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Immature platelet fraction (IPF) as a prognostic biomarker towards platelet count recovery in adult dengue patients: A systematic review and meta-analysis

I Komang Hotra ADIPUTRA[1], Giovanca Verentzia PURNAMA[1], Richard Christian Suteja[1], Cokorda Agung Wahyu PURNAMASIDHI[2] I Ketut Agus SOMIA[3]

[1]Department of Undergraduate Medicine, Faculty of Medicine, Udayana University, Bali, Endonesia
[2]Department of Tropical and Infectious Diseases, Faculty of Medicine, Udayana University Academic Hospital, Bali, Endonesia
[3]Department of Tropical and Infectious Diseases, Faculty of Medicine, Udayana University Prof. Dr. I.G.N.G. Ngoerah General Hospital, Bali, Endonesia

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Abstract

Dengue is a viral infection spread by arthropods, damaging platelets and causing thrombocytopenia. An increased production of platelets from bone marrow to compensate thrombocytopenia can be measured using IPF (immature platelet fraction). Therefore, this study aims to synthesize information about the potential of immature platelet fraction as a prognostic biomarker towards predicting platelet recovery. We searched articles from online databases (PubMed, Cochrane, Google Scholar, and Scopus) using the keywords dengue and immature platelet fraction. Three independent reviewers were screened, and data about the prognostic potential of IPF% for platelet count were extracted. IPF% generally moves in a manner mirroring platelet count change. IPF% increase and platelet count decrease were generally seen until day 4-8, followed by a reversal – IPF% decrease and platelet count increase on the following days. Previous research also showed that platelet recovery may be seen within 24 to 48 hours post maximum IPF% measurement. This systematic review identified IPF% as a significant prognostic to platelet recovery in adult dengue patients. Knowledge about how to utilize IPF% will help clinicians avoid prescribing unnecessary platelet transfusions.

Keywords: Immature platelet fraction, dengue, prognosis, systematic review, meta-analysis

1. Introduction

1.1. Rationale

Dengue infection is a major tropical disease which reportedly inflicted a burden of 390 million cases and 25 thousand deaths each year in more than 100 countries (1–3). These large numbers can be attributed to the pathogen's ability to ride female *Aedes aegypti* as transmission vectors. Symptoms due to dengue infection vary through a wide spectrum, from mild dengue fever to severe dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS) (4). These symptoms were aggravated in the presence of immunity towards the dengue serotype distinct from the one it is infected with at the moment through antibody-dependent enhancement (ADE) (5).

A central mechanism towards dengue pathogenesis is infection of endothelial cells, thus causing vascular dysfunction through impairment of physiological functions and increasing vascular permeability Microvascular leakage consequently decreases intravascular fluid volume, at times also changing its viscosity depending on whether blood is also leaking or not (6). Parallel to this mechanism, compensation through coagulation occurs in various parts of the body. The overuse of thrombocytes may induce thrombocytopenia, a major criterion for measuring dengue severity (7).

Though the disease is generally self-limiting, the case is not always true for all patients. Excessive microvascular leakage may inherently cause hypovolemia and impaired perfusion towards vital organs. Treatment is generally supportive and symptomatic through IV fluid and drug loadings. A major breakthrough in dengue treatment involves transfusion of pure platelets to prevent bleeding (8). Platelet concentrates gained through apheresis may occur as a lifesaving procedure by inducing rapid haemostasis in sites of vascular injury (9). However, transfusions carry their own risks: alloimmunization, immunosuppression, disease transmission, and many more (8). Therefore, the use of transfusion is generally reserved for life-threatening conditions, which is clinically relative under each physician's subjective discretion.

Immature platelet fraction (IPF%) serves as a relatively new parameter for measuring young reticulated platelets in circulation (8). Reticulated platelets, alongside several other biomarkers, may serve as an assessment towards thrombopoiesis within the bone marrow (10). Reticulated platelets were regarded by experts as 'hyperactive' platelets, which exhibit significantly higher thrombogenicity. Their levels were found to be proportional towards platelet turnover rate, thus indirectly correlated to patients' dengue severity (11). In conclusion, IPF% levels theoretically rise when there are

*Correspondence: purnamasidhi@unud.ac.id

less thrombocyte in the bloodstream than needed, and it is theoretically a good measure towards thrombopoiesis and platelet recovery. Evaluation of IPF% as a predictor of platelet recovery is expected to save patients from unnecessary transfusions and their adverse effects (12).

1.2. Objectives

This study aims to synthesize information about the prognostic powers of IPF% towards predicting platelet recovery 24 and 48 hours post-IPF% measurement in adult dengue patients admitted to any clinical setting. The prognostic power may help physicians in making therapeutic decisions in real-life clinical settings.

2. Materials and Methods

2.1. Study Design

This study is a systematic review and meta-analysis conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).(13) Protocols applied in this study were registered with PROSPERO (CRD42023395232), a prospective international register of systematic reviews prior to commencement. However, it must be noted that the PROSPERO protocol was automatically published, and the PROSPERO team has not checked its eligibility due to the streamlining of COVID-19-related protocols.

2.2. Search Strategy and Inclusion Criteria

Online databases searched were PubMed, Cochrane, Google Scholar, and Scopus. This was done on February 17, 2023. The delay in online database search was because we waited for PROSPERO approval. The search in the Scopus database was assisted by Harzing's Publish or Perish® version 8.6.4. Search keywords included (Dengue AND Immature Platelet Fraction [MeSH]) and were set not to strictly follow PICOTS due to the scarcity of studies on the topic. Full search terms can be seen on supplementary files (S1). We only included articles that described adult dengue patients diagnosed using standard methods mentioned in guidelines (positive anti-dengue IgM, NS1, or positive RT-PCR) written in English. We did not impose restrictions regarding the year of publication.

2.3. Study Selection

After downloading the data acquired from the established search protocols into Microsoft Excel®, three reviewers (GVP, IKHA, and RCS) independently screened each article's title and abstract for study eligibility and inclusion-exclusion criteria. The screening was then be continued on retrievable full-text articles, respectively. Disagreement or uncertainty between the three researchers was resolved by discussion. For studies with repeated measurements, we included results with the longest interval between IPF% measurement and dengue.

2.4. Data Extraction

Three reviewers (GVP, IKHA, and RCS) independently extracted data from the studies that were agreed to be included. Extracted data were summarized in a separate Microsoft Excel® sheet. Disagreement or uncertainty between the three reviewers was resolved by discussion. Data gathered within the standardized sheet were the study's first author, year of publication, country, study design, number of participants, age, sex, dengue diagnosis and additional criteria, and findings.

2.5. Outcomes

Primary outcomes assessed include any findings that illuminate the prognostic potential of IPF% towards platelet count. This includes the number of platelet count improvement after a certain time interval, certain IPF% value, and correlation analysis.

2.6. Assessment of Study Quality

Three independent reviewers (GVP, IKHA, and RCS) assessed the risk of bias within the studies with quality in prognostic studies (QUIPS) tool and quality of evidence using GRADE criteria. The results were then visualized with the help of ROBVIS. Disagreement or uncertainty between the three researchers was resolved by discussion.

2.7. Statistical Analysis

A random-effect meta-analysis was synthesized with a pooled proportion within a 95% confidence interval. This statistical analysis will be applied to measure the combined proportion of patients showing platelet recovery after certain IPF% values. A forest plot would be drawn to visualize effect and heterogeneity if the number of studies eligible for synthesis was adequate. Heterogeneity (I^2) was measured and defined as low (<25%), moderate (26-75%), and high (>75%). Funnel plots and Egger tests were considered for the assessment of publication bias. Statistical analysis was conducted using MedCalc® version 20.0.1.

3. Results

3.1. Bibliographic Search and Study Selection

This literature study searched and identified 139 potential articles. We excluded 21 articles due to duplication when search results from different databases were merged. After that, we excluded 105 articles due to wrong PICO or study design. In total, there were 13 articles eligible for full-text screening. We also excluded four and two irretrievable articles, resulting in only seven full-text articles eligible for qualitative and quantitative synthesis. The flow diagram per PRISMA guidelines can be seen in (Fig 1) (14).

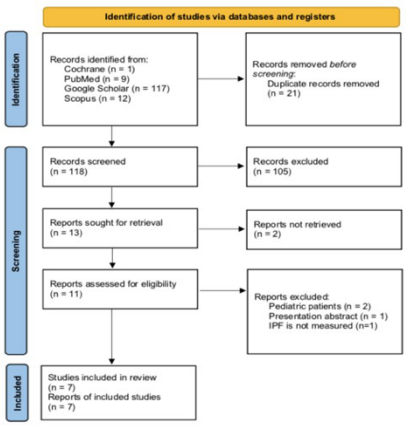

Fig. 1. PRISMA Flowchart

3.2. Characteristics of Included Studies

Details of the included studies can be seen in Table 1. It must be noted that most of these studies were carried out during the COVID-19 pandemic (8,10,15–18) and all of them were done in developing Asian countries with high incidents of dengue infections.(8,10,12,17–20) Agarwal (2021) and Dadu (2014) did not report the demographic characteristics of the subjects included in the study (10,12). Dadu (2014) and Wayez (2020) measured IPF% using XE-2100 (Sysmex®), Agarwal (2021) measured IPF% using XN-1000 (Sysmex®), while the rest of the studies used XN-2000 (Sysmex®) to measure IPF%.

Table 1. Characteristics of included studies

Author (Year)	Country	Study Design	Number of Participants (% Male)	Age in years (Mean ± SD / Med, Q1-Q3)	Severe; N (%)	Dengue diagnosis & additional criteria	IPF% Measurement Method	Findings
Agarwal (2021)	India	Retrospective	140 (-)	-	-	Positive for NS1 and/or IgM	XN-1000 (Sysmex®)	IPF% has a significant positive correlation to platelet count change 48 hours post IPF% measurement. An IPF% cut-off of 6.1% yields following accuracy after certain period of time towards platelet count recovery (> 20.000 cells/mm^3 increase): - 2 days (Sen 85.37%, Spe 38.38%, Acc 52.14%) - 4 days (Sen 82.41%, Spe 78.13%, Acc 81.43%) - 6 days (Sen 77.42%, Spe 100.00%, Acc 80.00%) After attaining peak IPF%, platelet count increases in 36.5% patients after 48 hours, 92.7% patients after 96 hours, and 100% patients after 6 days.
Chakraborty (2020)	Bangladesh	RCT	33 (79%)	30±9	-	Positive for NS1 and antibody (IgM/IgG) without severe comorbidity	XN-2000 (Sysmex®)	IPF% were steady from day 0-3, before decreasing throughout later days. Platelet count were relatively steady from day 0-2, before increasing throughout later days. Trends are shown on Chakraborty (2020) Fig 3A.
Dadu (2014)	India	Prospective	32 (-)	-	-	Positive for NS1 or IgM. Platelet count <150.000/mm^3 with falling platelet trend and had not received blood transfusion	XE-2100 (Sysmex®)	After attaining peak IPF% peak, 84.3% patients showed platelet count recovery within 24 hours and 100% within 48 hours. Platelet count recovery was seen in 93.75% patients with IPF ≥ 10% within 48 hours. Platelet count recovery was seen in 93.75% patients with rising IPF% trend (IPF% change ≥ +10%) within 48 hours and 100% patients with falling IPF% trend (IPF% change ≤ -10%) within 24 hours.

Looi (2021)	Malaysia	Prospective	287 (60.6%)	[a]NS: 37.16±15.43 S: 44.44±20.16	25 (8.7%)	Positive in any of below: - NS1 ELISA (Standard Diagnostics®) - IgM or IgG ELISA (Standard Diagnostics®) - iTaq Universal SYBR Green One-Step Kit for RT-PCR (Bio-Rad®)	XN-2000 (Sysmex®)	Platelet count decreased from admission to day 5, remained low until day 7 and day 8 after onset of fever; thereafter, platelet count increased from day 9 onwards towards normal values. IPF% increased from admission to day 8, before decreasing gradually to day 10 and then decreasing rapidly thereafter. Trends are shown on Looi (2021) Fig 1.
Puspita (2019)	Indonesia	Prospective	30 (60%)	24.83±9.18	4 (13.3%)	Positive for NS1 or IgM and fever of < 6 days	XN-2000 (Sysmex®)	IPF% is significantly correlated with platelet count change 2 days post IPF% measurement (R 0.746, p < 0.01).
Shah (2021)	India	Retrospective & prospective	124 (71.8%)	[b]34.1	4 (3.0%)	Positive for NS1 and/or IgM with platelet count <100.000/mm^3	XN-2000 (Sysmex®)	In patients with IPF > 10.0%, 90.9% showed platelet recovery within 24 hours and 93.5% within 48 hours. After attaining peak IPF%, 96.1% patients showed platelet recovery within 24 hours and 97.4% within 48 hours. In addition, 64% patients with severe thrombocytopenia in this study can be prevented from receiving platelet transfusions by using an IPF cut-off > 10%
Wayez (2020)	India	Prospective	106 (55.7%)	[c]15-30 (66.0) 31-45 (20.8) 46-60 (10.4) >60 (2.8)	-	Positive for NS1 and/or IgM with platelet count <100.000/mm^3	XE-2100 (Sysmex®)	IPF% is significantly correlated with platelet count change 24 hours post IPF measurement (R 0.133, *p < 0.05*) and 48 hours post IPF% measurement (R 0.303, *p < 0.01*).

[a]NS: Non-Severe, S: Severe, [b]Mean, [c]Measured in years (%)

3.3. Patient Characteristics

A total of 752 subjects were included from a total of all five studies. Males constitute 60.0% to 78.8% of total subjects across all studies.(8,12,16–21) The largest study was conducted by Looi (2021), with a total of 287 subjects (60.6% were male) (20). Though not all studies reported the proportion of severe cases, we recorded a total of 40 subjects with severe dengue. Though all studies uniformly diagnose dengue infection via positive NS1, IgM/IgG, and/or RT-PCR, some studies impose a maximum platelet count as an inclusion criterion.

3.4. General Findings

Agarwal (2021) found that IPF% significantly correlates to platelet count change 48 hours post IPF% measurement. An IPF% cut-off of 6.1% yields following accuracy after a certain period of time towards platelet count recovery (> 20.000 cells/mm^3 increase): 2 days (Sen 85.37%, Spe 38.38%, Acc 52.14%), 4 days (Sen 82.41%, Spe 78.13%, Acc 81.43%), 6 days (Sen 77.42%, Spe 100.00%, Acc 80.00%). After attaining peak IPF%, platelet count increases in 36.5% of patients after 48 hours, 92.7% after 96 hours, and 100% after 6 days (10).

Chakraborty (2020) found that IPF% were steady from day 0-3 before decreasing throughout later days. Platelet counts were relatively steady from day 0-2 before increasing throughout later days. Trends are shown on Chakraborty (2020) Fig 2.(17)

Dadu (2014) found that after attaining peak IPF% peak, 84.3% of patients showed platelet count recovery within 24 hours and 100% within 48 hours. Platelet count recovery was seen in 93.75% of patients with IPF ≥ 10% within 48 hours. Platelet count recovery was seen in 93.75% of patients with a rising IPF% trend (IPF% change ≥ +10%) within 48 hours and

100% of patients with a falling IPF% trend (IPF% change ≤ -10%) within 24 hours (12).

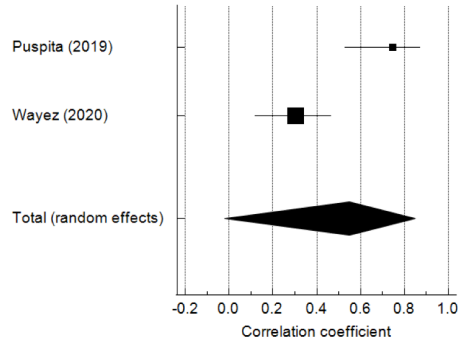

Fig. 2. Forest Plot of Predictive Value of IPF% to Platelet Count Change

Looi (2021) found that Platelet count decreased from admission to day 5, and remained low until day 7 and day 8 after the onset of fever; thereafter, platelet count increased from day 9 onwards towards normal values. IPF% increased from admission to day 8 before decreasing gradually to day 10 and then decreasing rapidly thereafter. Trends are shown in Looi (2021) Fig 1 (20).

Puspita (2019) found that IPF% is significantly correlated with platelet count change 2 days post IPF measurement (R 0.746, $p < 0.01$).(19)

Shah (2021) found that in patients with IPF% > 10, 90.9% of patients showed an increase in platelet count at 24 hours and 93.5% at 48 hours, respectively. After attaining peak IPF%, 96.1% of patients showed an increase in platelet count at 24 hours and 97.4% at 48 hours, respectively. In addition, 64% of patients with severe thrombocytopenia in this study can be prevented from receiving platelet transfusions by using an IPF% cut-off >10 (8).

Wayez (2020) found that IPF% is significantly correlated with platelet count change 24 hours post IPF measurement (R 0.133, $p < 0.05$) and 48 hours post IPF% measurement (R 0.303, $p < 0.01$) (18).

3.5. Daily IPF% and Platelet Count Changes

Agarwal (2021), Chakraborty (2020), and Looi (2001) reported the daily progression of IPF% and platelet count.(10,17,20) Visualization of progress can be seen in Fig. 3. IPF% change is shown on the blue bar, while platelet count change is shown on the purple bar. Dotted bars represent an increase, lined bars represent a decrease, and blank bars represent stagnancy/no change.

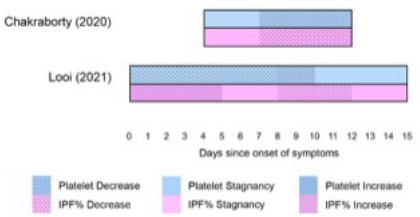

Fig. 3. Relative Daily Change in Platelet

(Fig. 3) puts into account the duration between the onset of fever and admission, therefore enabling comparison between the literature. Agarwal (2021) was not included in the figure because the study did not report the duration between fever onset and the day of admission.(10) Although not absolute, it is obvious that we can see a mirroring in the IPF% and platelet count progression. IPF% increase and platelet count decrease were seen until day 4-8, followed by a reversal – IPF% decrease and platelet count increase on the following days. Though the observation period did not span widely, pathophysiologic theory combined with observation results from Looi (2021) showed that by the end of week 2 – day 14 – IPF% and platelet count levels reverted to the normal range (20).

3.6. Pooled Correlation of Predictive Value of IPF% to Platelet Count Change

Puspita (2019) and Wayez (2020) reported Pearson's correlation coefficient of IPF% to platelet count post-IPF measurement. Pooled Pearson's correlation coefficient of these values can be seen in Fig. 3. Complete weight proportions per study can be seen in supplementary files (S3).

Pooled Pearson's correlation coefficient was insignificant (ES 0.549, 95% CI -0.019, 0.849). We found a high level of heterogeneity (I^2 = 88.97). This may be due to the non-linear relationship between IPF% and platelet count. This is supported by the fact that the analyzed studies did not explain the non-linear relationship between the variables. Studies could improve on this by considering the natural course of the disease and the time of measurement relative to the onset of symptoms at each measurement point.

3.7. Pooled Proportion of Platelet Recovery Post Maximum IPF% Values

Dadu (2014), Shah (2021), and Agarwal (2021) reported the proportion of patients achieving platelet recovery post maximum IPF% values. The pooled proportion of these values can be seen in the figures.

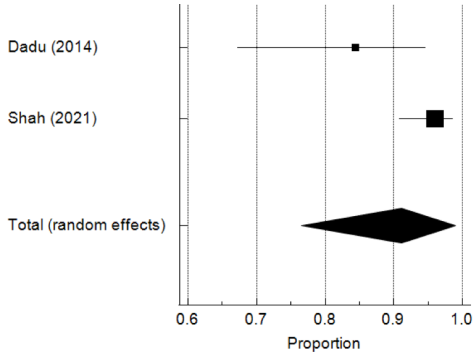

Fig. 4. Forest Plot of Proportion of Patients with Platelet Recovery 24 Hours Post Maximum IPF% Value

Pooled proportion and detailed calculations of platelet recovery 24 hours post maximum IPF% values can be seen in Fig. 4. Complete weight proportions per study can be seen in supplementary files (S4). A total of 157 subjects across 2 studies showed that 91.317% (95% CI 77.368-98.954) patients

experienced platelet recovery 24 hours post maximum IPF% values. However, we noted a high level of heterogeneity (I^2 = 98.55%).

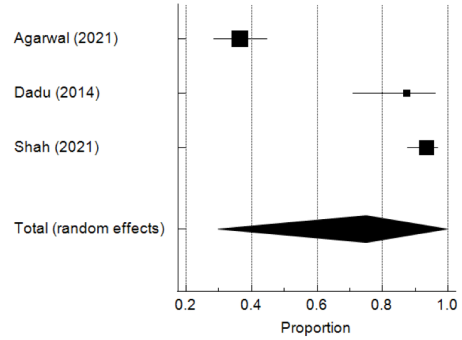

Fig. 5. Forest Plot of Proportion of Patients with Platelet Recovery 48 Hours Post Maximum IPF% Value

Pooled proportion and detailed calculations of platelet recovery 48 hours post maximum IPF% values can be seen in Fig. 5 and Supplementary File 5 (S5). A total of 296 subjects across 3 studies showed that 69.356% (95% CI 63.790-74.534) patients experienced platelet recovery 48 hours post maximum IPF% values. However, we noted a high level of heterogeneity (I^2 = 98.35%).

It must be noted that the 2 analyses above (Fig. 4 and 5) resulted from a disease-oriented way of thinking. In the clinical setting, the term 'maximum IPF% values' is always uncertain for any physician, as the future results are, of course, not yet available. The lack of information about the future progression of the IPF% values is a major factor towards why these analyses might not be clinically significant.

3.8. Pooled Proportion of Platelet Recovery Post Certain IPF% Values

Therefore, researchers developed another way to utilize the predictive capabilities of IPF% measurement. This includes using certain IPF% values as cut-off points. The pooled proportion of platelet recovery post certain IPF% values can be seen in Fig. 6.

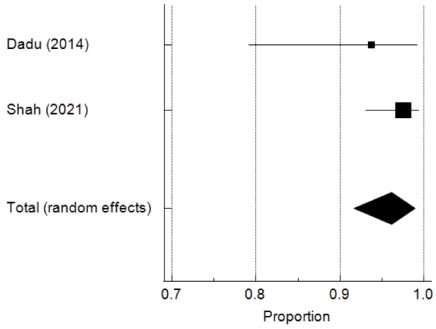

Fig. 6. Forest Plot of Proportion of Patients with Platelet Recovery 48 Hours Post IPF% ≥10%

Pooled proportion and detailed calculations of platelet recovery 48 hours post maximum IPF% values can be seen in Fig. 6 and Supplementary File 6 (S6). A total of 156 subjects across 2 studies showed that 96.161% (95% CI 91.678-98.967) patients experienced platelet recovery 48 hours post maximum IPF% values. We noted a low level of heterogeneity (I^2 = 20.59%).

3.9. Risk of Bias Assessment

The risk of bias was assessed using the quality in prognostic studies (QUIPS) tool. Complete reports of the risk of bias can be seen in Fig. 7 and 8.

We noted that not all studies measured the potential effect of confounding variables. This might bias the results of these studies. Overall, these studies pose a moderate up to high risk of bias; therefore, their results must be verified through further studies.

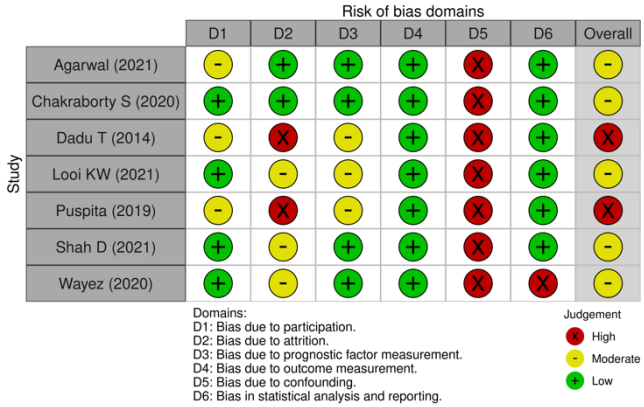

Fig. 7. Traffic Light Plot for Risk of Bias

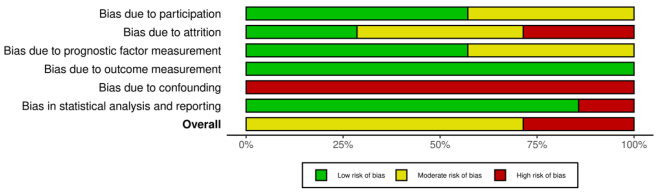

Fig. 8. Overall Risk of Bias

3.10. Quality of Evidence Assessment

The quality of evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool. The complete report on the quality of the evidence assessment can be seen in Table 2.

Due to studies included in our analyses being cohorts, we noted that the quality of evidence was mostly moderate to very low.

Table 2. Quality of Evidence

Author (year)	Quality of Evidence
Agarwal (2021)	Moderate
Chakraborty S (2020)	Moderate
Dadu T (2014)	Very low
Looi KW (2021)	Moderate
Puspita (2019)	Low
Shah D (2021)	Moderate
Wayez (2020)	Moderate

4. Discussion

Dengue infection caused by the Dengue virus of the Flavivirus family was transmitted through mosquitoes such as Aedes aegypti.(22,23) They are categorized based on their serotypes, namely DENV-1, DENV-2, DENV-3, and DENV-4.(24) Infection towards one serotype induces lifelong immunity, while subsequent infection by different serotypes induces antibody-dependent enhancement towards disease severity (25). In the last few decades, dengue has evolved from a sporadic disease to an epidemic in middle to lower-income countries (24).

Although most dengue infections are asymptomatic, typical symptoms are flu, fever, arthralgia, myalgia, cluster-type headache, and maculopapular rashes (26). The severity of dengue infection is classified by WHO based on the patient's few physical examinations and symptoms. Grade I is defined as fever without constitutional symptoms, and the only haemorrhagic manifestation is a positive tourniquet test and/or easy bruising. Grade II adds spontaneous bleeding, while grade III adds circulatory failure manifested by rapid and/or weak pulse, narrowing of pulse pressure or hypotension, cold and/or clammy skin, and restlessness. Grade IV happens when the patient has profound shock with undetectable blood pressure or pulse (27).

These viruses have one main nonstructural protein (NS1) that will induce platelet apoptosis, thus modulating macrophages and mononuclear cells to cause endothelial damage (22,23). This exhausts thrombocyte levels within the blood, as they are forced to be used to prevent vascular leakage. Aside from increasing thrombocyte turnover, DENV antigen from *Flavivirus* also decreases thrombocyte formation by reducing the proliferation of hematopoietic cells and inhibiting progenitor cells in the bone marrow. Combined, thrombocytopenia in dengue patients can cause severe bleeding and shock (7). The bone marrow compensates for thrombocytopenia by forming new thrombocytes called reticulated platelets counted in immature platelet fraction (IPF%). IPF% is a proportion of immature platelets divided by total platelets in peripheral blood (28). In cases that involve a decrease in platelet numbers as a marker of disease progression, IPF% can be utilized as an indicator of platelet recovery. This means that, theoretically, IPF% can be used in systemic inflammatory diseases such as sepsis. The immature platelet will mature in about 24 hours; thus, after IPF% reach its peak, platelet recovery will appear within 48-72 hours (20). Adequate compensation, though not immediately, protects the body from severe vascular leakage and septic shock.

Aside from dengue infection, IPF% has been used as a prognostic factor on numerous diseases, such as myelodysplastic syndrome, sepsis, disseminated intravascular coagulation (DIC), coronary acute syndrome, and many more. All studies reported that IPF% is a significant prognostic factor towards platelet count recovery (29–32).

This systematic review identified IPF% as a significant prognostic to platelet recovery in adult dengue patients. IPF% generally moves in a manner mirroring platelet count change. IPF% increase and platelet count decrease were generally seen until days 4-8, followed by a reversal – IPF% decrease and platelet count increase on the following days. Previous research has also shown that platelet recovery may be seen within 24 to 48 hours post maximum IPF% measurement. However, these disease-oriented analyses might not be clinically relevant for daily use. Therefore, analyses using IPF% cut-off of 10.0% and 6.10% were also done; producing results showing that platelet recovery may be seen within 24 to 48 hours post maximum IPF% measurement. Knowledge about how to utilize IPF% will help clinicians avoid prescribing unnecessary platelet transfusions.

This study is limited due to its scope of not including grey literature. Included studies also did not report the outcome in a single type of measurement (e.g., some with sensitivity and specificity analyses, some with correlation coefficient), although they all were an attempt to measure the predictive power IPF% measurement.

We recommend further studies to accommodate the possible effects of confounding variables through prospective studies. Further research in a different time frame (i.e., post COVID-19 pandemic) and in different regions (i.e., developing countries, South American countries) whilst specifying/considering the major DENV serotype might aid clinicians in gaining a personalized understanding of the disease progression.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: I.K.H.A., I.K.A.S., Design: R.C.S., C.A.W.P., Data Collection or Processing: I.K.H.A., G.V.P., R.C.S., Analysis or Interpretation: I.K.H.A., G.V.P., R.C.S., Literature Search: I.K.H.A., G.V.P., R.C.S., C.A.W.P., I.K.A.S., Writing: I.K.H.A., G.V.P.

Ethical Statement

This article requires no ethical clearance. The data used were those made public by respective authors.

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