Severe Thrombocytopenia Associated with Dengue Fever and its Management by Using Platelet Concentrators

ABSTRACT

To assess the efficacy of platelet concentrators in the treatment of severe thrombocytopenia associated with dengue infection. The study examines several literature articles according to the manner of data collecting. The information acquired was based on the analysis's objectives. All data were gathered from numerous journals, magazines, research papers, and publications. The sites visited were Google Scholar, PubMed, and others. The relationship between Dengue infection and thrombocytopenia demonstrates the intricacies of dengue etiology and stresses the importance of targeted treatment strategies. This study investigated many pathways implicated in dengue-induced platelet decrease, including direct platelet infection, megakaryocyte suppression, and immune-mediated clearance. The findings indicate that medicines focused on these pathways have the potential to minimize the severe clinical effects of dengue.Furthermore, platelet concentrators have shown promise in the treatment of thrombocytopenia, offering a viable alternative for reducing bleeding risks and improving patient outcomes. Continued research into the molecular links between DENV and platelet biology is crucial for developing more effective treatments and, ultimately, improving clinical dengue fever care.

INTRODUCTION

Dengue fever, the most rapidly expanding vector-borne disease in the world, has risen markedly during the twenty-first century [47]. This is an illness caused by dengue virus (DENV), which is mainly transmitted by Aedes aegypti mosquito [48]. DENV infection can occur in different patterns, ranging from mild febrile illness to severe dengue characterized by capillary leakage, hemorrhage and organ failure[49].

Severe dengue also involves thrombocytopenia, a condition defined as abnormally low blood platelet levels that can worsen bleeding and complicate clinical management of this disease[50].

The mechanisms responsible for DENV-induced thrombocytopenia are still not fully elucidated despite intensive researches. The objective of this study is to shed light on the postulated pathways through which DENV influences platelet production and function leading to thrombocytopenia and assess if it’s possible to treat this syndrome with platelet concentrators.

1.AIM AND OBJECTIVE OF THE STUDY

Aim:

To evaluate the effectiveness of platelet concentrators in the management of severe thrombocytopenia associated with dengue fever.

Objectives:

1. To assess the prevalence and severity of thrombocytopenia in patients with dengue fever.
2. To investigate the clinical outcomes associated with severe thrombocytopenia in dengue fever patients.

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3. To evaluate the efficacy of platelet concentrators in increasing platelet counts in patients with severe thrombocytopenia
4. To elucidate the mechanisms through which dengue virus (DENV) infection induces thrombocytopenia

2. METHODOLOGY

The study reviews various literature article by method of data collection. information gathered based on the objectives of the analysis. All the data were collected through various journal, magazine, research paper and publications. The site followed was google scholar, pub med etc.

3. OBSERVATIONS AND RESULTS

Dengue fever is one of the most common vector-borne virus diseases seen in tropical and subtropical countries. Colombia has one of the highest dengue case rates in the Americas. Severe dengue virus (DENV) infection causes capillary leakage, hemorrhage, and organ compromise, ultimately leading to death. Many efforts have been made over the years to develop a vaccine that provides protective immunity, but they have only been partially effective because such immunity must defend against four unique virus serotypes. Absolute platelet count is a laboratory marker used to track the clinical course of DENV, which is frequently accompanied by thrombocytopenia. Although this discovery is extensively reported in terms of the disease's natural history, there are multiple possibilities as to why this rapid drop occurred, and several in vivo and ex vivo models have been utilized to understand how DENV infection affects platelets and their precursors. DENV infects and activates platelets, allowing them to be eliminated by phagocytic cell identification and peripheral marginalization. Infection, however, has an effect on bone marrow precursors via modifying megakaryopoiesis. The goal of this paper is to investigate multiple hypothesized pathways of DENV-induced thrombocytopenia in order to better understand the pathophysiology and clinical manifestations of this highly relevant viral illness.[34]

It is caused by an arthropod-borne virus transmitted by the vector Aedes aegypti. Dengue fever and dengue hemorrhagic fever have arisen major global public health concerns in recent decades. Dengue viruses (DV) belong to the Flaviviridae family and have four serotypes: DV-1, DV-2, DV-3, and DV-4. The study only included dengue-positive patients who had received platelet transfusions. This study did not include non-dengue patients or dengue patients who did not receive platelet transfusions [33].

One of the most significant viral diseases spread by vectors in tropical and subtropical areas is dengue. In the Americas, Colombia has one of the highest dengue case rates. Severe dengue virus (DENV) infection manifests as organ damage, bleeding, and capillary leakage, which ultimately results in death. Many attempts have been made over the years to create a vaccine that ensures protective immunity; however, their efforts have only been partially successful because the immunity in question would need to ensure protection against four different virus serotypes. Since thrombocytopenia is frequently associated with DENV infection, the absolute platelet count is a laboratory indicator used to track the disease's clinical development. While the natural course of the disease is well-explained by this discovery, there are a number of theories explaining why the number of platelets and their precursors decreased so quickly. Several in vivo and ex vivo models have also been utilized to understand the impact of DENV infection on platelets. DENV causes infection and stimulates platelets, making it easier for phagocytic cells to recognize and eliminate them through peripheral margination. Nevertheless, infection also modifies megakaryopoiesis, which impacts the precursors in the bone marrow. This article's goal is to investigate several hypothesized mechanisms of DENV-induced thrombocytopenia in order to gain a deeper understanding of the pathogenesis and clinical manifestations of this extremely important viral infection.[1]

Dengue has a broad clinical spectrum and is a significant public health concern. Dengue is divided into three categories by the World Health Organization: probable dengue, dengue with warning signs, and severe dengue. If severe dengue is not treated promptly, it can lead to major morbidity and fatality. Severe dengue is characterized by plasma leakage, severe bleeding, or organ dysfunction. Dengue has no known cure; supportive care is the only available treatment. The cornerstone of dengue management during its critical phase is prudent fluid resuscitation. The first choice of fluid is crystalloids. Transfusions

of platelets as a preventive measure are not advised. When dengue is severe, organ involvement needs to be closely monitored and treated. It is important to diagnose secondary hemophagocytic lympho-histiocytosis, a potentially fatal dengue complication, as particular treatment with steroids or intravenous immunoglobulin may improve results. There is currently no anti-dengue medication on the market, however a number of substances with this potential are being investigated.[2]

Common tropical viral diseases like dengue frequently result in thrombocytopenia, which can cause bleeding and necessitate blood transfusions. This is expensive in low-income environments. Using a relatively novel parameter—the immature platelet fraction—which represents platelet regeneration by the bone marrow, we carried out observational research. Platelet count and immature platelet fraction were found to be strongly correlated in our study of 124 dengue patients. We also found that 96.1% and 97.4% of patients, respectively, had an increase in platelet count at 24 and 48 hours. In 64% of patients with an IPF level of 10% or above, platelet transfusion was avoided in the absence of bleeding.[29]

Anucleated blood cells called platelets are produced from bone marrow megakaryocytes and are essential for thrombosis and hemostasis. Platelets are made up of specialized storage organelles termed alpha-granules, which are rich in cytokines such as transforming growth factor β (TGF-β), CXCL (also known as interleukin 8; IL-8), and C-X-C motif ligand (CXCL) 1/4/7. Platelets that have been activated degranulate and release their contents into the plasma. Numerous viral diseases, such as the human immunodeficiency virus (HIV), the H1N1 influenza, the hepatitis C virus (HCV), the Ebola virus (EBV), and the dengue virus (DENV), frequently cause platelet activation. The production of cytokines such as TNF-α, CXCL8, CCL5 (also known as Regulated on Activation, Normal T Expressed and Secreted, RANTES), CXCL1/5, and CCL3 encourages the formation of a pro-inflammatory state and draws additional immune cells to the infection site. Additionally, platelets interact with neutrophils and monocytes, assisting in their activation to produce various cytokines that exacerbate inflammation. In addition, when platelets are activated, they release substances called fibrinopeptides, CCL5, and CXCL4 (sometimes referred to as platelet factor, PF4), which are vital regulators of the host's ability for multiple viruses to replicate and spread. Studies suggest that CXCL4 can both inhibit as well as enhance HIV1 infection. Data from our lab show that CXCL4 inhibits interferon (IFN) pathway and promotes DENV replication in monocytes in vitro and in patients significantly. Inhibition of CXCL4 mediated signaling results in increased IFN production and suppressed DENV and JEV replication in monocytes. In this review, we discuss the role of platelets in viral disease progression with a focus on dengue infection. Research indicates that CXCL4 has the ability to both promote and inhibit HIV-1 infection. Our lab's findings demonstrate that CXCL4 strongly stimulates DENV replication in monocytes both in vitro and in patients, while also inhibiting the interferon (IFN) pathway. When CXCL4-mediated signaling is inhibited, monocytes produce more IFN and have less DENV and JEV replication. We address the function of platelets in the development of viral diseases in this review, concentrating on dengue infection.[6]

On platelet surfaces, the DENV NS1 protein and its domains stimulate the production of P-selectin and the αIIbβ3 complex. When a small amount of collagen, epinephrine (EPI), or adenosine diphosphate (ADP) is added, DENV NS1 causes a stable platelet aggregation. Interestingly, upon incubation with the NS1 protein domains, only EPI was able to cause the development of platelet aggregates.[3]

Study by Quirino-Teixeira suggest that CXCL4 can both inhibit as well as enhance HIV1 infection. Data from our lab show that CXCL4 inhibits interferon (IFN) pathway and promotes DENV replication in monocytes in vitro and in patients significantly. Inhibition of CXCL4 mediated signaling results in increased IFN production and suppressed DENV and JEV replication in monocytes. In this review, we discuss the role of platelets in viral disease progression with a focus on dengue infection. Dengue sickness, which can appear mildly, develop into severe dengue, or be asymptomatic, is caused by an infection with the dengue virus (DENV). Thrombocytopenia is a crucial feature of DENV infection that can be seen in both moderate and severe cases, while severe patients have the lowest platelet counts. This study compiles data on various pathways linked to changes in platelet quantity and function, which can result in thrombocytopenia as well as platelet-mediated immunological and inflammatory responses. Studies suggest that CXCL4 can both inhibit as well as enhance HIV1 infection. Data from our lab show that CXCL4 inhibits interferon (IFN) pathway and promotes DENV replication in monocytes in vitro and in patients significantly. Inhibition of CXCL4 mediated signaling results in increased IFN

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production and suppressed DENV and JEV replication in monocytes. In this review, we discuss the role of platelets in viral disease progression with a focus on dengue infection. In this context, we draw attention to the possibility that peripheral platelet consumption or bone marrow suppression may be the cause of the drop in platelet counts. We talk about how stromal cell and hematopoietic progenitor infection contributes to bone marrow suppression. In relation to the peripheral consumption of platelets, we discussed DENV's direct infection of platelets, platelet adherence to leukocytes and vascular endothelium, and anti-platelet antibody-mediated platelet clearance. Additionally, we examined the role that platelets play in dengue immunity and pathogenesis by translating and secreting host and viral proteins, as well as by forming platelet-leukocyte aggregates. Therefore, this review presents key results about thrombocytopenia and platelet activation during dengue illness, and it also shows many pathways linked to low platelet counts.[7]

Physicians frequently treat febrile patients with thrombocytopenia, particularly in the monsoon and peri monsoon seasons. Protozoa, bacterial, and viral infections can result in thrombocytopenia, either in conjunction with or independently of disseminated intravascular coagulation. Frequent presentations of fever with thrombocytopenia include dengue, malaria, scrub typhus and other rickettsial diseases, meningococci, leptospira, and several viral infections. These patients may occasionally go on to experience a stormy course with multiorgan dysfunction that necessitates admission to an intensive care unit and is linked to a high rate of morbidity and mortality.1,2 Because infections affect both platelet survival and generation, they result in a drop in platelet count.3. When sepsis with disseminated intravascular coagulation is present in bacterial infections, thrombocytopenia may develop. Hemophagocytic histiocytosis, which involves the phagocytosis of platelets and leucocytes in the bone marrow histiocytes, can also occur in sepsis patients. Sepsis can result from bacterial infections that are either Gram-positive or Gram-negative. Increased IgG linked with platelets has been linked. In meningococcemia, platelets often stick to vascular surfaces that have been injured.[5]

A study by Looi, K. W et all suggest that during the first week of sickness, all patients experienced a declining trend in platelet count, which was accompanied by an increasing trend in the percentage of immature platelets to total platelets (IPF%) for more than three days before platelet recovery. On days 3–5 following the beginning of fever, patients with severe dengue exhibited a significantly higher IPF% in comparison to those with non-severe dengue. On day five, the reticulocyte count dramatically increased in patients with severe dengue.[8]

By the study of Tulara, N. K, it was observed that, upon admission, 97% of the patients with serologically confirmed positive cases had thrombocytopenia (count <100,000/mm3), and no patient had bleeding issues. Only one patient (<1%) out of the 112 serologically confirmed dengue cases had platelet transfusion; his platelet counts were <7000/mm3, and he had petechiae all over his body. Nine patients (8.03%) had a platelet count of less than 100,000/mm3, 28 patients (25%) had a count of less than 20,000/mm3, 52 patients (46%) had a count of less than 40,000/mm3, and 79 patients (70.53%) had a count of less than 50,000/mm3. Platelet transfusion was administered since only one patient in the research population exhibited petechiae, and the remaining 28 patients (25%) and 9 patients (8.03%) had platelet counts less than 20,000/mm3.The clinical characteristics of all other patients with platelet counts <20,000/mm3 were closely watched, and repeated manual platelet counts were performed. There was no transfusion administered to these individuals.[26]

One of the most prominent clinical symptoms of dengue virus infection is a decrease in white blood cells and platelets in human peripheral blood (leukopenia and thrombocytopenia, respectively), which can greatly hamper dengue virus clearance by the immune system. The etiology of thrombocytopenia and leukopenia during dengue infection is unknown, however it could be due to severe suppression of bone marrow populations such as hematopoietic stem cells and megakaryocytes, which are the progenitors of white blood cells and platelets, respectively. We investigated whether dengue virus infection of megakaryocytes causes bone marrow suppression, including megakaryocyte population ablation. We measured dengue virus infection and replication using three different models: in vitro, in a human megakaryocyte cell line containing viral receptors; ex vivo, in primary human megakaryocytes; and in vivo, in humanized mice. All three systems enable dengue virus infection and replication in vivo, including virus strains from serotypes 1, 2, and 3, as well as clinical symptoms; all tests detected viral RNA and/or

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active viruses 7-14 days after infection. Although cell viability did not significantly decrease in vitro, mature megakaryocytes were significantly depleted in vivo. Vogt, M. Bet al conclude that megakaryocytes can create dengue viruses in the bone marrow niche, and that a decrease in cell numbers may disrupt bone marrow homeostasis.[40]

It was observed by Khare, RK et al, a patient's risk of complications after being admitted with dengue fever can be predicted using their platelet count. Despite being evident at an early stage of the illness, leukopenia and the rate of complications do not significantly correlate. Our investigation indicated no significant correlation between hemorrhagic and non-hemorrhagic manifestations with low platelet count which was existent in previous literature. To ensure program sustainability, a focus on community-based methods of larval source reduction has been made in recent years. Comprehensive health education and community outreach are necessary for community ownership and participation in preventative programs. Regretfully, this method is extremely cumbersome.
[42]

The results of the study by Logia, Pet al,showed that higher aPTT, temperature above 38.3°C, and an increase in sequential organ function assessment score were found to be independent risk factors for CSB. Patients at risk of developing CSB can be identified using a clinical prediction score that is generated from these criteria.[44]

Shabir, Met al concluded that there is a positive correlation between platelet count and bleeding complications in dengue patients; however, certain types of bleeding, such as melena, hematemesis, hemoptysis, and per vaginal bleeding, are not directly associated to blood platelet counts.
[45]

Patel, K. B., Ranapurwala et al noted that dengue cases commonly present with fever 32.65% or fever with chills / rigidity 66.33%, headache 37.76%, body aching 44.90%, and bleeding symptoms such as petechiae 5.10% and bleeding from the gums, nose, and rectum 5.15%. In dengue-positive cases, 18% had ascites, and 7% have pleural effusion. The severity of dengue infection is significantly associated with hemoconcentration, a decrease in total WBC count, platelet count, and plateletcrit. Platelet count was directly linked to plateletcrit in dengue-positive cases.[46]

Irshad, Z., Shabbir, Aet al concluded that while platelet count can be a predictor of disease and how it will proceed, it cannot be used to rule out disease progression. Dengue fever remains a serious health concern in Pakistan.[41]

The results of anobservational study by Isharat, Set al showed that dengue fever can be treated symptomatically in accordance with WHO standards, and platelet transfusion is only necessary in cases of bleeding diathesis or when the platelet count is less than 10,000/cumm[39].

Dogra, A., et al investigated 20 patients were diagnosed as dengue confirmed cases using serological testing methods. Out of 20 patients, 12 (60%) had dengue fever, with platelet counts ranging from 50,000 to 80,000/µl. Two Dengue fever patients with Petechial spots and platelet counts ranging from 50,000/µl received preventive Single Donor Platelet Transfusions. Eight patients (40%) had Dengue hemorrhagic fever and a platelet count of less than 20,000/µl. These patients received single donor platelet transfusions. Six patients responded positively, with CCI levels exceeding 30,000/µl, whereas two patients did not respond.[43]

A study was carriedbyJayashree, K., et al to investigate the correlation between the severity of dengue fever in pediatric patients and their platelet counts. Each platelet counts and the recovery parameter of DF/DHF/DSS were found to be predictive. More than 2.5 billion people are at risk of contracting dengue, an arboviral illness that mostly affects tropical nations. An estimated 100 million cases of dengue fever (DF) and 2.5 to 5 lakh cases of dengue hemorrhagic fever (DHF) are reported to the World Health Organization (WHO) annually. Two main features of DHF are increased vascular permeability and severe thrombocytopenia.[9]

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The results of the study by Tewari, K., et al, there were 57 youngsters ranging in age from 6 months to 77 years old and 443 adults. 115 individuals, or 23%, had positive NS1 results. Severe bodily aches (97.4%) and fever (99.8%) were the most frequent presentations. 429 instances (85.6%) had DF, 55 cases (11.1%) had DFWS, 10 cases (2%) had SD with severe bleeding, and 6 cases (1.2%) had SD with severe plasma leakage. In 412 cases (82%), OPD care was required, and in 88 cases (18%), hospitalization was required. In 16 (3.2%) of the patients, intravenous fluid resuscitation was required. At presentation, 335 individuals (67%) had thrombocytopenia. In 46 cases (9.2%), a platelet transfusion was required.Ten patients with significant bleeding from SD and three patients with DFWS received packed red blood cell (PRBC) transfusions. Three SD patients with significant plasma leaks and two SD patients with serious bleedings died.[32]

Patel, G. Ret al concluded that coagulation problems were found in 42.8% of the patients. Overall, the most prevalent coagulation abnormality was extended aPTT (40.8%), followed by low fibrinogen (38.7%), high D-dimer (31.2%), elevated INR (26.0%), and prolonged PT (19.2%). 19.9% of patients showed signs of bleeding. Patients with bleeding had significantly greater levels of PT, INR, aPTT, and D-dimer ($P<0.01$) and lower levels of fibrinogen ($P<0.001$) than those without bleeding. Patients with bleeding reported significantly greater rates of coagulation anomalies compared to those without bleeding ($P<0.01$).[36]

Jayanthi, H. K et al noted that the most frequent consequence was transaminitis (12.12%), which was followed by acute renal damage (2%). According to our research, the complication rate rose as the platelet count dropped ($P = 0.0006$). Comparing our study to other studies where there was no association between the two, we found that the length of stay in the hospital rose (P equals 0.00597) as the platelet count decreased. Similar to prior studies, there was no link seen between thrombocytopenia and leucopenia and complications ($P = 0.292$).[31]

The results of the study byMakroo, R. N et al, upon admission, 84.88% of the patients in the serologically confirmed instances had thrombocytopenia (counts fewer than 100,000/cumm), and 22 (9.7%) of them had bleeding. A total of 96 (42.6%) dengue patients underwent platelet transfusions. Of these, 47 patients (20.88%) had a platelet count of less than 20,000/cumm, 43 patients (19.11%) had a platelet count between 21 and 40,000/cumm, and 6 patients (2.66%) had a platelet count between 41 and 50,000/cumm. Eighteen patients out of 49 with a platelet count >20,000/cumm experienced hemorrhagic symptoms, requiring platelet transfusion, such as petechiae, gum bleeding, epistaxis, etc. 31 patients, nevertheless, had platelet transfusions that weren't appropriate.[10]

It was observed by Rajapakse, S et al, between 1990 and 2013, the incidence of dengue fever increased seven times worldwide. During epidemics, total mortality rates can be considerable despite a low case fatality rate (<1%) because of the large number of affected individuals. In dengue, there is an unknown chance of clinically substantial bleeding, which frequently leads to a negative outcome. The evidence supporting preventive and therapeutic measures for bleeding in dengue illness is the main topic of this systematic review. We looked through PubMed, CINAHL, the Cochrane Library, Embase, and Google Scholar for prospective or retrospective randomized, quasi-randomized, and non-randomized trials with a control group and an intervention meant to reduce or prevent bleeding in dengue illness. Eleven studies with 1904 participants across 12 trial arms met the eligibility requirements. These evaluated the effectiveness of plasma transfusion (one RCT), recombinant activated factor VII (one RCT), anti-D globulin (two RCTs), immunoglobulin (one RCT), and interleukin 11 (one RCT) as prophylactic or therapeutic measures for bleeding. There were also two randomized controlled trials (RCTs) and three non-randomized studies examined. A meta-analysis was not carried out since there was a great deal of variation in the study designs and results reported. As of right now, no data suggests that any of the aforementioned therapies could be helpful in treating or preventing clinically serious dengue hemorrhage.[18]

The results of the study by Hassan, J., Borhany, M et al, 200 patients were chosen, with a mean age of 28.68 years (±13.28) and a preponderance of males (147/200). Mean platelet count, hemoglobin, and hematocrit at baseline for bleeding and non-bleeding individuals yielded significant results; bleeding individuals had a platelet count of 24,000 at baseline, while non-bleeding individuals had a platelet count of 29,000, which demonstrated a significant link with bleeding (P-value =.027). 76 patients (38%) received

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platelets by transfusion. Nevertheless, other from the platelet count, none of the specialized hemostasis indicators were associated with bleeding, necessitating platelet infusions.[14]

A study byManagoli, N., Garg, N et al was determined that on the first day following afebrile, 10 patients (9.26%) had platelet counts between 35,000 and 40,000/cu, 42 patients (38.89%) had platelet counts between 30,000 and 35,000/cu, and 56 patients (51.85%) had platelet counts between 25,000 and 30,000/cu. Day 2 following afebrile, 8 patients (7.41%) had platelet counts between 35,000 and 40,000/cu, 36 patients (33.33%) had platelet counts between 30,000 and 30,000/cu, and 64 patients (59.26%) had platelet counts between 25,000 and 30,000/cu. On the third day following afebrile, 56 patients (51.85%) had platelet counts between 35,000 and 40,000/cu, 42 patients (24.93%) had platelet counts between 30,000 and 35,000/cu, and 24 patients (22.22%) had platelet counts between 25,000 and 30,000/cu.According to the RPI of the same patients on the same day, on day 1, 11 patients (10.19%), 74 patients (68.52%), 22 patients (20.37%), and 1 patient (0.93%) had RPIs of 2.5–3.5, 3.5–4.5, and 4.5–5.5. After becoming afebrile, on day 2, there were 2 patients (1.85%), 83 patients (76.85%), 21 patients (19.44%), and 2 patients (1.85%) with RPI 2.5-3.5, RPI 3.5-4.5, and RPI >5.5. On day 3, there were 0 patients (0.00%), 92 patients (85.19%), 14 patients (12.96%), and 2 patients (1.85%) with RPI 2.5-3.5. [15]

Khatri, Set al concluded that he frequency of dengue infection linked to several serotypes is on the rise globally. According to epidemiological research, secondary dengue infections have a higher incidence of severe dengue. One of the early indicators of plasma leakage is a sharp decline in platelet count along with an increase in hematocrit over baseline. The purpose of this study was to evaluate the usefulness of platelet indices in dengue fever patients with thrombocytopenia, including mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit. Between April and September 2014, a cross-sectional study using platelet histograms was conducted in a hospital setting among dengue patients who had thrombocytopenia. All laboratory-confirmed patients of dengue infection with thrombocytopenia admitted to Kasturba Medical College in Manipal, Karnataka during the study period were included in the study population. Within two hours of venipuncture, the blood samples taken from thrombocytopenia-affected dengue patients with serological confirmation were examined using an automated analyzer. In dengue fever cases with thrombocytopenia, the platelet histograms (MPV, PDW, and Plateletcrit) produced by the Beckman Coulter counter LH755TM and LH780TM series were evaluated. It was found that the mean platelet volume (MPV) was 9.01 fL (SD = 0.09). The median plateletcrit was 0.47 (IQR 0.2–0.8) and the mean platelet distribution width was 17.2% (SD = 0.98). No one who took part in the trial experienced bleeding symptoms. No appreciable alterations in platelet parameters were found in dengue cases with thrombocytopenia in the current investigation.[19]

The results of the study byAsha, J, there were 250 samples in all. In dengue patients, the investigation revealed normal PDW and MPV, low platelet counts and PCT, and elevated PLCR and IPF. Based on platelet transfusion, there were statistically significant changes in PIs (greater MPV, PDW, PLCR, and IPF, lower platelet count and PCT).[23]

A study by Brahma, Aet al showed that the mean MPV was substantially lower (p value < 0.0001) on the day before, when the platelet count was less than 20,000/cu.mm, in comparison to the mean MPVs of all patients.[27]

Gupta, Set al studied 68 patients ranged in age from 12 to 75 years old (mean age: 35.6 years), with a male to female ratio of 1.4:1. The most common clinical symptoms were a 100% fever, 98.53% myalgia and arthralgia, 86.76% rash, 92.65% petechiae, and other bleeding manifestations. 24 patients (35.29%) who did not belong to any specific age group experienced shock during the critical phase, which is three to seven days following the onset of fever. There was a significant correlation (p = 0.004) between the presence of acute bleeding and shock. Shock patients had a mortality rate of 45.8% (n = 11). A notable plasma leak was observed as a pleural effusion (n = 14). The study shows that a total of twenty-eight individuals (n = 28) had fluid accumulation in their serous cavities, sixteen of whom were in shock. When 11 patients were admitted, the mean hemoglobin percentage was above 50%, with a mean of 43.47%. Thrombocytopenia (n = 49) with a platelet count < 50,000/µl at presentation was the most often observed result. 54 individuals exhibited an increase in AST > ALT, and 24 patients had blood bilirubin levels greater than 2 mg/dl, indicating hepatic impairment. Three patients experienced acute renal failure, and

24 patients with blood creatinine > 1.4 mg/dl showed signs of renal impairment. There were eleven (16.17%) deaths among the patients under study (ten male and one female), with no discernible trend related to age. Eleven of the patients who passed away had platelet counts ranging from 20,000 to 49,000/µl; three patients had platelets exceeding 50,000/µl, and one patient had a level < 20,000/µl.Seven of the eleven patients who passed away had platelet transfusions for their hemorrhagic symptoms, and all eleven were in shock when they were first seen.[24]

Zeb, S., Qaisar, Oet al noted that out of the total suspected cases, people tested positive, with men making up the majority (65.3%) compared to women (34.7%). White blood cells, platelets, and hemoglobin levels were the lowest at 6.9 g/dl, 2400 g/dl, and 43000 g/dl, respectively. 9.4% of patients had low hemoglobin levels, 25.3% had white blood cell counts that were below normal, and 30.4% had platelet counts that were below normal. Fewer patients than usual were found to have lower mean platelet volumes and platelet crits.[28]

Kantharaj, Aconcluded that to diagnose dengue fever and forecast its course, platelet indices, or PI, may be used as predictive instruments. It is necessary to raise awareness among clinicians and transfusionists regarding the limitations and usefulness of these indices in routine clinical practice. Based on these indices, transfusion decisions may also serve to reduce clinician anxiety by helping to rationalize the requirement for red cell and platelet transfusions in dengue and enhance the blood center's readiness to supply the appropriate blood components for transfusion. However, platelet indices are not frequently reported or tested for in clinical practice, which is likely why they are not employed in ordinary clinical practice.One measure that is being used more and more to evaluate dengue patients' recovery from thrombocytopenia is IPF, but it can only be performed on 5-part differential machines, which makes it challenging to routinely adopt in all labs and hospitals. Furthermore, no specific disease state can be predicted or identified by platelet indices. The majority of these research are retrospective and include small study populations; prospective validation of the cutoff values is lacking. Large epidemiological, randomized, control trials are therefore required to conclusively demonstrate the value of these measures in dengue.[12]

When bleeding from thrombocytopenia complicates a dengue episode, platelet transfusions are frequently given. Whether this technique leads to an increase in clot strength is unclear, though. In this study by Sundar, V, 74 dengue patients' levels of bleeding control and improved clot strength as determined by thromboelastography were evaluated in relation to platelet transfusion. The impact of one unit of single donor aphaeresis units or weight-based random donor platelets was investigated. A mean platelet count increase of 10,210 cells per mm3 from pretransfusion values was seen 24 hours after transfusion of weight-based random donor platelets. This rise approached borderline statistical significance ($p = 0.031$).At 24 hours, the mean platelet augmentation of patients receiving single donor platelets was 22,874 cells per mm3, with a significant statistical significance ($p < 0.001$). However, in thromboelastography, there was no discernible increase in clot strength. In the random donor platelet group, the mean increment in the maximum amplitude value at 24 hours was only 2 mm, whereas in the single donor group, it was 5 mm. Neither of these increments reached statistical significance. In addition, most of the patients continued to hemorrhage even after receiving platelets. This study found that while the absolute platelet counts increased following platelet transfusion, the clot strength did not improve in dengue patients experiencing bleeding complications.[13]

Lee, T. H., Wong, J. G et al noted that out of 788 patients 486 got platelet transfusions as a preventative measure. The prevalence of clinical bleeding did not significantly differ between the two groups (18.2% in the non-transfused group vs. 23.5% in the transfused group; $P = 0.08$). In comparison to the non-transfused group, patients in the transfused group required a median of 1 day longer to reach a platelet count of 50,000/mm3 or above (3 days vs. 2 days, $P <0.0001$). In the non-transfused group, the median length of hospital stay was 5 days, but in the transfused group, it was 6 days ($P<0.0001$). The percentage needing ICU admission (non-transfused 0.66% vs. transfused 1.23%, $P = 0.44$) and death (non-transfused 0% vs. transfused 0.2%, $P = 0.43$) did not differ significantly.[11]

It was observed by Archuleta, S., Chia, P. Y et al 158 out of 360 patients had inadequate platelet recovery. Once baseline features and platelet transfusion were taken into account, age, white cell count, and day of illness at study entry were found to be significant predictors of poor platelet recovery.

Regardless of transfusion, patients with poor platelet recovery were in hospitals for longer periods of time, but there was no discernible difference in other clinical outcomes. Patients with poor platelet recovery were more likely to hemorrhage if given a prophylactic platelet transfusion (odds ratio 2.34, 95% confidence interval 1.18-4.63). We detected a significant interaction between platelet recovery and transfusion.[4]

A study by Sethi, S. M et al, out of the total dengue patients, 32.7% received platelets through transfusion (group 1), whereas 67.3% did not (group 2). Minor bleeding episodes differed significantly between the transfused group and the non-transfused group (65(31.1%) vs. 59(13.7%); p=0.000). In a similar vein, 1(0.2%) versus 4(1.9%) patients in group 2 (p=0.024) died. In group 1, the mean hospital stay cost was Rs26,733±5,780, while in group 2, it was Rs5,266±3,627 (p=0.000).[16]

The results of the study byNasir, A et al the average age of the 107 patients was 53 years (±19.05), with 44 (41.1%) female and 63 (58.9%) male. Platelets were requested for 93 patients (86.7%), platelets and fresh frozen plasma for 3 patients (2.8%), platelets and whole blood for 9 patients (84.4%), and whole blood for 2 patients (1.9%). 35 patients (32.7%) had therapeutic platelet transfusions, while 72 patients (67.3%) received prophylactic platelet transfusions.[21]

Kansay, S etalconcluded that 25,703/cumm was the average platelet count at which platelet transfusion was started. The average quantity of random donor platelets (RDPs) transfused fell dramatically in 2015 (5.4 vs. 4.3 in 2013) as a result of SDAP transfusions to patients with high-risk variables overlaid on their platelet counts and extremely low platelets. The average duration of hospitalization was comparable for patients on RDP alone and for those on RDP and SDAP combined (5.48 vs. 5.54), but it was much shorter (3.6) for patients on SDAP alone. The total cost of hospitalization was greater for patients getting transfusions of SDAP.[25]

Machado, A. A studied 323 patients, 52 underwent transfusion, with 52% of them lacking criterion (n = 27), while 271 did not receive transfusion, with 4.4% (n = 12) having criteria. Hospitalization expenses (median US$ 674.3 vs. US$ 478, p = 0.293) were 41% greater in the transfused group without criteria than in the group with criteria. The mean duration of hospitalization was greater for patients who did not receive a transfusion but still fulfilled the WHO criteria for transfusion (n = 12) than for those who did not receive a transfusion (3.8±3.4 days versus 3.6±3.1 days; p = 0.022). Hospital stay and costs were used as the dependent variables in the GLM analysis, which explained roughly 33.4% (R2 = 0.334) of the hospitalization duration and 79.3% (R2 = 0.793) of the costs. Hospital stays with transfusions lasted 1.29 days longer (p = 0.0007; IRR = 1.29) and were 5.1 times more expensive than patients who did not receive blood components (IRR = 5.1; p<0.001; median US$ 504.4 vs US$ 170.7). On the other hand, compared to patients who were not transfused in accordance with WHO standards (without criteria), patients who were transfused in accordance with WHO criteria saw a cost decrease of about 96% (IRR = 0.044; p<0.001; β = -3.12).[17]

Bhat, A et al noted that at 4 hours post-transfusion, the respondents' median post-transfusion platelet increments (PPI) and corrected count increments (CCI) were 25,000/µL (5,000-80,000/µL) and 18,000/µL (range 8,000/µL-47,500/µL), respectively. The respondents' median PPI and CCI at 24 hours were 45,000/µL and 28,863/µL, respectively. The non-responders' median CCI was 850/µL at 4 hours after transfusion and 1,425/µL at 24 hours. Respondents' PPI was noticeably greater at 24 hours than that of non-respondents. For responders, an average of 4 units of platelets were transfused, but for non-responders, an average of 8 units [22]

Manoharan, A et al concluded that only 34 (77.3%) of the 44 serologically identified dengue cases that underwent platelet transfusion shown a satisfactory response, while 10 (22.7%) of the patients who had bleeding symptoms or hyperpyrexia had a poor reaction or were refractoriness.[30]

The results of the study byThimmarayan, G et al,the majority of platelet transfusion cases were in the age range of 31 to 40 years, followed by the third and second decades. Females outweigh males in platelet transfusion cases. Considering platelet transfusion standards, 42 (39%) patients with a platelet count of 20,000/cu. mm in the absence of bleeding or sepsis received an inappropriate transfusion. CONCLUSION Platelet products are inexpensive, valuable, and time-consuming to prepare, thus there is

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a need to follow excellent platelet transfusion techniques, particularly in poor countries such as India. Irrational use of platelets puts the patient at risk. A periodical transfusion-related audit or the formation of a committee comprised of physicians and transfusion medicine specialists is an effective strategy to improve transfusion practices.[33]

Buddharaju, C. D. V. B., et al observed that at 24 hours post-transfusion, SDP transfusions resulted in significantly higher platelet increases compared to RDP transfusions ($p<0.01$). However, both groups' corrected count increment and % recovery were practically identical, and the difference was statistically insignificant.[37]

A study by Rao, C. A et al, 100 out of 200 patients received FFP transfusion alone, resulting in a substantial increase in platelets (p-value < 0.001), while 26 patients had SDP transfusion alone, resulting in a mean increase in platelets (p-value = 0.023). Out of 200 patients, 74 received FFP followed by SDP, resulting in a mean platelet increase with a p value of <0.001. The mean length of hospital stay with FFP followed by SDP shows a significant p-value.[38]

The results of an observational study by Chikkaveeraiah, S. K e al found that dengue fever can be managed symptomatically using WHO standards. Platelet transfusions are only recommended when platelet count is less than 10000/cumm or in bleeding diathesis, regardless of platelet count.[35]

Archuleta, S et al noted that 158 out of 360 patients had inadequate platelet recovery. Once baseline features and platelet transfusion were taken into account, age, white cell count, and day of illness at study entry were found to be significant predictors of poor platelet recovery. Regardless of transfusion, patients with poor platelet recovery were in hospitals for longer periods of time, but there was no discernible difference in other clinical outcomes. Patients with poor platelet recovery were more likely to hemorrhage if given a prophylactic platelet transfusion (odds ratio 2.34, 95% confidence interval 1.18–4.63), according to our analysis of the substantial interaction between platelet recovery and transfusion.[20]

CONCLUSION

The link between Dengu infection and thrombocytopenia shows the complexities of dengue pathogenesis and emphasizes the significance of focused therapy options. This study examined many routes involved in engue induced platelet reduction, including direct platelet infection, megakaryocyte suppression, and immune-mediated clearance. The findings show that therapies concentrating on these processes have the potential to reduce the severe clinical consequences associated with dengue. Furthermore, platelet concentrators have showed potential in treating thrombocytopenia, providing a realistic alternative for lowering bleeding risks and improving patient outcomes. Continued study into the molecular relationships between DENV and platelet biology is critical for creating more effective medicines and, eventually, improving clinical dengue fever care.

ETHICAL APPROVAL

It is not applicable.

REFERENCE

1. Losada, P. X., DeLaura, I., & Narváez, C. F. (2022). Dengue Virus and Platelets: From the Biology to the Clinic. *Viral immunology*, *35*(5), 349–358. https://doi.org/10.1089/vim.2021.0135
2. Tayal, A., Kabra, S. K., & Lodha, R. (2023). Management of Dengue: An Updated Review. *Indian journal of pediatrics*, *90*(2), 168–177. https://doi.org/10.1007/s12098-022-04394-8
3. García-Larragoiti, N., Kim, Y. C., López-Camacho, C., Cano-Méndez, A., López-Castaneda, S., Hernández-Hernández, D., Vargas-Ruiz, Á. G., Vázquez-Garcidueñas, M. S., Reyes-Sandoval, A., & Viveros-Sandoval, M. E. (2021). Platelet activation and aggregation response to dengue virus nonstructural protein 1 and domains. *Journal of thrombosis and haemostasis : JTH*, *19*(10), 2572–2582. https://doi.org/10.1111/jth.15431

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4. Archuleta, S., Chia, P. Y., Wei, Y., Syed-Omar, S. F., Low, J. G., Oh, H. M., Fisher, D., Ponnampalavanar, S. S. L., Wijaya, L., Kamarulzaman, A., Lum, L. C. S., Tambyah, P. A., Leo, Y. S., & Lye, D. C. (2020). Predictors and Clinical Outcomes of Poor Platelet Recovery in Adult Dengue With Thrombocytopenia: A Multicenter, Prospective Study. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *71*(2), 383–389. https://doi.org/10.1093/cid/ciz850
5. Parikh F. (2016). Infections and Thrombocytopenia. *The Journal of the Association of Physicians of India*, *64*(2), 11–12.
6. Singh, A., Bisht, P., Bhattacharya, S., &Guchhait, P. (2020). Role of Platelet Cytokines in Dengue Virus Infection. *Frontiers in cellular and infection microbiology*, *10*, 561366. https://doi.org/10.3389/fcimb.2020.561366.
7. Quirino-Teixeira, A. C., Andrade, F. B., Pinheiro, M. B. M., Rozini, S. V., &Hottz, E. D. (2022). Platelets in dengue infection: more than a numbers game. *Platelets*, *33*(2), 176-183.
8. Looi, K. W., Matsui, Y., Kono, M., Samudi, C., Kojima, N., Ong, J. X., ... & Lum, L. C. S. (2021). Evaluation of immature platelet fraction as a marker of dengue fever progression. *International Journal of Infectious Diseases*, *110*, 187-194.
9. Jayashree, K., Manasa, G. C., Pallavi, P., & Manjunath, G. V. (2011). Evaluation of platelets as predictive parameters in dengue fever. *Indian Journal of Hematology and Blood Transfusion*, *27*, 127-130.
10. Makroo, R. N., Raina, V., Kumar, P., & Kanth, R. K. (2007). Role of platelet transfusion in the management of dengue patients in a tertiary care hospital. *Asian journal of transfusion science*, *1*(1), 4.
11. Lee, T. H., Wong, J. G., Leo, Y. S., Thein, T. L., Ng, E. L., Lee, L. K., & Lye, D. C. (2016). Potential harm of prophylactic platelet transfusion in adult dengue patients. *PLoS neglected tropical diseases*, *10*(3), e0004576.
12. Kantharaj, A. (2018). Role of red cell and platelet indices as a predictive tool for transfusions in dengue. *Global Journal of Transfusion Medicine*, *3*(2), 103-108.
13. Sundar, V., & Bhaskar, E. (2019). Effect of platelet transfusion on clot strength in dengue fever with thrombocytopenia related bleeding: a thromboelastography-based study. *Transfusion Medicine and Hemotherapy*, *46*(6), 457-461.
14. Hassan, J., Borhany, M., Abid, M., Zaidi, U., Fatima, N., & Shamsi, T. (2020). Coagulation abnormalities in dengue and dengue haemorrhagic fever patients. *Transfusion Medicine*, *30*(1), 46-50.
15. Managoli, N., Garg, N., Raheja, R., Jacob, A. J., Atodaria, K., Patel, F., ... & Kumar, L. (2017). Limited role of platelet transfusion in dengue management and the value of reticulocyte production index as a measure of clinical improvement. *International Journal of Scientific Study*, *4*(12), 187-191.
16. Sethi, S. M., Khalil, A., Khan, M. R. N., Khatri, A., Rehman, A. U., Muhammad, A. J., & Murtaza, G. (2017). Clinical outcomes of prophylactic platelet transfusion in patients with dengue: A retrospective study of patients at a tertiary care hospital in Karachi. *J. Pak. Med. Assoc*, *67*, 1374-1378.
17. Machado, A. A. V., Negrao, F. J., Croda, J., de Medeiros, E. S., & Pires, M. A. D. S. (2019). Safety and costs of blood transfusion practices in dengue cases in Brazil. *Plos one*, *14*(7), e0219287.
18. Rajapakse, S., de Silva, N. L., Weeratunga, P., Rodrigo, C., & Fernando, S. D. (2017). Prophylactic and therapeutic interventions for bleeding in dengue: a systematic review. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *111*(10), 433-439.
19. Khatri, S., Sabeena, S., Arunkumar, G., & Mathew, M. (2018). Utility of platelet parameters in serologically proven dengue cases with thrombocytopenia. *Indian Journal of Hematology and Blood Transfusion*, *34*, 703-706.
20. Archuleta, S., Chia, P. Y., Wei, Y., Syed-Omar, S. F., Low, J. G., Oh, H. M., ... & Lye, D. C. (2020). Predictors and clinical outcomes of poor platelet recovery in adult dengue with thrombocytopenia: a multicenter, prospective study. *Clinical Infectious Diseases*, *71*(2), 383-389.
21. Nasir, A., Sarwar, M., Fatima, M., Noor, H., Imran, A., Malik, N. A., ... & Chughtai, A. S. (2022, April). Blood Transfusion Practices in Dengue Fever: A Cross Sectional Single Center Study During a Dengue Outbreak in Pakistan. In *Proceedings* (Vol. 36, No. 2, pp. 1-6).

22. Bhat, A., Chowdappa, V., &Masamatti, S. S. (2016). Effectiveness of pooled platelet transfusion in concordant and discordant groups among dengue patients. *Journal of Clinical and Diagnostic Research: JCDR*, *10*(7), EC21.
23. Asha, J., Baiju, N. M., Innah, S. J., Rafi, A., & John, B. M. (2023). Comparison of platelet indices in dengue fever patients based on platelet transfusion: A prospective observational study in a tertiary care center. *Asian Journal of Transfusion Science*, *17*(1), 21.
24. Gupta, S. S., Singh, R. K., & Gupta, A. K. (2016). Dengue: Clinical profile and management in reference to platelet transfusion. *EDITORIAL BOARD*, *17*(3), 185.
25. Kansay, S., & Singh, H. (2018). Effect of introduction of single-donor apheresis platelets in dengue management: A comparative analysis of two consecutive dengue epidemics. *Journal of Laboratory Physicians*, *10*(02), 173-178.
26. Tulara, N. K. (2019). Dengue fever and thrombocytopenia–A prospective Observational Study at Tertiary Care Centre. *Eastern Journal of Medical Sciences*, 45-48.
27. Brahma, A., Ghosh, P. K., Goswami, U., & Majumdar, S. (2019). Utility of mean platelet volume to predict significant thrombocytopenia and complications in dengue. *Int J Trop Dis*, *2*, 026.
28. Zeb, S., Qaisar, O., Babar, N., Sardar, A., Bilal, M., & Shuaib, S. L. (2023). Significance of Platelets and its Indices in Patients with Dengue Fever. *Pakistan Journal of Medical & Health Sciences*, *17*(02), 475-475.
29. Shah, D., Khataniar, M., Sawhney, A., Nautiyal, M., Desai, R., & Kakar, A. (2021). An observational study to see the correlation between trends of platelet counts and immature platelet fraction in dengue infection. *Tropical Doctor*, *51*(3), 378-381.
30. Manoharan, A., Janarthanam, V., Srivastava, R., Sowmya, S., & Gandhi, N. (2016). Effectiveness of platelet transfusion in dengue fever. *Int J Res Rev*, *3*, 5-9.
31. Jayanthi, H. K., & Tulasi, S. K. (2016). Correlation study between platelet count, leukocyte count, nonhemorrhagic complications, and duration of hospital stay in dengue fever with thrombocytopenia. *Journal of family medicine and primary care*, *5*(1), 120.
32. Tewari, K., Tewari, V. V., & Mehta, R. (2018). Clinical and hematological profile of patients with dengue fever at a tertiary care hospital–an observational study. *Mediterranean journal of hematology and infectious diseases*, *10*(1).
33. Thimmarayan, G., &Janarthanam, V. (2016). Rationale use of platelet transfusion in dengue fever-experience from a Tertiary Care Hospital. *Journal of Evolution of Medical and Dental Sciences*, *5*(70), 5054-5058.
34. Losada, P. X., DeLaura, I., & Narváez, C. F. (2022). Dengue virus and platelets: from the biology to the clinic. *Viral Immunology*, *35*(5), 349-358.
35. Chikkaveeraiah, S. K., Reddy, R., & Kumar, A. (2016). A prospective observational study of dengue fever with thrombocytopenia with reference to treatment. *Int J Res Med Sci*, *4*, 902-907.
36. Patel, G. R., Thanvi, I., Nadeem, M., &Kanwaria, R. (2023). Coagulation abnormalities and their relationship with bleeding manifestations in patients with dengue-A single center observational study. *Asian Pacific Journal of Tropical Medicine*, *16*(2), 65-71.
37. Buddharaju, C. D. V. B., Chandrakanth, G., Reddy, K. V. S., Reddy, V. L., & Som, L. S. (2022). A comparative study of the transfusion effect of single donor apheresis platelets versus random donor platelets in the management of severe dengue infection in children. *International Journal of Contemporary Pediatrics*, *9*(6), 595.
38. Rao, C. A., & Reddy, M. (2021). Role of Fresh Frozen Plasma (FFP) and Single Donor Platelets (SDP) in Treatment of Dengue and Dengue like illness. *Journal of Chalmeda Anand Rao Institute of Medical Sciences Vol*, *21*(1), 34.
39. Isharat, S., Sharma, A., Goru, B., & Molla, M. A. (2022). An audit of clinical cases of dengue fever and the usage of platelets in such cases in a Tertiary Care Hospital in Hyderabad. *Global Journal of Transfusion Medicine*, *7*(2), 139-143.
40. Vogt, M. B., Lahon, A., Arya, R. P., Spencer Clinton, J. L., & Rico-Hesse, R. (2019). Dengue viruses infect human megakaryocytes, with probable clinical consequences. *PLoS neglected tropical diseases*, *13*(11), e0007837.
41. Irshad, Z., Shabbir, A., Shaikh, A., Hasan, S. M., & Abid, M. (2019). Association of thrombocytopenia and prolonged bleeding time in dengue with the clinical outcome of the patient. *Pakistan Armed Forces Medical Journal*, *69*(5), 1029-34.

42. Khare, R. K., & Raj, P. (2017). Dengue Fever With Thrombocytopenia and It's Complications: A Hospital Based Study. *Journal of Advanced Medical and Dental Sciences Research*, *5*(3), 72.
43. Dogra, A., & Kaushik Rana, D. D. G. (2021). To Study the Effectiveness of Platelet Transfusion in Management of Dengue Patients in Tertiary Care Hospital. *Annals of the Romanian Society for Cell Biology*, 5988-5992.
44. Logia, P., Selvam, V., Parasuraman, V., Renuka, M. K., & Rajagopalan, R. E. (2023). Predictors of Clinically Significant Bleeding in Thrombocytopenic Dengue Patients Admitted to Intensive Care Unit: A Retrospective Study. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine*, *27*(12), 888.
45. Shabir, M., Nisar, S., Urooj, Z., Sohail, M., Khan, M. S., & Khan, D. H. (2022). Thrombocytopenia and its Relationship with Bleeding Manifestations in Dengue Patients-A Tertiary Care Hospital Experience. *Pakistan Armed Forces Medical Journal*, *72*(6), 2021-24.
46. Patel, K. B., Ranapurwala, M. F., & Patel, A. N. (2022). Utility of Red Cell and Platelet Indices Evaluation of Severity of Dengue Infection. *Annals of Pathology and Laboratory Medicine*, *9*(5).
47. Sarker, R., Roknuzzaman, A. S. M., Haque, M. A., Islam, M. R., & Kabir, E. R. (2024). Upsurge of dengue outbreaks in several WHO regions: Public awareness, vector control activities, and international collaborations are key to prevent spread. *Health science reports*, *7*(4), e2034. https://doi.org/10.1002/hsr2.2034
48. Islam, M. T., Quispe, C., Herrera-Bravo, J., Sarkar, C., Sharma, R., Garg, N., Fredes, L. I., Martorell, M., Alshehri, M. M., Sharifi-Rad, J., Daştan, S. D., Calina, D., Alsafi, R., Alghamdi, S., Batiha, G. E., & Cruz-Martins, N. (2021). Production, Transmission, Pathogenesis, and Control of Dengue Virus: A Literature-Based Undivided Perspective. *BioMed research international*, *2021*, 4224816. https://doi.org/10.1155/2021/4224816
49. Rodriguez-Manzano, J., Chia, P. Y., Yeo, T. W., Holmes, A., Georgiou, P., & Yacoub, S. (2018). Improving Dengue Diagnostics and Management Through Innovative Technology. *Current infectious disease reports*, *20*(8), 25. https://doi.org/10.1007/s11908-018-0633-x
50. de Azeredo, E. L., Monteiro, R. Q., & de-Oliveira Pinto, L. M. (2015). Thrombocytopenia in Dengue: Interrelationship between Virus and the Imbalance between Coagulation and Fibrinolysis and Inflammatory Mediators. *Mediators of inflammation*, *2015*, 313842. https://doi.org/10.1155/2015/313842

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