The Interdependence of nonstructural proteins (NS1) in development of dengue fever and its effects on the haematological and immune systems in the South east Asian population.

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ABSTRACT
Dengue fever is known as a viral infection that is spread by several vectors, the most important of which is the Aedes mosquito (such as Aedes aegypti and Aedes albopictus) and is caused by the dengue virus (RNA virus) of the family Flaviviridae. DENV-1, DENV-2, DENV-3, and DENV-4 has main four serotype of the virus, In 2013 the fifth serotype was discovered DENN-5. Countries allocate a large budget to combat the disease because the disease has become a major public health problem, especially in recent decades due to the worsening of cases and the increase in numbers, especially among the population of Southeast Asia. The purpose of this review is to provide an overview of the dengue virus and investigate the role of non-structural proteins, in increasing disease severity. This study dealt with the damage resulting from the increase in disease severity on the hematological and immune systems, and explored the possibility that genetic factors contribute to the severity of the disease. In conclusion, there are differing opinions about the association of disease severity in dengue virus infection with non-structural proteins, but a significant role appears to exist for genetic factors in increasing the severity of the disease. due to the lack of focus on this type of research, the study recommends focusing on the role of NS1 (One of the non-structural proteins) in order to obtain exploratory results that contribute to reducing the severity of the disease or developing effective prevention methods against infection.

INTRODUCTION

Infection with dengue, a reemerging disease caused by dengue viruses, This disease now affects a large percentage of the world's population. The disease can range from a mild fever with no symptoms to a severe fever that causes death [1]. As of 2020, the World Health Organization has divided dengue into two main categories, The first category is called mild dengue fever, which is without signs, and the second category is severe dengue fever, which is accompanied by many warning signs, with a sub-classification of dengue fever, which may be with or without warning signs. The purpose of this division is to help medical personnel identify critical cases that require intensive medical assistance and reduce the risk of infection to reduce the number of mrrtality[2]. The following warning signs can be considered as symptoms of mild dengue fever, which include a severe headache, pain behind the eyes, muscle and joint pain, nausea and vomiting, swollen glands, and a rash. In the case of severe dengue fever, the following signs appear, which are more serious, and include severe abdominal pain, persistent vomiting, rapid breathing, bleeding from the gums or nose, fatigue, insomnia, an enlarged liver, and blood in the vomit or stool. It usually requires intensive care for the patient to avoid mortality[3].

More than half of the human race worldwide is susceptible to dengue fever, which is caused by one of four closely associated serotypes of the dengue virus and is prevalent in tropical and subtropical climates. The sickness progresses through three distinct stages: the acute phase (days 0–5) after fever beginning, the critical phase (days 6–8) after fever onset, and the recovery phase (days 22–28) after fever onset. During the crucial stage of severe dengue, patients encounter vascular leakage, thrombocytopenia, and bleeding, in contrast to mild dengue patients who usually recover without incident after 6-8 days. This ongoing intravascular volume loss from plasma leakage can quickly cause hypotension and circulatory failure, which can be fatal [4, 5][6]. Viruses and their human hosts immunological mechanisms may aid in the progression of the illness susceptibility, and despite numerous attempts to develop effective treatments for severe dengue over the past decade, it remains difficult to do so because of the unclear causes of the switch from mild to severe dengue during the critical phase [7]. Despite the fact that various vaccine candidates are being tested with different levels of effectiveness, dengue fever currently lacks a specific therapy.

This research paper will discuss the potential impact of non-structural proteins of the virus, specifically NS1, in predicting the development of dengue fever in the population of Southeast Asia, as the region is tropical with high rainfall and a climate suitable for disease vectors. The spread of dengue disease poses a serious threat to public health. Dengue fever is on the rise in Southeast Asia, and this research paper looks at how non-structural proteins could amplify the sickness and cause harm to the immunological and hematological systems. The study's overarching goal was to lessen the strain on healthcare providers and improve illness control and management by identifying NS1 (a nonstructural protein) as a biomarker for disease development and the change from mild to severe.

DENGUE VIRUS GENOME

Multiple interactions between dengue virus and host cell machinery are involved in the complicated process of viral replication. So as to generate Understanding the mechanisms involved in dengue virus production is crucial for the discovery of a useful biomarker and the prediction of illness progression.

A group of researchers studied the shape of the dengue virus.They identified an even, viral surface. A nucleocapsid with a viral genome and numerous C-protein copies follows an envelope glycoprotein dimer on the virus's surface. A type-1 cap at the 50 ends and no poly'A' tail characterize the 10,900-nucleotide single-stranded RNA genome [8]. Three structural proteins envelope E,contains 495 amino acids , pre-membrane-membrane PrM/M contains75 amino acids, and capsid C, contains100 amino acids. and seven nonstructural NS proteins like NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 are encoded in the genome. The N′ terminus of viral polyprotein contains structural proteins and the C′ terminus non-structural proteins. The immature DENV virion has a spiky 60 nm surface, while the adult virion is smooth and 40 nm wide [9,10]. Nonstructural proteins replicate the virus, while structural proteins build the dengue fever virion (figure 1).

The passage accurately conveys that RNA's reverse complementary sequences are present in the genomes of flaviviruses, including DENV, and enable long-range RNA-RNA interactions [11][11][12][13][14][15][16][17]. Viruses rely on two sets of complimentary sections and neighboring nucleotides—the 5'-3'CS and 5'-3'UAR areas—to complete genome cyclization, a crucial step in viral replication. Figure 1 shows the location of the 5'-3'CS inside the ORF of the DENV genome [18]. It is crucial to understand genome cyclization as it occurs during viral replication.

[19].

The passage accurately conveys that mismatches in complementary areas do not affect the ability of viral RNA to be translated, but they can significantly reduce the amount of RNA that can be synthesized, sometimes to undetectable levels.

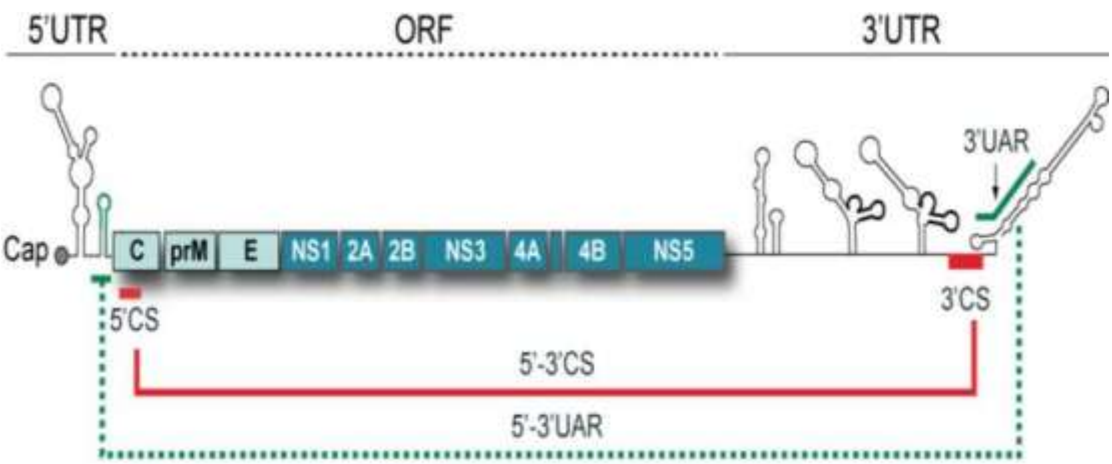

FIGURE 1. The Dengue virus genome, depicted schematically. The open reading frame with structural proteins (C-prM-E) and non-structural proteins (NS1-NS2AB-NS3-NS4AB-NS5), as well as the 5' and 3' untranslated regions (UTRs) of the virus. Dashed lines denote the placement of the 5'-3'UAR sequence and solid lines show the location of the 5'-3'CS sequence.

PATHOGENESIS OF DENGUE FEVER

An increased vascular permeability is a hallmark of severe dengue, which can develop in a small subset of patients (often those with subsequent infections).

, which can lead to shock, plasma leakage, and contracted intravascular volume. Only the peritoneal and pleural spaces are affected by the leaking and occurs within 24 to 48 hours. Unlike inflammation that usually accompanies pleural and peritoneal space leakage, there is a lack of inflammation, and patients recover quickly from shock without complications, suggesting alterations in vascular function rather than endothelial damage in its structural form as the root cause [20].

according to Avirutnan et al., increased immune reactivity during a secondary infection with dengue virus can lead to an exaggerated cytokine response, which alters vascular permeability. An antibody-dependent augmentation describes this effect. Virus proteins such as NS1 may also regulate vascular permeability and complement activation.
[21][22][23].

Although the relative importance of the several cytokines that enhance permeability remains unknown, they have all been linked to the escalation of severe dengue. Research suggests a possible connection between the pattern of cytokine production and the ability of dengue-specific T cells to cross-recognize. Despite seemingly lacking in their cytolytic power, cross-reactive T-cells secrete more cytokines like tumour necrosis factor (TNF), interferon (IFN), and chemokines. [24].

Multiple studies have shown that severe dengue patients tend to have higher levels of viral load than those with mild dengue. Furthermore, these studies have also found that the levels of viral protein NS1 are elevated in severe cases [25]. The levels of viral load have been observed to correspond with indicators of disease severity, thrombocytopenia, pleural effusion count, and other similar factors. According to these results, viral load might have a major role in deciding how bad dengue fever is.

the dengue virus appears to be able to activate multiple systems simultaneously, including immune systems, procoagulant and anticoagulant systems, and other clotting mechanisms. The severity of the sickness and the amount of bleeding noticed may be influenced by the degree and timing of these systems' activity. However, the exact immuno-pathogenetic mechanisms underlying these observations have not yet been identified. Because of this intricacy, scientists from all walks of life face new challenges [26].

It is crucial to conduct further research to fully understand the intricate and insufficiently understood disease progression mechanism, which involves the situation with the host, virus, and vector, all of which are influenced by various societal, economic, behavioural, and demographic factors. The complexity of the disease also challenges scientists working in various fields. Additionally, the effectiveness of prevention and control programmes relies on a comprehensive understanding of the changing patterns and NS1 levels of the virus.

DENGUE FEVER IN SOUTH-EAST ASIA

That is correct.. Both mild and severe dengue fever are major global health issues because they impact so many people, especially in tropical and subtropical areas. About 2-2.5 billion people call dengue-endemic regions home, and the disease has already made its way to more than 90 nations, according to the World Health Organization (WHO). Dengue fever affects around 49 million people annually, with more than 25,000 fatalities and an estimated 500,000 instances of severe dengue that necessitate hospitalization. The increasing global incidence of dengue is a cause for concern, and efforts to prevent and control the disease are ongoing [27]. The majority of nations in Southeast Asia experience frequent and cyclical epidemics, as well as a heavy burden of dengue fever and its severe forms [28].

The dengue virus is mostly transmitted by the Aedes mosquito, has a global range and has led to the spread of dengue to all tropical and subtropical regions of the world [29]. Dengue is one of the most pressing health and economic problems in Southeast Asia. The current dengue epidemic in the area should guide efforts to control the disease [30][31][32].

With 1.2 billion people at risk, or 53% of the global dengue population, South East Asia is home to 11 nations with virus endemicity. Recurrent epidemics of dengue, both mild and severe, affect several countries in the area. Tropical and subtropical climates, together with human activities, have contributed to the dengue epidemic that has gripped the area in recent decades. The danger of dengue vector and viral transmission has grown due to recent migrations that have made use of contemporary modes of transportation. Most migrants do not have access to healthcare, water, or sanitation, and cities are overcrowded as a result of unplanned development and large-scale migration from rural regions. Trash collection in densely populated areas fosters the growth of dengue vectors. The deforestation and fragmentation of landscapes brought about by fast industrial and commercial growth have contributed to an increase in mosquito bites and dengue transmission. Due to the lack of a reliable method for predicting the severity or rate of disease transmission, dengue fever has expanded from lowlands in the south to higher altitudes [33,34].

STRUCTURE OF NS1 (NON-STRCTURAL PROTEIN 1)

Many researchers have realized that knowing the structure of NS1 contributes to understanding how it serves a role in determining the path of the virus (Figure 2). displays the three-dimensional structure of NS1 together with an overview of the highlighted important functional regions. Researchers led by Akey were able to clearly see the dimer and hexamer structures of dengue virus NS1. They did this by using a baculovirus expression method to make full-length, glycosylated NS1 [35]. The crystal structure of dengue virus NS1 revealed the three domains found in the NS1 monomer—the roll, the wing, and the central ladder. There are three domains, the smallest of which is the "β-roll" domain. Two separate subdomains, disulfide bonding on the inside, and two glycosylation sites make up the "wing" domain. A discontinuous subdomain connects it to the "β-roll," and a disulfide bond, resembling a wing protruding from the core "β-ladder" domain, connects it to the rest of the domain. According to Akey et al., the "β-ladder" is the primary structural component of NS1, and every monomer has nine β-chains organized in a ladder-like pattern [35]. Youn et al. (2012) also discovered that a WNV NS1 dipeptide (Arg10-Gln11) is in a loop of the β-roll and interacts with the NS4B transmembrane protein[36]. This suggests that hydrophobic protrusions are likely the sites where the dimer NS1 connects with the endoplasmic reticulum (ER) protein transport across the membrane and the replication complex NS4A/B [37].

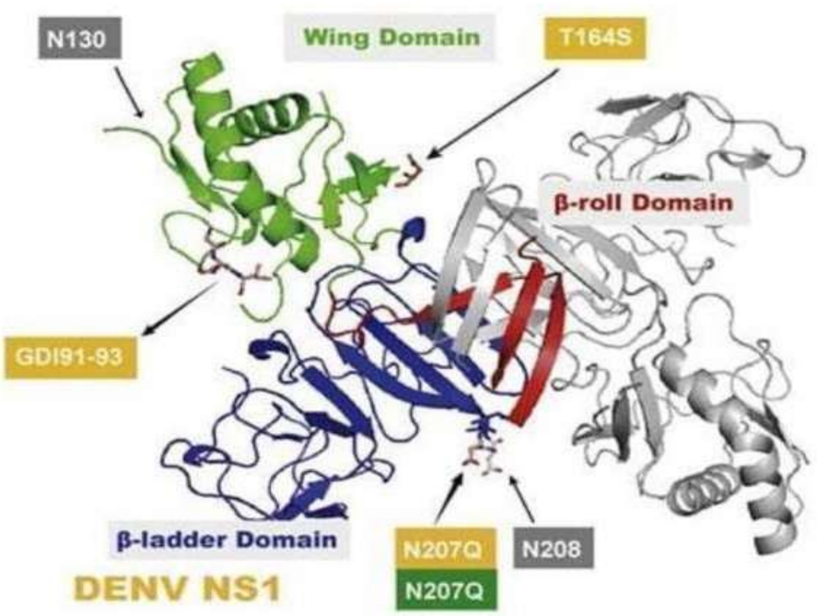

Figure 2. displays a three-dimensional model of the dengue genome, which includes the encoded NS1 component. dimer of NS1: One monomer in the DENV NS1 dimer is gray in color, while the other is separated into three domain-specific colors: β-roll (red), wing (green), and β-ladder (blue), as seen in the 3D structure.

NS1'S MULTIFACETED ROLE

1- The role of NS1 in Viral Replication: A multifunctional protein with a molecular weight of about 54 kDa and 230 to 250 amino acids, NS1 is a byproduct of the eighth vRNA segment's collinear transcription and is highly conserved. A viral protein with a disorganized C-terminus tail, two globular domains, and a linker region. [38]. A signal region located at the C-terminus of structural envelope protein E guides a highly conserved glycoprotein that is produced by NS1 to the lumen of the endoplasmic reticulum. [39]. Deletion of the first YFV NS1 glycosylation site decreases viral replication and limits secretion of NS1, leading to the hypothesis that NS1 is involved in viral RNA replication and illness progression [38]. There is a significant role for the dengue virus NS1 glycosylation site (Asn-207) and Cys residues in the viral life cycle. Glycosylation site (Asn-207) and Cys sites (Cys4, Cys55, Cys291) mutations considerably reduced viral replication [40]. Therefore, NS1 can be considered an important protein in the process of viral replication.

2- The role of NS1 as a marker of dengue infection: Anemia caused by dengue fever is highly correlated with serum NS1 levels [41]. are noticeable when a fever begins and reach their climax up to five days later. When symptoms first appear, it may take up to 12 days before NS1 is detected.

One of the most intriguing and conserved non-structural proteins released into the bloodstream after dengue virus infection. It has found employment for decades as a virus diagnostic test to identify dengue early on [42]. The relevance and pathophysiology of NS1-induced vascular leakage are still up for debate, nevertheless, since it has only recently been brought up. A number of investigations have shown that individuals with severe dengue had elevated NS1 levels [43,44]. In the event that NS1 stimulates toll like receptor 4 immune cell activation [45], drives monocytes to release IL-10 [46], or disrupts endothelial glycocalyx components, which increases vascular permeability [47], the condition may deteriorate. The researchers found no correlation between NS1 positive and serious diseases [48], but they did find a correlation between lower NS1 levels and more severe symptoms [49].

3- The role of NS1 in Immune Evasion: Upon the onset of symptoms, patients' serum will contain dengue fever nonstructural protein 1 (NS1), the sole nonstructural protein released by virus-infected cells[50,51] . Evidence suggests that increased amounts of secreted NS1 are associated with dengue severity [52], immune evasion [53-57], and deleterious inflammatory responses [58,59]. The ability of NS1 to evade the host immune system is dependent on its several interactions By attaching to proteins in the host complement system, for instance factor H, C4, and C1s, NS1 prevents the activation of the complement. Moreover, NS1 has the ability to disrupt TLR signaling pathways, particularly TLR3 and TLR4, thereby impeding the activation of the complement cascade. This, in turn, diminishes inflammation and stops the complement from lysing the virus. NS1 inhibits these pathways, which in turn reduces type I interferon and other pro-inflammatory cytokines, thereby decreasing antiviral activity in infected and neighboring cells. Dengue virus infections rely on NS1's capacity to enhance vascular permeability, which compromises the integrity of endothelial cells. Leaks in blood vessels can cause hemorrhagic fever and shock. NS1 modifies the immune system and evades cell death, impacting macrophages and dendritic cells. Critical antiviral responses block the virus's ability to evade detection, allowing infected cells to survive and multiply virally [60].

4- The role of NS1 in Pathogenicity and Vascular Leakage: In humans, the innate immune system is crucial for maintaining environmental stability and serving as the initial barrier against pathogen invasion. Immune signaling pathways, including type I interferon (IFN), are activated when dengue virus is identified by host pattern recognition receptors (PRRs)[61]. When the dengue virus invades, the body's adaptive immune responses may develop similar strategies. The antiviral responses are initiated during viral infections by PRRs that detect viral components, known as molecular patterns associated with pathogens and then produce type I interferons (IFNs)[62]. But many viruses have developed new ways to fight IFN production in order to evade the antiviral response. TLRs or RLRS pathways initiate the antiviral response, which some flavivirus non-structural proteins, particularly NS1, can counteract. This allows flaviviruses to elude the host immune system.

5-The role of NS1 in potential vaccines and drug targets: The highly conserved secreted glycoprotein called dengue virus nonstructural protein 1 (NS1) plays a significant role in the development of dengue fever. Unlike antibodies against dengue envelope proteins, those targeting NS1 do not induce antibody-dependent enhancement (ADE), making them a more secure target for immunization. Bailey et al. (2019) have demonstrated the protective effects of ZIKV NS1 monoclonal antibody (mAb) AA12 in mice against lethal viral challenge[63]. Modhiran et al. (2021) discovered that mAb 1G5.3, which is specific to dengue virus NS1, provides protection against dengue virus. These promising findings raise the possibility that dengue virus NS1 could serve as a target for a vaccine[64]. In 2021, Ooi and Lok discovered that DNA vaccines and NS1-based subunits effectively reduced the death rate caused by dengue in mouse models[65].

THE EFFECTIVENESS OF VIRAL (NS1) PROTEIN

When an infection occurs on its own, the 45-54 kDa glycoprotein known as nonstructural protein 1 (NS1) is released into the bloodstream as a soluble hexameric complex. More and more evidence points to sNS1's central function in infection-related regulation, immune evasion, and inflammatory responses [66,67]. The presence of the hexameric NS1 protein in the serum of infected individuals at varying levels allows for the early detection of dengue [68,69].

In addition, secreted NS1 (sNS1) has a role in the development and defense of dengue virus. For the purpose of aiding viral immune evasion, it connects various complement regulators and the components that make them up [70-75]. In addition, there is evidence that immune complexes formed by NS1 and anti-NS1 antibodies, which are produced in large quantities during infection, can impede the regulation of vascular permeability and trigger an inflammatory response [76,77].

There is a high degree of homology between the 352-aa protein encoded by the 1056-nt flavivirus NS1 genes [78]. Within and outside of cells, it exists as a secreted extracellular species (sNS1) or on cell membranes (mNS1) [79,80].Virus replication requires intracellular NS1, which is found in viral-induced vesicle packets along with dsRNA and other components of the viral replication complex [81-84]. We don't know what this protein does to help viruses replicate. Research has connected the protein and antibodies elicited by secreted and cell surface-associated NS1 to several processes, including protection, disease, and innate immune evasion [85-89]. A large number of cells are bound to sNS1 and its interactions with host cell proteins are mediated by cell surface glycosaminoglycans [90-93].

Extensive study on dengue virus multiplication and disease development has left us in the dark regarding the effects of NS1 on the blood and immune systems [94]. Research suggests that NS1 may affect endothelial cells and platelet function, leading to increased vascular permeability and severe dengue. It is possible that NS1's interactions with antibodies and complement proteins play a role in disease progression. Additional research is necessary to fully comprehend the mechanisms by which NS1 causes dengue and to develop effective treatments [94].

THE ROLE OF GENETIC FACTORS IN PATHOGENESIS OF SEVERE DENGUE

Viral components, host genetics, and the immunological response interact to cause severe dengue. Plasma leakage, severe bleeding, and organ damage can kill in severe dengue. Most dengue patients are asymptomatic or mild febrile, but a tiny number progress to severe dengue [95].

The dengue virus-host immune response relationship is critical to illness progression [96] Some immune system components are modulated by the virus, including the complement pathway [97], T cell activation [98], and cytokine production [99]. This can lead to an imbalance in the immune response, resulting in severe symptoms such as plasma leakage and organ damage. Additionally, virus's ability to escape host immunity by altering the expression of its own proteins further contributes to the pathogenesis of severe dengue.

There are three structural proteins (the envelope, the capsid protein, and the precursor membrane) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) that result from the translation of the viral RNA genome into a long polypeptide [100].

NS1 is one of the most conserved and puzzling non-structural proteins. It is necessary for RNA replication and viral contagiousness, As a viral marker for early dengue identification, it has been utilized for decades [101]. It enters the bloodstream during dengue virus infection. NS1-induced vascular leakage was just recently studied, and the pathophysiology and extent of NS1's contribution are still debated. It may boost monocyte IL-10 production, activate immune cells via toll-like receptor 4 or alter endothelial glycocalyx components, increasing vascular permeability in order to worsen the condition[102].

On the other hand, Duong, Veasna, et al. indicated that the viral protein was associated with disease severity [101]. ALLONSO, Diego, et al. He had other opinions and denied that NS1 is associated with the severity of the disease [102]. These contradictory results are considered an unaddressed research gap and indicate the need for further studies.

the different studies to have different findings or conclusions, especially in a complex disease like dengue fever where many factors can influence disease severity. Therefore, further studies are needed to fully understand the role of NS1 in disease severity and its potential as a diagnostic and therapeutic target.

CONCLUSION

Dengue fever is caused by the transmission of the Dengue virus, an RNA virus belonging to the Flaviviridae family. The mosquitoes Aedes aegypti and, to a lesser extent, Aedes albopictus are the vectors for this infection.

Dengue fever has grown into a major public health concern, with potentially fatal consequences, and its occurrence has been steadily rising due to the lack of a viable vaccine that can protect against all serotypes.

This highlights the need for additional studies to investigate the role of factors and proteins/genetics of the host like cytokines and interferons in determining vulnerability to or protection from dengue virus infection. Since the viral (NS1) protein is crucial to dengue virus biology, is abundant in patient sera, and activates macrophages and peripheral blood mononuclear cells, this review aims to give a general outline of the virus and assess the function of non-structural proteins in aggravating disease severity, particularly in the Southeast Asian population. This study dealt with the damage resulting from the increase in disease severity on the hematological and immune systems, and explored the possibility that genetic factors contribute to the severity of the disease. In conclusion, there are differing opinions about the association of disease severity in dengue virus infection with non-structural proteins, but a significant role appears to exist for genetic factors in increasing the severity of the disease. However, due to the lack of focus on this type of research, the study recommends focusing on the role of NS1 in order to obtain exploratory results that contribute to reducing the severity of the disease or developing effective prevention methods against infection.

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CONTRIBUTIONS

Contributions from all authors were substantial in the following areas: ideation, design, data acquisition, analysis, and interpretation; writing the article or critical revision for important intellectual content; acceptance of the work for submission to the journal in question; final approval of the published version; and acceptance of full responsibility for all parts of the work. Everyone on the writing team meets the criteria set out by the International Committee of Medical Journal Editors (ICMJE), Supervision and final approval: Dr. Dzul Azri Mohamed Noor.

ETHICAL APPROVAL

This study does not involve experiments on animals or human subjects or other.

DATA AVAILABILITY

All the data generated and analyzed are included within this manuscript.

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