Immature Platelet Fraction (IPF) as A Prognostic Biomarker Towards Platelet Count Recovery in Adult Dengue Patients: A Systematic Review and Meta-Analysis

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ABSTRACT

Background and Objectives. Dengue is a viral infection spread by arthropod which will damage platelets and caused thrombocytopenia. An increase production of platelets from bone marrow to compensate thrombocytopenia can be measured using IPF (immature platelet fraction). Therefore, this study aims to synthesise information about the potential of immature platelet fraction as a prognostic biomarker towards predicting platelet recovery.

Materials and Methods. We search article study from online databases (PubMed, Cochrane, Google Scholar, and Scopus) using keywords dengue and immature platelet fraction. Three independent reviewers were screened and extracted data about prognostic potential of IPF% towards platelet count.

Results. 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 researches had also shown that platelet recovery may be seen within 24 to 48 hours post maximum IPF% measurement.

Conclusions. 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 to avoid prescribing unnecessary platelet transfusions.

Keywords: Immature Platelet Fraction; Dengue; Prognosis; Systematic Review; Meta-Analysis

Abbreviations:

- IPF: Immature platelet fraction
- DHF: Dengue hemorrhagic fever
- DSS: Dengue shock syndrome
- IV: intravenous
- GRADE: Grading of Recommendations Assessment, Development, and Evaluation
- QUIPS: Quality in Prognostic Studies

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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 varies 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 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.[6] 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 criteria to measure 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 platelet 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 carries its 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 to measure young reticulated platelets in circulation.[8] Reticulated platelets alongside with several other biomarkers may serve as an assessment towards thrombopoiesis within the bone marrow.[10] Reticulated platelets was regarded by experts as 'hyperactive' platelets which exhibits significantly higher thrombogenicity.[11] Their levels were found to be proportional towards platelet turnover rate, thus is indirectly correlated to patients' dengue severity.[11] In conclusion, IPF% levels theoretically rises when there were less thrombocyte in the bloodstream than those needed, and is theoretically 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 synthesise 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.

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 hasn't 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 was done on February 17, 2023. The delay in online database search was due to the await of PROSPERO approval. The search in Scopus database was assisted by Harzing's Publish or Perish® version 8.6.4. Search keywords included (Dengue AND Immature Platelet Fraction [MeSH]) and was set not to strictly follow PICOTS due to the scarcity of studies done on the topic. Full search terms can be seen on supplementary files (S1). We only include articles which described adult dengue patients diagnosed using standard methods mentioned in guidelines (positive anti-dengue IgM, NS1, or positive RT-PCR) written in English. We don't impose restrictions regarding 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 will then be continued on retrievable full-text articles, respectively. Disagreement or uncertainty between the three researchers were 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 agreed to be included. Extracted data were summarized in a separate Microsoft Excel® sheet. Disagreement or uncertainty between the three reviewers were resolved by discussion. Data gathered within the standardised sheet were 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 which gives light to 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 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 were resolved by discussion.

2.7 Statistical Analysis

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

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 excluded again 4 articles and 2 irretrievable articles, resulting in only 7 full-text articles eligible for qualitative and quantitative synthesis. Flow diagram per PRISMA guidelines can be seen on figure 1.[14]

Insert Figure 1 here

3.2 Characteristics of Included Studies

Details of included studies can be seen in table 1. It must be noted that most of these studies were carried during the COVID-19 pandemic,[8,10,15–18] and all of them were done in developing Asian countries with high incident of dengue infections.[8,10,12,17–20] Agarwal (2021) and Dadu (2014) didn't report demographic characteristics of 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%.

Insert Table 1 here

3.3 Patient Characteristics

A total of 752 subjects were included from a total of all 5 studies. Of them, male constitutes from 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% 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.[10] Chakraborty (2020) found that 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.[17]

Dadu (2014) found that 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.[12]

Looi (2021) found that 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.[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% patients showed increase in platelet count at 24 hours and 93.5% at 48 hours, respectively. After attaining peak IPF%, 96.1% patients showed increase in platelet count at 24 hours and 97.4% at 48 hours, respectively. In addition, 64% 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 on figure 2. IPF% change is shown on blue bar, while platelet count change is shown on purple bar. Dotted bars represent an increase, lined bars represent a decrease, while blank bars represent stagnancy / no change.

Insert Figure 2 here

Figure 2 puts into account the duration between onset of fever and admission, therefore enabling comparison between literatures. Agarwal (2021) was not included in the figure due to the study not reporting duration between fever onset and 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 didn't 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 revert back to 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 on figure 3. Complete weight proportions per study can be seen on supplementary files (S2).

Insert Figure 3 here

Pooled Pearson's correlation coefficient was found to be not significant (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 these studies analysed didn't explain about the non-linear relationship of both variables. Studies could improve on this by putting into account the natural course of the disease and time of measurement relative to the onset of symptoms at each point of measurement.

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. Pooled proportion of these values can be seen on the following figures:

Insert Figure 4 here

Pooled proportion and detailed calculations of platelet recovery 24 hours post maximum IPF% values can be seen on figure 4. Complete weight proportions per study can be seen on

supplementary files (S3). 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 ($I^2 = 98.55\%$).

Insert Figure 5 here

Pooled proportion and detailed calculations of platelet recovery 24 hours post maximum IPF% values can be seen on figure 5 and supplementary files (S4). 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 (figure 4 and 5) were a result of a disease-oriented way of thinking. In clinical setting, the term 'maximum IPF% values' is always uncertain for any physician, as the results from the future are of course not available yet. The lack of information about the future progression of the IPF% values is a major factor towards why these analyses might not be clinically important.

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 on the following figures:

Insert Figure 6 here

Pooled proportion and detailed calculations of platelet recovery 48 hours post maximum IPF% values can be seen on figure 6 and supplementary files (S5). 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 ($I^2 = 20.59\%$).

3.8 Risk of Bias Assessment

Risk of bias was assessed with the quality in prognostic studies (QUIPS) tool. Complete reports of the risk of bias can be seen on Figure 7 and 8.

Insert Figure 7 and 8 here

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

3.9 Quality of Evidence Assessment

Quality of evidence was assessed with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool. Complete report of the quality of evidence assessment can be seen on table 2.

Insert Table 2 here

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

DISCUSSION

Dengue infection caused by *Dengue virus* of the *Flavivirus* family were 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 had evolved from a sporadic disease to an epidemic one in middle to lower income countries.[24]

Although most dengue infection are asymptomatic, typical symptoms were flu, fever, arthralgia, myalgia, cluster type headache, and maculopapular rashes.[26] The severity of dengue infection is classified by WHO based on few physical examinations and symptoms felt by the patient.[27] Grade I is defined as fever without constitutional symptoms, the only haemorrhagic manifestation is positive torniquet test and/or easy bruising.[27] 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.[27] Grade IV happens when the patient had profound shock with undetectable blood pressure or pulse.[27]

These viruses have one main non-structural protein (NS1) which will induce platelets 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 on preventing vascular leakage. Aside from increasing thrombocyte turnover, DENV antigen from *Flavivirus* also decrease thrombocyte formation by reducing proliferation of hematopoietic cells and inhibit progenitor cells in bone marrow. Combined, thrombocytopenia in dengue patients which can cause severe bleeding and shock.[7] The bone marrow compensates thrombocytopenia by forming new thrombocyte 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 which involves a decrease of platelet as a marker of disease progression, IPF% can be utilized as indicator of platelet recovery. This means that theoretically, IPF% can be used in systemic inflammatory diseases such as sepsis. 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]

CONCLUSION

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 day 4-8, followed by a reversal – IPF% decrease and platelet count increase on the following days. Previous researches had also shown that platelet recovery may be seen within 24 to 48 hours post maximum IPF% measurement. However, this disease-oriented analyses might not be clinically relevant for daily

use. Therefore, analyses which uses IPF% cut-off of 10.0% and 6.10% were also done; producing results which also shows that platelet recovery may be seen within 24 to 48 hours post maximum IPF% measurement. Knowledge about how to utilize IPF% will help clinicians to avoid prescribing unnecessary platelet transfusions.

LIMITATIONS AND RECOMMENDATIONS

This study is limited due to its scope of not including grey literatures. Included studies also didn't 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 possible effects of confounding variables through prospective studies. Further research in a different time frame (i.e., post COVID-19 pandemic) and in different region (i.e., developing countries, South American countries) whilst specifying / putting into account the major DENV serotype might aid clinicians in gaining personalized understanding of the disease progression.

CONFLICT OF INTEREST

The author declared that there was no conflict of interest during the making of this paper.

There is also no funding granted to the authors.

AUTHOR'S CONTRIBUTIONS

Conceptualization, GVP, IKHA and RCS; methodology, RCS; software, RCS; validation, CAWP, IKAS; formal analysis, GVP, IKHA, RCS; investigation, GVP, IKHA, RCS; resources, GVP, IKHA, RCS; data curation, GVP, IKHA, RCS; writing—original draft preparation, GVP, IKHA, RCS; writing—review and editing, GVP, IKHA, RCS; visualization, GVP, IKHA, RCS; supervision, CAWP, IKAS; project administration, GVP; funding acquisition, none. All authors have read and agreed to the published version of the manuscript.

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TABLES

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	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 trend and had not received blood transfusion		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	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.

						One-Step Kit for RT-PCR (Bio-Rad®)		
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	India	Prospective	106	[c]15-30 (66.0)	-	Positive for NS1	XE-2100	IPF% is significantly correlated with platelet

(2020)	(55.7%)	31-45 (20.8) 46-60 (10.4) >60 (2.8)	and/or IgM with platelet count <100.000/mm^3	(Sysmex®)	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 (%)

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

FIGURES

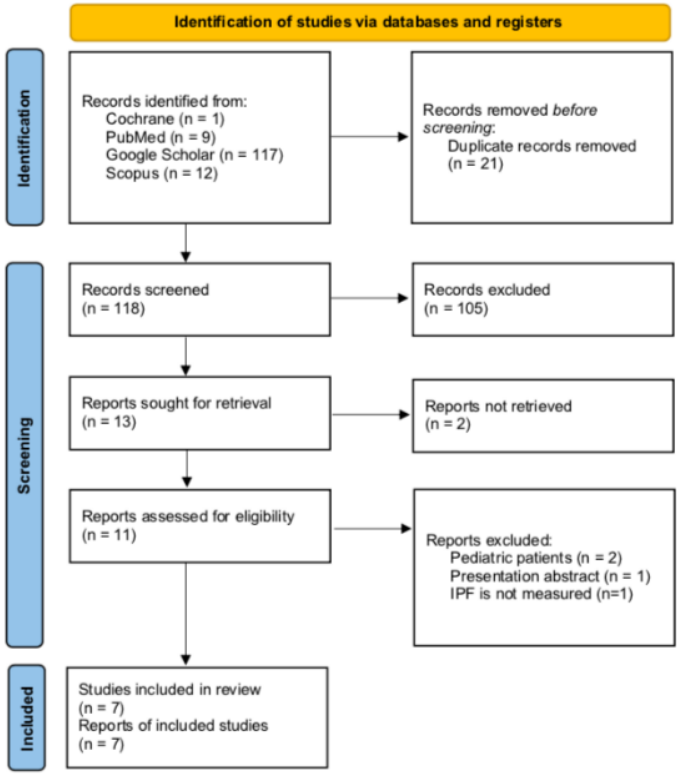

Figure 1. PRISMA Flow Diagram

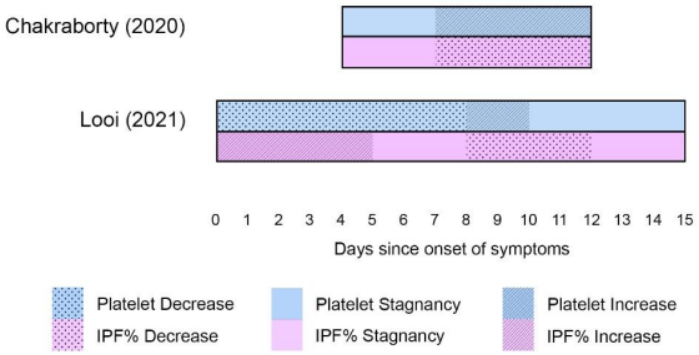

Figure 2. Changes in IPF% and Platelet Count

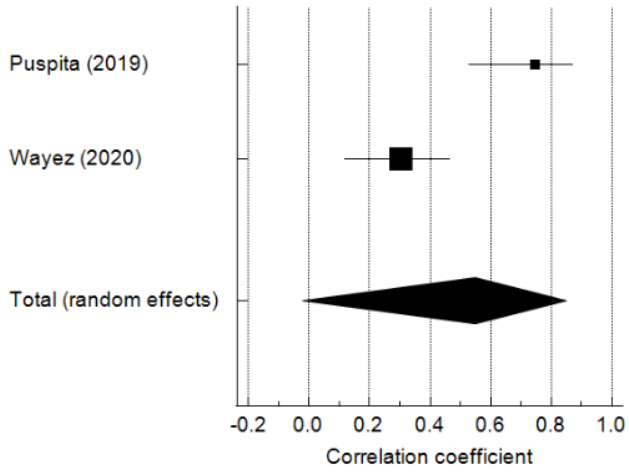

Figure 3. Pooled Pearson's Correlation Coefficient 48 Hours Post IPF Measurement

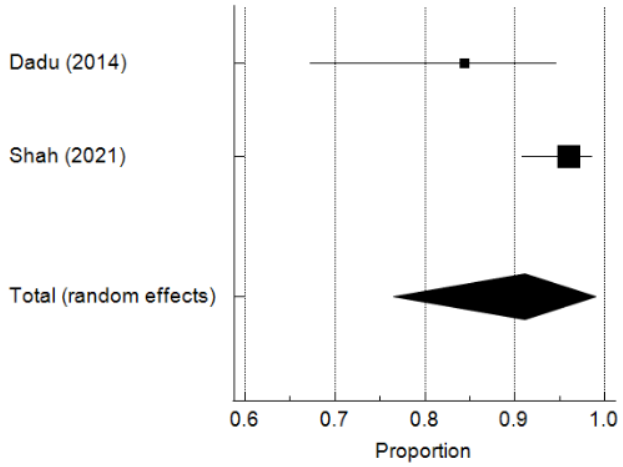

Figure 4. Pooled Proportion of Platelet Recovery 24 Hours Post Maximum IPF% Values

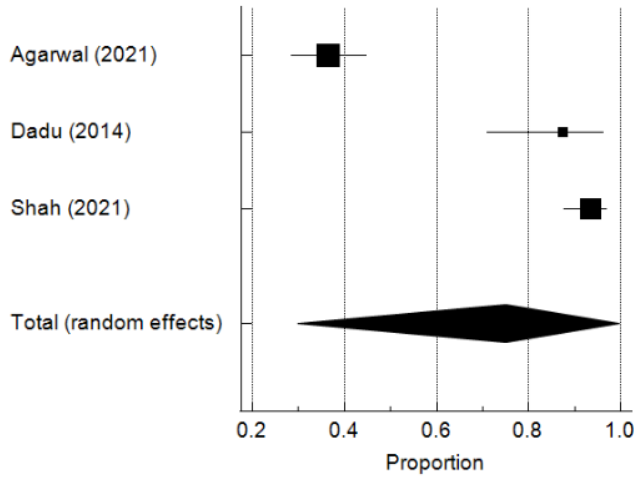

Figure 5. Pooled Proportion of Platelet Recovery 48 Hours Post Maximum IPF% Values

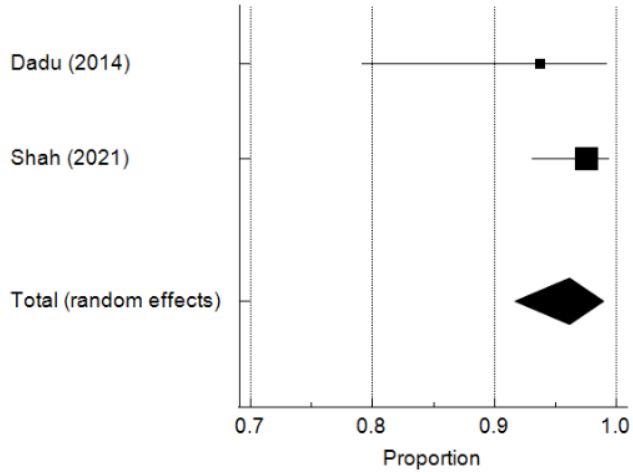

Figure 6. Pooled Proportion of Platelet Recovery 48 Hours Post IPF% > 10.0

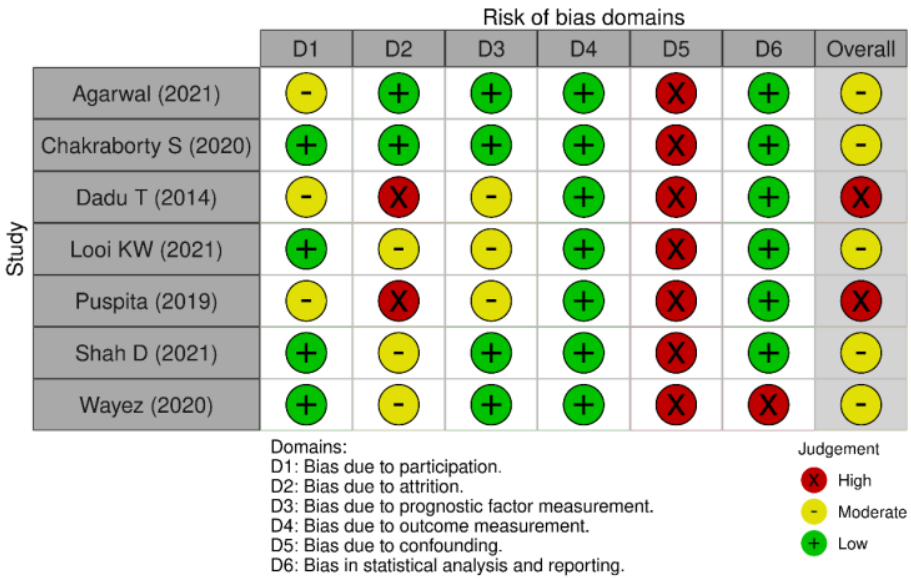

Figure 7. Risk of Bias Assessment using Quality in Prognostic Studies (QUIPS) Tool Visualization

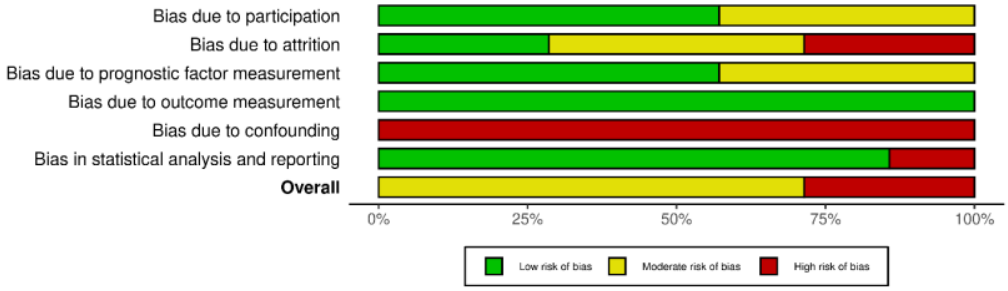

Figure 8. Risk of Bias Assessment using Quality in Prognostic Studies (QUIPS) Tool Summary