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Immature Platelet Fraction: A Novel Hematological Parameter for Predicting Prognosis of Dengue Patients

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Abstract

Objective: Therefore, the aim of our study is to evaluate IPF as an early recovery indicator of platelet count in dengue patients with thrombocytopenia.
Methodology: This study was conducted at Chughtai Institute of Pathology, Lahore from October 2022 till December 2023. A total of 199 patients, with NS1 antigen were included in the study. Immature platelet fraction (IPF) and total platelet count were measured by Sysmex XN 1000 on day 1 and day 5 of the infection. IPF and its co relation with platelet count on day 1 and day 5 of infection was analyzed. Data was analyzed by using SPSS version 23.00. Paired sample t-Test was used to assess correlation between the two main variables.
Results: Out of 199 patients, 104 (52.3%) were males and 95 (47.7%) were females. Mean age of the patients was 39 years. There was a strong correlation between IPF values and the recovery of total platelets. IPF values tended to be higher at low values of platelet counts ($p<0.001$) at Day 1 whereas IPF decreased on Day 5 with an increase in platelet count showing statistically significant correlation
Conclusion: IPF is a good prognostic marker for recovery of platelets in DENV infection. It is a reliable and cost-effective tool that can help clinicians avoid unnecessary platelet transfusion.
Key words: Dengue infection, Immature platelet fraction.

Introduction

Dengue virus (DENV) is one of the major health concerns in Pakistan. In DENV infection the degree of thrombocytopenia determines the severity of the disease and is mainly used to as an indicator for platelet transfusion. Immature platelet fraction (IPF) is a new hematological parameter that measures reticulated platelets and directly measures thrombopoiesis.

Dengue virus (DENV) is an arthropod borne ribonucleic acid (RNA) virus which belongs to the family of Flaviviridae, genus Flavivirus. It infects around 200 million people worldwide annually and is responsible for around 20,000 deaths.[1] Dengue infection has different manifestations which mainly include dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue cases that do not fit into these classical presentations are labeled as "expended dengue syndrome" (EDS).[2] The global burden of DENV is on the rise since last few decades. DENV is endemic in more than 100 nations with greatest burden occurring in south east and south Asia.[3] DENV is also endemic in Pakistan and has become a major health concern. A number of factors have played integral role in this endemicity like unplanned urbanization, overpopulation, climate change, poor sanitation facilities, lack of public health support and lack of awareness for vector control among general public.[4]

DENV infection is a febrile infection with variable symptoms including migraine, retroorbital pain, myalgia, joint pains, diarrhea and thrombocytopenia.[5] Severity of thrombocytopenia depends upon the severity of DENV infection, more severe the disease lower is the platelet count in DENV infection. Thrombocytopenia occurs usually due to bone marrow suppression caused by infection of hematopoietic progenitor cells or by direct infection of platelets with DENV. Certain host factors also lead to leucocyte-platelet aggregates formation and clearance of platelets by anti-platelet antibodies.[6] Only thrombocytopenia is not a good predictor of hemorrhagic complications in DENV infection as not all patients with thrombocytopenia in DENV infection bleed. Bleeds like melena, hemoptysis, vaginal bleeds and hematemesis have not been well established with degree of thrombocytopenia.[7] Mostly hematocrit and platelet

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counts are used by clinicians to assess disease progression. Therefore, there is a need to have a hematological maker that can be used to predict the disease outcome in DENV infection.

Immature platelets are released in peripheral blood immediately after their formation and mature within two days after their release. This lag time between this maturation is a good estimate of bone marrow activity.[8] Immature platelet fraction (IPF) is a new hematological parameter that measures reticulated platelets in the peripheral blood. These reticulated platelets are the immature large platelets with RNA and are functionally more active. IPF is a direct measure of thrombopoiesis.[9] Sysmex XN1000 is an automated hematology analyzer which apart from giving 5-part differential count, has an additional feature of measuring IPF without using any other specific reagent.[10]

The normal range of IPF is 1-9% and according to Madhusudan et al IPF can be used to predict platelet recovery in DENV patient so that unnecessary platelet transfusions can be avoided which leads to alloimmunization, transfusion transmitted infections and graft vs host disease.[11] Therefore, the aim of our study is to evaluate the role of IPF as an early recovery indicator of platelet count in dengue patients with severe thrombocytopenia. This will avoid unnecessary testing and transfusion in patients with dengue.

Methodology

This cross-sectional observational study was performed at the Department of Hematology, Chughtai Institute of Pathology from October 2022 till December 2023 after taking approval from Institutional Review Board (IRB), vide reference number CIP-1149. After a thorough literature search, a sample size of 199 was calculated via WHO sample size calculator, keeping the margin of error at 5%, a confidence level at 95%, and prevalence of dengue.[4] Sampling was done using a non-probability consecutive sampling technique.

Inclusion Criteria: Dengue patients of both genders and any age whose NS1 antigen was positive and platelet count was below 150 x 109/L were included in the study.

Exclusion Criteria: Patients who had received platelet transfusion were excluded from the study.

Written consent was obtained before enrolling all patients, and their confidentiality was ensured at all levels. Approval of the institutional ethical committee was also procured before starting the project. Patients with dengue infection, confirmed by positive NS1 antigen were sampled on Day 1 and Day 5 of their illness. 2 ml of venous blood sample was taken from each patient in Ethylenediamine tetra acetic acid (EDTA) tube following standard sampling procedures. Immature platelet fraction (IPF) and total platelet count were measured by a hematology analyzer Sysmex XN 1000. The patient´s hemoglobin levels, hematocrit, and total leukocyte count were also measured on both days. IPF and its correlation was studied with total platelet count. We evaluated the trend of IPF as an early recovery indicator of platelet count in dengue patients with thrombocytopenia and its relationship with severe dengue. Data was analyzed by using Statistical Package for the social sciences (SPSS) version 23.00. Mean ± SD was calculated for continuous variable. Frequency and percentage were calculated for categorical variables. Paired sample t-Test was used to assess correlation between the two main variables.

Results

The total of 199 patients were included in our study. Out of these, 104 (52.3%) were males and 95 (47.7%) were females. Mean age of the patients was 39 years ranging from 12.0 to 70.0 Years.

All 199 patients were diagnosed cases of Dengue. Mean of all hematological parameters of the patients measured at Day 1 and Day 5 are shown in Table I.

Table I: Mean hematological parameters.

Parameters	Mean (range) (n)
Hemoglobin - Day 1	16.1 (12.0-20.0) g/dL
Hemoglobin - Day 5	12.3 (2.0-16.0) g/dL
Hematocrit - Day 1	45.8 (35.0-58.0) %
Hematocrit - Day 5	36.6 (30.0-45.0) %
Total leukocyte count - Day 1	2.4 (1.0-6.0) x10^9/L
Total leukocyte count - Day 5	7.3 (2.0-11.0) x10^9/L

We found a strong correlation between IPF values and the recovery of total platelets in our patients. IPF values tended to be higher at low values of platelet counts ($p<0.001$) at Day 1. The highest recorded value of IPF on Day 1 was 35 (normal range: 0.5 - 7) and the lowest platelet count was 34 (normal range 150-450). IPF decreased on Day 5 with an increase in platelet count showing statistically significant correlation as shown in

Table II. A comparison of the means of IPF and total platelet count on Day 1 and Day 5 is shown in Figure I.

Table II: Paired sample t-Test.

Variables	Mean (n)	Range (n)	p-value
IPF - Day 1	20.2	10.0 - 35.0	<0.001
PLT - Day 1	78.5	34.0 - 143.0	
IPF - Day 5	7.6	2.0 - 17.0	<0.001
PLT - Day 5	131.9	10.0 - 190.0	

196 (98.4%) of patients showed improvement in platelet counts at Day 5 of illness as compared to Day 1 after a raised IPF count was recorded on Day 1. Trends of IPF and total platelet count on Day 1 and Day 5 is shown in Figure II.

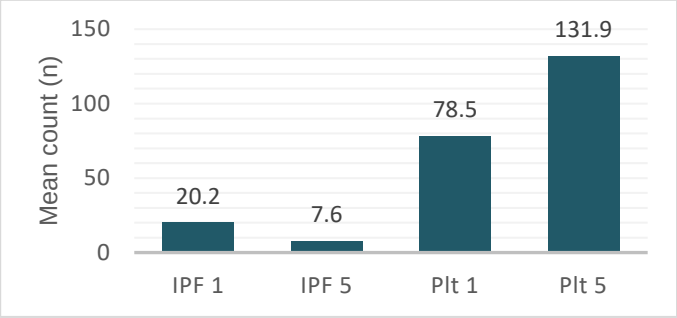

Figure I. Comparison of mean IPF and mean platelet count. (Day 1 and Day 5)

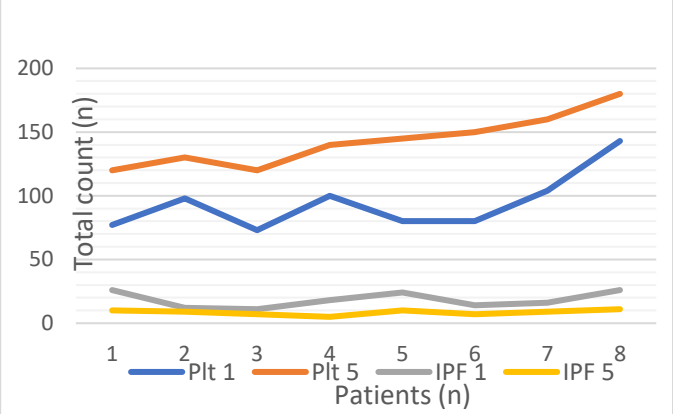

Figure II. Total platelets and IPF trend. (Day 1 and Day 5)

Discussion

As par WHO guidelines thrombocytopenia is the most potent indicator of clinical severity of DENV infection and thrombocytopenia is defined as platelet count less than 150 x 10^9/L. It has been demonstrated by several researches that platelet counts drastically fall by the 4th day of DENV infection and start improving by 7th day.[12] Thrombocytopenia is worrisome for both the patient and the clinician as the bleeding risk increases with the severity of thrombocytopenia. The decision of platelet transfusion to manage thrombocytopenia in DENV infection is very difficult at times as risk stratification between bleeding risk and adverse effects of transfusion have to be done.

In a study conducted by Fatima et al on-dengue patients, the mean Hb, hematocrit and platelet count in dengue patients is quite similar to the hemoglobin, hematocrit and platelet count in our study i.e. hemoglobin 15.8 g/dl, hematocrit 46% and platelet count of 27 x 10^9/L at the time of diagnosis.[13]

In a study conducted in Karachi, it was found out that IPF was higher in dengue patients (normal value 1-7%). In our study also IPF was raised both on day 1 (mean IPF 20.2%) and day 5 (mean IPF 7.6%) of the infection.[14]

In our study, higher IPF value at day 1 of infection and lower value on day 5 of infection with improved platelet count on day 5 indicates that high IPF value means that thrombopoiesis is active and there is no need for prophylactic platelet transfusion as platelet count will improve in few days. The same is supported by a Das et al who state that platelet transfusion has minimal benefit in treating patients with DENV infection and should be avoided.[15]

According to Deepak et al also IPF had strong correlation with recovery of platelets in patients with febrile thrombocytopenia. Their study showed an increase in IPF which favored an increase in platelet count on day 4 and day 5 of the disease.[16] In another study conducted in India, IPF and platelet counts were recorded for 7 days and it was found out that almost 90% of the children infected with DENV recovered their platelet counts within 24 to 48 hours after their IPF valued peaked during this time frame.[17]

In a study conducted in Ramathibodi Hospital it was observed that IPF ≥10% significantly improved the platelet count within 72 hours.[18] This theory was also supported by Dadu et al who found out that platelet count improved after 24-48 hours when IPF was more than 10%.[19] Likewise, another study conducted in India showed that there is 67% chance of platelet recovery within 48 hours when IPF is 6.25% and the chance of 100% recovery occurs when IPF is 10.6%.[20] Our study also indicates more the value of IPF greater are the chances of quicker recovery.

Conclusion

In our study we conclude that IPF is a good prognostic marker for recovery of platelets in DENV infection. It is a reliable and cost-effective tool that can help clinicians avoid unnecessary prophylactic platelet transfusion. This will lessen the burden on the blood banks of the country especially during the outbreaks of DENV infection. Adverse reactions due to platelet transfusions can also be avoided. Therefore, we recommend that IPF should be used regularly to monitor platelet recovery in DENV infection and this parameter should be made available in all parts of the country specially in remote areas of Pakistan where transfusion facilities are suboptimal.

Limitations: The limitation of the study is that this study was solely laboratory based and clinical symptoms of the DENV infection were not taken into consideration.

References

1. Murugesan A, Manoharan M. Dengue Virus. In: Emerging and Reemerging Viral Pathogens. Elsevier; 2020. p. 281-359. https://doi.org/10.1016/B978-0-12-819400-3.00016-8
2. Umakanth M, Suganthan N. Unusual Manifestations of Dengue Fever: A Review on Expanded Dengue Syndrome. Cureus. 2020 Sep 27; https://doi.org/10.7759/cureus.10678
3. Yang X, Quam MBM, Zhang T, Sang S. Global burden for dengue and the evolving pattern in the past 30 years. J Travel Med. 2021 Dec 29;28(8). https://doi.org/10.1093/jtm/taab146
4. Ali L, Gul Z, Ijaz A, Khalid N, Zeb F, Afzal S, et al. An overview of dengue viral infection circulating in Pakistan. J Vector Borne Dis [Internet]. 2022;59(2). Available from: https://journals.lww.com/jvbd/fulltext/2022/59020/an_overview_of_dengue_viral_infection_circulating.1.aspx https://doi.org/10.4103/0972-9062.331412
5. Khan NT, Hussain S. Prevalence of Thrombocytopenia in Dengue Fever Patients. Research Horizon. 2021 Dec 30;1(6):254-62. https://doi.org/10.54518/rh.1.6.2021.254-262
6. Quirino-Teixeira AC, Andrade FB, Pinheiro MBM, Rozini SV, Hottz ED. Platelets in dengue infection: more than a numbers game. Platelets. 2022 Feb 17;33(2):176-83. https://doi.org/10.1080/09537104.2021.1921722
7. Shabir MM, Nisar S, Urooj Z, Sohail M, Khan MS, Khan DH. Thrombocytopenia and its Relationship with Bleeding Manifestations in Dengue Patients-A Tertiary Care Hospital Experience. Pakistan Armed Forces Medical Journal. 2022 Dec 1;72(6):2021-4. https://doi.org/10.51253/pafmj.v72i6.4553
8. Looi KW, Matsui Y, Kono M, Samudi C, Kojima N, Ong JX, et al. Evaluation of immature platelet fraction as a marker of dengue fever progression. International Journal of Infectious Diseases. 2021 Sep;110:187-94. https://doi.org/10.1016/j.ijid.2021.07.048
9. Ahmad W, Lubna Z, Mohsin A, Nishat A. Study of platelet indices in dengue fever with thrombocytopenia and correlation of immature platelet fraction (IPF) with platelet recovery. Archives of Hematology Case Reports and Reviews [Internet]. 2020 Jan 24;5(1):001-5. Available from: https://www.peertechzpublications.org/articles/AHCRR-5-121.php https://doi.org/10.17352/ahcrr.000021
10. Imitiaz I, Minhas AM, Fatima M, Imran A, Malik NA, Chughtai AS. HIGH FLUORESCENCE LYMPHOCYTE COUNT AS AN EARLY PREDICTOR OF SEVERE THROMBOCYTOPENIA IN DENGUE INFECTION. Pakistan Journal of Pathology [Internet]. 2022 Jun 30;33(2):57-60. Available from: https://pakjpath.com/index.php/Pak-J-Pathol/article/view/697 https://doi.org/10.55629/pakjpathol.v33i2.697
11. Madhusudan S, Prabhavathi R, Ranganath K, Sandhya V. Study of Immature Platelet Fraction as a Predictor of Platelet Recovery in Pediatric Dengue Patients. J Cardiovasc Dis Res. 2022;13(05):1655-9.
12. Luh Pradnya Ayu Dewantari, I Gusti Nyoman Gde Bidura, I Gusti Bagus Teguh Pramana. Immature platelet fraction as predictor of platelet recovery in dengue fever. World Journal of Biology Pharmacy and Health Sciences. 2022 Dec 30;12(3):239-43. https://doi.org/10.30574/wjbphs.2022.12.3.0254
13. Fatima M, Younas A, Imran A, Nasir A, Malik NA, Chughtai OR, et al. Pseudobasophilia: A Helpful Screening Tool in Diagnosis of Dengue 1. Vol. 36, Z.M.C. 2022. https://doi.org/10.47489/PSZMC-825361-31-34
14. Hassan J, Waheed S, Abid M, Shamsi TS. High Fluorescence Lymphocyte Count and Immature Platelet Fraction; "Can these Two Parameters Reliably Distinguish between Dengue and ITP?" National Journal of Health Sciences [Internet]. 2021 Oct 29;6(1):17-21. Available from: https://njhsciences.com/wp-content/uploads/2021/10/Article3.pdf https://doi.org/10.21089/njhs.61.0017
15. Das S, Abreu C, Harris M, Shrader J, Sarvepalli S. Severe Thrombocytopenia Associated with Dengue Fever: An Evidence-Based Approach to Management of Thrombocytopenia. Case Rep Hematol. 2022 Aug;12. https://doi.org/10.1155/2022/3358325
16. Deepak P, Kumar MS, Harshika Ch. Immature Platelet Fraction as a Predictor of Recovery of Platelets in Febrile Thrombocytopenia Patients. APIK Journal of Internal Medicine. 2023;11(4):228-32. https://doi.org/10.4103/ajim.ajim_70_22
17. S AB, E A, YS, Naidu A, N. S. Immature platelet fraction in children infected with dengue fever. Int J Contemp Pediatrics. 2018 Dec 24;6(1):5. https://doi.org/10.18203/2349-3291.ijcp20185151
18. Chuansumrit A, Apiwattanakul N, Sirachainan N, Paisooksantivatana K, Athipongarporn A, Tangbubpha N,

Kadegasem P, Tangnararatchakit K, Yoksan S. The use of immature platelet fraction to predict time to platelet recovery in patients with dengue infection. Paediatr Int Child Health. 2020 May;40(2):124-128. doi: 10.1080/20469047.2019.1697574. Epub 2019 Dec 6. PMID: 31809660.
https://doi.org/10.1080/20469047.2019.1697574

19. Dadu T, Sehgal K, Joshi M, et al. Evaluation of the immature platelet fraction as an indicator of platelet recovery in dengue patients. Int J Lab Hematol. 2014;36:499-504. https://doi.org/10.1111/ijlh.12177
20. Suman FR, D'Cruze L, Rejendran R, et al. Dengue: platelet and immature platelet dynamics a study done at a tertiary care centre from South India. Int J Recent Trends Sci Technol. 2014;12:620-623.