Review Article

Role of immature platelet fraction (IPF) in sepsis patients: A systematic review

Abubakar Tauseef[1], Maryam Zafar[2], Wafa Arshad[2], Joseph Thirumalareddy[1], Akshat Sood[1], Umar Farooque[2], Sunil Nair[1], Mohsin Mirza[1]

[1]Internal Medicine Department, Creighton University Hospital Program, Omaha, Nebraska, USA, [2]Internal Medicine Department, Dow University of Health Sciences, Karachi, Pakistan

Abstract

Sepsis is extremely common amongst critically ill patients and requires early diagnosis. Hence, identifying a biomarker that could acknowledge sepsis at its prior stage is of vital significance. Immature platelets are a percentage of circulating platelets that contain RNA and is a newer parameter that is measured using automated hematology analyzers in diagnosing sepsis. This review article discusses 10 articles that reveal the role of immature platelet fraction in predicting the onset of sepsis and its relationship with mortality in sepsis. Literature search was done using PubMed, Scopus and Google Scholar and words like platelet indices and immature platelet fraction were typed in the search bar. The aim of this review article is to present a precise form of data that talk about immature platelet fraction (IPF) and its association with the severity and mortality of sepsis. Five out of 10 articles suggest that immature platelet fraction can predict the onset of sepsis and eight out of 10 articles suggest that increased IPF values are associated with high mortality.

Keywords: Immature platelet fraction, mortality, review, sepsis, severity

Introduction

Sepsis is an extremely complicated lethal syndrome of organ dysfunction caused by dysregulated inflammatory host response to a staggering systemic infection.[1] In spite of expanding information regarding its pathogenesis, death rates as high as 30% are still being detected, even with the best possible management.[2] Early finding is one of the most significant difficulties in the management of sepsis, as deferral in sepsis acknowledgement increases sepsis-related mortality.[2] Microcirculatory changes and coagulation abnormalities are thought to play vital roles in sepsis by activating platelets and resulting in end-organ damage.[3] Besides hemostasis, platelets also play a key role in inflammatory diseases, which especially come to action in sepsis. Immature platelets, also known as reticulated platelets, are portrayed by higher RNA content compared to mature platelets.[4] Immature platelet fraction (IPF) estimates platelet production and accordingly differentiates between thrombocytopenia associated with bone marrow collapse due to toxic agents or a systemic infection.[4] The wide range of conventional and innovative parameters offered by the modern age of hematological analyzers typically include CBC, RET and differential leukocyte count and recently IPF provides a more clear cut assessment of red blood cells and platelet production.[5,6] Two diverse hematology analyzers XE- and XN- Series (Sysmex) or CELLDOWN Sapphire (Abbott) were used to perform automated estimations of immature platelets.[2] The evaluation of IPF gives significant data for the analysis and development of patients with sepsis. According to Korean data, reference values for IPF in men and women are 0.5–3.2% and 0.4–3.0%, respectively.[7] Moreover, IPF% corresponds with the positivity of blood cultures and in general surge before the beginning of sepsis. It is the main marker whose qualities appear

Address for correspondence: Dr. Abubakar Tauseef, 6815, Giles Road, Apt# 403, Papillion, NE 68133, USA.
E-mail: abubakartauseef@creighton.edu

Received: 22-11-2020 **Revised:** 24-12-2020
Accepted: 13-02-2021 **Published:** 02-07-2021

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_2293_20

How to cite this article: Tauseef A, Zafar M, Arshad W, Thirumalareddy J, Sood A, Farooque U, *et al*. Role of immature platelet fraction (IPF) in sepsis patients: A systematic review. J Family Med Prim Care 2021;10:2148-52.

to shift autonomously from those of ordinary coagulation tests.[6] According to the newer studies, immature platelet fraction may be a valuable prognostic factor to assess the seriousness of the disease and mortality in patients with sepsis.[2]

Objective

The aim of this article is to assess the importance of IPF in septic patients besides the typical biomarkers used such as CBC, WBC count, Pro- calcitonin, and CRP, which currently are the best markers for diagnosing and monitoring sepsis and its role in diagnosing sepsis at an early stage to decrease mortality and morbidity that can happen if the patient ends up with septic shock secondary to sepsis.

Methods

Information for this review article was mainly gathered from PubMed, Medline, Scopus, and Google Scholar. The keywords searched were immature platelet fraction, sepsis, platelet indices, and platelets in sepsis. The results revealed around 20 studies in the English language mainly from 2005 to 2020. Most of the studies were cohort, cross-sectional, and were conducted in the intensive care unit. A total of 10 articles were tabbed and were from the years 2010 to 2020. This was followed by a detailed, extensive analysis of these studies elaborating the outcomes of each article. The point of this article was to give the extensive data starting 2010 and to survey the significance of immature platelet fraction in diagnosing sepsis in the beginning phases and in predicting mortality. Ethical approval was taken before starting the literature search. The table below mentions the outcomes of each article and is composed in an ascending manner in terms of years for a better understanding.

Roberto Alberto De Blasi, *et al.*[4]

This was an observational prospective cohort study held at Sant' Andrea University Hospital, from December 2010 till April 2011 and included 64 ICU patients. It was ensured that the patients who were selected had no sepsis at the time of admission, which was confirmed within the first 24 hours of admission through diagnostic investigation for sepsis, septic shock, and severe sepsis using the sepsis criteria. Patients who showed signs of sepsis were excluded. The control group consisted of 31 septic patients diagnosed within 12 hours of ICU admission. Blood samples were taken within one hour of admission into the ICU and daily for seven days. Along with IPF, CRP, and PCT measurements, routine laboratory tests were also done which includes WBC count, APTT, PT, and INR [Table 1].

Of the patients who were enrolled, 31 patients showed no signs of sepsis and 42 patients had developed sepsis in the seven-day period. Of the 42 positive patients, 25 had positive blood cultures and nine were excluded due to low platelet count and in whom sepsis was not confirmed, leaving behind 33 septic patients in total. The septic control group that had 31 patients had 21 cases with positive blood cultures. The cut-off value for IPF% was 4.7%.

The only marker that proved to be effective in predicting sepsis in patients that initially had no sepsis but developed during the study was IPF. IPF showed to have a sensitivity of 56.2% and a specificity of 90%. Of the 31 patients who did not develop sepsis, only two had increased IPF values. This study showed that IPF increased two days before the onset of sepsis and only one patient developed sepsis six days after having increased IPF, which proves that platelet activity begins with an increment in thrombopoiesis before sepsis manifests clinically. IPF compared with other biomarkers used in this study (PCT and CRP) proved to administer beneficial information regarding sepsis if measured at an earlier stage when signs of systemic inflammatory response syndrome develop than when sepsis becomes evident. IPF was also seen to be inversely proportionate with platelet count.

Doaa Okasha, MD, *et al.*[8]

This investigation was intended to prospectively assess the estimation of IPF as an indicator of clinical result and mortality in patients prone to sepsis. It consisted of two populations of patients, one being admitted in the ICU due to neutropenia and the other one due to other reasons apart from neutropenia. There was a total of 104 neutropenic patients and 138 without neutropenia. This study revealed that IPF was higher in the 138 nonneutropenic patients than the neutropenic patients, which indicates that IPF was valuable in predicting the development of sepsis in those patients whose bone marrow was not compromised due to chemotherapy. High IPF was related to a longer stay in the hospital, death, and poor hemodynamic status [Table 1].

Rodolfo Monteiro Enz Hubert, *et al.*[5]

This was a retrospective study which aimed to evaluate the performance of IPF and IRF as biomarkers in terms of diagnosing sepsis and severity. It was a 30-day study in the intensive care unit and consisted of 41 patients in total. Of the 41 patients, 23 patients were diagnosed with sepsis and 14 were diagnosed with isolated SIRS. Twelve patients out of the 23 had severe sepsis and 11 had nonsevere sepsis. IPF was measured using an automated hematology analyzer. Patients with complicated sepsis presented with increased levels of IPF than patients with noncomplicated sepsis. IPF showed to be related to sepsis severity and was most accurate for diagnosing the presence of sepsis out of all the routine laboratory tests. IPF was also raised in septic patients when compared with healthy individuals. In terms of severity, lactate and IPF were the only biomarkers to give significant results between serious sepsis and nonserious sepsis [Table 1].

Qin Wu, MD, *et al.*[9]

This prospective study was held in a surgical critical care center of a Chinese tertiary care hospital in Jiangsu Province, China, which enrolled 68 septic shock patients and 68 controls. Diagnosis of sepsis was made based on the diagnostic criteria

of the American college of Chest Physicians/Society of Critical Care Medicine. The patients with sepsis were divided into two groups dependent on survival at 28 days. No difference was seen in terms of age, sex, comorbidities, primary disease, renal replacement therapy, mechanical ventilation, and infection between survivors and nonsurvivors. Reticulated platelets were measured within two hours of admission, using venous blood samples and flow cytometry, which revealed that RP was raised in patients who died with sepsis than in those who did not. RP was also compared with procalcitonin and lactate, which are currently the best biomarkers to diagnose sepsis, and RP ended up being superior to the two of them as far as anticipating mortality in septic patients. Kaplan–Meier survival curves were made based on an RP cutoff of 8.77%, which showed significant differences between survivors and nonsurvivors. The sensitivity and specificity between the survivors and nonsurvivors based on the cutoff value (RP of 8.77%) were 88% and 84%, respectively. The positive and negative predictive values were 66% and 95%, respectively [Table 1].

Tomohiro Murono, MD, *et al.*[10]

This prospective observational study was conducted from October 2013 to February 2015. Of 149 patients, 101 patients were having sepsis and 48 did not. IPF was measured on the day of admission and daily for 5 days using an hematology analyzer. In this observational investigation, IPF was able to predict a decrease in platelet count in sepsis, which suggests that increment in IPF levels are coagulopathy-related platelet consumption and not due to elevated thrombopoiesis. This study also revealed that elevated IPF is related to increased mortality in patients with sepsis, making it a beneficial marker for identifying thrombocytopenia. Hence, it is helpful in identifying the severity of and mortality due to sepsis [Table 1].

Sang Hyuk Park, *et al.*[3]

The aim of this article was to assess if IPF is a beneficial biomarker in differentiating between septic and nonseptic patients and severity of sepsis. This study was conducted in Asan Medical Center from March 2013 to July 2013 and a total of 312 patients were randomly enlisted who were divided into five groups. The groups consisted of 47 nonseptic patients, 50 nonseptics but with local infection, 64 uncomplicated sepsis, 61 with severe sepsis, and 90 septic shock patients. When septic patients were differentiated from nonseptic, PCT and CRP acted best in terms of specificities and positive predictive value. But IPF showed the best sensitivity and accuracy upon using 3.1% as the cutoff. However, IPF was unable to differentiate between complicated and uncomplicated sepsis, unlike various other studies.

Table 1: A quick review of articles used to write this review article

Author	Topic	Outcome
Roberto Alberto De Blasi, *et al.*[4]	Immature platelet fraction in predicting sepsis in critically ill patients.	IPF% values were higher for the patients who had sepsis at admission and during the study than in patients in whom sepsis never developed.
Doaa Okasha, *et al.*[8]	Immature platelet fraction predicts outcome and sepsis development in critically ill patients	IPF was raised in non- neutropenic patients than in neutropenic patients and was able to predict the development of sepsis in patients who did not have neutropenia.
Rodolfo Monteiro Enz Hubert, *et al.*[5]	Association of immature platelet fraction with sepsis diagnosis and severity.	IPF showed to be higher in sepsis than in healthy individuals. Moreover, it also showed to be higher in severe sepsis compared to non-severe sepsis.
Qin Wu, MD, *et al.*[9]	An elevated percentage of reticulated platelet is associated with increased mortality in septic shock patients	RP%, also known as IPF, was shown to be higher in patients who died with sepsis compared to patients who survived with sepsis. The sensitivity was 88% and specificity was 84% between survivors and non-survivors.
Tomohiro Murono, MD, *et al.*[10]	Immature platelet fraction predicts coagulopathy-related platelet consumption and mortality in patients with sepsis	The IPF upon the arrival of ICU admission was highest in patients in whom the platelet counts significantly declined and was less raised in patients in whom the platelet count was only slightly decreased.
Sang Hyuk Park, *et al.*[3]	Immature platelet fraction in septic patients: Clinical relevance of immature platelet fraction is limited to the sensitive and accurate discrimination of septic patients from non- septic patients, not to the discrimination of sepsis Severity	IPF turned out to be the most sensitive biomarker amongst other biomarkers in terms of differentiating sepsis from non- sepsis but was unable to discriminate sepsis severity.
Sabrina Buoro, *et al.*[6]	Innovative hematological parameters for early diagnosis of sepsis in adult patients admitted in intensive care unit	IPF was compared with CRP, in which IPF proved to give significant clinical data for predicting the onset of sepsis.
Qin-hua Liu, MS, *et al.*[11]	Clinical significance of measuring reticulated platelets in infectious diseases	RP% showed the best results when patients with serious sepsis were compared with non- serious septic patients. RP% gave best results when used with CRP, and PCT in terms of sensitivity and specificity of early diagnosis of infectious diseases.
M H Djuang, *et al.*[12]	Immature platelet fraction in bacterial sepsis severity assessment	IPF had no significance in discriminating between the PCT groups yet showed a positive correlation with MPW and PDW.
Nathan Jones, *et al.*[13]	Immature platelet indices alongside pro- calcitonin for sensitive and specific identification of bacteremia in the intensive care unit	IPF showed to be beneficial in differentiating between bacteremia from non- bacteremia patients. IPF was able to predict sepsis in this study quicker than CRP and lactate.

Sabrina Buoro, *et al.*[6]

This was a case control study held in the ICU of the General Hospital of Bergamo (Italy) from February 2014 to March 2014. This study enrolled 62 patients, of whom 41 were nonseptic and 21 were septic after their admission into the ICU, which was confirmed using the International Sepsis Definitions Conference guidelines along with a SOFA score. Blood tests were carried out twice daily from the day of admission till the day of discharge. Date of sepsis onset was described as the index date and up to five controls were arbitrarily chosen from patients who were without sepsis on the index date. IPF was compared with CRP and RET and athough CRP showed a decent diagnostic act, IPF displayed an equivalent act to differentiate between patients who eventually developed sepsis from individuals who did not. Altogether, this study exhibited that patients who were diagnosed with sepsis had elevated IPF two days before the onset which makes it a reliable marker in predicting sepsis [Table 1].

Qin-hua Liu, MS, *et al.*[11]

The aim of this study was to investigate the relationship between reticulated platelets (RP) and sepsis along with other biomarkers in diagnosing sepsis. The study began in December 2015 and was held until August 2016 and had 190 patients enrolled in the infectious group, of which 104 were male and 86 were female (age range: 18–91). Of the 190 patients, 89 patients were diagnosed with sepsis, of whom 39 had complicated sepsis, 18 had septic shock, and 70 were controls. According to this study, RP proved to be helpful in predicting the development of sepsis upon using 5.5% as the cutoff value and proved to be more useful than other routine laboratory tests. RP%, when combined with PCT, displayed a sensitivity of 90.41% and specificity of 90.90%, respectively. It was highest when RP%, PCT, and CRP were used altogether for diagnosis of sepsis [Table 1].

M. H. Djuang, *et al.*[12]

In this cross-sectional study conducted in Medan, 64 septic patients were recruited of whom 40 were male and 24 were female and all were above the age of 18. The aim of this study was to study the correlation between IPF and PCT in assessing the severity of sepsis. The patients were divided into three subgroups according to their PCT levels. The cutoff value for PCT in healthy individuals is <0.05, and in this study, the results were only significant if the *P* value is under 0.05. According to this study, IPF did not show any significant results when compared with platelet count, plateletcrit, MPW, and PDW in assessing sepsis severity and showed a *P* value of 0.644, whereas platelet count and plateletcrit showed *P* values of 0.04 and 0.03, respectively [Table 1].

Nathan Jones, *et al.*[13]

This study was conducted in the ICU of the Warrington District General Hospital between October 2018 and May 2019. It consisted of 82 patients, out of which 45 were male and 37 were female with the average age of 55.2 years. This study aims to compare IPF, AIPC, PCT, lactate, and CRP in terms of differentiating between bacteremia and nonbacteremia. In the eight patients who were positive for bacteremia, IPF and AIPC showed exceptional outcomes than in patients who did not have bacteremia and were able to accomplish much quicker than CRP and lactate [Table 1].

Discussion

This systematic review includes a total of 10 observational studies, with most studies supporting the fact that IPF is associated with increased sepsis severity and mortality. Most studies were able to support the fact that IPF can predict development of sepsis and assess severity of sepsis. Two studies reported that IPF cannot assess the severity of sepsis when compared with PCT.[3,12] De Blasi, *et al.*[4] reported that IPF was seen to be elevated two days before the onset of sepsis in critically ill patients in the ICU. Similar results were noted by Buoro *et al.*,[6] who observed elevated levels of IPF two days before sepsis was diagnosed. Moreover, Enz Hubert *et al.*[5] in his retrospective study reported that IPF was able to diagnose sepsis and discriminate between complicated and noncomplicated sepsis. Nathan Jones, *et al.*[13] also reported that RP was able to diagnose sepsis in patients with bacteremia quicker than CRP and lactate. However, Sang Hyuk Park, *et al.*,[3] announced in his study that IPF can diagnose sepsis but not differentiate between complicated and noncomplicated sepsis. This was also reported by M. H Djuang, *et al.*,[12] that IPF when combined with PCT did not show significant results in assessing the severity of sepsis when compared with other platelet indices. Qin-hua Liu, *et al.*[11] reported that immature platelets were beneficial in predicting sepsis after using 5.5% as the cutoff. Overall, five studies were able to prove the value of IPF in predicting sepsis.[4,6,8,10,11] Regarding mortality, Qin Wu[9] reported that IPF was higher in patients who died with sepsis than in patients who survived. These discoveries are of central significance as they allow early acknowledgment of sepsis and commencement of antimicrobials, which might contribute to improving the result of septic patients. Although the accessible information in the literature propose that IPF could be a significant biomarker for early analysis of sepsis, most of the investigations have restricted test size. Moreover, the values of IPF can vary upon using an XE-2100 instrument instead of the XN series which may alter the results.[3] IPF tends to be higher in people with ITP due to platelet destruction and lower in immunocompromised people due to bone marrow suppression.[7] The purpose of this review article is to display a concise dossier about how IPF may play a vital role in predicting sepsis and its association with mortality, as early recognition of sepsis is key and may help in improving the high mortality rates due to sepsis. This study is of great significance for the physicians as this study proved the fact by extensive data that patients with raised IPF are at higher risk for developing severe sepsis and mortality caused by sepsis. Upon obtaining IPF levels, we can diagnose a patient as having sepsis even when the other sepsis markers are not even

elevated which might lead to the detection of sepsis at early stage and hence result in the early management of sepsis and decrease in mortality caused by severe sepsis or septic shock.

Key points

Sepsis is a life-threatening illness which requires early diagnosis. This systematic review proposes that immature platelet fraction plays a pivotal role in sepsis and may be a predictor of the disease and gives 100% accuracy when combined with other biomarkers that are currently in use. Many articles also suggest that higher values of IPF may be associated with higher rates of mortality. Also, increased IPF level is correlated with the increase in the stay at hospitals.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Assinger A, Schrottmaier WC, Salzmann M, Rayes J. Platelets in sepsis: An update on experimental models and clinical data. Front Immunol 2019;10:1687.
2. Thorup CV, Christensen S, Hvas AM. Immature platelets as a predictor of disease severity and mortality in sepsis and septic shock: A systematic review. Semin Thromb Hemost 2020;46:320-7.
3. Park SH, Ha SO, Cho YU, Park CJ, Jang S, Hong SB. Immature platelet fraction in septic patients: Clinical relevance of immature platelet fraction is limited to the sensitive and accurate discrimination of septic patients from non-septic patients, not to the discrimination of sepsis severity. Ann Lab Med 2016;36:1-8.
4. De Blasi RA, Cardelli P, Costante A, Sandri M, Mercieri M, Arcioni R. Immature platelet fraction in predicting sepsis in critically ill patients. Intensive Care Med 2013;39:636-43.
5. Enz Hubert RM, Rodrigues MV, Andreguetto BD, Santos TM, de Fátima Pereira Gilberti M, de Castro V, *et al.* Association of the immature platelet fraction with sepsis diagnosis and severity. Sci Rep 2015;5:8019.
6. Buoro S, Manenti B, Seghezzi M, Dominoni P, Barbui T, Ghirardi A, *et al.* Innovative haematological parameters for early diagnosis of sepsis in adult patients admitted in intensive care unit. J Clin Pathol 2018;71:330-5.
7. Schmoeller D, Picarelli MM, Paz Munhoz T, Poli de Figueiredo CE, Staub HL. Mean platelet volume and immature platelet fraction in autoimmune disorders. Front Med (Lausanne) 2017;4:146.
8. Okasha D, Sarig G, Benyamini N. Immature Platelet Fraction Predicts Outcome and Sepsis Development in Critically Ill Patients Admitted to a General Intensive Care Unit, Washington: American Society of Hematology 2014;21:1-7.
9. Wu Q, Ren J, Hu D, Jiang P, Li G, Anjum N, *et al.* An elevated percentage of reticulated platelet is associated with increased mortality in septic shock patients. Medicine 2015;94:e814.
10. Muronoi T, Koyama K, Nunomiya S, Lefor AK, Wada M, Koinuma T, *et al.* Immature platelet fraction predicts coagulopathy-related platelet consumption and mortality in patients with sepsis. Thromb Res 2016;144:169-75.
11. Liu QH, Song MY, Yang BX, Xia RX. Clinical significance of measuring reticulated platelets in infectious diseases. Medicine (Baltimore) 2017;96:e9424.
12. Djuang MH, Ginting F, Hariman H. Immature Platelet Fraction in Bacterial Sepsis Severity Assessment; Earth and Environmental Science 2018;125:012024.
13. Jones N, Tridente A, Dempsey-Hibbert NC. Immature platelet indices alongside procalcitonin for sensitive and specific identification of bacteremia in the intensive care unit. Platelets. 2020:1-9. doi: 10.1080/09537104.2020.1809646.