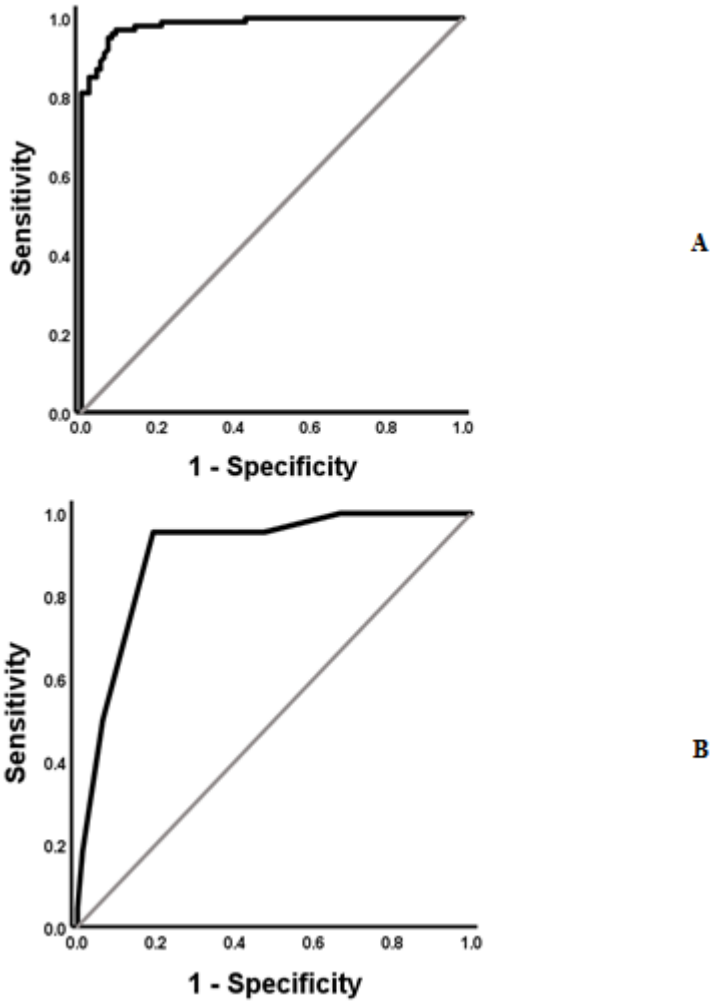

Figure (1): ROC curve of PMI for discrimination between (A) TTN cases and control groups, (B) TTN cases whose required oxygen less than and more than 48 hours

PMI showed significant positive correlations with platelet count (p<0.001), significant negative correlations with duration of oxygen therapy (p<0.001) **(Figure 2)**.

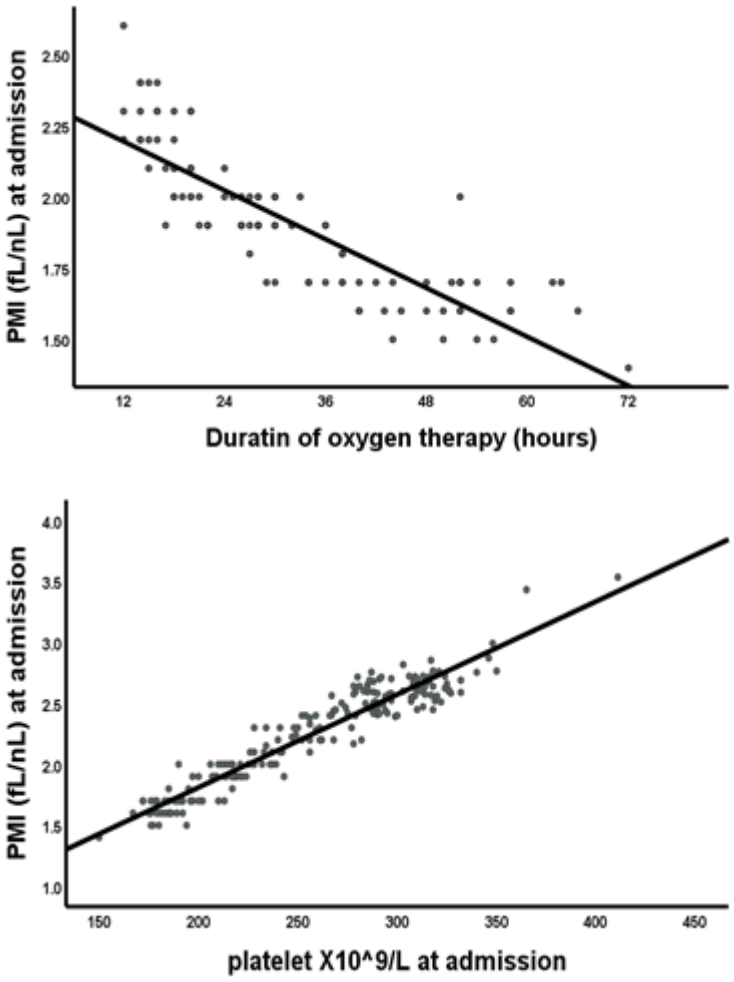

Figure (2): Correlation of PMI with (A) duration of oxygen therapy, (B) platelet count among all studied TTN cases

DISCUSSION

Transient tachypnea of the newborn (TTN) is a benign, self-limited condition that can present in full-term or late preterm infants *(Jha et al., 2021)*. TTN consists of tachypnea (respiratory rate above 60/min), mild to moderate respiratory distress that gradually improves during the first 48 to 72 hours of life *(Bulut et al., 2022)*. TTN is due to delay in clearance of fetal lung fluid after birth *(McGillick et al., 2017)*. Low platelets count that presents in the first 72 hours of life develops usually due to chronic fetal hypoxia *(Weyrich and Zimmerman, 2013).*

In the present study, there were no significant differences between TTN cases

and healthy control groups regarding gravidity and parity, and this agreed with *Algameel (2020)* who found no significant association of late preterm birth who are susceptible to respiratory distress and TTN with parity, which in line with data reported by a case control study in 5 Italian Centers *(Mandruzzato et al., 2013)*.

The current study showed that TTN cases were significantly associated with higher frequency of CS when compared to our healthy control group. This was in agreement with *Weintraub et al. (2013)*. However, the very high percentage of C.S in both groups indicates the abuse of C.S.

The present research showed that WBCs did not differ significantly between both groups, which agreed with *Çiğri et al. (2021)*. TTN cases showed significantly lower hemoglobin and hematocrit than control group which agreed with *Okur et al. (2016)* that had found anemia in TTN cases.

In the current study, MPV did not differ significantly between both groups which agreed with *Go et al. (2020)*. Our TTN cases showed significantly lower platelet count and PMI than control group, which were in agreement with *Cosar et al. (2017)* and *Ilhan and Bor. (2019)*, while *Çiğri et al. (2021)* noticed no significant difference in terms of platelet count and PMI between TTN and healthy control groups.

The present study revealed no significant association in our TTN cases between the duration of oxygen therapy requirement and neonatal demographic, anthropometric data, vital signs, APGAR scores which were in agreement with *Babaei et al. (2019)*. While *Bak et al. (2012)* showed that the longer oxygen requirement was associated with younger gestational age, lower birth weight and higher proportion of acidosis.

Amoung our TTN cases, the current study reported that increased duration of oxygen therapy was significantly associated with decreasing platelet count and PMI, while MPV did not differ significantly which agreed with *Bolat et al. (2021)* who reported that PMI was negatively correlated with duration of oxygen therapy. The current study showed a significant negative correlation between PMI and platelet count with duration of oxygen therapy which agreed with *Buchiboyina et al. (2016)* and *Ilhan et al. (2019)*. The present study found that, platelet count and PMI after remission of TTN improved significantly when compared to TTN infants on admission, these results agreed with *Ilhan et al., 2019.*

ROC curve of PMI was conducted in the current study for prediction of TTN occurrence. PMI showed sensitivity of 96%, specificity of 92%, AUC was 0.984, and the best cut off value was established as 2.37 fL/nL. Moreover, PMI was excellent predictor for TTN severity. The optimal PMI cut-off to predict prolonged duration of oxygen therapy (>48 h) was1.75 fL/nL, with sensitivity of 95.5%, specificity of 80.8%, AUC was 0.903.

There were some limitations in our study as small sample size, since we investigated the treatment outcomes that developed in the early period We recommend extending the period of observation to the whole period of the hospitalization of the neonates to carry out longer follow-up periods.

Lower PMI and platelet count are associated with longer duration of oxygen treatment in patients with TTN which may allow clinicians to predict the severity of TTN.

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دور مؤشر كتلة الصفائح الدموية في التنبوء بحدة متلازمة تسرع التنفس العابر لدي الاطفال حديثي الولادة

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خلفيـــة البحـــث: يعـــد مـــرض تســـرع التـــنفس العـــابر لـــدي الاطفـــال حـــديثي الـــولادة حالـــة مرضـــية حميـــدة والتـــي تظهـــر أعراضـــها بعـــد الـــولادة مباشـــرة فـــي صـــورة ضـــيق الـــنفس خفيـــف إلـــي معتـــدل، ويتحســـن تـــدريجيا خـــلال يـــومين. كمـــا يعـــد متوســـط كتلـــة الصـــفائح الدمويـــة مؤشـــر لوظيفـــة الصـــفائح الجيـــدة حيـــث أن الصـــفائح كبيـــرة الحجـــم نشطة إنزيميا أكثر من صغيرة الحجم.

الهـــدف مـــن البحـــث: تقيـــيم دور متوســـط كتلـــة الصـــفائح الدمويـــة فـــي مـــدي ســـوء حـــالات تسرع التنفس العابر لدي حديثي الولادة.

المرضـــي وطـــرق البحـــث: أجريـــت الدراســـة علـــي مائـــة طفـــل مـــن حـــديثي الـــولادة المصـــابين بمتلازمـــة تســـرع التـــنفس العـــابر فـــي وحـــدة العنايـــة المركـــزة لحـــديثي الـــولادة فـــي مستشـــفي الازهـــر الجـــامعي بـــدمياط فـــي الفتـــرة مـــن أكتـــوبر 2020 الـــي ديســـمبر2021، وكـــان متوســـط إعطـــاء الاكســـجين بـــين حـــالات الدراســـة لمـــدة 28 ســـاعة وكـــان بنســـبة 36% أقـــل مـــن 24 ســـاعة، وبنســـبة 42% لمـــدة 24-48 ســـاعة، وبنســـبة 22% لمدة أكثر من 48 ساعة.

نتـــائج البحـــث: أظهـــرت نتـــائج الدراســـة دلالـــة احصـــائية هامـــة بـــين زيـــادة مـــدة إعطـــاء الاكســـجين لحـــالات الدراســـة ونقـــص عـــدد الصـــفائح ومتوســـط كتلـــة الصـــفائح، بينمـــا لا يوجـــد دلالـــة علـــي متوســـط حجـــم الصـــفائح, وبعـــد هـــدوء تســـرع التـــنفس العـــابر للحالـــة يعـــود متوســـط الكتلـــة والحجـــم وعـــدد الصـــفائح للمعـــدلات الطبيعيـــة والتـــي لـــم تتـــاثر بمـــدة إعطاء الاكسجين.

الاســـتنتاج: متوســـط كتلـــة الصـــفائح الدمويـــة يعـــد مؤشـــرا هامـــا لمـــدي خطـــورة مـــرض تسرع التنفس العابر لحديثي الولادة.