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Deciphering the Impact of Dengue Serotypes on Liver Function Tests (LFTs), Kidney Function Tests (KFTs) and Complete Blood Counts (CBC): A Comprehensive Analysis

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ABSTRACT

The primary aim of this review article is to elucidate the differential impacts of dengue stereotypes on liver function tests (LFTs), kidney function tests (KFTs) and complete blood counts (CBC) through a comprehensive analysis of existing literature. By doing so, it seeks to enhance the understanding of dengue's pathophysiology and inform more targeted clinical management strategies. This review systematically searched and analyzed peer-reviewed studies, meta-analyses and case reports from databases such as PubMed, Scopus and Web of Science. The inclusion criteria focused on studies that explicitly examined the relationship between dengue serotypes and alterations in LFTs, KFTs and CBC parameters. Data were synthesized qualitatively, highlighting patterns of organ involvement across different serotypes. All dengue stereotypes were associated with some degree of liver impairment, as evidenced by elevated levels of AST and ALT. Stereotype-specific patterns were less clear, though some studies suggested DENV-2 might cause more significant liver enzyme elevations. Kidney function impairment was less commonly reported but tended to be more severe with DENV-3 and DENV-4, with cases of acute kidney injury requiring dialysis. Thrombocytopenia was a universal finding across all serotypes, while leukopenia was more pronounced with DENV-1 and DENV-3. Hematocrit levels were often elevated, indicating hemo concentration. The review highlights the need for clinicians to consider the potential for differential organ involvement based on the dengue serotype, which can influence management strategies, especially in regions where multiple serotypes circulate. It also underscores the importance of further research into serotype-specific pathophysiological mechanisms to improve patient outcomes. Additionally, the findings advocate for the development of rapid stereotyping methods in clinical settings to refine prognosis and tailor supportive treatments more effectively. Understanding the impact of different dengue serotypes on laboratory parameters is crucial for several reasons that significantly enhance patient care and public health responses: Knowledge of how specific dengue serotypes affect laboratory parameters such as LFTs, KFTs and CBC can aid in the early and accurate diagnosis of the infection. This is particularly important in regions where dengue is endemic and other febrile illnesses may present similarly. Identifying serotype-specific effects on laboratory parameters can help tailor patient management strategies. For instance, recognizing that a particular serotype is more likely to cause severe thrombocytopenia or elevated liver enzymes can prompt closer monitoring and intervention, potentially reducing the risk of severe complications like hemorrhagic fever or acute liver failure. Certain dengue serotypes may be associated with more severe disease manifestations. Understanding these associations can help healthcare providers assess the risk of progression to severe dengue, enabling more proactive management of high-risk patients. Knowledge of the differential impacts of dengue serotypes can inform public health strategies, including vaccine development and deployment. Vaccines that can effectively target the most clinically significant serotypes in a region could substantially reduce the disease burden. Insights into how different serotypes influence laboratory parameters can guide future research, including the development of targeted therapeutics and improved diagnostic tools. This could lead to better clinical outcomes and more efficient use of healthcare resources. As global travel and climate change increase the geographic spread of dengue, understanding the clinical implications of different serotypes becomes vital for regions newly encountering the disease. This knowledge can help prepare healthcare systems worldwide for effective dengue management. In summary, grasping the nuances of how dengue serotypes impact laboratory parameters is fundamental for advancing clinical practice, improving patient outcomes and guiding public health policies.

INTRODUCTION

Dengue fever, caused by the dengue virus (DENV), represents a significant public health challenge globally. It is a mosquito-borne viral infection found in tropical and subtropical climates worldwide, predominantly in urban and semi-urban areas^[1]. The World Health Organization (WHO) estimates that there are 390 million dengue infections per year, of which 96 million manifest clinically. The disease spectrum ranges from mild febrile illness to severe flu-like symptoms and can progress to fatal severe dengue, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)^[2]. The global incidence of dengue has grown dramatically in recent decades. A complex interplay of factors, including urbanization, increased international travel, climate change and inadequate mosquito control, has facilitated the spread of the *Aedes aegypti* mosquito and the dengue virus, increasing the disease's impact. Dengue now poses a significant economic and health burden in over 100 countries. Dengue fever stands as a formidable vector-borne disease, primarily spread through the bite of infected *Aedes* mosquitoes, most notably *Aedes aegypti*. Originating from a family of viruses known as Flaviviridae, dengue has escalated from a sporadic illness affecting specific geographic locales to a pervasive global health menace. The World Health Organization (WHO) underscores the dramatic surge in dengue cases over the past few decades, now estimating up to 400 million infections annually worldwide. This figure starkly contrasts with the 1950s, when severe dengue epidemics were relatively uncommon^[3,4]. The disease manifests in a wide clinical spectrum, ranging from asymptomatic and mild dengue fever to severe forms, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). These severe forms can lead to plasma leakage, severe bleeding, or organ impairment, marking a significant cause of morbidity and mortality in affected populations^[5]. The global burden of dengue is particularly heavy in tropical and subtropical regions, where environmental conditions favor the breeding of *Aedes* mosquitoes. Urbanization, increased global travel, climate change, and the geographic expansion of these mosquitoes have facilitated the wider spread and increased incidence of dengue. The socioeconomic impact of dengue is profound, straining healthcare systems, impeding economic productivity and affecting the quality of life in endemic areas^[6]. Despite ongoing efforts to control the disease through vector management, public health strategies and the development of dengue vaccines, challenges remain. The complexity of the dengue virus, with its four distinct serotypes, complicates the immune response and vaccine development. Infection with one serotype provides lifelong immunity to that serotype but not to the others and sequential infections increase the risk

of severe dengue. In light of these challenges, the global health community continues to prioritize dengue as a critical public health issue, necessitating concerted efforts to enhance surveillance, prevention, and treatment strategies. The quest for more effective vaccines and therapeutics is ongoing, alongside initiatives to reduce mosquito populations and public health campaigns to raise awareness and promote protective measures among at-risk populations^[7,8]. Dengue virus exists as four distinct serotypes (DENV-1, DENV-2, DENV-3 and DENV-4), each capable of causing the full spectrum of dengue disease. These serotypes are part of the Flavivirus genus, which also includes other significant viruses such as the Yellow Fever virus, West Nile virus and Zika virus^[8,9]. The existence of multiple serotypes has significant implications for disease epidemiology, vaccine development and clinical management. The serotypes are closely related but genetically distinct. Infection with one serotype provides lifelong immunity to that serotype but confers only temporary and partial immunity to the others. Subsequent infections by different serotypes increase the risk of developing severe dengue, attributed to a phenomenon known as antibody-dependent enhancement (ADE). The diversity among the dengue serotypes contributes to the complexity of disease management and vaccine development. Understanding the distinct and common features of each serotype, including their pathogenesis and impact on the host, is critical for improving dengue treatment and prevention strategies. Although the four dengue serotypes share approximately 65% of their genomic sequence, the differences are sufficient to ensure that infection with one serotype typically provides lifelong immunity only to that specific serotype^[10,11]. Partial and temporary cross-immunity to the other serotypes may occur immediately following infection, but this wanes over time. Crucially, subsequent infections by different serotypes are associated with an increased risk of severe dengue manifestations, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), due to a phenomenon known as antibody-dependent enhancement (ADE)^[8,12]. The global distribution of dengue serotypes is uneven, with certain serotypes predominating in specific regions at different times. This distribution is dynamic and influenced by factors such as human movement, mosquito migration patterns, and environmental changes. The co-circulation of multiple serotypes in many dengue-endemic areas complicates efforts to control the disease and poses challenges for vaccine development. The clinical manifestations of dengue infection can range from asymptomatic to severe, life-threatening disease, regardless of the infecting serotype. However, some studies suggest that certain serotypes may be more likely to lead to severe disease outcomes. For instance, DENV-2 and DENV-3 have

been frequently associated with severe dengue cases in some outbreaks, although this can vary depending on the population and previous exposure patterns^[13]. The presence of four dengue serotypes complicates vaccine development efforts. An ideal dengue vaccine would need to provide balanced protection against all four serotypes to prevent disease enhancement associated with partial immunity. The first dengue vaccine, Dengvaxia (CYD-TDV), has been licensed in several countries but is recommended only for individuals who have been previously infected with dengue virus due to concerns about increased risk of severe dengue in seronegative individuals^[14,15]. Ongoing research aims to better understand the interactions between the dengue serotypes and the human immune system, to improve disease prediction models and to develop more effective and safer vaccines. Advances in genetic sequencing and immunology hold promise for unraveling the complex dynamics of dengue virus infection and immunity, leading to improved public health strategies and clinical outcomes for those affected by dengue worldwide. The management of dengue fever, a mosquito-borne viral disease caused by the dengue virus, heavily relies on supportive care and close monitoring of the patient's clinical status. Laboratory tests, including Liver Function Tests (LFTs), Kidney Function Tests (KFTs) and Complete Blood Counts (CBC), play a pivotal role in monitoring the disease's progression, guiding treatment decisions and predicting potential complications. These tests provide valuable insights into the impact of the dengue virus on various organ systems and the patient's overall health. LFTs are a group of blood tests that assess the health of the liver by measuring the levels of liver enzymes, proteins and bilirubin in the blood. In dengue infection, liver involvement is common, often resulting in hepatocellular damage. This is indicated by elevated levels of liver enzymes, such as Alanine Amino transferase (ALT) and Aspartate Amino transferase (AST)^[16]. Monitoring these enzymes can help assess the extent of liver damage and guide the management of liver-related complications. Severe liver impairment can be a feature of severe dengue and warrants immediate medical attention. KFTs measure the levels of substances in the blood that indicate kidney health, including creatinine and urea. Dengue virus infection can lead to acute kidney injury (AKI), characterized by a sudden decline in kidney function^[17]. This can result from dehydration, rhabdomyolysis (a condition involving muscle breakdown), or direct viral effects on the kidney. Monitoring kidney function is crucial, especially in severe cases of dengue, to prevent and manage renal complications and ensure appropriate fluid management. The CBC is a comprehensive blood test that provides important information about the types and numbers of cells in the blood, including red

blood cells, white blood cells and platelets^[18,19]. In the context of dengue fever, CBC is particularly important for detecting:

Thrombocytopenia: A decrease in platelet count is a hallmark of dengue fever, contributing to bleeding tendencies and, in severe cases, to dengue hemorrhagic fever. Monitoring platelet levels helps assess the risk of bleeding and guide the need for transfusions^[20].

Leukopenia: A decrease in white blood cell count, particularly of neutrophils, can occur in dengue fever, indicating the body's response to viral infection^[21].

Hemoconcentration: An increase in hematocrit levels can indicate plasma leakage, a serious complication associated with severe dengue. It necessitates careful fluid management to prevent shock. In summary, LFTs, KFTs, and CBC are essential components of the clinical management of dengue fever. These tests provide critical insights into the disease's effects on the body, guide treatment decisions and help identify patients at risk for severe complications, thereby facilitating timely and appropriate interventions. The objectives of this comprehensive review on the impact of dengue serotypes on Liver Function Tests (LFTs), Kidney Function Tests (KFTs) and Complete Blood Counts (CBC) are to:

Synthesize Existing Knowledge: Compile and synthesize current research findings on how different dengue serotypes affect LFTs, KFTs and CBC parameters. This involves examining variations in laboratory parameters among patients infected with different dengue serotypes and understanding the clinical implications of these variations.

Highlight Patterns of Organ Involvement: Identify and discuss patterns of organ involvement and damage in dengue fever, with a focus on liver and kidney function and hematological changes. This includes analyzing how specific serotypes may predispose to more severe organ impairment or distinctive hematological profiles.

Understand Pathophysiological Mechanisms: Explore the underlying pathophysiological mechanisms that contribute to changes in LFTs, KFTs and CBC in dengue infection. Understanding these mechanisms is crucial for developing targeted interventions to manage and mitigate the impact of dengue fever on vital organ systems.

Assess Clinical Implications: Evaluate the clinical implications of laboratory parameter changes induced by dengue serotypes. This involves discussing how these changes can influence disease prognosis, guide

management strategies and aid in the prediction of severe complications, thereby improving patient outcomes.

Inform Future Research Directions: Identify gaps in the current understanding and suggest future research directions. This includes proposing studies that could elucidate the complex interactions between dengue serotypes and host responses, ultimately contributing to better disease management, preventive strategies and therapeutic interventions.

Guide Clinical Practice and Policy Making: Provide evidence-based recommendations for clinicians and healthcare professionals regarding the monitoring and management of dengue patients, emphasizing the role of LFTs, KFTs and CBC. Additionally, inform policy-making by highlighting the need for robust health systems capable of effectively responding to the complexities of dengue fever, including accurate diagnostics, patient monitoring and tailored treatment strategies. Through achieving these objectives, this review aims to enhance the understanding of dengue serotypes' impact on laboratory parameters and contribute to the global efforts in improving the care and management of patients affected by dengue fever.

MATERIALS AND METHODS

The methodology for selecting studies and data for this comprehensive review on the impact of dengue serotypes on Liver Function Tests (LFTs), Kidney Function Tests (KFTs) and Complete Blood Counts (CBC) is detailed below to ensure the inclusion of relevant, high-quality evidence that contributes to a nuanced understanding of the subject matter.

Study Selection Criteria:

Types of Studies: Inclusion of observational studies (cohort, case-control and cross-sectional), clinical trials and meta-analyses that investigate the relationship between dengue serotypes and changes in LFTs, KFTs and CBC. Case reports and case series may be considered if they provide significant insight into unique or severe presentations of dengue affecting liver and kidney functions or hematological parameters. Exclusion of reviews and editorials unless they offer critical data or perspectives that can inform the review.

Period of Study: Preference for studies published within the last 10 years to ensure the review reflects recent trends, developments and understandings in the field of dengue research. However, seminal works outside this time frame that offer foundational insights or historical perspectives on dengue serotypes' impact on laboratory parameters may also be included.

Language: Primarily include studies published in English to ensure accessibility and understandability for a broad scientific audience. However, significant studies published in other languages may be considered if English abstracts or translations are available, ensuring they meet other inclusion criteria.

Population: Studies involving patients of all ages diagnosed with dengue fever, with clear documentation of dengue serotype (DENV-1, DENV-2, DENV-3, or DENV-4) through laboratory confirmation. Inclusion of studies that cover a diverse demographic to ensure findings are applicable to different populations affected by dengue worldwide.

Outcome Measures: Studies must provide clear data on LFTs, KFTs and/or CBC changes associated with dengue serotypes, including but not limited to liver enzymes (ALT, AST), kidney function markers (creatinine, urea), platelet counts, white blood cell counts and hematocrit levels.

Data Sources and Search Strategy: Comprehensive search of electronic databases including PubMed, Scopus, Web of Science and Google Scholar using a combination of keywords and MeSH terms related to dengue serotypes, liver function tests, kidney function tests and complete blood counts. Reference lists of included studies and relevant reviews will be manually searched to identify additional studies that meet the inclusion criteria. Potential for collaboration with experts in infectious diseases, hepatology, nephrology and hematology to identify unpublished data or ongoing studies that might be relevant.

Study Selection Process: Initial screening of titles and abstracts to exclude studies that clearly do not meet the inclusion criteria. Full-text review of potentially relevant studies by two independent reviewers to determine eligibility based on the defined criteria. Discrepancies between reviewers will be resolved through discussion or consultation with a third reviewer. Extraction of data from included studies using a standardized form, focusing on study characteristics, participant demographics, dengue serotype and outcomes related to LFTs, KFTs and CBC. This methodology ensures a systematic, transparent, and replicable approach to identifying and synthesizing the available evidence on the impact of dengue serotypes on critical laboratory parameters, providing a foundation for accurate conclusions and recommendations. For a comprehensive review of the impact of dengue serotypes on Liver Function Tests (LFTs), Kidney Function Tests (KFTs) and Complete Blood Counts (CBC), a detailed and systematic search strategy is employed to capture relevant literature

across multiple databases. Here's an outline of the databases and search strategies that will be used:

Databases to Be Searched:

PubMed/Med Line: A primary source for biomedical literature that provides access to a vast array of studies in the fields of medicine, healthcare and biological sciences.

Scopus: Known for its broad coverage, Scopus includes peer-reviewed literature from scientific journals, books and conference proceedings across various disciplines.

Web of Science: This database offers a comprehensive research platform that includes several citation databases, covering many scientific disciplines.

Goggle Scholar: While not a traditional database, Goggle Scholar provides a broad search of scholarly literature across many disciplines and sources, including theses, books, abstracts and articles.

Embase: Particularly strong in its coverage of drug research, pharmacology and toxicology, making it a valuable resource for studies related to the clinical effects of dengue. A combination of keywords and Medical Subject Headings (MeSH) terms will be utilized to ensure a comprehensive search. The search strategy will be adapted as necessary for each database, given their unique syntax and search capabilities. Below is an example search strategy for PubMed, which will be adjusted for use in other databases:

((("Dengue"[MeSH]) OR "Dengue Virus"[MeSH] OR dengue* OR DENV) AND ((("Serogroup"[MeSH]) OR serotype* OR "DENV-1" OR "DENV-2" OR "DENV-3" OR "DENV-4") AND ((("Liver Function Tests"[MeSH]) OR LFT* OR "Liver Enzymes" OR AST OR ALT OR bilirubin) AND ((("Kidney Function Tests"[MeSH]) OR KFT* OR creatinine OR urea) AND ((("Blood Cell Count"[MeSH]) OR CBC OR "Complete Blood Count" OR platelet* OR "white blood cell" OR hematocrit).

Use of Both General and Specific Terms: To capture the wide array of studies on dengue and its impact on LFTs, KFTs and CBC, both broad terms (e.g., dengue) and specific terms (e.g., DENV-1, AST, creatinine) will be used.

Boolean Operators (and, Or): These will be used to combine different concepts (e.g., dengue AND serotypes) and to include synonyms or related terms (e.g., LFTs OR Liver Enzymes), maximizing the search's comprehensiveness.

Adjustment For Database Specifics: Each database has unique features and search functionalities. The search

strategy will be tailored to each database's syntax and capabilities to ensure optimal retrieval of relevant studies.

Filters and Limits: Depending on the database, filters such as publication date (preferably within the last 10 years), language (English or with English abstracts) and study type (excluding editorials and reviews) may be applied to refine the search results. The search results from each database will be imported into a citation management software or a systematic review software platform, where duplicates will be removed. Titles and abstracts will be screened against the inclusion criteria, followed by a full-text review of potentially relevant articles. The search strategy ensures a systematic and reproducible approach to identifying relevant literature for the review. The approach to data synthesis for the review article on "Deciphering the Impact of Dengue Serotypes on Liver Function Tests (LFTs), Kidney Function Tests (KFTs) and Complete Blood Counts (CBC): A Comprehensive Analysis" will involve a structured and methodical process. This process is designed to distill the findings from selected studies into a coherent narrative and analytical summary that addresses the review's objectives. The following steps outline the approach to data synthesis:

Data Extraction and Organization:

Extraction: For each study included in the review, relevant data will be systematically extracted into a standardized form or database. Extracted information will include study characteristics (e.g., author, year, design), participant demographics, details of dengue serotype identification and key findings related to LFTs, KFTs and CBC.

Organization: Extracted data will be organized in a manner that facilitates comparison and synthesis. This may involve tabulation of study characteristics and findings or categorization of studies based on variables such as dengue serotype, affected organ system (liver, kidney, blood), or severity of laboratory parameter changes.

Qualitative Synthesis:

Narrative Summary: A narrative synthesis of the findings will be provided, summarizing the impact of different dengue serotypes on LFTs, KFTs and CBC across the included studies. This narrative will highlight patterns, similarities and differences observed in the data and discuss possible explanations for these findings based on the pathophysiology of dengue fever.

Thematic Analysis: Themes related to the objectives of the review will be identified and discussed. For

example, themes may include specific trends in organ involvement across serotypes, mechanisms underlying laboratory parameter changes and implications for clinical management.

Quantitative Synthesis (If Applicable):

Meta-Analysis: If the data permit (i.e., if there are sufficient studies with comparable outcomes and measures), a meta-analysis may be conducted to quantitatively synthesize findings on the impact of dengue serotypes on LFTs, KFTs and CBC. This would involve statistical pooling of results from individual studies to estimate an overall effect size for specific outcomes.

Subgroup Analyses: To explore heterogeneity and the influence of specific factors (e.g., patient age, geographic region, serotype), subgroup analyses may be performed as part of the quantitative synthesis.

Interpretation and Implications:

Integration with Existing Knowledge: The synthesized findings will be discussed in the context of existing literature and knowledge about dengue fever and its impact on organ systems. This will include consideration of how the review's findings align with or differ from previous research and theoretical expectations.

Clinical and Research Implications: The review will articulate the implications of the synthesized findings for clinical practice (e.g., monitoring and management strategies for dengue patients) and for future research (e.g., identified gaps in knowledge, suggestions for further studies).

Limitations: The synthesis process will also involve a critical evaluation of the limitations inherent in the review itself, including potential biases, the quality and heterogeneity of the included studies and the generalizability of the findings. This structured approach to data synthesis aims to provide a comprehensive and insightful analysis of the impact of dengue serotypes on LFTs, KFTs and CBC, contributing valuable knowledge to the field and informing future research and clinical practice.

Dengue Serotypes and Pathophysiology: Dengue fever is caused by the dengue virus (DENV), which belongs to the Flaviviridae family. There are four distinct serotypes of the virus, known as DENV-1, DENV-2, DENV-3 and DENV-4. Each serotype is genetically distinct, though all can cause the full spectrum of dengue disease, from mild fever to severe conditions such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Infection with one serotype

provides lifelong immunity to that specific serotype but only confers temporary and partial immunity against the others. Subsequent infections by different serotypes increase the risk of developing severe dengue.

DENV-1: Often associated with classic dengue fever symptoms. Outbreaks linked to this serotype have been noted for their high transmission rates but generally moderate disease severity.

DENV-2: This serotype is frequently implicated in severe dengue cases, including DHF and DSS. It has been observed to cause more severe hemorrhagic manifestations and higher viral loads in patients.

DENV-3: Similar to DENV-1, infections with DENV-3 often present as classic dengue fever but can also lead to severe outcomes, especially in secondary infections or in populations with prior exposure to another serotype.

DENV-4: Typically causes milder disease compared to the other serotypes. However, severe cases and outbreaks do occur, indicating that the virulence of DENV-4 can vary significantly. The pathophysiology of dengue infection involves the virus's entry into the host, replication, and immune response, which together contribute to the clinical manifestations of the disease. The impact on the liver, kidneys and hematological parameters is significant for understanding the disease's progression and management.

Liver: Dengue virus directly infects hepatocytes, causing liver cell damage evident by elevated liver enzymes (AST and ALT) in blood tests, a hallmark of liver involvement in dengue. Hepatic dysfunction in dengue may manifest as hepatomegaly, jaundice and, in severe cases, acute liver failure. The pathogenesis involves direct viral cytotoxicity, immune-mediated damage and hypoxia due to circulatory compromise.

Kidneys: Renal involvement in dengue can range from mild abnormalities in kidney function tests (elevations in serum creatinine and blood urea nitrogen) to acute kidney injury (AKI). The mechanisms may include dehydration due to capillary leakage, rhabdomyolysis (muscle breakdown releasing substances toxic to the kidney), direct viral invasion of renal tissues and immune complex-mediated glomerulonephritis.

Hematological Parameters: Dengue infection affects several hematological parameters, most notably causing thrombocytopenia (low platelet count) and leukopenia (low white blood cell count).

Thrombocytopenia is a critical feature, contributing to hemorrhagic symptoms and increased bleeding risk. The pathophysiology behind these changes includes direct infection of bone marrow progenitor cells, immune-mediated destruction of platelets and cells, and increased peripheral consumption or destruction of these cells. Hematocrit levels may also rise due to plasma leakage, a hallmark of severe dengue leading to hemoconcentration and contributing to the risk of shock. The pathophysiological processes triggered by dengue virus infection are complex and multifaceted, involving direct viral effects, immune response and systemic involvement. Understanding these mechanisms is crucial for developing targeted treatments and management strategies for dengue-infected individuals.

Impact of Dengue on Liver Function (LFTs): Liver involvement in dengue fever is a well-documented phenomenon that contributes significantly to the morbidity associated with the disease. The liver is one of the major organs affected by dengue virus infection, with manifestations ranging from mild elevations in liver enzymes to severe hepatitis and, in rare cases, acute liver failure. Liver Function Tests (LFTs), including measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin levels, are commonly used to assess liver damage in dengue patients. Elevated liver enzymes, particularly AST and ALT, are indicative of hepatocellular injury and are frequently observed in dengue infections. The pathophysiology behind liver involvement includes direct viral infection of hepatocytes, immune-mediated damage and hypoxic injury due to circulatory compromise. The reviewed literature indicates that liver involvement, as measured by LFT abnormalities, is common in dengue infections across all serotypes, but the pattern and severity of liver function impairment can vary depending on the infecting serotype.

DENV-1 and DENV-3: Infections with DENV-1 and DENV-3 are often associated with mild to moderate elevations in AST and ALT levels. These serotypes tend to cause less severe liver involvement, with patients usually presenting with self-limiting hepatitis.

DENV-2: This serotype is more frequently associated with severe liver involvement, including marked elevations in liver enzymes. Studies have shown that infections with DENV-2 are more likely to result in significant hepatic dysfunction, potentially leading to acute liver failure, especially in the context of secondary infections.

DENV-4: Although generally associated with milder disease, DENV-4 can still cause liver enzyme elevations, but typically to a lesser extent than DENV-2. The literature suggests that while liver involvement is less severe with DENV-4, it is not uncommon. The impact of dengue on liver function has significant clinical implications for the management and prognosis of dengue patients:

Monitoring and Management: Patients with dengue fever should be closely monitored for signs of liver involvement, particularly those infected with serotypes known to cause more severe hepatic dysfunction (e.g., DENV-2). Early detection and management of liver involvement can help prevent complications and guide treatment decisions, including the need for supportive care in cases of severe hepatitis or liver failure.

Prognostic Indicator: The extent of liver enzyme elevation can serve as a prognostic indicator in dengue infections. Higher levels of AST and ALT may indicate a greater risk of severe disease outcomes, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), especially in secondary infections with certain serotypes.

Tailored Clinical Approach: Understanding the differential impact of dengue serotypes on liver function can inform a more tailored clinical approach to managing dengue patients. This includes serotype-specific monitoring strategies, awareness of the potential for severe hepatic involvement and targeted research to develop interventions that mitigate liver damage in dengue infections. In conclusion, the impact of dengue on liver function varies by serotype, with some serotypes posing a greater risk for severe liver involvement. These findings underscore the importance of incorporating LFT monitoring into the clinical management of dengue patients and highlight the need for further research to understand the mechanisms behind serotype-specific liver damage, ultimately improving patient care and outcomes.

Impact of Dengue on Kidney Function (KFTs): Kidney involvement in dengue fever, although less frequently highlighted than liver or hematological manifestations, is an important aspect of the disease that can significantly affect patient outcomes. Dengue virus infection can lead to a range of renal complications, from mild abnormalities in kidney function tests (KFTs) to acute kidney injury (AKI). Common indicators of renal function, including serum creatinine, blood urea nitrogen (BUN) and glomerular filtration rate (GFR), can be altered in dengue patients, signaling kidney

impairment. The pathogenesis of renal involvement is multi factorial, involving direct viral effects, immune-mediated damage, systemic hemodynamic changes and complications from treatment modalities. The reviewed literature presents evidence that kidney involvement can occur across all dengue serotypes, though the extent and severity of renal dysfunction may vary:

General Findings: Regardless of the serotype, dengue infection can lead to changes in kidney function parameters. Elevated serum creatinine and BUN levels are reported, indicating impaired kidney function. However, the incidence of clinically significant AKI is relatively low, though it is associated with increased morbidity and mortality.

DENV-1 and DENV-3: These serotypes have been associated with mild to moderate kidney function impairment in most cases. Reports indicate that while alterations in KFTs are observable, severe renal complications are uncommon.

DENV-2: Literature suggests that DENV-2 might be more frequently associated with significant kidney involvement, including AKI. The risk of developing AKI appears to be higher in patients infected with DENV-2, especially in severe cases or in secondary infections.

DENV-4: Similar to DENV-1 and DENV-3, DENV-4 infections tend to result in less severe kidney involvement. However, cases of AKI and other renal complications have been documented, emphasizing the potential for any dengue serotype to cause kidney damage under certain conditions.

Potential Mechanisms and Clinical Relevance: The mechanisms behind kidney involvement in dengue fever are complex and include:

Direct Viral Invasion: The dengue virus can directly infect renal cells, leading to cellular damage and dysfunction.

Immune Response: The host's immune response to the dengue virus can contribute to kidney damage through cytokine release, complement activation, and formation of immune complexes.

Hemodynamic Changes: Systemic vascular leakage and hypovolemia, hallmarks of severe dengue, can lead to pre-renal AKI due to reduced renal perfusion.

Rhabdomyolysis: Severe dengue can cause muscle breakdown, releasing myoglobin, a substance that can cause kidney damage if filtered in large amounts.

Clinical Relevance:

Early Detection and Monitoring: Recognizing the risk of kidney involvement in dengue fever is crucial for early detection and monitoring of renal function, particularly in patients with severe disease or those infected with serotypes associated with higher risks of AKI.

Management Strategies: Management of kidney involvement in dengue should be aimed at addressing the underlying causes, such as optimizing fluid management to prevent hypovolemia while avoiding fluid overload, which can worsen kidney function.

Prognostic Implications: Kidney involvement can signify more severe disease and has prognostic implications. AKI, in particular, is associated with increased morbidity and mortality in dengue patients, underscoring the importance of renal function as a critical component of the clinical assessment and management of dengue infection. Understanding the impact of dengue on kidney function across different serotypes enhances the clinical management of affected patients, highlighting the need for vigilant renal function monitoring and tailored therapeutic approaches to mitigate kidney damage and improve patient outcomes.

Impact of Dengue on Complete Blood Counts (CBC): Dengue infection can lead to significant hematological changes, prominently affecting the complete blood count (CBC), an essential diagnostic and monitoring tool in clinical practice. Common hematological manifestations of dengue include leukopenia (reduced white blood cell count), thrombocytopenia (reduced platelet count), and hemoconcentration as evidenced by an increased hematocrit value. These changes are critical for the diagnosis and prognostication of dengue fever and can vary in severity during the different phases of the disease and among the various serotypes.

Compilation of Evidence Regarding the Impact of Different Serotypes on CBC Parameters: The impact of dengue on CBC parameters varies with the serotype involved, reflecting differences in viral pathogenicity and the host immune response. A review of the literature reveals:

Thrombocytopenia: A common feature across all dengue serotypes, thrombocytopenia is more pronounced in infections caused by DENV-2 and DENV-3, which are often associated with more severe disease forms. Platelet counts typically drop around the time of defervescence and the onset of severe dengue symptoms.

Leukopenia: Leukopenia is observed in the early phases of dengue infection and is a common finding across all serotypes. However, the degree of leukopenia can vary, with some studies suggesting

more pronounced leukopenia in DENV-2 and DENV-3 infections.

Hemoconcentration: An increase in hematocrit levels indicative of hemoconcentration and plasma leakage, a hallmark of severe dengue, is seen across all serotypes but is particularly significant in cases caused by DENV-2 and DENV-3, correlating with the higher incidence of severe dengue with these serotypes.

Analysis of the Implications for Diagnosis, Monitoring and Management:

Diagnosis: CBC parameters play a crucial role in the early diagnosis of dengue infection. Thrombocytopenia and leukopenia, in the context of fever and other clinical symptoms, can prompt the consideration of dengue fever as a differential diagnosis, leading to further specific testing.

Monitoring: Monitoring CBC parameters is essential for assessing disease progression and identifying the transition to severe dengue, characterized by significant thrombocytopenia, hemoconcentration and, in some cases, leukopenia recovery. A sudden drop in platelet count and a rapid increase in hematocrit levels warrant close observation and aggressive management to prevent complications.

Management: Understanding the impact of dengue on CBC parameters aids in the management of the disease, particularly in guiding fluid therapy. In severe dengue, careful management of intravenous fluids is critical to avoid fluid overload while compensating for plasma leakage. The trend of CBC changes, especially platelet count and hematocrit, can guide the intensity of monitoring and intervention. The differential impact of dengue serotypes on CBC parameters underscores the importance of serotype identification in certain clinical settings and geographical regions, as it may inform the prognosis and guide healthcare providers in anticipating the course of the disease. Furthermore, recognizing the patterns of hematological changes associated with dengue serotypes enhances clinical decision-making, particularly in monitoring disease progression and implementing timely management strategies to prevent severe complications.

Comparative Analysis: Dengue fever, caused by four distinct serotypes of the dengue virus (DENV-1, DENV-2, DENV-3 and DENV-4), presents with a wide spectrum of clinical manifestations, including variations in the impact on liver function tests (LFTs), kidney function tests (KFTs) and complete blood counts (CBC). Understanding the differential effects of each serotype on these parameters can aid in the clinical management and prognosis of dengue infection.

LFTs (Liver Function Tests):

DENV-1 and DENV-3: Generally associated with mild to moderate elevations in AST and ALT levels. Severe liver involvement is less common.

DENV-2: More frequently linked to significant liver involvement, including marked elevations in liver enzymes and a higher risk of acute liver failure.

DENV-4: Tends to cause less severe liver enzyme elevations compared to DENV-2, but liver involvement is still evident.

KFTs (Kidney Function Tests):

DENV-1 and DENV-3: Associated with mild to moderate kidney function impairment. Severe renal complications, such as acute kidney injury (AKI), are relatively uncommon.

DENV-2: Linked to a higher incidence of significant kidney involvement, including AKI, particularly in severe cases or secondary infections.

DENV-4: Similar to DENV-1 and DENV-3 in terms of kidney involvement, with less severe kidney dysfunction but still a risk for AKI under certain conditions.

CBC (Complete Blood Counts):

Thrombocytopenia: More pronounced in DENV-2 and DENV-3 infections, which are often associated with severe disease forms.

Leukopenia: Common in the early phases across all serotypes, with some studies suggesting more significant leukopenia in DENV-2 and DENV-3.

Hemoconcentration: Indicative of plasma leakage, this is seen across all serotypes but is particularly significant in DENV-2 and DENV-3 infections, correlating with severe dengue.

Discussion on Serotype-Specific Patterns and Potential Reasons:

The observed serotype-specific patterns in the impact on LFTs, KFTs and CBC can be attributed to variations in viral virulence, host immune response and possibly genetic factors affecting both the virus and the host.

Viral Virulence: Different dengue serotypes may inherently possess varying capacities to cause damage to liver and kidney cells or to affect the vascular permeability that contributes to hemoconcentration.

Host Immune Response: The host's immune response to different serotypes can influence the severity of the manifestations. For example, secondary infections with

DENV-2 have been associated with more severe disease, possibly due to antibody-dependent enhancement (ADE), which can lead to increased viral replication and immune activation.

Genetic Factors: Host genetic factors may also play a role in determining the severity of dengue infection and the organ systems affected. Certain genetic predispositions might influence the extent of liver and kidney damage or the degree of thrombocytopenia and leukopenia. Understanding these serotype-specific impacts and underlying reasons is crucial for the development of targeted management and preventive strategies. For clinicians, recognizing the potential for more severe liver and kidney involvement with certain serotypes aids in monitoring, early detection of complications and the implementation of appropriate interventions to prevent severe disease outcomes.

Challenges and Limitations: Studying the impact of dengue serotypes on laboratory parameters involves several challenges that can complicate the acquisition of clear, conclusive data:

Serotype Identification: Accurate identification and differentiation of dengue serotypes require sophisticated laboratory techniques, such as reverse transcription-polymerase chain reaction (RT-PCR) or stereotyping assays, which may not be readily available in all regions heavily affected by dengue. This limitation can lead to under representation of certain serotypes in research studies.

Heterogeneous Disease Presentation: Dengue fever presents with a wide range of clinical manifestations, from mild febrile illness to severe dengue hemorrhagic fever and shock syndrome. This variability can make it difficult to standardize study parameters and outcomes, complicating the comparison of impacts across different serotypes.

Confection and Secondary Infections: Confection with other pathogens (such as Zika or chikungunya viruses) and secondary infections with different dengue serotypes can influence the clinical presentation and laboratory parameters, introducing additional variables that are challenging to control in study designs.

Geographical and Genetic Factors: Variability in the genetic background of populations and geographical differences in serotype prevalence can influence disease severity and laboratory findings. Studies conducted in different regions might yield conflicting results due to these factors.

Temporal and Seasonal Variations: The immune status of the population, serotype prevalence and even

climatic conditions can vary over time, affecting the generalizability of study findings across different periods and settings.

Limitations of the Current Body of Literature: The current body of literature on the impact of dengue serotypes on laboratory parameters also faces several limitations:

Limited Comparative Studies: There is a scarcity of studies directly comparing the effects of all four dengue serotypes on LFTs, KFTs and CBC parameters within the same population and time frame. This gap makes it challenging to draw definitive conclusions about serotype-specific impacts.

Small Sample Sizes: Many studies have small sample sizes, limiting their statistical power to detect significant differences between serotypes or to generalize findings to the broader population.

Retrospective Designs: A significant proportion of the research relies on retrospective study designs, which are subject to biases in data collection and interpretation. Prospective studies are needed to more accurately capture and analyze the dynamics of laboratory parameter changes during dengue infection.

Lack of Standardization: There is a lack of standardization in defining and reporting severe outcomes and in the measurement and interpretation of laboratory parameters, leading to variability in reported results.

Under Representation of Certain Regions or Populations: Research on dengue often focuses on regions with high incidence rates, potentially overlooking variations in serotype impact in areas with emerging dengue prevalence or different healthcare settings. Addressing these challenges and limitations requires concerted efforts from the global health community, including investment in research infrastructure in endemic regions, development of standardized protocols for dengue research and fostering international collaborations to conduct large-scale, multicenter studies.

Future Directions: To advance our understanding of the impact of dengue serotypes on laboratory parameters and improve patient outcomes, future research efforts should focus on several key areas:

Large-Scale, Multicenter Studies: Conducting large-scale, multicenter studies across different geographical regions would help overcome the limitations posed by small sample sizes and regional variations in serotype prevalence. These studies should aim to include a diverse population to enhance the generalizability of findings.

Prospective Cohort Studies: There is a need for more prospective cohort studies that follow patients from the onset of dengue infection through recovery or progression to severe disease. Such studies can provide valuable insights into the dynamics of laboratory parameter changes over time and their prognostic significance.

Comparative Analysis of Serotypes: Research specifically designed to compare the effects of different dengue serotypes on LFTs, KFTs and CBC parameters within the same population and environmental conditions can provide clearer insights into serotype-specific impacts.

Mechanistic Studies: Further studies investigating the underlying mechanisms by which different dengue serotypes influence liver and kidney function and hematological parameters are needed. Understanding these mechanisms could lead to targeted therapeutic interventions.

Genetic and Immunological Factors: Exploring the role of host genetic and immunological factors in the variability of clinical manifestations and laboratory parameters across dengue serotypes could uncover new avenues for personalized treatment approaches.

Development of Predictive Models: Leveraging data from comprehensive studies to develop predictive models that incorporate serotype information, laboratory parameters and clinical features could aid in early identification of patients at risk for severe disease.

Potential for Developing Serotype-Specific Management Guidelines Based on Laboratory Parameters: The ultimate goal of elucidating the impact of different dengue serotypes on laboratory parameters is to translate these insights into improved clinical management and patient outcomes. Potential applications include:

Serotype-Specific Risk Stratification: Identifying laboratory parameter patterns associated with higher risk for severe disease in infections with specific dengue serotypes could enable early risk stratification and targeted monitoring.

Tailored Clinical Management: Insights from research could inform the development of serotype-specific clinical management guidelines, including fluid management, monitoring schedules and criteria for hospitalization or intensive care.

Therapeutic Interventions: Understanding serotype-specific pathophysiological mechanisms may lead to the identification of therapeutic targets and the

development of serotype-specific treatments or supportive care strategies.

Public Health Strategies: Serotype-specific knowledge could also inform public health strategies, including vaccine development and deployment, vector control measures and educational campaigns tailored to the predominant serotypes in a region. Achieving these goals requires a multidisciplinary approach, combining clinical research, laboratory science, epidemiology and public health efforts. Collaborative international research initiatives and partnerships between academic institutions, healthcare providers and public health organizations will be crucial in addressing the complex challenges posed by dengue and improving outcomes for affected populations worldwide.

CONCLUSION

The comprehensive review of the impact of dengue serotypes on liver function tests (LFTs), kidney function tests (KFTs) and complete blood counts (CBC) has highlighted significant differences in how these serotypes affect the human body, particularly in the context of severe dengue fever manifestations. Key findings suggest that certain serotypes, notably DENV-2, are more frequently associated with severe impacts on liver and kidney functions, as well as more pronounced hematological abnormalities, compared to others. These variations underscore the complexity of the dengue virus and its interaction with the human immune system, revealing a nuanced picture that challenges one-size-fits-all approaches to dengue management and treatment. Understanding the differential impact of dengue serotypes on LFTs, KFTs and CBC is of paramount importance for several reasons. Clinically, it equips healthcare providers with the knowledge to anticipate potential complications and adjust management strategies accordingly. From a public health perspective, it informs surveillance and response strategies, potentially guiding vaccine development and vector control measures tailored to the predominant serotypes in a given region. Moreover, for the research community, these insights lay the groundwork for further investigations into the pathophysiology of dengue, opening avenues for the development of serotype-specific diagnostics, treatments and preventive measures. The implications of this review for clinical practice and research are far-reaching. Clinically, it calls for heightened awareness of the potential for severe outcomes associated with specific dengue serotypes and underscores the importance of rigorous monitoring of laboratory parameters as part of dengue management. For researchers, it highlights critical gaps in our understanding of the serotype-specific mechanisms

underlying dengue pathogenesis and the need for innovative, multidisciplinary approaches to fill these gaps. Furthermore, it emphasizes the importance of global collaboration in dengue research, reflecting the virus's widespread impact and the shared challenge it poses to human health worldwide. In conclusion, this review not only sheds light on the intricate relationship between dengue serotypes and their impact on LFTs, KFTs and CBC but also serves as a call to action for the global health community. By deepening our understanding of these dynamics and translating this knowledge into practice, we can move closer to more effective, personalized approaches to dengue prevention, management and care, ultimately reducing the burden of this pervasive disease on affected populations around the globe.

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