

Health Economic Evaluation

The use of immature granulocyte and other complete blood count parameters in the diagnosis of transient tachypnea of the newborn

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ABSTRACT

Background: Although Transient tachypnea of the newborn (TTN) is one of the most common causes of respiratory distress in the newborn period, there is no laboratory parameter used to diagnose it. Immature granulocyte (IG) measurement is accepted as a useful indicator that can be used in early detection of many infectious conditions, especially neonatal sepsis. In this study, it was aimed to determine if IG and other complete blood count (CBC) parameters could be used as laboratory findings supporting TTN diagnosis.

Materials and methods: This study, which was retrospectively planned, was conducted in the neonatal intensive care unit (NICU) a public hospital between January 1, 2019 and January 31, 2021. Randomly selected 50 infants hospitalized with the diagnosis of TTN, constituted the patient group of the study. 50 infants hospitalized with the diagnosis of hyperbilirubinemia and did not have any additional problems accepted as the control group. IG and other CBC parameters of infants in the patient and control groups were compared in the study.

Results: There was no significant difference between the patient and control groups in terms of demographic data and types of delivery ($p > 0.05$). The rate of delivery by elective cesarean section (C/S) was significantly higher than the rate of normal spontaneous vaginal (NSV) delivery in the patient group ($p < 0.001$). The IG number and percentage, WBC (white blood cell) count, RDW (red cell distribution width), number and percentage of NRBC (nucleated red blood cell), neutrophil and lymphocyte ratio, count and percentage of basophil and PLR (platelet/lymphocyte ratio) of the patient group was significantly higher than the control group ($p < 0.05$).

Conclusion: According to the findings obtained in the study, it was concluded that IG and other CBC parameters may be used to support clinical and imaging findings to diagnose transient tachypnea of the newborn.

1. Introduction

Transient tachypnea of the newborn (TTN), a clinical syndrome associated with respiratory distress, was first defined in 1966 by Avery et al. [1,2]. It is known to be the most common (40%) cause of respiratory distress in late preterm and term infants [3]. Although real frequency of TTN is not exactly known; it is estimated that 0.33–0.50% of infants develop this disease at birth [4].

Elective C/S, low gestational age, male sex, low birth weight, low Apgar score, maternal asthma, maternal sedation during delivery and perinatal asphyxia are the main known risk factors for TTN [5,6]. However, the etiology of TTN is not exactly known yet. Delay in the removal of fetal lung fluid in the early postnatal period and the resulting enlargement of interstitial spaces, alveolar air retention and decreased lung compliance have been suggested in the pathogenesis of TTN [7].

Transient tachypnea of the newborn is expressed as a benign and self-

limiting disease. Usually, the disease is expected to be resolved within 24–72 h with short-term oxygen therapy ($\text{FiO}_2 < 40\%$). If respiratory distress symptoms persist longer than 72 h in TTN, other possible diagnoses should be investigated [8]. In addition factors like associated hypoxemia, respiratory failure and pulmonary air leak syndromes may increase the risk of morbidity [9–11]. It has been reported that in the first 1 year of life the risk of hospitalization due to respiratory syncytial virus bronchiolitis in infants undergoing TTN in the neonatal period is higher than in infants without TTN [12].

2. Material and method

2.1. Study design

This retrospective study was conducted between January 1, 2019 and January 31, 2021, in the Neonatal Intensive Care Unit (NICU) of a

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public hospital in Kastamonu/Turkey. The study consisted of 50 randomly selected infants diagnosed with TTN. 50 infants, treated for hyperbilirubinemia and had no additional problems with similar age, gestational week and gender distribution characteristics were the control group of the study.

The study was registered at researchregistry (<https://www.researchregistry.com/browse-the-registry#home/registrationdetails/616008cdd3ff83001fe5d5dbd/>).

2.2. Exclusion criteria

Infants with birth asphyxia (pH < 7.1 in umbilical cord blood gas, HCO₃>12, base deficit < -10.5, min Apgar score <3), congenital lung anomaly, diseases that can change CBC parameters and inflammatory markers (ex: sepsis, malignancy); infants born before 36 weeks and without CBC data were excluded from the study.

2.3. Data collection

Data on laboratory tests, age and gender of the patients were obtained from the hospital Laboratory Information System. CBC parameters of the patients at their first hospitalization (before the treatment) were measured with Automatic hematological analyzer (XN-1000-Hematology-Analyzer-System Corporation, Japan).

2.4. Ethics

Prior to the study, the requisite approvals were obtained from Kastamonu University Ethics Committee (2020-KAEK-143-99).

2.5. Statistical analysis

“Statistical Package for Social Sciences 18.0 for Windows” (SPSS Inc., Chicago, USA) were used for the data analysis. In the descriptive statistics of the data, for categorical variables number and % were used. For numerical variables, median (25 Percentiles, 75 Percentiles) values were used.

For the comparison of the data between the groups in cases that did not show normal distribution, the Mann Whitney *U* test was used. The chi-square test was used to determine whether there was a significant difference between the two groups in terms of age and gender. Area Under Curve (AUC), cut-off, sensitivity and specificity values was determined by Receiver Operating Characteristic (ROC) analysis and Youden's index. P-Value<0.05 was considered statistically significant in the interpretation of the data.

3. Results

Our study was carried out with a total of 100 infants (50-patient group/50-control group). 30 (60%) of the infants in the patient group were male and 20 (40%) were female. Males were significantly higher than females (p < 0.05). In the control group, there were 29 (58%) male,

Table 1
The Demographic data of infants (patient and control groups).

	Patient Group	Control Group	P
Gender (n, %)			
Male	30 (60)	29 (58)	0.2
Female	20 (40)	21 (42)	
Mean maternal age (year)	26.53 ± 5.68	27.92 ± 5.75	0.8
Mean gestational week	37.4 ± 1.49	37.6 ± 1.89	0.4
Delivery Type (n, %)			
C/S	40 (80)	38 (76)	
Elective	37 (74)		0.6
Emergency	3 (6)		
NSV	10 (20)	12 (24)	

21 (%42) female infants. There was no significant difference between the groups in terms of gender distribution (p > 0.05). (Table 1).

Mean maternal age was 26.53 ± 5.68 years and 27.92 ± 5.75 years in the patient and control groups, respectively. The mean gestational week was 37.4 ± 1.49 weeks in the patient group and 37.6 ± 1.89 weeks in the control group. No significant differences were found between the groups in terms of mean maternal age and mean gestational week (p > 0.05) (Table 1).

The delivery type of 80% of the patient group was C/S (74% elective, 6% emergency) 20% was NSV (Normal Spontaneous Vaginal), 76% of the control group was C/S and 24% was NSV. There was no significant difference between the two groups in terms of delivery type (p > 0.05) (Table 1). The rate of elective C/S delivery in the patient group was significantly higher than the rate of NSV delivery (p < 0.001) (Table 2). The birth weight of the infants ranged between 2500 and 4000 g, and there was no significant difference between the groups in terms of birth weight (p > 0.05).

The WBC, RDW, NRBC, neutrophil count, lymphocyte count, basophil count and percentage, monocyte percentage, PLR, IG number and percentage were found to be statistically significantly higher in the patient group than in the control group (Table 3) in the comparison of CBC parameters. There was no statistically significant difference between the groups in terms of other CBC parameters. Platelet mass index (PMI) was calculated with the formula of “platelet count x mean platelet volume (MPV)/103 (fl/nl)” [13], and no statistically significant difference was found between the two groups (p > 0.05).

ROC curve analysis was performed to determine the cut-off values of CBC parameters for predicting the TTN diagnosis (Fig. 1). ROC curve analysis values of CBC parameters, which are especially important in predicting the diagnosis of TTN, are listed in Table 4.

In the study, we concluded that the development of pneumothorax and use of chest tube among the infants in the patient group was only 2 (4%). We did not conclude any other complications or mortality.

4. Discussion

The C/S is the most frequently performed surgical operation worldwide. Over the past few decades, the rate of CS delivery has been risen rapidly. The long standing WHO advice of 10–15% of deliveries by CS, but this percent is exceeded in many high-income places (average rate of 27%) and low to middle-income settings (up to 29%) [14].

In the study of Eyi et al. in Turkey, the overall C/S ratio was found to be 51.2% [15]. Elective C/S delivery has been defined as a modifiable risk factor for TTN in the literature [16]. The fact that the activation of the hypothalamic-pituitary-adrenal axis induced by labor and the resulting increase in corticosteroid hormone levels does not occur in elective C/S delivery is thought to delay lung maturation [17]. In the study of Özkiliç et al.; 53.4% of infants were born with elective C/S and 24.4% were born with NSV [18]. Kheir et al. Concluded in their study that, 68.7% of infants diagnosed with TTN were born with elective C/S [19]. Similarly, in our study, it was determined that elective C/S delivery was significantly higher than NSV delivery.

The immature granulocytes (IG) in peripheral blood reflect an active bone marrow response to bacterial infection. IG are classified as promyelocytes, myelocytes, and metamyelocytes by microscopic examination [20,21]. The advances in technology have enabled automated hematology analyzers to identify and count IGs, resulting in improved quality and cost in the laboratory [22].

In our study, we concluded that the number and percentage of IG was significantly higher in the patient group than in the control group. As a

Table 2
The Comparison of delivery types in the patient group.

Patient Group	Elective C/S	NSV	P
n, %	37 (74)	10 (20)	<0.001

Table 3
The Comparison of CBC parameters of groups.

CBC parameters	Patient Group	Control Group	P
Median (IQR)			
WBC	17.1(12.6; 20.4)	11.43(9.93; 15.06)	<0.001
RDW_SD	59.5(56.5; 65.8)	57.6(51.8; 63.3)	0.022
RDW_CV	16.5(15.9; 18.1)	15.7(14.8; 17.2)	0.007
NRBC#	0.55(0.15; 1.45)	0.01(0.00; 0.13)	<0.001
NRBC%	3.2(0.9; 10.6)	0.1(0.00; 0.67)	<0.001
NEUT#	7.42(4.37; 11.4)	4.37(2.76; 8.68)	0.014
LYMPH#	6.01(4.23; 8.42)	5.11(3.74; 6.66)	0.012
BASO#	0.17(0.12; 0.22)	0.1(0.06; 0.13)	<0.001
MONO%	10.7(8.1; 13.4)	8.7(7.8; 10.6)	0.008
BASO%	1.1(0.8; 1.4)	0.8(0.57; 1.1)	0.009
IG#	0.38(0.25; 0.69)	0.11(0.06; 0.28)	<0.001
IG%	2.3(1.7; 3.4)	1.0(0.6; 2.02)	<0.001
PLR	56.2(42.4; 68)	44.6(32.5; 57)	0.009

WBC: White blood cell, RDW: Red cell distribution width, NRBC: Nucleated red blood cells, NEUT: Neutrophil LYMPH: Lymphocyte, BASO: Basophil, MONO: Monocyte, IG: Immature granulocyte, PLR: Platelet/lymphocyte ratio.

result of the ROC analysis, the cut-off value of the IG number for TTN was found to be 0.23 (78% sensitivity, 72% specificity), and the cut-off value of the IG percentage was found to be 1.65 (76% sensitivity, 68% specificity). In the light of these findings, we think that neonatal transient tachypnea may be an infectious/inflammatory condition that stimulates the bone marrow and causes IG production.

Yorulmaz et al. [23] reported that the WBC count, neutrophil count, lymphocyte count, and RDW ratio were significantly higher in infants hospitalized in NICU due to neonatal sepsis compared to infants hospitalized due to neonatal jaundice and had no other problems. We found that the same parameters were significantly higher in infants with a diagnosis of TTN than in the control group. Considering these results, we think that TTN may be an infectious/inflammatory condition like neonatal sepsis. The positive effect of starting empirical antibiotic therapy for TTN in the NICU on the patient’s clinic supports this thought.

Ilhan et al. [13] concluded a negative correlation between platelet count and PMI and the duration of tachypnea in TTN ($r = -0.43$, $p < 0.001$). They reported that as the platelet count and PMI decreased in

infants with TTN, the duration of tachypnea was prolonged. In our study, PLR was significantly higher in infants with TTN compared to the control group, but there was no significant difference between the two groups in terms of platelet count and PMI.

Nucleated red blood cell (nRBC), a premature red blood cell, is an indicator of hematopoiesis in a newborn infant and has been known to be associated with hypoxia [24,25]. In different studies, it was concluded that NRBC was an important marker showed that newborn babies went through the hypoxic process.

In their study, Boskabadi et al. [26] found that NRBC increased significantly in the first 6 h in infants with hypoxic ischemic encephalopathy. According to Sarah et al. [27] the high NRBC in infants in the NICU was an indicator for severe hypoxia; and they stated a significant relationship between the number of NRBCs and mortality. In our study, we found that the NRBC level was higher in infants with TTN compared to infants in the control group who did not experience hypoxia. According to this result we thought that infants with TTN had gone through an important hypoxic period. Ozkilinc et al. [18] reported that only one infant (2.2%) developed pneumothorax due to TTN. In our study, we found that pneumothorax developed in only 2 (4%) infants which was consistent with the literature.

In summary, we found that IG and other CBC parameters can be useful to support clinical and imaging findings to diagnose TTN.

Limitations of the Study: One of the main limitations of the study is that it has been carried out retrospectively. Therefore, prospective studies are required to reach more definite conclusions about the functionality of these parameters in diagnosing the disease.

Table 4
The ROC curve analysis values of TTN patients.

	Cut-off	AUC	95%CI	p	Sensitivity	Specificity
WBC	12,06	,727	0,62-0,82	,000	84	58
NRBC#	0,19	,823	0,73-0,90	,000	74	80
NRBC%	0,55	,810	0,72-0,89	,000	82	72
BASO#	0,13	,745	0,64-0,84	,000	68	76
IG#	0,23	,765	0,49-0,66	,000	78	72
IG%	1,65	,753	0,50-0,65	,000	76	68

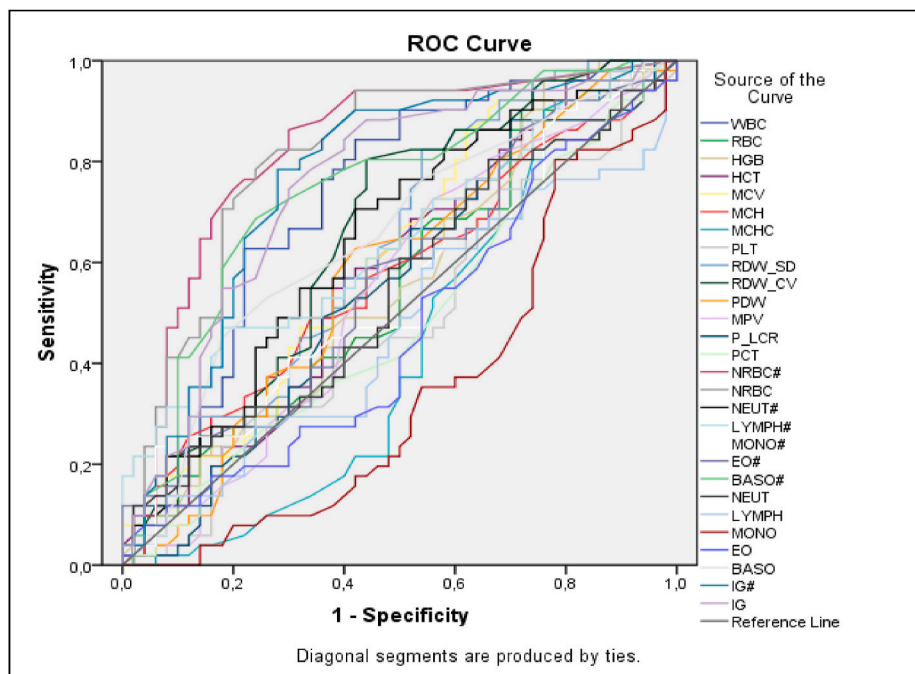


Fig. 1. The ROC Curve analysis of CBC parameters of TTN patients.

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Ethical approval

Since the study did not include human subject ethical approval was not taken.

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Author contribution

EC: Designing the study, analysis and interpretation of data, collecting data and final approval of the version.

SG, EY: Review the written material and edited. Revising critically.

All of the authors have read and approved the final manuscript.

Consent

None.

Registration of research studies

1. Name of the registry:
2. Unique Identifying number or registration ID:
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

MD. Emrah CIGRI.

Declaration of competing interest

The authors have no conflict of interest.

References

- [1] J.A. Whitsett, W.R. Rice, B.B. Warner, S.E. Wert, G.S. Pryhuber, Acute respiratory disorders, in: M.G. MacDonald, M.D. Mullet, M.M. Seshia (Eds.), *Avery's Neonatology: Pathophysiology and Management of the Newborn*, Lippincott Williams Wilkins, Philadelphia, 2005, pp. 553–577.
- [2] M.E. Avery, O.B. Gatewood, G. Brumley, Transient tachypnea of the newborn: possible delayed resorption of fluid at birth, *Am. J. Dis. Child.* 111 (1966) 380–385.
- [3] T.N. Raju, R.D. Higgins, A.R. Stark, K.J. Leveno, Optimizing care and outcome for late-preterm (near-term) infants: a summary of the workshop sponsored by the National Institute of Child Health and Human Development, *Pediatrics* 118 (3) (2006) 1207–1214.
- [4] A.K. Hansen, K. Wisborg, N. Ulbjerg, T.B. Henriksen, Risk of respiratory morbidity in term infants delivered by elective caesarean section: cohort study, *BMJ* 336 (2008) 85–87.
- [5] S. Ozkiraz, Z. Gokmen, S.B. Boke, H. Kilicdag, D. Ozel, A. Sert, Lactate and lactate dehydrogenase in predicting the severity of transient tachypnea of the newborn, *J. Matern. Fetal Neonatal Med.* 26 (2013) 1245–1248.
- [6] A. Derbent, M. Tatli, M. Duran, et al., Transient tachypnea of the newborn: effects of labor and delivery type in term and preterm pregnancies, *Arch. Gynecol. Obstet.* 283 (2011) 947–951.
- [7] A. Kumar, B.V. Bhat, Epidemiology of respiratory distress of newborns, *Indian J. Pediatr.* 63 (1996) 93–98.
- [8] B. Kasap, N. Duman, E. Ozer, M. Tatli, A. Kumral, H. Ozkan, Transient tachypnea of the newborn: predictive factor for prolonged tachypnea, *Pediatr. Int.* 50 (1) (2008) 81–84.
- [9] D.I. Tudehope, M.H. Smyth, Is "transient tachypnoea of the newborn" always a benign disease? Report of 6 babies requiring mechanical ventilation, *J. Paediatr. Child Health* 15 (3) (1979) 160–165.
- [10] H.L. Halliday, G. McClure, M.M. Reid, Transient tachypnoea of the newborn: two distinct clinical entities? *Arch. Dis. Child.* 56 (5) (1981) 322–325.
- [11] T.L. Gross, et al., Transient tachypnea of the newborn: the relationship to preterm delivery and significant neonatal morbidity, *Am. J. Obstet. Gynecol.* 146 (3) (1983) 236–241.
- [12] H. Santtu, S. Liina, G. Mika, P. Olli, A. Sture, H. Otto, Transient tachypnea of the newborn is associated with an increased risk of hospitalization due to respiratory syncytial virus bronchiolitis, *Pediatr. Infect. Dis. J.* 38 (4) (2019) 419–421.
- [13] O. Ilhan, M. Bor, Platelet mass index and prediction of severity of transient tachypnea of the newborn, *Pediatr. Int.* 61 (7) (2019) 697–705.
- [14] A. Hasan, A. Deyab, K. Monazea, et al., Clinico-pathological assessment of surgically removed abdominal wall endometriomas following cesarean section, *Ann Med Surg (Lond)* 62 (2021 Jan 21) 219–224.
- [15] E.G. Eyi, L. Mollamahmutoglu, An analysis of the high cesarean section rates in Turkey by Robson classification, *J. Matern. Fetal Neonatal Med.* 34 (16) (2021 Aug 18) 2682–2692.
- [16] A. Buchiboyina, B. Jasani, M. Deshmukh, S. Patole, Strategies for managing transient tachypnea of the newborn—a systematic review, *J. Matern. Fetal Neonatal Med.* 30 (2016) 1524–1532.
- [17] M. Kurek Eken, G. Sahin Ersoy, S. Cetinkaya, C. Cam, A. Karateke, The effect of labour pain in caesarean delivery on neonatal and maternal outcomes in a term low-risk obstetric population, *J. Obstet. Gynaecol.* 38 (2017) 27–31.
- [18] M.C. Ozkılıç, E.E. Yalınbaş, Geç preterm ve term yenidoğanlarda yenidoğanın geçici takipnesi gelişmesi ile kortizol, epinefrin ve tiroid hormonları düzeyleri arasındaki ilişki, *Güncel Pediatri* 18 (3) (2020) 358–369.
- [19] A.E. Kheir, T.A. Ahmed, Prevalence, risk factors and short term outcome of infants with transient tachypnea of the newborn in Sudan, *Eur J Pharm Med Res* 3 (2016) 23–26.
- [20] D.P. Frings, B. Montag, A. Heydorn, M. Friedemann, W. Pothmann, A. Nierhaus, Immature granulocytes, immature myeloid cells and outcome in adult severe sepsis and septic shock, in: *Proceedings of the 16th Annual Congress of the European Society of Intensive Care Medicine (ESICM '03)*, October 2003. Amsterdam, Netherlands.
- [21] C. Iddles, J. Taylor, R. Cole, et al., Evaluation of immature granulocyte count in the diagnosis of sepsis using the Sysmex XE-2100 analyser, *Sysmex Journal International* 17 (2007) 20–29.
- [22] S. Balamurugan, K. Treshul, S. Jayapria, M. Jeya, R.K. Ramesh, Automated measurement of immature granulocytes: performance characteristics and utility in routine clinical practice, *Pathol. Res. Int.* 2012 (2012) 483670.
- [23] A. Yorulmaz, M. Yücel, S. Sert, Yenidoğan sepsis olgularında hematolojik parametrelerin tansal değeri, *Ortadoğu Medical Journal* 10 (3) (2018) 252–262.
- [24] G. Buonocore, S. Perrone, D. Gioia, Nucleated red blood cell count at birth as an index of perinatal brain damage, *Am. J. Obstet. Gynecol.* 181 (1999) 1500–1505.
- [25] B. Thilaganathan, S. Athanasiou, S. Ozmen, S. Creighton, N.R. Watson, K. H. Nicolaides, Umbilical cord blood erythroblast count as an index of intrauterine hypoxia, *Arch. Dis. Child. Fetal Neonatal Ed.* 70 (1994) F192–F194.
- [26] H. Boskabadi, M. Zakerihamidi, M.H. Sadeghian, A. Avan, M. GhayourMobarhan, G.A. Ferns, Nucleated red blood cells count as a prognostic biomarker in predicting the complications of asphyxia in neonates, *J. Matern. Fetal Neonatal Med.* 30 (2017) 2551e6.
- [27] U.M. Sarah, B. Kaitlyn, A.F. Henry, T.L. Kristen, Association of nucleated red blood cell count with mortality among neonatal intensive care unit patients, *Pediatrics and Neonatology* 61 (2020) 592–597.