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Review Article

Internal Medicine Section

Potential Role of Immature Platelet Fraction in Dengue Fever: A Narrative Review

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ABSTRACT

Dengue fever has emerged as a major international public health concern with a dramatic global increase in its frequency over the past few decades. It may present as a mild illness to a life-threatening condition with the major pathophysiological hallmark being plasma leakage as a result of increased vascular permeability and haematological abnormalities. The unpredictable nature and progression of the disease has led to research of novel haematological markers like Immature Platelet Fraction (IPF) which may help enhance the precision and efficacy of dengue management strategies by guiding the need for blood transfusion and blood lab monitoring, decreasing financial cost and hospital stay. This review provides detailed information about the immunopathogenesis of dengue, which is responsible for the fatal complexities and also gives the definition and uses of IPF by the healthcare workers. It aims to delve into the evolving role of IPF in the management of dengue, exploring its potential applications in assessing disease severity, predicting haemorrhagic tendencies and guiding therapeutic interventions. The review informs the readers about the implications and significance of the use of IPF in the treatment of dengue and how this technique can potentially reduce disease severity by timely diagnosis and treatment.

Keywords: Aedes, Dengue virus, Haemostatic shock, Platelets, Thrombocytopenia, Transfusion, Vector-borne diseases

INTRODUCTION

Dengue fever, caused by the Dengue Virus (DENV) and spread by *Aedes* mosquitoes, is a significant global health issue. According to the World Health Organisation (WHO), 100-400 million infections occur annually, affecting nearly half of the world's population [1].

In developing countries with tropical climates, the risk of dengue has surged in recent years due to factors such as rapid urbanisation, lifestyle changes, and inadequate water management and storage practices. According to the National Centre for Vector Borne Diseases Control (NCVBDC) in 2022, a staggering 2,33,251 dengue cases were documented resulting in 303 fatalities in India [2]. These statistics highlight the dire need for improved approaches to dengue management, particularly in regions where the disease is endemic.

The patients infected with the DENV present with clinical features like break bone fever, arthralgia, headache, retro-orbital pain, and maculopapular rash over the chest and abdomen [3]. Dengue manifests in several clinical forms and severe, potentially life-threatening complications including Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [4] which present with haemorrhagic manifestations like haemoconcentration and thrombocytopenia [5]. The unpredictable progression of the disease, poses significant challenges for healthcare professionals.

Role of platelets in dengue is evident; thrombocytopenia contributes to bleeding diathesis, notably in severe cases [6]. Moreover, the host's immune response during secondary DENV infection can trigger a cascade of events, including complement activation, release of proinflammatory cytokines and T-cell mediated elimination of infected cells culminating in shock, vasculopathy and thrombopathy [7].

Patients with dengue may undergo a steep fall in platelet count, warranting platelet transfusion. There are no clear guidelines regarding the same [8]. According to WHO, platelet transfusion is not the main treatment for dengue. Prophylactic transfusion is unnecessary if platelet count is >10,000/mm³. Prophylactic platelet transfusion is indicated when platelet levels are <10,000/mm³ without bleeding manifestations, prolonged shock with coagulopathy and abnormal coagulogram. In case of systemic bleeding, platelet

transfusion may be required in addition to red cell transfusion [9]. One intriguing development in dengue management is the exploration of the Immature Platelet Fraction (IPF) as a potential diagnostic and prognostic tool. IPF is an automated method for the quantification of reticulated platelets by automated analysers [6]. Thus, it is a relatively novel, haematological parameter, offering valuable insights into platelet production and maturation period.

The transfusion may be avoided altogether when the platelet count is set to rise. IPF monitoring shows promise in guiding transfusion decisions and reducing unnecessary transfusions [10]. The limited role of IPF in dengue patient management is due to research gaps. If associated with platelet recovery, it could help reduce costs and duration of hospital stay. This review addresses the clinical challenges of dengue and the potential benefits of IPF in its management. It synthesises research to explore IPF's role in predicting platelet recovery, improving dengue management precision, and reducing unnecessary transfusions by elucidating thrombocytopenia mechanisms.

Literature Search

A literature search of online databases including PubMed, Web of Science, Google Scholar, Scopus, and Cochrane was done using the keywords- Dengue, IPF, platelet count, and plateletcrit to retrieve studies. PubMed yielded 1086 results for the keywords dengue and thrombocytopenia, Web of Science yielded two results, Google Scholar yielded 31,900 and Cochrane yielded three results. On PubMed, we found 371 results for IPF and one on Cochrane. The keywords- IPF and dengue together accrued 10 results on PubMed. After going through the articles, 35 appropriate studies were included in the current review after a multistep approach was used for the selection of articles, which was based on shortlisting of titles, abstracts, and full texts using inclusion/exclusion criteria, methodology, findings, and limitations for analysis of the results. The studies were further subjected to the following selection criteria: i) those studies that clearly articulated their research design, methods, sample size, and sampling techniques; ii) the studies that were published in English in a peer-reviewed journal; and iii) studies that commented on one of the clinical applications on the role of IPF in dengue.

Immunopathogenesis of Dengue

Dengue fever is a major public health problem and one of the major concerns of dengue fever is thrombocytopenia. The pathophysiological hallmark of dengue is plasma leakage as a result of increased endothelial permeability [11]. Following this leakage (pleural or ascetic), critical plasma volume loss occurs from the blood vessels which in turn leads to hypovolaemic shock [12-14]. Constant haematological abnormalities occurring in dengue include bone marrow suppression, leucopenia, thrombocytopenia and complications like Haemophagocytic Syndrome (HPS) [15]. Enhanced immune response of the host to a secondary DENV infection is a feature of DHF and leads to many consequences. These immune mechanisms are complement activation, immune complex formation, increased histamine release, and a massive release of many cytokines into the circulation leading to shock, vasculopathy, thrombopathy, and Disseminated Intravascular Coagulation (DIC) [14,16]. Thrombopathy consists of thrombocytopenia and platelet dysfunction.

Numerous processes, such as peripheral platelet degradation and bone marrow suppression, have been connected to DENV associated thrombocytopenia. Studies have demonstrated that anti-platelet antibodies cause the premature death of platelets in the peripheral circulation [17-19] and that DENV-infected haematopoietic progenitors or bone marrow stromal cells decrease haematopoiesis. Dengue patients have been found to exhibit a specific pathophysiological process of haemostatic shock, which includes severe thrombocytopenia, prolonged coagulation profiles, reduced coagulation factors, abnormal fibrinolysis, and reduced natural anticoagulant [Table/Fig-1] [11-20].

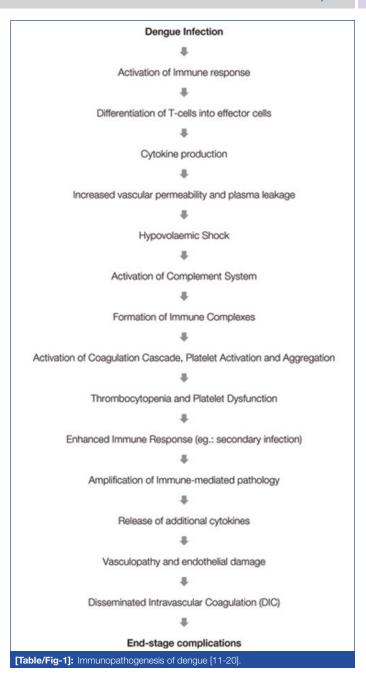
Immature Platelet Fraction (IPF)

Experienced medical professionals closely monitor haematological patterns to navigate their patients through the evolving stages of dengue infection and to provide suitable supportive care. While there isn't a targeted cure for dengue or its severe form, timely interventions have demonstrated effectiveness in reducing mortality rates. Consequently, there's been significant exploration into identifying new indicators that can forecast the restoration of platelet levels in dengue fever [21].

The IPF is a new haematological parameter that determines the percentage of new platelets released by the bone marrow by measuring reticulated platelets in peripheral blood. IPF measures the immature platelets as a fraction of the total number of platelets in peripheral blood. Immature platelets are young and reticulated because they contain higher Ribonucleic Acid (RNA) than mature platelets and are larger. Modern haematological analysers utilise this principle to measure immature platelets in peripheral blood as they absorb dyes more readily [22].

Various Uses of Immature Platelet Fraction (IPF)

Patients with dengue may experience a significant decline in platelet counts due to thrombocytopenia, necessitating platelet transfusion for which no specific guidelines exist. Blood transfusions should be administered as soon as significant bleeding in a haemodynamically unstable dengue patient is suspected or confirmed, according to recommendations made by the WHO. The practice of transfusing fresh frozen plasma and/or platelet concentrate for thrombocytopenia or severe bleeding in haemodynamically stable dengue patients, however, is not supported by any evidence. When there is severe bleeding or when the platelet count is fewer than 10,000/µL but there is no bleeding, it is customary to consider blood transfusion [23]. The transfusion may be avoided when the platelet count is set to rise. This brings us to the issue of how we can reliably predict the rise in the platelet count. IPF count holds great promise of being this predictor and by monitoring the IPF value [24], unnecessary transfusions can be avoided since it has an increased risk of alloimmunisation, immunosuppression, transmission of infectious diseases, and graft vs. host disease. IPF has also been found to be useful in determining the aetiology of thrombocytopenia which helps in identification and tailored management of the underlying condition.



It will therefore be much quicker to determine the underlying cause of thrombocytopenia and enable more efficient treatment and management of thrombocytopenic patients if this marker is included more frequently in hospital diagnostic testing panels and defined ranges are standardised [25]. IPF has also been used to confirm engraftment post-chemotherapy stem cell transplantation and in assessing the forthcoming sepsis and its recovery [26].

Preference of Immature Platelet Fraction (IPF) as a Marker in Dengue Patients

The IPF is a good reliable, consistent clinical utility marker. It can be measured even in very low platelet count, where the other platelet recovery parameters like Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) cannot be consistently measured [27]. The paucity of research and information now available means that IPF is not involved in the management or follow-up of dengue patients. If there is evidence linking IPF to platelet count recovery, it could play a part in managing dengue fever and reducing the need for unnecessary blood transfusions, blood test monitoring, hospital stays that are shorter, and lower associated costs [9]. A retrospective study was done by reviewing 12 articles to find out the association between the status of IPF and the recovery of patients in confirmed dengue cases that included daily/regular monitoring of IPF levels of the patients [Table/Fig-2].

S. No.	Author's name; year	Place of study	Sample size	Objective	Methodology	Findings
1	Looi KW et al., 2021 [21]	Malaysia	287	The study evaluated the trend of IPF as an early recovery indicator of platelets in dengue patients with thrombocytopenia, and its relationship with severe dengue in conjunction with reticulocyte count.	This single-centred prospective observational study was carried to evaluate the Immature Platelet Fraction (IPF) as a marker for dengue fever progression. Blood samples were collected from patients diagnosed with dengue fever, and IPF levels were measured using an automated haematology analyser. The progression of dengue was monitored by correlating IPF levels with clinical outcomes and other laboratory parameters. The data were statistically analysed to determine the significance of IPF as a predictive marker.	This study in 287 patients with confirmed dengue showed that IPF% increased for more than three days prior to platelet recovery.
2	Jeon K et al., 2020 [29]	South Korea	167	The study assessed the role of the IPF in differentiating hyperdestructive/consumptive thrombocytopenia from hypodestructive thrombocytopenia and its potential use as a predictive marker for platelet recovery.	This study was a retrospective analysis of 262 patients diagnosed with thrombocytopenia. Researchers measured the Immature Platelet Fraction (IPF) using an automated blood cell analyser. Patients were then categorised into groups based on the underlying causes of their thrombocytopenia, such as bone marrow suppression, increased platelet destruction, and other conditions. Statistical analyses were performed to evaluate the effectiveness of IPF in identifying the cause of thrombocytopenia and predicting the patients' platelet recovery.	The IPF was significantly higher in the hyperdestructive/consumptive thrombocytopenia group (266.7% of the control group value) than in the hypoproductive group; this difference can be used as a guide to distinguish the cause of thrombocytopenia in real-world practice.
3	Abeysuriya V et al., 2022 [27]	Sri Lanka	240	The objective was to assess the predictive value of IPF% on days 2 and 3 of illness for recovery from dengue-related thrombocytopenia.	The study was a prospective analysis involving 208 patients with dengue-related thrombocytopenia. Researchers measured the IPF using an automated haematology analyser. They monitored the patients' platelet counts and IPF levels to assess the IPF's effectiveness in predicting early platelet recovery during the course of dengue infection.	An IPF% on day 2 of illness of >7.15% had a sensitivity of 80.0% and specificity of 70.4% for prediction of platelet recovery (defined as platelet count ≥60×10³/L) on day 7 of illness. An IPF% of >7.25% on day 3 of illness had a sensitivity of 88.9% and specificity of 47.1% for predicting platelet recovery >60×10³/L on day 8 of illness. The IPF% was significantly lower in patients with severe dengue. Platelet recovery was observed within 48 h after the peak IPF% was reached, regardless of severity.
4	Ahmad J et al., 2022 [22]	Malaysia	84	This study aimed to evaluate the role of IPF% and to identify its cut-off value in predicting platelet recovery in dengue patients with thrombocytopenia.	The study by Ahmad et al., aimed to determine a cut-off value for IPF in predicting platelet recovery in dengue patients with thrombocytopenia. The methodology likely involved measuring IPF levels using an automated haematology analyser and monitoring platelet counts in dengue patients over time. Statistical analysis was likely performed to establish the cut-off value for IPF as a predictor of platelet recovery.	About 83% of dengue patients in our study achieved platelet recovery after reaching peak IPF% compared to 16.7% who didn't achieve platelet recovery. Based on AUC for the ROC curve, the cut-off IPF% value of 10.55% could predict platelet recovery for dengue patients with the sensitivity and specificity of 69% and 67%, respectively. When the value of peak IPF% is more than 10.55%, the platelet count of dengue patients will increase >20×10°/L within 48 hours. The increasing trend of IPF% was concomitant with progressive recovery, suggesting that IPF% could be a promising tool to predict increasing platelet count thrombocytopenia in the first week of illness, and thereafter, the trends of these two parameters were reversed, supporting the results of previous studies.
5	Kumar VV et al., 2016 [30]	India	45	To find out the association between the status of IPF and the recovery of platelets in patients with dengue.	Platelet count and IPF were estimated using Sysmex XE-2100 (Sysmex, Kobe, Japan). Complete blood count was recorded simultaneously, and peripheral smears were studied in all these cases with a note for the presence of large platelets on smear.	Among the recovery of platelets, 86.4% showed recovery within 24 hours and the rest with 48 hours after attaining peak IPF value. A single value IPF more than 10% was indicative of platelet recovery within 24-48 hours. A positive correlation was observed among IPF level and the recovery of platelets in those patients with dengue.
6	Chuansumrit A et al., 2019 [31]	Thailand	64	To determine a predictor for platelet recovery in patients with dengue infection.	Platelet count and IPF from daily blood samples of patients with dengue infection during hospitalisation and 1-4 weeks after discharge were retrospectively analysed.	The median IPF among normal children was 3.6% with a 95 percentile of 9.9%. In dengue patients, an IPF of ≥10.0% after defervescence was associated with a subsequent platelet count of ≥60×10 ⁹ /L within 72 hours.
7	Agarwal M et al., 2021[32]	India	140	The aim of this study was to establish the relationship between IPF and increase in platelet count in patients with dengue who suffer from thrombocytopenia.	The patient's details were retrieved from the hospital in the patient management system. The platelet counts and IPF were retrieved from Sysmex XN1000 haematology analyser. The values of platelet and IPF were available for 1st, 3rd, 5th and 7th day of admission for each patient. The patients were grouped into five categories according to their platelet count on the day of the admission. 2 High risk <20,000/cu mm, moderate>20,000-40,000/cu mm, low risk >40,000-1,00,000/cu mm, no risk >1,00,000-1,50,000/cu mm, Normal >1.5 lacs/cu mm. A platelet count of <1,50,000 was considered as thrombocytopenia.	There was statistically significant (p<0.01) improvement in platelet values within 48 hrs when the IPF was more than 6.1%. Total patients with low IPF i.e., ≤6.1% was 44 in which 6 (13.6%) showed improvement in platelets (>20,000) on day 3 but 38 (86.4%) patients didn't show improvement in platelet count.

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8	3	Lavanya N and Jayanthi BV, 2022 [33]	India	37	To evaluate the relationship between the IPF and platelet recovery and the consistency of its expression.	The present study was a retrospective observational study done at the Institute of Pathology, Madras Medical College between November 2018 to December 2018. Total 37 patients having fever with thrombocytopenia in dengue and other haematological causes were included for analysis. The platelet count, IPF, Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and Plateletcrit (PCT) was evaluated at the time of admission and once in every 24 hours and plotted in Excel spreadsheet.	About 86.4% were recovered in 24 hours after attaining the peak, 89.1% showed recovery in 24-48 hours of the rise of the IPF compared to the previous value and 94.5% recovered within 24 hours after the fall in the IPF value. It was observed that 81.8% were recovered when the IPF value ≥10% within 24-48 hours. IPF readings are able to appreciate even in low platelet count levels but the other platelet recovery parameters did not. IPF is a consistent and reliable marker which can be measured even when the platelet count is low and it also predicts the platelets recovery. It is a promising marker that helps in guiding the decision towards platelet transfusion.
9)	Goel G et al., 2021 [34]	India	162	To assess and establish the clinical utility of IPF in differentiating the two major causes of thrombocytopenia i.e., decreased production and increased destruction of platelets along with determining its significance in monitoring thrombocytopenic patients.	The collected samples were analysed within 2 to 3 hours of collection using Mindray BC-6800.	The normal reference range for IPF was calculated from the findings of 101 controls and found to be ranging from 0.7 to 5.7%. A value of IPF above 5.7% was considered abnormally raised. The IPF was significantly higher in cases with increased destruction of platelets than in cases with decreased production of platelets (cut-off 5.95%).
1	1()	Asha J et al., 2023 [35]	India	250	This study aimed to compare Platelet Increments (PIs) in patients with dengue fever to assess their role in the outcome such as hospital stay and platelet transfusion requirements.	A group of 250 dengue patients was studied over a period of 18 months. The platelet parameters i.e., platelet count, MPV, PDW, Platelet Large Cell Ratio (PLCR), PCT and IPF were measured with Sysmex XN-1000 and followed-up every 24 h. The clinical features, duration of hospital stay and platelet transfusion requirement details were collected.	The normal IPF value is in between 1.1% and 6.1%. More than two-third (68.4%) of patients had high IPF, 30.8% had normal and 0.8 had low IPF values as the baseline. From day 2 to 10, the majority of patients had high IPF values. On day 5, there was a decrease in the percentage of patients having IPF >6.1%. The median value of IPF is 8 (range 0.7%-28%) and the mean value was 10.1%±6.9%.

[Table/Fig-2]: Details of studies made on impact of IPF in management of dengue [21,22,27,29-35].

Among the numerous studies published on the role of IPF in dengue, the most noteworthy evidence was obtained from research conducted by Looi KW et al., Faculty of Medicine, University of Malaysia [21]; Wayez A et al., Aligarh Muslim University [28] and Dadu T et al., PD Hinduja Hospital [24]. These studies recommend monitoring IPF levels daily in confirmed dengue patients Non-structural protein 1 (NS1) antigen positive. Looi KW et al., investigated the pattern of IPF as an early indicator of recovery in dengue patients with thrombocytopenia. Their study, involving 287 patients, revealed that the IPF percentage exhibited a consistent rise for over three days preceding platelet recovery. They tracked the levels of IPF daily in confirmed dengue cases. They observed that a sudden rise in IPF% is accompanied by a fall in platelet count from day 2 to day 3 of illness. For the remaining patients, platelet recovery occurred within 24 to 48 hours. The escalating trajectory of IPF percentage correlated with advancing recovery, indicating its potential as a reliable tool for predicting platelet count. Overall, an increasing trend of IPF during the first week of illness was concurrent with progressive thrombocytopenia. Beyond this initial phase, the trends of IPF and thrombocytopenia reversed, indicating stages of disease progression and recovery [21]. In a retrospective analysis conducted by Wayez A et al., they drew the conclusion that the value of IPF more than 8% can be used as a predictive marker for platelet recovery since the platelet count tends to recover within 24 to 48 hours in such dengue fever patients [28]. Dadu T et al., found that levels of IPF in confirmed dengue patients with positive NS1 tests heightened IPF levels and were linked with platelet recovery in nearly 93% of patients within 24-48 hours. Additionally, nearly all patients achieved recovery within 24 hours following the decline in IPF levels [24]. Jeon K et al., examined the function of IPF in distinguishing between different types of thrombocytopenia and its potential utility as a predictive indicator for platelet recovery. They discovered that IPF levels were notably elevated in the hyper-destructive thrombocytopenia group, reaching 266.7% of the control group value [29].

A study by Abeysuriya V et al., aimed to evaluate the predictive capability of IPF on the second and third days of dengue fever for the resolution of dengue-related thrombocytopenia. An IPF percentage exceeding 7.15% on the second and third days of illness demonstrated a sensitivity of 80% and a specificity of 70.4% in predicting platelet recovery, defined as a platelet count exceeding 60×10⁹/L [27]. In the study conducted by Ahmad J et al., it was observed that 83% of dengue patients attained platelet recovery subsequent to reaching the peak IPF percentage, in contrast to 16.7% who did not experience recovery. Utilising the Area Under the Curve (AUC) for the Receiver Operating Characteristic (ROC) curve, a cut-off IPF percentage value of 10.55% was identified as capable of predicting platelet recovery for patients, with a sensitivity of 69% and a specificity of 67% [22]. In the study conducted by Kumar VV et al., it was observed that 86.4% of platelet recoveries occurred within 24 hours after reaching the peak IPF value, with the remainder recovering within 48 hours. A single IPF value exceeding 10% served as an indicator of recovery within the 24 to 48-hour timeframe. Additionally, a positive association was identified between IPF levels and platelet recovery in dengue patients [30]. Chuansumrit A et al., conducted a study that similarly concluded that an IPF exceeding 10% in patients with dengue fever correlated with a subsequent rise in platelet count within 72 hours [31]. Agarwal M et al., showcased a statistically notable enhancement in platelet levels within a 48-hour timeframe when the IPF exceeded 6.1% [32]. Lavanya N and Jayanthi BV, conducted a research investigation aimed at assessing the clinical significance of IPF in individuals with thrombocytopenia. Their findings revealed that 86.4% of patients experienced recovery within 24 hours after reaching the peak IPF value, and IPF values were attainable even at low platelet counts. In contrast to conventional platelet recovery markers, they noted that 81.8% of patients exhibited recovery when the IPF value exceeded 10% within a 24 to 48-hour period [33]. Goel G et al., evaluated the clinical effectiveness of IPF in distinguishing between the two primary causes of thrombocytopenia: hyperdestructive and hypodestructive. They found that IPF levels were notably elevated in instances of heightened platelet destruction, suggesting escalated production and consequent platelet replenishment [34]. Asha J et al., aimed to compare platelet indices among dengue fever patients to elucidate their relevance in outcomes such as hospital duration and necessity for platelet transfusions. Following an analysis of 250 patients spanning 18 months, the study revealed the following observations: the majority (68.4%) of patients exhibited elevated IPF levels initially, with 30.8% displaying normal levels and 0.8% exhibiting low IPF values as a baseline. Throughout days 2 to 10, most patients maintained elevated IPF levels. However, by day 5, there was a reduction in the proportion of patients with IPF levels exceeding 6.1%. The median IPF value was eight (ranging from 0.7% to 28%), with a mean value of 10.1±6.9% [35].

These studies suggest that there is a positive correlation between IPF and platelet count in the initial days of dengue fever. Hence, whenever IPF is above the normal limit, it will indicate thrombocytopenia and once it reaches its peak and starts down trending, it correlates with recovering platelet counts. Hence, the decreasing IPF trend can be a good predictor of an increasing trend in platelet count.

Implications and Significance

The results from the reviewed studies collectively suggest that platelet recovery in dengue patients is related to thrombocytopenia. Daily monitoring of IPF levels can provide clinicians with critical insights into the timing of platelet recovery, allowing them to make informed decisions regarding platelet transfusions. The observed correlation between IPF and platelet count in the early stages of dengue illness further highlights the clinical utility of IPF. By identifying an increasing trend in IPF levels, healthcare providers can anticipate a subsequent increase in platelet count. This anticipation may reduce the need for empirical platelet transfusions and minimise the unnecessary burden on blood banks during dengue outbreaks. Furthermore, the differentiation between hyperdestructive and hypodestructive thrombocytopenia based on IPF levels offers additional diagnostic value. Early identification of hyperdestructive thrombocytopenia can prompt more targeted and tailored interventions to manage severe cases effectively.

Overall, incorporating IPF as a frontline anticipatory approach in the management of thrombocytopenia during dengue outbreaks can improve patient outcomes, optimise healthcare resources, and enhance the overall efficiency of dengue fever management.

CONCLUSION(S)

The results of the examined studies offer strong evidence in favour of IPF's role as a reliable indicator of platelet recovery in thrombocytopenia-affected dengue patients. Clinicians can be better equipped to make timely and informed decisions regarding platelet transfusions when they monitor IPF levels on a daily basis in confirmed dengue cases with positive NS1 testing. Improved outcomes during dengue outbreaks can be achieved by healthcare practitioners through the efficient management of thrombocytopenia in dengue patients through the use of IPF as a useful diagnostic and predictive tool lessening the requirement for empirical platelet transfusions and the needless strain on blood banks during dengue outbreaks.

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