

Incidence of Thrombocytopenia in NICU and Its Association with Immature Platelet Fraction and Absolute Immature Platelet Count: A Cross-sectional Study

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ABSTRACT

Introduction: Neonatal Thrombocytopenia (TCP) is frequently encountered in the Neonatal Intensive Care Unit (NICU), occurring either due to decreased production or increased destruction of platelets. This condition often leads to increased platelet transfusions in a NICU setting. Immature Platelet Fraction (IPF) and Absolute Immature Platelet Count (AIPC) are hypothesised to be surrogate markers of bone marrow activity and can help in differentiating between TCP caused by decreased production or increased destruction.

Aim: To estimate the incidence of neonatal TCP in newborns admitted to a tertiary care NICU and to investigate the association of IPF percentage and AIPC values with the cause of TCP.

Materials and Methods: This cross-sectional study was conducted in the Department of Paediatrics and Neonatology at Dr. D.Y. Patil Medical College, Navi Mumbai, Maharashtra, India, from April 2021 to May 2022. All 46 newborns admitted to the NICU with TCP were enrolled in the study. The total number of NICU admissions during the study period was used

to calculate the incidence. The Complete Blood Count (CBC) with reticulocyte count and peripheral smear was examined using the impedance technique. The IPF and AIPC values were determined using an automated CBC counter based on flow cytometry principles. Statistical analysis was performed using the Chi-square test.

Results: The study included a total of 46 neonates with TCP, with an incidence rate of 6.14%. Among the patients with TCP, 18 (39.13%) had mild, 17 (36.95%) had moderate, and 11 (23.91%) had severe TCP. The majority of neonates (21.7%) had a significant maternal history of Pregnancy Induced Hypertension (PIH). Of the neonates with TCP, 42 (91.3%) had high IPF and 4 (8.6%) had normal IPF. Regarding AIPC, 29 (63.04%) had normal values, 11 (23.91%) had high values, and 6 (13%) had low values. No significant association was found between IPF and AIPC values and the diagnosis of TCP in this study.

Conclusion: The present study concludes that IPF and AIPC investigations cannot be recommended as markers to confirm the cause of TCP.

Keywords: Bone marrow, Disseminated intravascular coagulation, Perinatal asphyxia, Platelet allo-antibodies, Neonatal intensive care unit

INTRODUCTION

TCP is one of the most prevalent haematological issues in newborns. While neonatal TCP is rare overall (0.7 to 0.9%), it is notably more common (18 to 35%) among newborns hospitalised in the NICU [1]. Early-onset TCP tends to be mild to moderate and resolves spontaneously, whereas late-onset TCP is often more complex and prolonged, aiding in predicting its duration and severity [2]. Various factors contribute to impaired platelet production, including inherited disorders and conditions involving bone marrow infiltration, leading to neonatal TCP. It is particularly prevalent in preterm neonates with placental insufficiency or foetal hypoxia, commonly associated with maternal pre-eclampsia and foetal intrauterine growth restriction [3].

Increased platelet destruction is a common cause of neonatal TCP. Maternal platelet alloantibodies are responsible for 15-20% of cases present at birth [4,5]. Disseminated intravascular coagulation accounts for 10-15% of cases, particularly in very ill infants, often associated with perinatal asphyxia and infection [6-8]. Neonates can develop autoimmune TCP due to placental transfer of maternal platelet autoantibodies in mothers with autoimmune disorders [9]. Non-immune neonatal TCP can result from various factors such as sepsis, Necrotising Enterocolitis (NEC), viral infections (e.g.,

rubella, herpes simplex, cytomegalovirus, echovirus, and human immunodeficiency virus), disseminated intravascular coagulation, exchange transfusion, and vascular malformations [2].

The majority of newborns who develop TCP due to unfavourable foetal environments experience impaired megakaryocytopoiesis at birth, predisposing them to worsening TCP when exposed to concurrent neonatal platelet consumptive "stress" [3]. IPF serves as a measure of bone marrow activity, aiding in the differentiation between decreased production and increased destruction of platelets in neonates with TCP [10]. IPF, expressed as a percentage of immature platelets, or AIPC, an absolute number per microliter of blood, are increased in consumptive TCP (e.g., disseminated intravascular coagulation, infection, NEC, and immune-mediated TCP) and certain inherited TCP syndromes (such as Wiskott-Aldrich syndrome), while they decrease with decreased platelet production (e.g., some syndromic causes of TCP, neonates with intrauterine growth restriction, and birth asphyxia). This aids in predicting aetiology and guiding management decisions [10].

IPF and AIPC are unique parameters made possible by recent diagnostic advancements in the field of haematology. Understanding the cause of TCP is crucial, as different approaches

and treatments will be utilised. Due to the high incidence of TCP in neonates admitted to the NICU, they often receive many, and at times un-indicated, platelet transfusions. Avoiding these un-indicated platelet transfusions is possible if the cause is understood [11]. Additionally, studies on IPF and AIPC in neonates are scarce. With this background, this cross-sectional study was planned to ascertain the incidence of TCP in babies admitted to the NICU of D. Y Patil Hospital in Navi Mumbai, Maharashtra, India, and to study the association of AIPC and IPF with the cause of TCP.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Department of Paediatrics and Neonatology at Dr. D.Y. Patil Medical College, Navi Mumbai, Maharashtra, India, from April 2021 to May 2022 on all newborns admitted to the NICU within the study period. The study was approved by the institutional ethical committee (IEC Approval Number-EC/NEW/INST/2019/473). Informed consent was taken from the parents/guardians of the children.

Inclusion criteria: All newborns admitted to the NICU with TCP were included.

Exclusion criteria: Newborns who received platelet transfusion before the IPF/AIPC investigation were excluded.

Procedure

Data collection: A detailed proforma was completed for newborns with TCP admitted to the NICU. The incidence of TCP in the NICU was calculated by dividing the number of TCP neonates by the total number of NICU admissions during the study period. The impedance technique was employed to assess CBC with reticulocyte count and peripheral smear. The automated CBC counter, based on the flow cytometry principle, was used to determine IPF% and AIPC. The IPF% is expressed as a percentage, representing the ratio of immature platelets to the total number of platelets multiplied by 100 [12]. AIPC is calculated by multiplying the IPF by the circulating platelet count and dividing by 100 [12].

Various tests were conducted to determine the aetiologies of TCP as clinically indicated. These tests included CBC, peripheral smear, C-Reactive Protein (CRP), Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), d-dimer, Liver Function Tests (LFT), Renal Function Tests (RFT), fibrin degradation products, serum

electrolytes, urine routine, stool routine, X-ray, Ultrasonography (USG), Magnetic Resonance Imaging (MRI), and High-Resolution Computed Tomography (HRCT). TCP was defined based on platelet count: mild TCP (platelet count: 100,000 to 149,000/ μ L) [13], moderate TCP (platelet count: 50,000 to 99,000/ μ L) [13], Severe TCP (platelet count: <50,000/ μ L) [13]. Additionally, IPF% was defined as 1 to 4.4%, and AIPC ranged from 2940 to 12820/ μ L [14,15].

STATISTICAL ANALYSIS

All data were entered into an excel sheet, and appropriate graphs and tables were made using Statistical Package for Social Sciences (SPSS) software version 20.0. Chi-square tests, mean, median, mode, and standard deviation will be calculated. A p-value <0.05 was considered significant.

RESULTS

The total number of patients admitted to the NICU during the study period was 814, out of which 50 patients developed TCP during the course of admission. Four children out of the 50 could not be included in the study as they received platelet transfusions before the IPF test could be ordered. The incidence of TCP was 6.14% in the present study.

There were more male babies with TCP than female neonates (male:female ratio 1.71:1). Out of 46 newborns, there were 29 male babies. Among the 46 patients with TCP, 18 (39.13%) had mild, 17 (36.95%) had moderate, and 11 (23.91%) had severe TCP. Of the 46 newborns, 18 had mild TCP, of which 10 (21.7%) were low birth weight and 8 (17.39%) were above 2500 gm. Moderate TCP was seen in 11 (23.9%) of low birth weight and 8 (17.3%) of normal weight newborns. Eight (17.39%) were low birth weight newborns, and 3 (6.5%) were normal weight with severe TCP [Table/Fig-1]. The mean number of days of life at which patients developed TCP was 22.57 days with a standard deviation of \pm 12.12 days.

In the present study, 11 (23.9%) neonates with a significant maternal history had mild TCP, while 9 (19.56%) with both moderate and severe TCP had a significant maternal history [Table/Fig-2].

Ten (21.7%) neonates had PIH as a significant maternal history, 5 (10%) had hypothyroidism, 4 (8%) had mothers with leaking PV for 24 hours, 4 (8%) had maternal TCP, and 3 (6%) had tuberculosis as a significant maternal history [Table/Fig-3].

	Thrombocytopenia (TCP)					
	Mild (N=18)		Moderate (N=17)		Severe (N=11)	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
Gender						
Male	12	26.08	10	21.73	7	15.21
Female	06	13.04	07	15.21	04	8.69
Total	18		17		11	
Birth weight						
Low birth weight	10	21.73	11	23.91	08	17.39
Normal weight	08	17.39	06	13.04	03	6.52
Total	18		17		11	
Gestational age						
Preterm	09	19.56	09	19.56	04	8.69
Full term	09	19.56	08	17.39	07	15.21
Total	18		17		11	

[Table/Fig-1]: Distribution of newborns admitted to NICU according to gender, birth weight, gestation and Thrombocytopenia (TCP) (N=46).

Significant maternal history	Thrombocytopenia (TCP)					
	Mild (n=18)		Moderate (n=17)		Severe (n=11)	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
Yes	11	23.9	09	19.56	09	19.56
No	07	15.21	08	17.39	02	4.34

[Table/Fig-2]: Distribution of newborns admitted to NICU according to significant maternal history and Thrombocytopenia (TCP) (N=46).

Significant maternal history	Thrombocytopenia (TCP)					
	Mild		Moderate		Severe	
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)
PIH	04	36.36	03	27.2	03	27.2
Hypothyroidism	01	9	01	9	03	27.2
PV Leaking since 24 hours	02	18.1	01	9	01	9
Maternal Thrombocytopenia (TCP)	01	9	03	27.2	0	0
Tuberculosis	02	18.1	0	0	01	9
Others (gestational diabetes mellitus, anomaly scan suggestive of Down's syndrome)	01	9	01	9	01	9

[Table/Fig-3]: Types of implant used for Internal Distraction Plating in Distal Radius Fractures; One patient can have more than one history.

The data in [Table/Fig-4] presents the distribution of IPF levels across different diagnosis for 46 cases. Elevated IPF levels (>4.4) were predominantly observed in diagnosis like sepsis, while lower IPF levels (1-4.4) were more evenly spread across various conditions. However, the chi-square analysis indicates no significant association between IPF levels and diagnosis, with a p-value of 0.47. This suggests that IPF levels do not significantly vary based on diagnosis among neonates with TCP in this cohort.

Diagnosis	IPF		Chi-square level and p-value
	Normal (1-4.4)	High >4.4	
Sepsis	02	17	Chi-square value: 4.5 Degree freedom: 5 p-value: 0.47
Meconium stained amniotic fluid	02	06	
Birth asphyxia	0	07	
Low birth weight with complications	0	05	
Small for gestational age	0	04	
Incidental (cause for TCP couldn't be elaborated)	0	03	
Total	04	42	

[Table/Fig-4]: Relationship between IPF and cause of TCP in neonates with diagnosis (N=46).

The table displays the distribution of AIPC levels categorised by diagnosis for 46 cases. Sepsis cases had 10 with normal AIPC and five with high AIPC, while other diagnosis varied in AIPC levels. However, the chi-square analysis reveals no statistically significant association between AIPC levels and diagnosis ($\chi^2=9.94$, $df=10$, $p=0.44$) [Table/Fig-5].

DISCUSSION

The current study described the incidence of TCP at D.Y. Patil Medical College, Navi Mumbai NICU. Additionally, laboratory variables such as AIPC and IPF were taken into account to correlate with TCP. The incidence of TCP at the NICU over the course of the study was 6.14%. In comparison, the study by Madavi D et al., reported an incidence of 45% [16]. The combination of effective infection control measures, differences in maternal and neonatal risk factor profiles, and variations in NICU admission profiles likely contributed to the lower incidence of TCP observed in the current study compared to

Diagnosis	AIPC			Statistical test
	Normal N (%)	High N (%)	Low N (%)	
Sepsis	10 (34.48)	05 (45.5)	04 (66.7)	Chi-square value: 9.94 Degree freedom: 10 p-value: 0.44 (statistically not significant)
Meconium-Stained Amniotic Fluid (MSAF)	7 (24.14)	0 (0)	01 (16.7)	
Birth asphyxia	6 (20.7)	01 (9)	0 (0)	
Low birth weight with complications	3 (10.4)	02 (18.2)	0 (0)	
Small for gestational age	1 (3.5)	2 (18.2)	1 (16.7)	
Incidental (cause for AIPC couldn't be elaborated)	2 (6.9)	1 (9)	0 (0)	
Total	29 (100)	11 (100)	6 (100)	

[Table/Fig-5]: Relationship between AIPC with diagnosis (N=46).

previous studies. Of the cases involved, 10.86% (5/46) had severe TCP, while 89.13% had mild to moderate TCP. Mild to moderate TCP has been discovered in 80% of cases in several studies, which is consistent with the findings of the present study [3,8,17].

In the current study, the most frequent maternal risk factor for TCP was Pregnancy-Induced Hypertension (PIH), observed in 10 neonates (21.73%). Khalessi N et al., and Patil S et al., found PIH as a maternal risk factor in 17.70% and 72.17% of newborns, respectively [18,19]. Impaired platelet production and low quantities of circulating megakaryocyte progenitors are key factors contributing to the mild to moderate TCP associated with PIH universally. In this research, PIH was linked with mild TCP. Leaking per vaginam was identified as another maternal risk factor in four newborns (8.69%) in the study conducted at the institute. Oren H et al., research showed a positive association between Premature Rupture Of Membranes (PROM) and TCP, which was consistent with the findings of the present study [20]. Early-onset newborn sepsis caused by the mother's PROM eventually results in neonatal TCP.

In the current study, sepsis emerged as the most common risk factor associated with TCP, followed by MSAF and birth asphyxia. Sepsis was identified in 19 infants (41.30%) among other neonatal risk factors. Studies conducted by Nandyal SS et al., and Khalessi

N et al., reported lower percentages of sepsis among TCP babies, at 22.25% and 24.1%, respectively, compared to the current study [18,21]. However, Gupta A et al., found a similar percentage of sepsis among TCP babies, at 42%, aligning with present findings [17]. Variations in the percentages may be attributed to differences in aseptic precautions and methods utilised across various institutions.

In the present study, 36.84% of septic neonates exhibited severe TCP. Studies by Patil S et al., Hanoudi BM and Zaccheaus AJ and Oburu JE showed similar associations between sepsis and severe TCP, mirroring the outcomes of the current study [18,22,23]. This research revealed that the majority of admissions to the NICU were due to septicemia, which constituted the overall etiological profile. Septicemia induces TCP through both increased consumption and decreased generation of platelets, typically resulting in severe TCP. Meconium Aspiration Syndrome (MAS) was present in eight infants (17.39%). Infants with MSAF may exhibit reduced platelet production due to prenatal hypoxia. Several factors, including placental insufficiency, intrauterine infections, and maternal PIH, can lead to meconium passage in amniotic fluid, each of which can influence platelet production and consumption [24].

TCP is commonly observed in Meconium Aspiration Syndrome (MAS). In the current study, MAS was associated with moderate to severe neonatal TCP. However, in the studies by Gupta A et al., and Nandyal SS et al., MAS was linked to mild TCP [17,21]. Multiple aetiologies could explain this disparity. Birth asphyxia affected seven newborns (15.21%). Neonates with birth asphyxia often experience impaired megakaryopoiesis and platelet production. In the present study, mild to moderate neonatal TCP was associated with birth asphyxia. Studies by Nandyal SS et al., and Gupta A et al., also linked birth asphyxia to severe TCP [17,21]. The severity of birth asphyxia and the extent of required resuscitation may account for this disparity. Fewer babies in the current study sample received extensive resuscitation, potentially leading to the predominance of mild to moderate TCP.

Comparison of the findings in the present study with contrast studies is given in [Table/Fig-6] [16-22].

Authors name (ref no)	Place/year of the study	Sample size	Incidence of TCP	Major responsible factors/causes for TCP
Madavi D et al., [16]	Nagpur/2021	140	45%	PIH, Prematurity, Sepsis
Gupta A et al., [17]	Mumbai/2011	258	42%	Sepsis
Khalessi N et al., [18]	Iran/2013	364	17.9%	Sepsis
Patil S et al., [19]	Gulbarga/2014	140	72.17%	Sepsis, Maternal PIH
Oren H et al., [20]	Turkey/1994	643	Not Specified	Prematurity, Sepsis
Nandyal SS et al., [21]	Karnataka/2016	155	63.8%	Prematurity, Sepsis
Hanoudi BM, [22]	Israel/2015	728	13.04%	Prematurity, Preeclampsia
Present study	Navi mumbai	814	6.14%	Sepsis, MSAF

[Table/Fig-6]: Comparison of the findings in present study with previous studies [16-22].

Out of the 46 patients evaluated, 42 exhibited elevated levels of IPF (91.30%). Assessing IPF helps determine whether TCP is due to increased platelet consumption or inadequate megakaryopoiesis

response from the newborn bone marrow. In the present study, the majority of cases with increased IPF suggest a predominance of consumptive disease. These findings align with earlier research indicating neonates have a higher rate of megakaryopoiesis, contributing to increased IPF [25]. However, TCP is common in NICUs, and the exact mechanisms leading to it are not fully understood. Studies involving critically ill individuals suggest that IPF can aid in diagnosing sepsis and may even serve as a more reliable inflammatory biomarker than CRP and Procalcitonin (PCT) [26-28].

Despite the significant attention given to other platelet indicators for their potential utility in newborn infections, studies on IPF remain scarce [29-32]. The current study aimed to determine if there is an association between IPF values and the cause of TCP. However, no association was found between IPF values and the cause of TCP in the present study findings. Similarly, no statistical significance was observed between AIPC and the diagnosis of TCP. Strauss G et al., conducted a study in the paediatric population to differentiate between Immune Thrombocytopenia (ITP) and Acute Lymphoblastic Leukaemia (ALL) based on IPF levels [33]. They found significantly high IPF levels in both patient populations, despite ALL being considered a hypoproliferative cause of TCP. This finding is similar to the present observation, where high IPF levels were found even in conditions such as intrauterine growth restriction, birth asphyxia, and MAS, which are predominantly considered hypoproductive marrow states. One possible explanation for this observation is that multiple factors could be contributing to TCP in a single patient [33]. Additionally, the high rate of megakaryopoiesis in neonates might also contribute to the high IPF levels observed in the present study.

Limitation(s)

The sample size was small due to the Severe Acute Respiratory Syndrome (SARS) Coronavirus Disease-2019 (COVID-19) pandemic and a decrease in the admission rate in the hospital. Large-scale multicenter studies are essential to throw light on the utility of IPF and AIPC in neonates with TCP.

CONCLUSION(S)

The study revealed a relatively low incidence of TCP (6.14%) compared to other reports, possibly influenced by stringent aseptic precautions during the COVID-19 pandemic. However, despite investigating the IPF and AIPC, no significant correlation was found with the cause of TCP. Further multicenter studies with larger sample sizes are warranted to ascertain the utility of IPF and AIPC in neonates with TCP. Additionally, the study identified sepsis as the most common risk factor associated with TCP, followed by MSAF and birth asphyxia, highlighting the importance of maternal and perinatal factors in TCP aetiology.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Dec 29, 2023
- Manual Googling: Mar 16, 2024
- iThenticate Software: May 20, 2024 (9%)

ETYMOLOGY: Author Origin

EMENDATIONS: 9

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: Dec 29, 2023

Date of Peer Review: Feb 06, 2024

Date of Acceptance: May 21, 2024

Date of Publishing: Sep 30, 2024