ROLE OF PLATELET MASS INDEX TO PREDICT THE DURATION OF TRANSIENT TACHYPNEA OF NEWBORN

By

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ABSTRACT

Background: *TTN is one of the most important causes of respiratory distress in the neonates, mostly it is a benign and self-limited condition but there is rare incidence of developing severe respiratory distress which denotes that the neonate had malignant transient tachypnea of newborn.*

Objective: *This an observational prospective case control study aimed to evaluate the role of platelet mass index (PMI) to predict the severity of Transient tachypnea of the newborn.*

Subjects and methods: *The study was performed on 100 neonates with evidence of TTN admitted in the Neonatal Intensive Care Unit (NICU) during the first 24 hours of life and divided according to duration of tachypnea into two groups , group A(50 neonates with duration of tachypnea > 48 hours) and group B (50 neonates with duration of tachypnea ≤ 48 hours).*

Results: *Platelet mass index (PMI) and platelet counts were significantly lower in the group of neonate with duration of tachypnea > 48 hrs than in the group of neonate with a duration of tachypnea ≤ 48 hrs ($p < 0.001$ and $p < 0.001$ respectively). Platelets count and PMI had an excellent discriminative power for predicting tachypnea > 48 hours (AUC, 962 and 0.970 respectively) the optimal cut-point for platelets count was 309.5 x 103 which produced sensitivity and specificity of 90.0%. While the optimal cut-point for PMI was 2395.25 fl/nl yielding sensitivity of 94.0% and specificity of 88.0%.*

Conclusion: *Lower PMI and lower platelet count are associated with longer duration of tachypnea in patients with TTN.*

Keywords: *Transient tachypnea of the newborn, platelet mass index.*

INTRODUCTION

TTN is the most common cause of respiratory distress in the neonates **(Isik et al., 2010)**. Transient tachypnea of the newborn (TTN) has a picture of lung edema due to delayed desorption of lung fluids **(Machado et al., 2011)**. The proposed etiology for TTN is the delayed lymphatic drainage of the pulmonary alveolar fluid due to lack of maturation of epithelial sodium channels **(Helve et al., 2009)**. The excess lung fluid in transient tachypnea of newborn results in decreased lung functions, tachypnea will occur to compensate for decrease gas exchange associated with increased lung fluid **(Strauss et al., 2010)**.

Neonates with TTN present within the first few hours of life with tachypnea and other signs of respiratory distress, increased oxygen requirement, and ABGs that do not reflect carbon dioxide retention. During management of transient tachypnea of the newborn, it is imminent to observe development of respiratory fatigue and signs of clinical deterioration that may suggest some other diagnosis **(Machado, et al., 2011)**.

Platelets mass index (PMI) is calculated by multiplying the platelet count by the mean platelet volume (MPV). It is related to platelet function because larger platelets are enzymatically more active than smaller platelets **(Gerday et al., 2009)**. Lower PMI and lower platelet count are associated with longer duration of tachypnea in neonates with TTN **(Ozkan Ilhan, 2019)**.

The study was conducted to determine relation between platelet mass index and the severity of transient tachypnea of newborn.

PATIENTS AND METHODS

Ethical consideration:

1. The study was approved by the Ethics Committee of the Faculty of Medicine, Fayoum, Egypt.
2. Informed, verbal consents were obtained from the parents of the neonates.
3. All the data of the study is confidential and the participants have the right to keep or withdraw from the study at any time.
4. The authors declared no potential conflict of interest with respect to the research authorship and/or publication of the article.
5. No financial disclosure regarding the study or publication.

Sample size:

Sample size was calculated according to the following equation, a sample size of 50 in each group was needed to achieve power of 80 % alpha error of 5 % and 0.57 as an effect size for platelet mass index between the two groups.

Inclusion criteria:

TTN was diagnosed based on the following clinical and **laboratory criteria:** Onset of tachypnea (respiratory rate > 60 beats/min) ≤ 6 h after birth; persistence of tachypnea ≥12 h; oxygen requirement >21%; and chest X- ray indicative of at least one of the following: Prominent central vascular markings, widened interlobar fissures of the pleural fluid, symmetrical perihilar congestion, and hyperaeration as evidenced by the flattening and depression of the diaphragmatic domes or increased anteroposterior diameter or both. **(Guglani L, et al, 2008)**.

Exclusion criteria:

Infants with respiratory disorders, such as meconium aspiration syndrome, congenital lung anomalies, RDS, pneumonitis (diagnosed on chest X- ray), congenital cardiac disease (diagnosed on echocardiography), asphyxia (umbilical artery pH < 7.0 or 10 min Apgar score < 5), and non-respiratory disorders (polycythemia, hypocalcaemia, and persistent hypoglycemia), that may lead to tachypnea were excluded from the study .We also did not include infants in the study who had causes of early onset thrombocytopenia including intrauterine growth retardation, culture proven early onset sepsis, congenital infection, disseminated intravascular coagulation, metabolic disease, congenital/inherited syndromes, thrombosis, alloimmunity and autoimmunity. None of the present infants were small for gestational age (birth weight < 10th percentile).

Study design:

One hundred full-term neonates were divided into two groups according to the duration of tachypnea:

- Group A: 50 neonates with duration of tachypnea > 48 hrs.
- Group B: 50 neonates with duration of tachypnea ≤ 48 hrs

Both study groups were recruited to the following:

1. Full history taking focusing on; gestational age, birth weight, mode of delivery, gender, maternal risk factor like maternal asthma, diabetes

mellitus and pregnancy induced hypertension.

2. Full clinical examination, grading of respiratory distress, and need of oxygen supplementation are collected for both groups,
3. Laboratory investigation: oxygen saturation, ABG (arterial blood gases), CBC (complete blood count), platelet count, PMI and MPV were compared between the groups during admission to the NICU; and reevaluated after remission of the TTN.

PMI calculation with this formula:

(PMI = [Platelet counts] × [mean platelet volume/103]) (fL/nL). **(Gerday et al, 2009)**.

Statistical analysis:

Data management will be performed using the Statistical Package for Social sciences (version 15.0; SPSS Inc., Chicago, IL, USA). Computer standard descriptive statistics (e.g., mean, standard deviation) will be used to summarize the data.

Nominal data will be analyzed using simple X2 test, while independent sample T-test procedure will be used to compare means for two groups of cases; for more than two groups, data will be evaluated with one-way analysis of variance (ANOVA).

RESULTS

Our study data will be demonstrated in the following tables and figures:

Table (1): Neonatal data of both study groups

	Group A		Group B		P-value
	Mean	**SD**	**Mean**	**SD**	
Gestational age (weeks)	38.5	1.3	38.4	1.2	0.578# (NS)
Birth Weight (kg)	3.3	0.4	3.2	0.5	0.286# (NS)
	N	**%**	**N**	**%**	
Mode of delivery					
C.S	35	70.0%	37	74.0%	0.824## (NS)
NVD	15	30.0%	13	26.0%	

#Independent-t test ##Chi-squared test

The above table shows insignificant difference between two groups as regarding, mean gestational age, mean birth weight and mode of delivery.

Table (2): Comparison between both study groups as regarding Maternal Risk Factors

	Group A		Group B		P-value#
	N	%	N	%	
Gestational Diabetes mellitus(DM)					
Yes	5	10.0%	2	4.0%	0.240 (NS)
No	45	90.0%	48	96.0%	
Maternal Pregnancy induced hypertension (PIH)					
Yes	3	6.0%	1	2.0%	0.309 (NS)
No	47	94.0%	49	98.0%	
Maternal Bronchial asthma (BA)					
Yes	4	8.0%	1	2.0%	0.169 (NS)
No	46	92.0%	49	98.0%	

#Chi-squared test

The above table shows insignificant difference between two groups as regarding maternal risk factors (gestational DM, PIH and maternal BA).

Table (3): Comparison between two study groups as regarding Platelets indices

	Group A			Group B			P-value#
	Mean	SD		Mean	SD		
	Median	IQR		Median	IQR		
MPV (fL)	7.8	0.8		7.9	0.8		0.241 (NS)
	7.5	7.2	8.1	7.8	7.3	8.3	
Platelets count (*1000/mm^3)	232.2	56.7		403.9	75.5		**<0.0001 (S)**
	208.5	190	290	401	350	451	
PMI (fL/nL)	1796.4	373.4		3198.3	635.1		**<0.0001 (S)**
	1720.9	1486.1	2179.7	3207	2664.3	3612	

#Mann-Whitney U test, #SD: Standard Deviation, #IQR Interquartile range

There is significant statistical difference between both groups as regarding, platelets count (p-value <0.0001) and PMI (p-value <0.0001.

No significant statistical difference is found between both groups as regarding MPV (p value = 0.241).

Table (4): Correlation between tachypnea and clinical data of neonates for two study groups

	Tachypnea		P-value
	Group A (N=50)	Group B (N=50)	
Gestational age(weeks)	38.5±1.3	38.4±1,2	0.578
Male gender	29 (58)	28 (56)	0.840
Weight(K.g)	3.3±0.4	3.2±0.5	0.286
C.S	35 (70)	37 (74)	0.824
Maternal age	29.3±2.5	28.9±3.3	0.561
Gestational .D.M	5 (10)	2 (4)	0.240
PIH	3 (6)	1 (2)	0.309
Bronchial asthma	4 (8)	1 (2)	0.169

The difference in demographic characteristics and clinical finding between two groups was insignificant.

Table (5): Comparison between respiratory distress and radiological finding, platelets indices of neonates for two study groups:

	Respiratory distress		
	Group A (N=50)	Group B (N=50)	P-value
RD grade I	0 (0)	4 (8)	0.040*
RD grade II	25 (50)	30 (60)	
RD grade III	25 (50)	16 (32)	
Chest x-ray finding	50 (100)	11 (22)	<0.0001*
MPV (fL)	7.8±0.8	7.9±0.8	0.241
Platelets count (*1000/mm3)	232.2±56.7	403.9±75.5	<0.0001*
PMI (fL/nL)	1796.4±373.4	3198.3±635.1	<0.0001*

There was significant difference between two groups as regarding chest x ray finding, PMI and platelets count in relation to respiratory distress.

Table (6): Correlations between platelet indices and neonatal RD grades, Weight (Kg), and Gestational age (weeks)

		MPV (fL)	Platelets count (*1000/mm^3)	PMI (fL/nL)
RD Grades	**R**	-0.050	**-0.206**	**-0.199**
	P-value	0.623	**0.040***	**0.048***
Weight (Kg)	**R**	0.175	-0.076	-0.013
	P-value	0.084	0.454	0.898
Gestational Age(weeks)	**R**	0.087	-0.036	0.002
	P-value	0.392	0.725	0.981

*Significant

RD grades was negatively correlated with platelets count (r = -0.206) and PMI (r = -0.199) which was statistically significant.

On the other hand, there was no statistically significant correlation between platelet indices and other parameters.

Table (7): Sensitivity and specificity of platelet indices for predicting duration of tachypnea

Parameter	AUC	P-value	Cut-off point	Sensitivity	Specificity
MPV (fL)	0.568	0.243	7.75	64%	50%
Platelets count (*1000/mm^3)	0.962	**<0.0001***	309.5	90%	90%
PMI (fL/nL)	0.970	**<0.0001***	2395.25	94%	88%

*Significant

This table shows that Platelets count and PMI had an excellent discriminative power for predicting tachypnea > 48 hours (AUC = 962 and 0.970, respectively).

Also, the optimal cut-point for platelets count was 309.5 which produced sensitivity and specificity of 90.0%. While the optimal cut-point for PMI was 2395.25 yielding sensitivity of 94.0% and specificity of 88.0%.

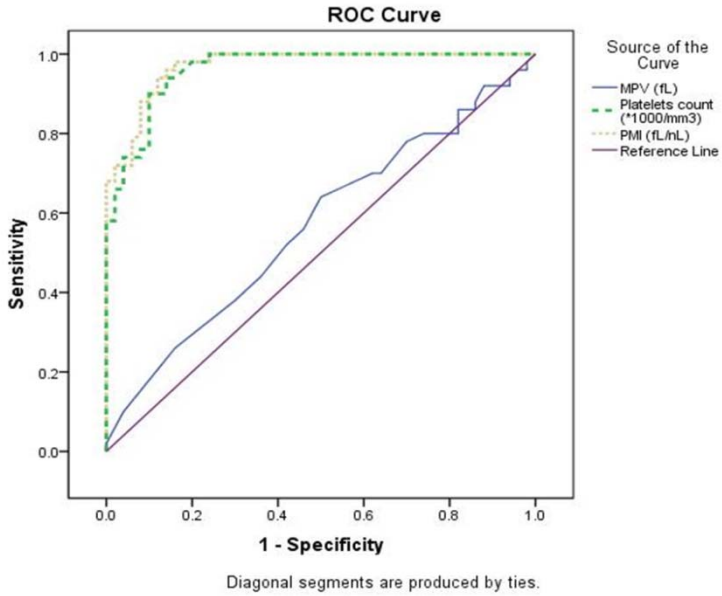

Figure (1): Sensitivity and specificity at platelet indices for predicting duration of tachypnea

Table (8): Sensitivity and specificity of platelet indices for predicting duration of oxygen supplementation

Parameter	AUC	P-value	Cut-off point	Sensitivity	Specificity
MPV (fL)	0.573	0.212	7.65	65.2%	50%
Platelets count (*1000/mm^3)	0.943	**<0.0001***	302	87%	88.9%
PMI (fL/nL)	0.963	**<0.0001***	2463.2	97.8%	81.5%

*Significant

This table shows that Platelets count and PMI also had an excellent discriminative power for predicting duration of oxygen supplementation (AUC = 943 and 0.963, respectively). Also, the optimal cut-point for platelets count was 302 which produced sensitivity of 87% and specificity of 88.9 %. While the optimal cut-point for PMI was 2463.2 yielding sensitivity of 97.8 % and specificity of 81.5%.

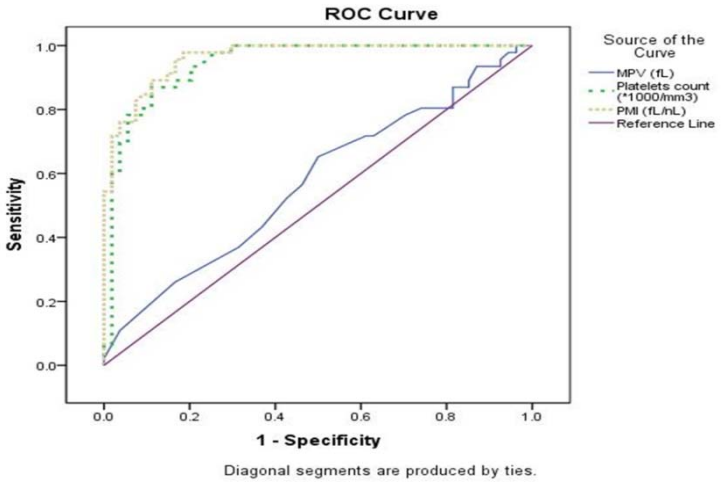

Figure (2): Sensitivity and specificity at platelet indices for predicting duration of oxygen supplementation

DISCUSSION

Transient tachypnea of the newborn (TTN) is one of the leading causes of neonatal respiratory distress and is therefore an important diagnosis to consider, identify correctly, and manage. It is mostly a benign, self-limited condition that presents shortly after birth and occurs in infants of any gestational age **(Machado et al., 2011)**. Diagnosis of TTN is based on an infant's clinical presentation, physical examination findings, and classic chest radiographic findings. The management consists of supportive care, with symptoms generally resolving by 24 to 72 hours of age **(Hagen, et al., 2017)**.

Our study is a case control study that was conducted on 100 full-term neonates who were born ± 37 weeks of gestational age and admitted immediately or shortly after birth in the neonatal intensive care unit (NICU) in Fayoum governorate hospitals by respiratory distress. Neonates were divided according to the duration of tachypnea into two groups, group A: 50 neonates with duration of tachypnea >48 hours. And group B: 50 neonates with duration of tachypnea ≤ 48 hours.

We observed that, platelet counts were significantly lower in the group with tachypnea duration of > 48 h compared to those with tachypnea duration of ≤ 48 h, which in agreement with **Sharm and Thapar, 2015** who demonstrated that TTN was significantly associated with

Thrombocytopenia **(Sharm and Thapar, 2015)**.

Also the results of **Boutaybi et al.,** observed early onset thrombocytopenia in term neonates with TTN **(Boutaybi et al., 2014)**.

Cosar et al., divided patients into two groups according to the duration of tachypnea (≤ 48 h and > 48 h), but no significant differences were found in their platelet count. Also he demonstrated that patients with severe TTN had significantly lower MPV levels. However, this study did not report any association between the MPV levels and severity of the TTN, which was consistent with the findings of the study **(Cosar et al., 2017)**.

As we observed, there was no significant association between MPV levels and severity of respiratory distress, however, platelet counts were significantly lower in severe TTN group. Therefore, we thought that the reason of lower PMI in severe TTN group was caused by platelet count rather than MPV levels.

PMI is associated with platelet functionality because larger platelets are enzymatically more active than the smaller platelets **(Gerday et al., 2009)**, **(Mangalpally et al., 2010)**. Recently, some studies that aimed at reducing unnecessary transfusions have suggested that the use of platelet mass index instead of platelet count should be used as an indicator of platelet transfusion **(Gerday et al., 2009)**, **(Paul et al., 2014)**. We noticed lower PMI levels in the group with more severe TTN but; no significant differences were noted in the MPV values between two study groups.

Results of the current study showed that there were no significant difference between two groups as regard gestational age, weight and gender.

On the other hand, **Günaydın et al., 2012**, found no significant differences observed as regarding gestational age and gender of neonate between newborns with or without TTN **(Günaydın et al., 2012)**. However, **Tutdbi et al., 2010** found that TTN is more frequent in male neonates **(Tutdbi et al., 2010)**.

Also, according to pregnancy induced hypertension (PIH) there was no significant difference between two groups. On contrast, Wei-Shan Chang et al demonstrated that Women with PIH have an increased risk of having infants who develop TTN compared with those without PIH **(Wei Shan Chang et al., 2018)**.

The present study had certain limitations. As this study is retrospective, the method and timing of obtaining CBCs was not sufficiently standardized. Moreover, our results might not be fully generalizable to infants with TTN in all hospitals and includes a relatively smaller sample size.

CONCLUSION

TTN is a common clinical condition in NICU. Early detection of TTN is highly appreciated to prevent worsening of the condition. We speculate that PMI, platelet count, and MPV levels are affected depending on the severity of TTN. Although low platelet count and low PMI levels are associated with longer duration of tachypnea in patients with TTN, we concluded that PMI is better than platelet count to predict severe TTN. Platelet mass index (PMI) might be useful for clinicians to predict duration and severity of TTN in NICU.

REFERENCES

1. **Isik DU, Bas AY, Demirel N, (2010):** Increased asymmetric dimethylarginine levels in severe transient tachypnea of the newborn. J Perinatol; 52:232.
2. **Machado LU, Fiori HH, Baldisserotto M. et al., (2011):** Surfactant deficiency in transient tachypnea of the newborn. J Pediatr 159: 750.
3. **Helve O, Pitkänen O, Janér C, Andersson S, (2009):** Pulmonary fluid balance in the human newborn infant. Neonatology.; 95: 347–52
4. **Strauss T, Maayan-Metzger A, Simchen MJ, Morag I, Shenkmean B, Kuint J, et al, (2010):** Impaired platelet function in neonates born to mothers with diabetes or hypertension during pregnancy. Klinische Pädiatrie. 222(3):154-157.
5. **Gerday E, Baer VL, Lambert DK, et al. (2009):** Testing platelet mass versus platelet count to guide platelet transfusions in the neonatal intensive care unit. Transfusion.; 49: 2034-9.
6. **Ozkan Ilhan (2019):** Platelet mass index and prediction of severity of transient tachypnea of the newborn, Pediatr Int. 697-705.
7. **Guglani L, Lakshminrusimha S, Ryan RM. (2008):** Transient tachypnea of the newborn. Pediatr Rev. 2008; 29: 59–65.
8. **Hagen, Eunice and Cheryl Lew, et al., (2017):** Transient tachypnea of the newborn; NeoReviews 18.3: e141-e148.
9. **Sharma A, Thapar K. (2015):** A prospective observational study of thrombocytopenia in high risk neonates in a tertiary care teaching hospital. Sri Lanka Journal of Child Health.: 44: 213-9.
10. **Boutaybi N, Razenberg F, Smits-Wintjens V, van Zwet EW, Rijken M, Steggerda S, et al. (2014):** Neonatal thrombocytopenia after perinatal asphyxia treated with hypothermia: A retrospective case control study. International Journal of Pediatrics. 2014; 2014:760654.
11. **Cosar H, Yılmaz O, Bulut Y,**

Temur M (2017): Red blood cell distribution width and transient tachypnoea of the newborn. HK J Paediatr (new series).2017; 22: 159-62.

12. **Mangalpally KK, Siqueiros-Garcia A, Vaduganathan M, Dong JF, Kleiman NS, Guthikonda S. (2010):** Platelet activation patterns in platelet size sub-populations: differential responses to aspirin in vitro. J Thromb Thrombolysis. 2010; 30: 251e62.
13. **Paul DA. Zisk JL, Mackley A, Clearly G, Chang E, Christensen RD, (2014):** Transfusing neonates based on platelet count vs. platelet mass: A randomized feasibility-pilot study. Platelets 2014; 25: 513– 6.
14. **Gunaydin, Ayca and Aksakal (2012):** Retrospective analysis on transient tachypnea of the newborn: is it associated with spinal anesthesia after cesarean section.Gaziantep Medical Journal, 18(2), 77-80.
15. **Tutdibi E, Gries K, Bücheler M, (2010):** Impact of labor on outcomes in transient tachypnea of the newborn: population-based study. Pediatrics125: e577.
16. **Wei Shan Chang et al. (2018):** Maternal pregnancy-induced hypertension increases the subsequent risk of transient tachypnea of the newborn: A nationwide population-based cohort study, Taiwan J Obstet Gynecol 57(4):546-550.