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Immature platelet fraction as predictor of platelet recovery in dengue fever

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Abstract

Dengue fever is caused by dengue virus—a mosquito-borne flavivirus and transmitted by Aedes aegypti and Aedes albopictus, and estimated 390 million cases of dengue infection occur each year globally, with 96 million cases being considered severe. Thrombocytopenia has always been one of the criteria used by WHO guidelines as a potential indicator of clinical severity. Thrombocytopenia is a common cause of concern in dengue to both patients and attending clinicians. To avoid hemorrhagic complications in dengue fever with thrombocytopenia, prophylactic platelet transfusions are administered. Even though it saves lives, platelet transfusions have their own dangers. In order to prevent unnecessary platelet transfusions, a lot of study has been done on Immature Platelet Fraction (IPF) as a predictor of platelet recovery. IPF is a measurement of reticulated platelets that represents the rate of thrombopoiesis. The rapid detection of IPF can lower the danger of platelet transfusion.

Keywords: Dengue fever; Thrombocytopenia; Immature Platelet Fraction (IPF); Predictor

1. Introduction

Dengue fever is anmosquito-borne viral infection that spreads rapidly and is a significant public health issue. Tropical and subtropical nations frequently see cases of dengue in primary care settings. More than 100 nations in Africa, America, the Eastern Mediterranean, South-East Asia, and the Western Pacific are affected by its endemicity [1]. It is caused by dengue virus—a mosquito-borne flavivirus and transmitted by Aedes aegypti and *Aedes albopictus.* An estimated 390 million cases of dengue infection occur each year globally, with 96 million cases being considered severe. There is a wide range of clinical symptoms associated with dengue virus infection, from low-grade fever or known as classic dengue fever to serious, potentially fatal complications known as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [2,3].

The course of dengue disease is closely related to several factors. The patient's immunological response, the viremia phase, and the haematological parameters in the peripheral blood are all important factors in how dengue disease develops. Along with a decline in the quantity of white blood cells and platelets, the phenomenon of increasing plasma leakage becomes one of the factors that determine the severity of the disease during the critical period [2]. Around 5% of cases of severe dengue illness are on the average and typically affect children and young people. For DHF and DSS to receive effective treatment and prevent developing a serious condition, early detection of dengue infection is crucial [3].

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2. The Course of Dengue Disease

Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Patients with asymptomatic infection are viraemic and thus may be a source of infection. Symptomatic dengue infection is a systemic and dynamic disease. The incubation period lasts for 5 to 7 days and the onset of the illness is abrupt. There are many different clinical presentations of it, both severe and less severe [1].

The severity of the disease usually becomes apparent during defervescence, that is, during transition from the febrile to the afebrile phase. This frequently happens when the critical phase begins, which typically happens after 72 hours of fever. The critical phase is distinguished by the pathophysiological feature of increased capillary permeability, which lasts approximately 24 to 48 hours and is more frequently found in secondary dengue infections. The recovery phase comes after this phase. Understanding the various stages of the disease and being aware of any potential clinical issues that can emerge during these periods are crucial for achieving a good clinical result [1].

It is essential to recognize and appropriately identify the early dengue infection disease signs. Initial laboratory results for acute dengue fever will show normal white blood cells and platelet counts, or in some cases, a mild increase in haematocrit (-10%) or moderate thrombocytopenia. After that, toward the end of the febrile phase, there is a drop in both neutrophils and total white blood cells. The critical phase of plasma leakage can be predicted using a decrease in the neutrophil to lymphocyte ratio and total white blood cell count (5000 cells/mm^3). Late in the febrile phase, prior to the onset of shock or the decrease in fever, there is a dramatic decrease in the platelet count below 100,000 [4]. Another early indicator is an increase in haematocrit (HCT) above the baseline. The elevated hematocrit and decreased platelet count indicate the transition from the viremia to the immunological phase of the disease [2]. Typically, clinically relevant plasma leakage lasts between 24 and 48 hours. Plasma leakage occurs to varying degrees. Blood pressure (BP) and pulse volume changes occur before increases in hemoglobin concentration. The severity of plasma leakage is indicated by the degree of hemoconcentration above the baseline haematocrit; however, this can be masked by early intravenous fluid therapy [1]. Haemoconcentration or a 20% increase in haematocrit from baseline is objective evidence of plasma leakage. Thrombocytopenia and haemoconcentration are constant findings in dengue fever [4].

3. Thrombocytopenia

Thrombocytopenia has always been one of the criteria used by WHO guidelines as a potential indicator of clinical severity. The definitions of thrombocytopenia generally refer to a rapid fall in platelet count or a platelet count fewer than 150,000 per microliter of blood in the most recent 2009 WHO guidelines. On the fourth day of the illness, the platelet count in DHF/DF showed a significant decline, according to a kinetic description. In reality, earlier research found that in people without shock with DHF, platelet counts declined mildly to moderately from the third day through the seventh day of the illness before returning to normal on the eighth or ninth day [5]. Thrombocytopenia in dengue is multifactorial. In the early stage, bone marrow hypo cellularity followed later by immune mediated destruction of platelets are proposed as the mechanisms for thrombocytopenia. Platelet dysfunction (the absence of adenosine diphosphate release) was initially demonstrated in patients with dengue hemorrhagic fever during convalescence. The platelet dysfunction could be due to exhaustion from platelet activation triggered by immune complexes [6].

The complex mechanism of thrombocytopenia is still controversial. Previous reports have shown that, during the early phase of disease, bone marrow displays hypocellularity and attenuation of megakaryocyte maturation. The precise mechanisms underlying DENV-induced bone marrow suppression during the acute phase remain unclear. However, three main factors have been suggested: (i) direct lesion of progenitor cells by DENV; (ii) infected stromal cells; and (iii) changes in bone marrow regulation. Activation of the complement system, enhanced peripheral sequestration, or platelet consumption during the ongoing coagulopathy process can all contribute to thrombocytopenia [4,5,6].

Thrombocytopenia and bleeding are the most often reported complications in dengue patients. Platelet dysfunction, endothelial cell damage, coagulation defects, and macrophage activation are caused by the cross-reactive antibodies anti-NS1, prM, and E viral proteins against platelets, endothelial cells, or coagulatory molecules. Vascular fragility resulting from impaired platelet functioning is what causes bleeding and plasma leakage in dengue hemorrhagic fever [8]. According to the guidelines, platelet transfusions should only be given in situations of severe thrombocytopenia or active bleeding. Although it was estimated that 13 to 56.2% of cases received inappropriate transfusions, the majority of platelet transfusions are a reaction and are not done for medical reasons. Thus, platelet transfusions should not be routinely performed in the management of dengue [9].

4. Prophylactic Platelet Transfusions

Thrombocytopenia is a common cause of concern in dengue to both patients and attending clinicians. To avoid hemorrhagic complications in dengue fever with thrombocytopenia, prophylactic platelet transfusions are administered. The estimation of platelet count and function, the underlying cause of thrombocytopenia, the state of the coagulation system, the presence or likelihood of bleeding, and the transfusion hazards all play a role in the decision to transfuse platelets [6]. There are no clear guidelines for management of thrombocytopenia and platelets are ordered as a routine in most hospitals. In contrast to therapeutic platelet transfusions, which are provided to patients who are experiencing clinical bleeding, prophylactic platelet transfusions are described as platelet transfusions delivered when there is no clinical bleeding. The majority of clinical guidelines advise giving platelet transfusions to patients who experience severe hemorrhagic symptoms or have extremely low platelet counts, defined as platelet counts below 10-20 x 10^9 L^{-1} without hemorrhage or 50 x 10^9 L^{-1} with bleeding or hemorrhage [5,8].

Although platelet transfusions save lives, they also carry their own risks. Alloimmunization, immunosuppression, allergic reactions, non-hemolytic febrile reactions, sepsis, infectious diseases transmission, and acute lung injury are complications that can result from prophylactic platelet transfusion [3,4,9].

5. Immature Platelet Fraction

To avoid hemorrhagic consequences, prophylactic platelet transfusion is administered to dengue fever patients with thrombocytopenia. Even though it saves lives, platelet transfusions have their own dangers [3]. Prophylactic platelet transfusion can cause complications such as alloimunization, immunosuppression, allergic reactions, non-hemolytic febrile reactions, sepsis, infectious disease transmission, and acute lung injury [4,9]. In order to prevent unnecessary platelet transfusions, a lot of study has been done on Immature Platelet Fraction (IPF) as a predictor of platelet recovery. IPF is a measurement of reticulated platelets that represents the rate of thrombopoiesis. The rapid detection of IPF can lower the danger of platelet transfusion. When an asymptomatic patient's platelet count is less than 20,000 cells/cum, prophylactic platelet transfusion is typically administered. There are no guidelines for when to transfuse platelets into individuals who are asymptomatic. However, prophylactic platelet transfusion for severe thrombocytopenia in hemodynamically stable patients has been demonstrated to be ineffective and unnecessary, according to WHO. To prevent unnecessary platelet transfusions, doctors can use IPF to predict platelet recovery in dengue fever patients [7].

A new parameter known as the Immature Platelet Fraction (IPF) automatically measures reticulate platelets in peripheral blood. Reticulate platelets are more recent platelets that are bigger, more physiologically active, and similar to red blood cell reticulocytes in that they contain RNA [10]. Immature platelets and reticulocytes are immediately released into the peripheral blood, where they mature within about 24 hours. Since these maturation processes take time, their presence in the blood can be viewed as a lagging signal of activity in the bone marrow. The absolute numbers and percentages represent the degree of activation and repression of the bone marrow, respectively. For example, in idiopathic thrombocytopenia, the destruction of peripheral platelets is associated with increased bone marrow cell production. Because the presence of immature platelets occurs two days before the increase in platelet count, the immature platelet fraction (IPF) has been utilized to assess platelet turnover in thrombocytosis [2].

Immature Platelet Fraction measurement offers an evaluation of bone marrow platelet production from a peripheral blood sample. Immature Platelet Fraction (IPF%) and Immature Platelet Fraction Count (IPF#) have been recognized as measures of thrombopoietic activity. IPF% and IPF# are theoretically similar to the percentage and total number of immature platelets in peripheral blood. An increase in IPF% is considered to indicate consumptive or destructive thrombocytopenic state, while a normal or decreasing IPF% is considered to indicate decreasing platelet production in the bone marrow. IPF# is considered to reflect real-time platelet production [11]. If there is an increase in platelet destruction and consumption, IPF will increase. In cases of bone marrow failure, IPF will decrease. The normal range for IPF is between 1.1 and 6.1 [3,4,7]. Other studies show that the usual reference range for IPF is between 1.6 and 7.1% in adults, while in children, it is between 1.0 and 6.8% [11]. Several studies reported that IPF >10% predicted platelet recovery within 48-72 hours [2,7]. The IPF will start to decrease the following day after reaching its peak value. A later increase in platelets is strongly predicted by this decrease in IPF. Therefore, the time lag for platelet recovery in that situation is between 24 and 48 hours if the platelets have not yet started to recover. According to studies, the lowest platelet count value, which indicates greater thrombopoiesis, associated with the biggest increase in IPF [12,13].

Fluid therapy in dengue fever patients with improved plasma leakage should not be overly aggressive and should be cautious because once plasma leakage improves there will be a shift back fluid to the intravascular, and may occur overload when fluid therapy is too aggressive. Fluid therapy in dengue patients still experiencing worsening plasma

leakage should be adequate to avoid going into shock. Therefore, one of the factors for fluid therapy in patients with DHF can be based on the data of IPF on DHF patients that are significantly connected favorably with platelet count changes in conjunction with the occurrence of plasma leakage [14]. Since IPF levels decline around 24-48 hours before improvement in platelet counts, unnecessary platelet transfusion can be prevented in such conditions [15].

The number and proportion of immature platelets indicate the rate of thrombopoiesis; these parameters' values fluctuate together with the rate of platelet formation. Immature platelets can be distinguished from their mature counterparts due to the high concentration of ribonucleic acid (RNA) in them. Using flow cytometry, Kienast and Schmitz made the initial demonstration of this in 1990. Since then, a number of modifications have been created using various flouro-chromes and multi-color flow cytometric analysis to provide easy, quick, and accurate assessment of reticulated platelets. Modern automated hematology analyzers with this sophisticated technique allow fluorescent dyes to identify RNA by penetrating the cell membrane through a breach created by surfactant. A percentage of the total platelet count (IPF%) is used to report it [12]. Automated haematology analyzers are able to determine the precise quantity of immature platelets and their proportions to mature platelets. It is simple to use dyes like thiazole orange to stain and measure the residual ribonucleic acid that is transmitted from megakaryocytic progenitor cells during platelet formation. For assessing thrombopoietic activity in patients with thrombocytopenia, flow cytometric examination of immature platelets is more helpful than other staining techniques [16].

6. Conclusion

Dengue fever is anmosquito-borne viral infection that is a significant public health issue. It is essential to recognize and appropriately identify the early dengue infection disease signs. Thrombocytopenia and bleeding are the most often reported complications in dengue patients. To avoid hemorrhagic complications in dengue fever with thrombocytopenia, prophylactic platelet transfusions are administered. But, platelet transfusions should only be given in situations of severe thrombocytopenia or active bleeding. Although platelet transfusions save lives, they also carry their own risks. In order to prevent unnecessary platelet transfusions, a lot of study has been done on Immature Platelet Fraction (IPF) as a predictor of platelet recovery. IPF indicates the amount of thrombopoiesis in thrombocytopenia patients and its measurement is useful in differential diagnosis and monitoring of platelet kinetics in thrombocytopenia patients. The IPF levels can predict the timing of platelet recovery which is within 1-2 days of IPF increase, so unnecessary platelet transfusion can be prevented in such conditions.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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