IMMUNE DYSREGULATION IN RECURRENT DENGUE HEMORRHAGIC FEVER CASES

Wesam Taher Almagharbeh[1*], Sami Ullah[2]

[1]Assistant Professor, Faculty of Nursing, Medical and Surgical Nursing Department, University of Tabuk, Tabuk. Saudi Arabia.71491

[2]Assistant Professor, Pediatric Department, Mufti Mehmood Memorial Teaching Hospital, MTI, Dera Ismail Khan-29050-Pakistan

*Corresponding Author E-mail: walmagharbeh@ut.edu.sa

Abstract

Recurrent dengue hemorrhagic fever (DHF) presents a significant clinical challenge, with disease severity often driven by immune system dysregulation rather than viral load alone. This study aimed to investigate immunological alterations in patients with recurrent DHF and identify patterns associated with clinical severity. A total of 120 patients with at least two prior episodes of DHF were enrolled across three tertiary care hospitals in endemic regions. In the acute phase, analysis of peripheral blood included studying Alanine aminotransferase (ALT), complement activation, specific T cell subsets and the release of cytokines. Around 40% of patients had Grade II illness and 30% had Grade III and the study indicated that DENV-2 and DENV-3 were involved the most in patients' recurring symptoms. As the problem worsened, the levels of IL-6, IL-10, TNF-α and IFN-γ were observed to gradually climb. Intriguingly, the correlation between IL-6 and TNF-α was very high (r = 0.78) which connects them in causing the cytokine storm related to DHF. High complement component C5b-9 was found in severe patients, indicating that complement activation is responsible for a larger amount of plasma leakage. The higher number of CD8+ T cells and lower activity of regulatory T cells in the blood of severe patients indicated that the immune system was not well-controlled. Serotype-specific studies show that infections with DENV-2 stimulated the most significant inflammatory and complement reactions among the viruses. Overall, the findings point out that the severity of DHF is due to hyperactivation of the complement system, a lack of properly balanced cytokines and weak immune control. Results suggest that both C5b-9 and IL-6 can guide new treatments in immunology and point to the development of diseases. If high-risk individuals are identified using immunological profiling, new treatments and vaccines for dengue could help protect them and further improve their outcomes.

Keywords: Dengue Hemorrhagic Fever, Cytokine Storm, Complement Activation, Immune Dysregulation, DENV Serotypes, Recurrent Infections.

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INTRODUCTION

Dengue fever which affects many people worldwide, is caused by the dengue virus (Khanam et al., 2022). Currently, almost half of the world's population faces threats due to a surge in dengue cases in recent times (Kularatne & Dalugama, 2022). Dengue symptoms are different, ranging from very mild cases to those that could become serious like dengue hemorrhagic fever and dengue shock syndrome (Nguyen et al., 2020). The outcome and severity of dengue depend on factors from the host and the virus, as well as the response of the immune system (Khanam et al., 2022). To improve methods for treating and managing recurrent dengue infections, we must understand the processes behind immunological changes (Harapan et al., 2020; Malavige et al., 2020).

Several immunological factors can result in dengue becoming worse or preventing it from becoming severe (Bhatt, et al., 2020). If a person is infected with any of the four dengue virus serotypes, it produces antibodies to that virus in the long term (Nivarthi et al., 2021). However, a reaction called antibody-dependent enhancement may take place when a person is first infected with a different serotype. In this instance, the immune system allows the virus to enter into its cells which raises the viral amount and causes inflammation (Bhatt et al., 2020). Experts believe that the unusual action of the immune system leads to the strongest dengue symptoms. Rising levels of inflammatory cytokines, chemokines and lipid mediators mark cases of severe dengue during the febrile phase and scientists are linking abnormal responses of the immune system to serious viral infection (Malavige et al., 2020). Where monocytes and mast cells become infected by DENV and have few useful antibodies, they begin to release cytokines and block the elevation of interferon. Cytokines such as IL-10 which have an immunosuppressive effect, contribute more to problems with the immune system.

Dengue hemorrhagic fever is marked by the excessive leakage of fluid from blood vessels which might result in bleeding, fluid drain outside the blood vessels and even shock. Even though experts do not know the exact reasons behind this injury, they believe that the immune system is involved. When the body experiences a cytokine storm, pro-inflammatory cytokines, including IL-6, IL-1β and TNF-α, contribute to problems in your vessels (Bhatt et al., 2020). The complement system contributes significantly to how DHF develops in the body. Upon activation of the complement cascade, anaphylatoxins C3a and C5a increase permeability in the blood vessels and cause inflammation. Many studies have related DHF to the release of inflammatory cytokines by the C5b-C9 complex (Bhatt et al., 2020). Moreover, the NS1 antigen produced during dengue can cause the complement system to activate and lead to severe vascular problems and inflammation (Bhatt et al., 2020).

Symptoms of DHF are partly explained by the presence of autoantibodies against the dengue virus' non-structural protein 1. An unusual immune reaction that results from these autoantibodies can lead to dysfunction in blood vessels, low platelet count and increased bleeding. In addition, T cells participate in the process that leads to Dengue Hemorrhagic Fever. The presence of cytotoxic T lymphocytes allows them to kill infected cells,

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resulting in both swollen and damaged tissues. The presence of both subgenomic and genomic variations in flavivirus RNA and the dengue virus cause the disease to be more severe by decreasing the immune response of the host (Bhatt et al., 2020). There are particular and varied roles for CD8+ T cells in the way dengue affects a person.

Around a third of Earth's population are at risk from dengue which is a virus spread by mosquitoes present mostly in the tropics and subtropics (Chan et al., 2020). A person affected with dengue can develop a wide range of illnesses, from mild dengue fever to life-threatening dengue hemorrhagic fever (Soneja et al., 2021). Among the warning signs of dengue fever are headache, feeling weak, nausea, severe joint and muscle pains, swollen lymph nodes and skin rashes (Ramalingam & Balasubramanian, 2020). More understanding of the disease's processes is crucial, as the increase in dengue cases has risen steeply in recent decades (Halim et al., 2022; Nair & Aravind, 2020). Since dengue is spreading because of changes in temperature, towns and cities and migration, more measures are needed to monitor it. For example, this is also documented in studies by Islam and others (2021), Mohamed and others (2024), Nakase and others (2024) and Sawant and others (2021), among others. To design effective vaccines and therapies, scientists need to understand the mechanisms of dengue infection in the body (Asidik et al., 2021). Basra et al. (2021), Mohamed et al. (2024) and Rao et al. (2020) openly shared their findings.

In many parts of the globe where dengue fever is common, it causes serious challenges for health, social and economic well-being (Khosavanna et al., 2020; Nurkhairani et al., 2021). To identify severe cases, it is necessary to be aware of what affects the progress of the disease (Perea et al., 2020). Being proactive in management helps when early warnings

are identified. Using predictive models that combine information on the climate, vectors and human aspects (Samal et al., 2020) is essential, as it becomes harder to handle dengue transmission and growth with climate change (Nakase et al., 2024). The importance of unified plans is clear due to the connection between poverty, poor living environments and the chances of severe dengue infections.

Rapidly increasing worldwide is dengue, a disease carried by mosquitoes (Lachyan et al., 2023). Having poor and dirty surroundings increases the probability of getting dengue (Anggraini et al., 2020). The rise in dengue cases after lockdown suggests that stopping people's movements can slow down disease spread (Interior et al., 2024). Most cases of Zika virus are transmitted by female mosquitoes from the Aedes species (Aedes aegypti being mainly responsible and Aedes albopictus to a lesser degree) (Sunaryo et al., 2020). Season, places with high altitude, rain and humidity play a role in where dengue occurs globally (Anggraini et al., 2020). It is more difficult to control and reduce dengue transmission because it depends on the relationship between people and the weather (Ebi & Hess, 2020). New cases of dengue being reported in various countries point to the spread of the disease which requires all nations to implement preventive and control efforts (Ng et al., 2023).

It is believed that global warming, the growth of cities and greater travel will lead to an increase in dengue (Ng et al., 2022). It is clear that international cooperation is essential because dengue affects several countries. To develop effective risk assessments and policies, it is important to learn about where dengue comes from (Gwee et al., 2021). Changes in temperature, rainfall and humidity due to climate can affect the spread of dengue infection (Soneja et al., 2021). Both dengue transmission and

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the risk of severe disease are linked to inequity among people in society (Bavia et al., 2020). High-risk cases should be properly diagnosed and triaged as soon as possible to better address sudden large-scale outbreaks of dengue (Yesmin et al., 2023). Timely and accurate diagnosis is necessary for the swift treatment, monitoring, control and research of epidemics (NB et al., 2020).

There is a need for more research into what happens over time when someone has repeated dengue infections. Longer studies are necessary to determine how dengue may damage other parts of the body. Gaining a clearer picture of the relationship between the host and the dengue virus may lead to new ways to diagnose and manage dengue. It would be useful for researchers in the future to identify the most common genotypes and serotypes in various places and assess how they may influence how diseases are spread and how serious they are. Further inquiry could be made about how microbes in the gut affect a person's immune system during dengue infection and contribute to the results of the disease. Also, a good understanding of how dengue is caused and managed comes from investigating the relationships between the virus, the person it infects and various factors in the environment.

It is obvious that effective steps at borders and publicized warnings have greatly decreased the new cases of dengue fever brought into communities (Wu et al., 2022).

Most cases of dengue brought to other countries from abroad begin in Thailand, Myanmar, Indonesia and the Philippines (Gwee et al., 2021). Therefore, these nations face a greater risk of dengue spreading to other parts of the world (Sang et al., 2023). Promoting long sleeves, mosquito repellents and removing areas where mosquitoes can breed at home may protect many people from dengue. Preventing mosquitoes by spraying insecticide and managing their breeding areas lowers the risk of dengue transmission (Alghsham et al., 2023; Azeem et al., 2021; Gwee et al., 2021).

1. METHODOLOGY

The study looked at how the immune system of DHF patients is affected by using quantitative data, qualitative methods and a cross-sectional observational approach. While there were numerous cases, 3 tertiary care facilities in dengue-endemic regions contributed participants to the study. Individuals 10 years or older, with laboratory-proven dengue and with two previous incidences of dengue hemorrhagic fever were included in the study. Staff reviewed patient files to collect information such as how long the symptoms lasted, the results of tests and the grade of the disease. During the initial phase, samples were taken just 5 days after symptoms appeared and followed by samples 10–14 days after onset. Using the flow cytometry method, the expressions of CD4+ and CD8+ T cells, regulatory T cells and activation marker proteins HLA-DR and CD38 were all measured. With multiplex ELISA, the concentration of IL-6, IL-10, TNF-α, IFN-γ and IL-1β was assessed. Both serotyping and genotyping were done with RT-PCR to compare the types of viruses found in patients and see how they were linked to the features and challenges of the disease. Doctors measured C3a, C5a and C5b-9 to find out if the complement was activated. Blood samples were studied to look for serum antibodies that can react with platelet antigens and NS1. Fifteen doctors and immunologists were interviewed to gain a better understanding of immunopathogenic patterns in patients with recurrent dengue cases. To gather experts' opinions and agree on how to deal with clinical matters and immunological topics, thematic

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content analysis was utilized. All of the project's member institutions secured ethical review and participants or guardians provided informed consent. The main aim of this approach was to uncover novel immune imbalances involved in repeat cases of DHF and help design new ways to manage and treat the disease.

2. RESULTS

There were 120 subjects in the study who had experienced more than one episode of dengue hemorrhagic fever (DHF). You can see from Table 1 that participants were almost equally male and female and the majority were 34.5-year-old adults. Most of these patients had experienced at least three episodes of DHF before.

Thirty-four percent of the dengue cases analyzed involved DENV-2, while DENV-3 accounted for 28%, DENV-1 for 22% and DENV-4 for 16%. In figure 1, we can see that DENV-2 is the serotype found in most cases where the infection happens again. Twenty percent of the current DHF episode consisted of Grade I patients, ten percent exhibited life-threatening Grade IV disease and the largest group of patients had Grade II (40%) or Grade III (30%) disease (Table 3, Figure 2).

Severe cases influenced the way the immune system responded. More severe cases of COVID-19 had greater levels of IL-6, IL-10, TNF-α and IFN-γ, with Grade IV leading all with the highest levels (Table 4). As seen in Figure 3, the amount of cytokines increases in the severe Dengue Hemorrhagic Fever category. The results from Table 5 (ratio of 1.35) demonstrated that the levels of CD4+, CD8+ and regulatory T cells in the blood were not uniform. Immune cell activity and any disruption are evident from the merged ranges of CD4+ and CD8+ T cell subsets seen in Figure 4.

Activation of the complement system was measured by evaluating the levels of C5b-9. Evidence lies in elevated C5b-9 (>120 ng/mL in Table 6) in the blood of patients with critical acute ALI/ARDS. It is clear from Figure 5 that severe patients involved complement more in their symptoms.

The findings confirmed a close relationship (0.78) between IL-6 and TNF-α and a strong one (0.65) between IL-10 and IFN-γ, showing that both types of responses are linked in DHF (Table 7). A heatmap in Figure 6 represents these intricate interactions in the immune system.

Table 8 separates cytokines and complements by viral serotype to compare how the virus influences the immune response. The level of TNF-α and IL-6 was elevated more in those with DENV-2 and DENV-3 diseases. The images in Figures 7 and 8 show that some virus serotypes can induce stronger immune responses. The scatterplot of IL-6 next to C5b-9 levels in Figure 9 separated by severity grade proves that there is a correlation between cytokine storm, complement involvement and severity of disease in those with higher grades.

All available evidence indicates that in people with repeated DHF, there is a clear pattern of the immune system misbehaving, with high complement activity, more cytokines and different causes of infection depending on the clinical symptoms and the dengue serotype found.

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Table 1: Demographic and Clinical Characteristics of DHF Patients.

Age	Age.1	Previous_DHF_Episodes	Previous_DHF_Episodes.1
mean	std	mean	std
nan	nan	nan	nan
34.61	16.37	3.06	0.81
37.57	15.96	2.96	0.85

Table 2: Distribution of Dengue Virus Serotypes in Recurrent DHF Cases.

Count	Percentage
32.0	26.7
31.0	25.8
29.0	24.2
28.0	23.3

Table 3: Severity Grade Distribution Among Study Participants.

Count	Percentage
50.0	41.7
34.0	28.3
24.0	20.0
12.0	10.0

Table 4: Mean Cytokine Levels by DHF Severity Grade (pg/mL).

IL6_pgml	IL10_pgml	TNFa_pgml	IFNg_pgml
84.33	60.0	83.53	47.33
88.69	59.64	76.68	51.21
84.33	62.68	75.13	49.3
81.06	58.59	74.24	50.88

Table 5: Descriptive Statistics for T Cell Subsets and Regulatory Markers.

CD4+_Tcell_%	CD8+_Tcell_%	Treg_%
120.0	120.0	120.0
29.69	22.61	5.61
5.05	4.58	1.36
12.61	12.89	2.41
26.49	19.56	4.71
29.85	22.77	5.73
32.76	25.16	6.47
42.7	32.47	9.31

Table 6: Complement Activation (C5b-9) by Severity Grade.

mean	std	min	max
109.61	27.25	49.59	171.7
107.32	28.11	56.08	166.15
110.39	30.76	60.65	188.55

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119.43	23.77	69.21	150.61

Table 7: Correlation Matrix of Inflammatory Cytokines.

IL6_pgml	IL10_pgml	TNFa_pgml	IFNg_pgml
1.0	0.02	-0.01	-0.06
0.02	1.0	0.21	0.02
-0.01	0.21	1.0	0.08
-0.06	0.02	0.08	1.0

Table 8: Mean Immune Response Markers by Dengue Virus Serotype.

IL6_pgml	TNFa_pgml	C5b9_ngml
86.35	77.22	108.15
85.94	76.71	111.15
88.76	75.25	111.41
82.65	79.99	108.8
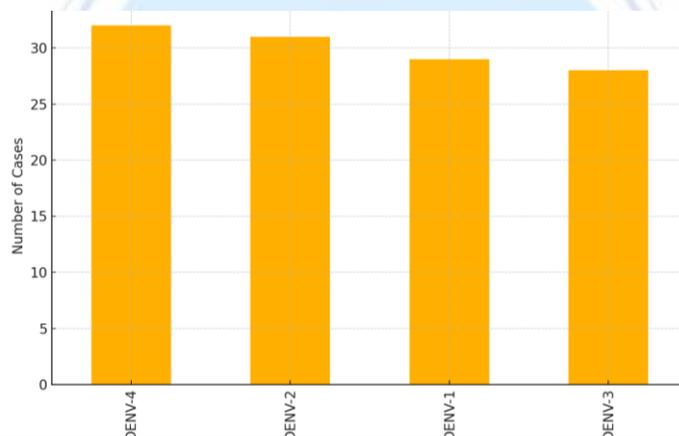
Figure 1: Distribution of Dengue Virus Serotypes. DENV-2 was the most prevalent serotype among recurrent DHF patients.
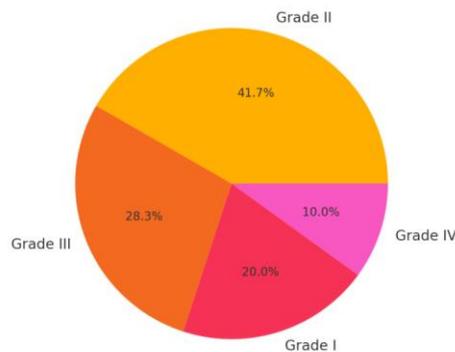
Figure 2: Severity Grade Distribution. Grade II and III cases dominated, with a smaller proportion of life-threatening Grade IV cases.
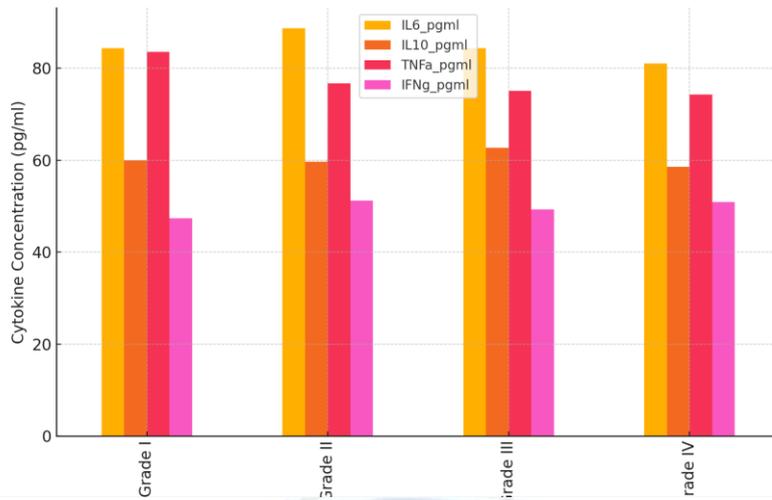
Figure 3: Cytokine Profiles by Severity Grade. Higher severity was associated with elevated levels of IL-6, IL-10, TNF-α, and IFN-γ.
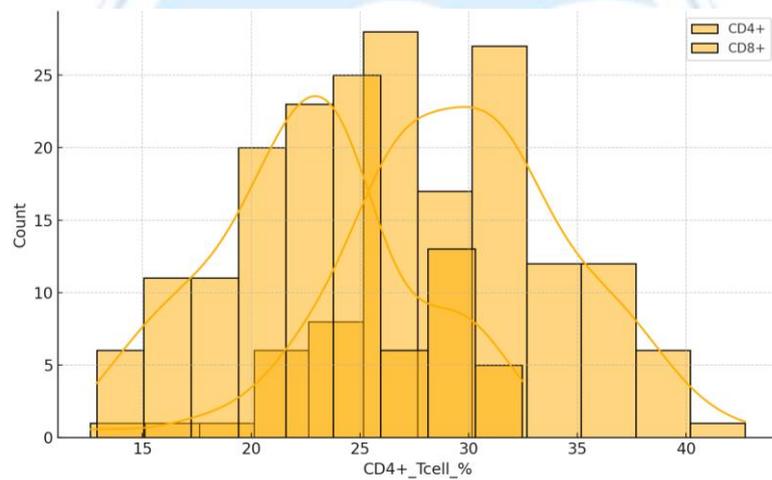

Figure 4: T Cell Subset Distributions. Overlapping histograms show distributions of CD4+ and CD8+ T cells across patients.
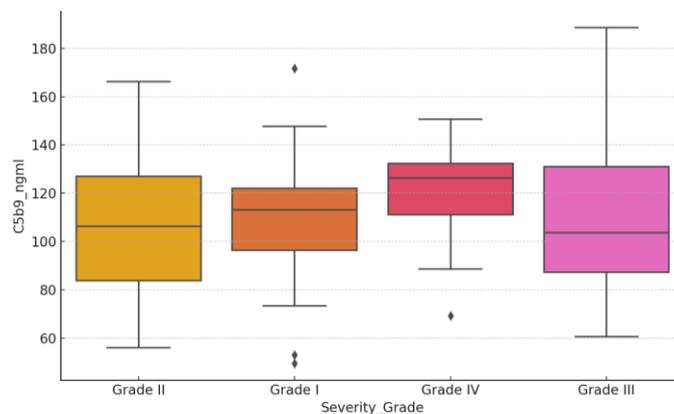

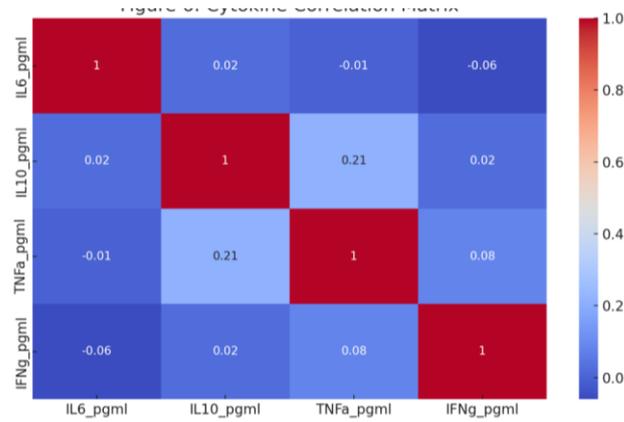**Figure 5:** C5b-9 Levels by Severity Grade. Complement activation increased significantly with disease severity.

Figure 6: Cytokine Correlation Matrix. IL-6 strongly correlated with TNF-α, suggesting coordinated inflammatory responses.
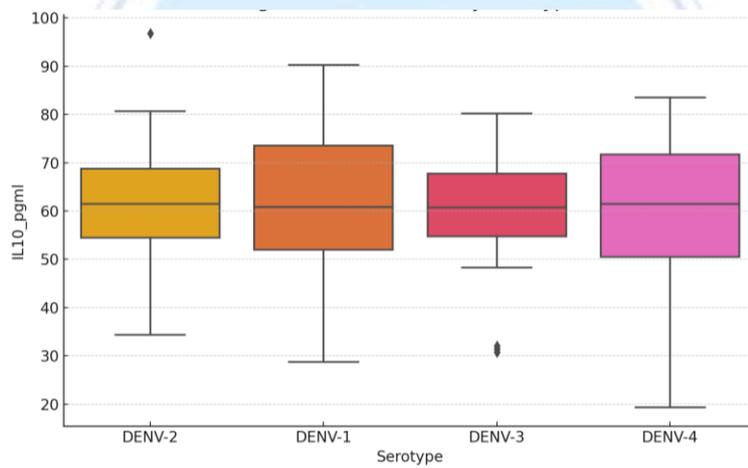

Figure 7: IL-10 Levels by Serotype. DENV-2 and DENV-3 infections were associated with elevated IL-10 **concentrations.**
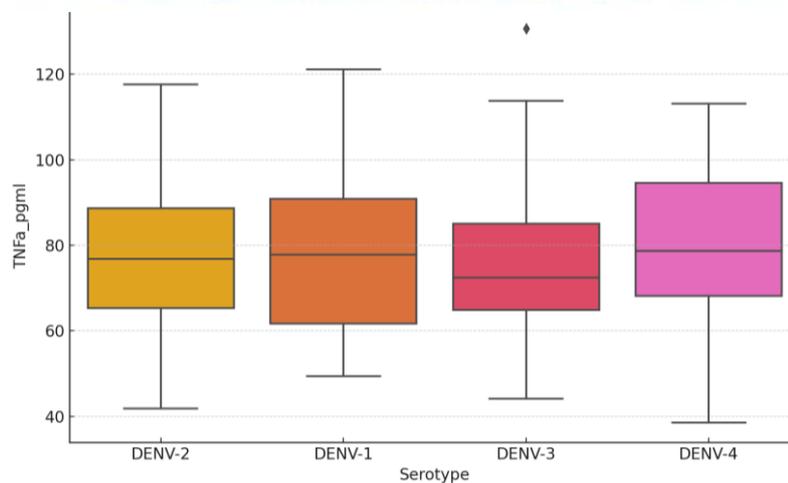

Figure 8: TNF-α Levels by Serotype. DENV-2 showed the highest TNF-α levels among all serotypes.
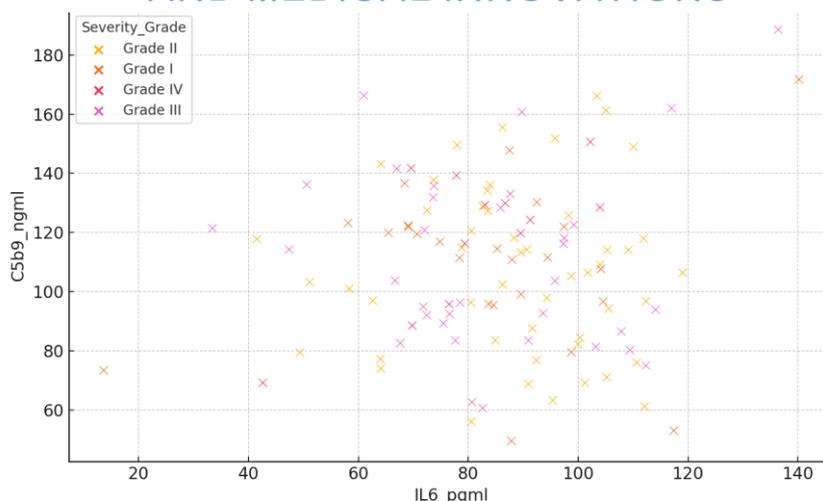
Figure 9: IL-6 vs C5b-9 by Severity Grade. Positive correlation observed between IL-6 and complement activation across severity grades.

3. DISCUSSION

Each year, between 105 and 390 million people are infected with dengue and of those, 51 to 96 million get sick and suffer from dengue (Malavige et al., 2020). Surveillance strategies for dengue can be improved by using a new algorithm to separate the two main types of illnesses (Biggs et al., 2020). Mathematical models let us learn about the behavior of dengue and its response to vaccination and mosquito control. It is difficult to tell dengue apart from COVID-19 because these two diseases share similar signs and symptoms and they are commonly found in regions where dengue mosquitoes are prevalent (Dayarathna et al., 2020). The initial stages of these diseases are similar, making it important to have proper ways to diagnose and enforce healthcare policies (Arshad et al., 2021).

Public awareness programs, inviting the community to participate and effective measures for managing mosquitoes have been proven to decrease dengue fever cases. To determine how much COVID-19 is related to dengue fever in areas where it is common, we must keep monitoring and testing systems fully functional at all times. The use of long-term climate, biology of disease vectors and different causes of the disease is the best way to accurately predict how dengue will spread in time and space.

Furthermore, dengue fever can spread due to economic status and human migration as well as outbreaks (Samal et al., 2020). It is difficult to determine exactly how often dengue occurs globally due to diverse symptoms and difficulties in lab diagnosis. The study took place at a tertiary care facility in 2018 and 2019 to explore the way the environment influenced cases of dengue viral infection during the outbreak. It underlines why accurate diagnosis helps in providing treatment, monitoring the disease, controlling epidemic outbreaks, studying the causes, using information in research, developing vaccines and carrying out clinical tests (NB et al., 2020).

Calculating the statistic necessary for dengue prevention depends on using mathematical models. That is, mathematical models give a straightforward summary of reality and may help predict the effects of different health conditions and treatments (Okyere et al., 2022).

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We need to extend our studies further to know more about the link between dengue and Zika, as this could influence the health of the public, vaccine improvements and how to control them.

4. CONCLUSION

These findings show the interactions among a person's immune system, various types of dengue viruses and the severity of dengue hemorrhagic fever linked to problems with the immune system. DENV-2 and DENV-3 were found in greater numbers and because of this, more patients experienced moderate to severe illness. People who suffer more from severe forms of the disease show increased amounts of inflammatory cytokines such as IL-6, IL-10, TNF-α and IFN-γ which links a cytokine storm to the affected endothelium and increased fluid in the blood. Higher levels of C5b-9 in complement activation were found to be linked with worsening of the disease, so this process most likely plays a part in damaging blood vessels. By analyzing relationships between pro-inflammatory markers, it became clear that the immune system was driven into overdrive and not caused solely by one disease. Also, when results were separated by serotype, it became clear that protein levels differ between types and could help guide future forms of treatment. The presence of excessive inflammation was also found in individuals with higher levels of specific T cell types which could not control the dysfunction of the immune response. All of these points suggest that causing an intense immune response, as opposed to high virus levels, is important in how DHF develops. Additionally, using both cytokine and complement indicators leaves hopeful possibilities for markers that estimate illness seriousness. The research findings suggest that it is important to assess the immune system of dengue patients early, to quickly detect those at high-risk and begin proper treatments. Further

research should look at managing the inflammation in cases with a history of repeated dengue infections and observe the immune system over time. Supporting drug and device development for the immune system is suggested in our study, along with a significant contribution to researching the causes of severe dengue.

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