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Laboratory Examinations in the Diagnosis of Dengue Hemorrhagic Fever: A Systematic Literature Review

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ABSTRACT

Dengue Hemorrhagic Fever (DHF) is an infectious disease caused by the dengue virus and remains a major public health problem in Indonesia. Early and accurate diagnosis is crucial for determining appropriate management and preventing fatal complications. This systematic literature review aimed to evaluate and synthesize evidence on laboratory diagnostic methods for DHF across Southeast Asia. A Comprehensive search was conducted across Pubmed, ScienceDirect, Scopus, Google Scholar and DOAJ for studies published between 2015 and 2025, using keyword such as "Dengue Hemorrhagic Fever," "Laboratory Diagnosis," and "Southeast Asia." Inclusion criteria encompassed peer-reviewed studies reporting empirical on hematological, serological, or molecular laboratory test for DHF, while reviews without empirical finding studies unrelated to dengue diagnosis were excluded. Found on database 40 after screening, 22 studies met the inclusion criteria ad were analyzed. NS1 antigen testing plays a crucial role in the early phase of infection, while IgM and IgG serological tests are useful in identifying the immunological phase of the disease. Meanwhile, RT-PCR is a highly sensitive method for directly detecting the presence of the virus. Combining several testing methods has been shown to improve diagnostic accuracy, both in terms of sensitivity and specificity. However, optimal implementation of these tests still faces challenges such as limited resources, cost, time, and differences in laboratory capabilities at various levels of health facilities. Therefore, strengthening laboratory capacity, standardizing testing methods, and implementing a combination testing strategy are needed to improve the reliability of dengue diagnosis. This approach is expected to support early detection, accelerate treatment, and strengthen efforts to control dengue outbreaks nationally.

INTRODUCTION

Dengue Hemorrhagic Fever (DHF) is a viral disease that remains a major problem in tropical and subtropical countries, including Indonesia. The dengue virus causes this disease. There are four serotypes: DEN-1, DEN-2, DEN-3, and DEN-4. All three are spread by the bites of the Aedes aegypti and Aedes albopictus mosquitoes. The World Health Organization (WHO) states that there are approximately 100 million cases of dengue fever worldwide each year. DHF is now common in Indonesia, and the number of cases increases rapidly during the rainy season due to increased mosquito vector populations. In Indonesia, the Ministry of Health reported over 114.720 confirmed cases of DHF in 2023, with higher incidence during the rainy season due the increased mosquito vector populations

The main signs of dengue fever include a sudden high temperature, headache, muscle and joint pain, and a skin rash. However, these signs are nonspecific and often resemble other viral diseases,

including chikungunya, malaria, and typhus. Therefore, identifying dengue fever solely based on clinical symptoms can sometimes lead to errors, especially in the early stages of the disease. Therefore, laboratory tests are crucial to ensure patients receive the correct diagnosis and medical treatment (Sheikh et al., 2022).

In dengue fever, laboratory tests perform two functions: directly detect the dengue virus in the body and monitor changes in blood parameters and biochemistry that occur due to the disease. Routine blood tests typically check platelet count, hematocrit, white blood cell count, and hemoglobin levels. A decrease in platelets and an increase in hematocrit are common signs that someone may have dengue fever, especially during the critical phase. However, these changes are not always clear-cut, so they need to be combined with serological or molecular tests. Serological techniques, including dengue IgM and IgG antibody detection tests, are used to assess the immunological response to dengue virus infection.

These tests are not particularly difficult to perform and are readily available in many laboratories. However, serological tests present challenges in the early stages of infection because antibodies are not developed until several days after the virus enters the body. On the other hand, NS1 antigen tests can detect early infection because the NS1 protein is produced in the blood soon after the virus replicates, usually within the first 0–5 days after symptoms appear. Furthermore, molecular tests such as Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) are now considered the most accurate and sensitive method for diagnosing dengue virus because they can directly detect dengue virus RNA. RT-PCR can also identify the type of virus causing the infection, which is crucial for tracking the spread of the disease and finding ways to stop it. However, RT-PCR can only be used in healthcare facilities with adequate laboratory equipment and sufficient funding (Datu, 2023)

These laboratory tests are difficult to use in the field due to their varying characteristics, cost, and sensitivity. In resource-limited settings, basic tests such as platelet count and hematocrit remain important, although they are not highly accurate in providing an early diagnosis. This issue underscores the need for a comprehensive assessment of the efficacy of each testing methodology across healthcare settings. In recent years, numerous studies have been conducted to examine the accuracy and reliability of various laboratory tests for diagnosing dengue fever. However, these results often fluctuate due to variations in study populations, sampling duration, and analytical methodologies used. Therefore, a comprehensive literature review is essential to integrate this data and provide a clearer understanding of the efficacy of dengue laboratory tests from various perspectives .

Literature reviews can also help identify areas that require further research, such as when there is insufficient evidence on how accurate tests are at different stages of the disease, how different viral serotypes affect results, or how other health issues impact laboratory results. Despite numerous studies in laboratory diagnosis of dengue, there remains a lack of consensus regarding the most reliable combination of test, their optimal timing, and their performance across different Southeast Asian populations, By understanding these elements, medical professionals and researchers can formulate more precise and contextually relevant diagnostic protocols specifically designed for endemic areas (Abdin & Pretis, 2023). Beyond diagnosis, laboratory tests are also crucial for monitoring how a condition worsens and how well a patient responds to treatment. Some test values can be used to determine whether a person is at risk for problems such as plasma leakage, severe bleeding, or dengue shock syndrome. Therefore, maximizing laboratory testing not only aids early diagnosis but also helps prevent the progression of dengue hemorrhagic fever.

Given the variability and limitations of existing diagnostic methods, as well as inconsistencies in reported sensitivity and specificity across different settings and dengue serotypes, a comprehensive synthesis of current evidence is needed. This systematic literature review aims to evaluate and integrate findings in Southeast Asia, with the goal of identifying the most effective and reliable testing strategies for early detection, accurate diagnosis, and improved patient management.

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METHOD

This study employed a literature review with a qualitative descriptive methodology. The aim was to collect, evaluate, and integrate various previous research findings on laboratory testing for the diagnosis of Dengue Hemorrhagic Fever (DHF) across Southeast Asia. The data used were secondary, drawn from various sources, including national and international journal articles, research reports, medical textbooks, and official publications from health institutions such as the WHO and the Ministry of Health. The literature search utilized various scientific databases, such as PubMed, ScienceDirect, Google Scholar, Scopus, and DOAJ.

The literature selection criteria included publications published within the last ten years (2015–2025), discussing laboratory testing in DHF patients, focusing on Southeast Asia (including Indonesia, Malaysia, Thailand, the Philippines, and Vietnam), and written in either Indonesian or English. The search approach used terms such as "Dengue Hemorrhagic Fever" OR "Dengue Hemorrhagic Fever" AND "Laboratory Examination" OR "Laboratory Diagnosis" AND "Southeast Asia." The search technique began by examining titles and abstracts for relevance. Then, all articles meeting the inclusion and exclusion criteria were selected.

Inclusion criteria for this study included studies discussing laboratory tests, including hematology, serology, or molecular testing in dengue cases, originating from Southeast Asian countries, and having received peer review. Articles unrelated to dengue diagnosis, studies that only discussed clinical characteristics without laboratory test findings, and review articles that did not provide empirical data were excluded.

Data analysis was conducted in several stages: selection of relevant articles, categorization by laboratory test type, thematic synthesis for comparative analysis of findings across Southeast Asian countries, and interpretation of results to determine the most effective laboratory tests for dengue diagnosis in the region. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart shows how many papers were found, screened, excluded, and finally analyzed during the literature selection process. The final results of this study include a narrative analysis and summary tables showing the various types of laboratory tests used, the sensitivity and specificity of each method, and their performance in Southeast Asian countries.

This study did not involve human participants or animals, as it relied entirely on secondary data from published literature, research reports, and official health publications. Ethical considerations included proper citation of all sources, accurate representation of study findings, and adherence to principles of transparency and academic integrity throughout the literature review process. All sources were critically appraised to ensure reliability validity, and compliance with copyright regulations.

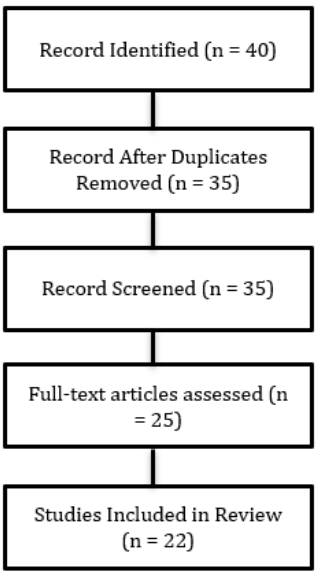

Figure 1. PRISMA Flow Diagram

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Table 1: Article Selection Proccess

Selection Stage	Number of Articles	Information
Found from database	40	Keywords: *Dengue* , *Laboratory Diagnosis* , *NS1* , *RT-PCR* , *Southeast Asia*
Duplication removed	35	Article selected after duplication removal
Title & abstract screening	35	10 eliminated due to epidemiological/clinical focus without specific lab
Full-text eligible	25	Assessing the suitability of laboratory detection
Studies *included*	22	Final article used in SLR

RESULTS

Based on observations from various literature and related studies, laboratory tests play a central role in the diagnosis and clinical monitoring of Dengue Hemorrhagic Fever (DHF). Observations indicate that the diagnosis of DHF cannot rely solely on clinical symptoms, as signs such as sudden high fever, muscle aches, skin rashes, and headaches often mimic other infectious diseases such as chikungunya, malaria, or typhus. Therefore, laboratory tests are key to ensuring an accurate diagnosis and determining the stage and severity of the disease (Sabottke & Spieler, 2020).

Observations of routine blood tests indicate that the two most important parameters in assessing the possibility of DHF are thrombocytopenia (a decrease in the platelet count) and hemoconcentration (an increase in the hematocrit). These two parameters reflect the plasma leakage process that is a key characteristic of DHF. However, not all patients exhibit a decrease in platelets or an increase in the hematocrit in the early stages of infection, so these tests must be repeated and combined with serological or molecular testing to improve diagnostic accuracy (Datu, 2023).

Serological testing is the most widely used diagnostic method because it is relatively easy, fast, and widely available in healthcare facilities. Observations indicate that dengue IgM and IgG tests are used to detect the presence of antibodies to the dengue virus. This test is effective after day 5 of infection, when antibodies begin to form. However, its limitation lies in its low sensitivity in the early acute phase of the disease, so a negative result at this stage cannot rule out dengue infection. Therefore, a combination with the NS1 antigen test is highly recommended. The NS1 protein is detectable in the blood from the first to the fifth day after symptom onset, making it an important indicator for early dengue diagnosis (Asra et al., 2025).

Furthermore, molecular tests such as Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) are the most sensitive and specific methods for detecting dengue virus RNA and determining the infecting serotype (DEN-1 to DEN-4). Observations indicate that RT-PCR is very useful for epidemiological studies and tracing the chain of virus transmission, but its cost and the need for sophisticated laboratory facilities make this method difficult to implement in areas with limited resources. Therefore, RT-PCR is more frequently used in reference laboratories or research centers.

Table 2. Summary of the Literature Review Findings

No	Author (Year)	Country/ Region	Examination Focus/ Method	Study Design	Key Findings
1	Datu (2023)	Indonesia	RT-PCR	Observational	RT-PCR shows high sensitivity for early diagnosis in the acute phase.
2	Datu (2023b)	Indonesia	RT-PCR vs Serology	Comparison of Methods	RT-PCR is superior on days 1–5 of fever compared to serology.

3	Aryasari et al. (2022)	Indonesia	NS1 Antigen	Cross-sectional	NS1 sensitivity varies based on the day of onset and the patient's immune status.
4	Banerjee et al. (2018)	Global	RT-PCR, NS1, Serology & Haematology	Review	Each method has a different role according to the phase of dengue infection.
5	Cavailler et al. (2016)	Cambodia	Early Biomarkers	Prospective	Haemo concentration & platelets <100,000 predict DHF early.
6	Chakravarti & Arora (2021)	India	Molecular Testing + Haematology	Review	The combination of molecular + haematology improves diagnostic accuracy.
7	Chen et al. (2022)	China	LAMP (Loop-mediated Isothermal Amplification)	Experimental	LAMP is fast, inexpensive, suitable for limited laboratory facilities.
8	Chong et al. (2021)	Malaysia	Dengue Fever Biosensor	Diagnostic Evaluation	New biosensor shows high accuracy & fast results.
9	Datta & Mukherjee (2023)	India	NS1	Review	NS1 is effective in the first 3 days but decreases in secondary infections.
10	Guzman et al. (2020)	Global	All lab methods	Review	Diagnosis of dengue fever remains challenging especially in recurrent infections.
11	Hunsperger et al. (2020)	Multi-Country	Serology	Evaluation Study	The performance of serology kits varies widely between regions.
12	Kumar et al. (2020)	India	Haematology (Platelets, WBC, HCT)	Clinic	Elevated haematocrit and low platelets are indicators of DHF.
13	Mahajan et al. (2021)	India	Rapid Diagnostic Test (RDT)	Multi-Site Evaluation	RDT sensitivity is influenced by clinical stage & kit variations.
14	Mallhi et al. (2015)	Malaysia	Haematology + Risk Factors	Retrospective	Increased haematocrit + atypical lymphocytes associated with DHF risk.
15	Melly & Anggraini (2022)	Indonesia	Serology + Haematology	Review	The combination of both methods increases the accuracy of diagnosis.
16	Muller et al. (2017)	Global	Molecular vs Serology	Review	RT-PCR is more accurate early, serology for the convalescent phase.
17	Ndiaye et al. (2023)	Senegal (Relevant SE Asia)	NS1 + IgM/IgG RDT	Field Trial	RDT performance is lower under field conditions.
18	Ngim et al. (2021)	Malaysia	Rapid Test	Passive Surveillance Study	Rapid tests still require clinical-laboratory confirmation.
19	Prodjosoewojo et al. (2019)	Indonesia	Automated Haematology Algorithm	Diagnostic Tool Study	Automated tools help differentiate dengue fever from other infections that cause fever.
20	Santiago et al. (2021)	Asia & America	Combination of NS1 + IgM/IgG	Clinical Evaluation	The combination increases the sensitivity and specificity of the diagnosis.
21	Suwarto et al. (2021)	Indonesia	Serum Biochemistry (SGOT/SGPT)	Clinic	Liver enzymes are significantly elevated in severe DHF cases.
22	Thomas et al. (2021)	Global	NS1 in secondary infections	Clinical Study	NS1 has lower accuracy in secondary dengue infections.

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Observations also indicate variations in results between studies due to differences in study populations, sampling times, and testing methods. This indicates the need for standardization of dengue fever laboratory testing protocols to ensure more consistent and comparable results across endemic areas. In addition to diagnosis, laboratory tests are also crucial for monitoring the course of the disease, such as detecting signs of plasma leakage, bleeding disorders, or the risk of dengue shock. Therefore, observations conclude that the effectiveness of dengue laboratory testing depends on the combination of methods used, sampling time, and the capabilities of health facilities. Basic tests such as a complete blood count remain essential for initial screening in primary care facilities, while a combination of NS1 and IgM/IgG provides higher diagnostic value in the acute and post-acute phases. Furthermore, RT-PCR remains the gold standard for confirmatory diagnosis and epidemiological mapping. Optimizing the use of a combination of laboratory tests according to health facility conditions is key to improving early detection, monitoring, and effective management of dengue cases in Indonesia.

DISCUSSION

Laboratory Tests as the Basis for Diagnosing Dengue Hemorrhagic Fever (DHF)

Laboratory tests play a crucial role in establishing a diagnosis of Dengue Hemorrhagic Fever (DHF), as the clinical manifestations of this disease are often nonspecific and difficult to distinguish from other infectious diseases such as chikungunya, typhoid, or influenza. Clinical diagnosis based solely on symptoms often leads to misinterpretation, especially in the early stages of the disease. Therefore, laboratory tests are necessary to confirm the presence of the dengue virus, assess the body's immune response to infection, and monitor physiological changes in the patient (Sabottke & Spieler, 2020).

Broadly speaking, laboratory tests for DHF cases are divided into two main groups: routine blood tests (hematology) and specific tests (serology or molecular). Routine blood tests are used to detect changes in blood components caused by dengue virus infection, while serology and molecular tests are used to directly identify the virus or antibodies (Version, 2022). Routine blood tests are the most frequently performed basic tests, especially in primary healthcare facilities. This examination includes platelet counts, hematocrit, leukocyte counts, and lymphocyte counts, each of which has its own diagnostic and prognostic role. According to Kumar et al. (2020), decreased platelet counts (thrombocytopenia) are a hallmark of dengue fever and typically occur on days 3 to 7 after fever onset. A significantly decreased platelet count (<100,000/µL) may indicate a critical phase of the disease, with an increased risk of bleeding and plasma leakage. Furthermore, an increase in hematocrit levels greater than 20% of normal is an indicator of hemoconcentration, indicating plasma leakage due to increased capillary permeability (Lancet et al., 2022).

In addition to platelets and hematocrit, leukocyte counts also exhibit characteristic changes in dengue fever. Leukopenia (<4,000/µL) is typically found, accompanied by a relative increase in atypical lymphocytes, indicating the body's immune response to the viral infection. These findings can help differentiate dengue fever from bacterial infections, which typically present with leukocytosis (an increase in the number of white blood cells) (Saha et al., 2023). dengue fever, in contrast to bacterial infections, which show an increased ESR (Saha et al., 2023). Furthermore, clinical chemistry tests, such as liver function tests (AST and ALT) and plasma albumin levels, can indicate the severity of the infection, as elevated liver enzymes and hypoalbuminemia due to plasma leakage are common in severe dengue fever (Asra et al., 2025).

Serological testing includes the detection of IgM and IgG antibodies to the dengue virus. IgM is typically detected from the fifth to seventh day after symptom onset, while IgG appears later but remains high in secondary infections (Mukherjee & Datta, 2024). On the other hand, NS1 antigen testing can detect infection earlier, as this antigen can be detected from the first to fifth day after fever onset. The presence of the NS1 antigen indicates an active infection, making this test highly useful for early detection of dengue fever cases.

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In addition to serological testing, the Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) technique is now considered the most sensitive and specific method for directly detecting dengue virus RNA. RT-PCR can also identify virus serotypes (DEN-1 to DEN-4), making it useful for epidemiological mapping and outbreak control (Sabottke & Spieler, 2020). However, technological limitations and cost often hinder RT-PCR implementation in healthcare facilities with limited resources. Thus, laboratory tests are not only used to establish a diagnosis but also serve as an important basis for monitoring the course of the disease. The combination of routine blood tests and serological/molecular testing provides a comprehensive picture of the patient's condition, enabling medical personnel to provide faster and more appropriate treatment. Optimizing these tests at all levels of healthcare is a crucial step in improving early detection and reducing dengue fever mortality in Indonesia.

Routine Blood Tests (Hematology) in the Diagnosis of Dengue Hemorrhagic Fever (DHF)

Routine blood tests, or hematology, are an essential component in the diagnosis of Dengue Hemorrhagic Fever (DHF). These tests play a role not only in establishing an initial diagnosis but also in monitoring disease progression and assessing the risk of complications such as bleeding and dengue shock. In the context of healthcare facilities in Indonesia—especially in endemic areas with limited resources—hematology tests are the primary diagnostic tool because they are quick, easy, and relatively inexpensive compared to molecular or serological tests (World Health Organization (Lancet et al., 2022).

In general, the main parameters in routine blood tests include platelet count, hematocrit, leukocytes, lymphocytes, erythrocyte sedimentation rate (ESR), and blood chemistry results such as albumin levels and liver function tests. Each parameter provides important physiopathological insights into how the body responds to dengue virus infection.

1. Platelet Count

Thrombocytopenia, or a decrease in platelet count, is a characteristic laboratory finding in dengue fever patients. Platelet decline begins to appear on days 3 to 7 after fever onset, which usually coincides with the critical phase of the disease (Singh et al., 2020). A normal platelet count ranges from 150,000 to 450,000/µL, but in dengue patients, it can drop to below 100,000/µL and even reach <50,000/µL in severe cases (Saha et al., 2023). Thrombocytopenia in dengue fever occurs due to three main mechanisms:

- Decreased platelet production in the bone marrow due to the direct effect of dengue virus infection on megakaryocytes.
- Increased platelet destruction by the immune system through the formation of antiplatelet antibodies.
- Increased platelet consumption due to activation of the coagulation system and plasma leakage.

Clinically, a significant decrease in platelets indicates a risk of bleeding and is one of the main criteria for diagnosing Dengue Hemorrhagic Fever (DHF). However, thrombocytopenia does not always align with the degree of bleeding, so it is important to monitor it alongside hematocrit levels and other clinical signs (Sabottke & Spieler, 2020).

2. Hematocrit (Packed Cell Volume)

Hematocrit reflects the percentage of red blood cell volume to total blood volume. In dengue fever, an increase in hematocrit of more than 20% above normal values indicates hemoconcentration due to plasma leakage from the blood vessels into the interstitial space (Lancet et al., 2022). This increase in hematocrit usually occurs simultaneously with a decrease in platelets, and the combination of these two results is a strong indicator of the possible onset of plasma leakage or dengue shock syndrome (DSS).

According to research by (Datu, 2023), patients with a hematocrit increase of ≥45% have a higher risk of circulatory impairment and shock compared to patients with normal hematocrit values. Therefore, serial monitoring of hematocrit values is crucial for assessing the effectiveness of intravenous fluid therapy and determining the indication for intensive care. In addition to being an indicator of plasma leakage, a very low hematocrit value can indicate anemia due to internal

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bleeding. Therefore, changes in hematocrit values, whether increasing or decreasing, provide important information about the patient's hemodynamic condition.

3. Leukocytes (White Blood Cell Count)

A leukocyte count test provides an overview of the body's immune response to dengue virus infection. One of the hematological characteristics of dengue fever is leukopenia, a decrease in the leukocyte count below 4,000/µL. This leukopenia usually appears on days 2 to 4 of infection, then begins to increase again during the recovery phase (Chorro et al., n.d.). The decrease in the leukocyte count in dengue fever is caused by bone marrow suppression due to direct dengue virus infection and increased leukocyte apoptosis (cell death). On the other hand, bacterial infections are generally characterized by leukocytosis (an increase in the leukocyte count), so this test can help differentiate dengue fever from acute bacterial infections such as typhoid or pneumonia (Murhekar et al., 2021). Specifically, the differential count often shows an increased proportion of atypical lymphocytes (reactive lymphocytes), which are immune cells that have changed shape due to viral activation. The presence of atypical lymphocytes is an indicator of active viral infection, including dengue (Fatoki et al., 2020).

4. Lymphocytes and Monocytes

In addition to total leukocytes, examination of white blood cell types such as lymphocytes and monocytes also provides important diagnostic information. In dengue virus infection, relative lymphocytosis—an increase in the percentage of lymphocytes in the peripheral blood—usually occurs, despite a decrease in the total leukocyte count. These lymphocytes play a role in the immune response to the virus and increase in number during the recovery phase (Mukherjee & Datta, 2024). Meanwhile, monocytes often increase during the acute phase of infection. These cells play a role in phagocytosis of viral particles and the production of pro-inflammatory cytokines. Increased monocyte activity is associated with systemic symptoms such as high fever, joint pain, and weakness.

5. Erythrocyte Sedimentation Rate (ESR)

The erythrocyte sedimentation rate (ESR) test is used to assess the level of inflammation in the body. In viral infections such as dengue fever, the ESR is usually normal or decreased, in contrast to bacterial infections, which generally show an increase. A consistently low ESR can help doctors rule out a secondary bacterial infection in patients with acute fever (Saha et al., 2023) . Although the ESR is not a specific parameter for dengue fever, its results can be used to support the differential diagnosis, especially in endemic areas where other infectious diseases are also common.

6. Plasma and Blood Chemistry Tests

In addition to basic hematological parameters, blood biochemistry tests also provide important information about the physiological status of dengue patients. In severe cases of dengue fever, plasma leakage occurs, characterized by decreased albumin levels (hypoalbuminemia) and increased liver enzymes such as AST (aspartate aminotransferase) and ALT (alanine aminotransferase). Elevated liver enzymes indicate impaired hepatocellular function due to dengue virus replication in liver tissue (Asra et al., 2025). In addition, some patients also exhibit hyponatremia (decreased serum sodium levels), which results from fluid loss through plasma leakage and impaired antidiuretic hormone regulation. These test results are important in assessing body fluid balance and determining intravenous fluid therapy strategies.

Clinical Implications of Hematology Tests

Interpreting routine blood test results has significant clinical implications for the management of dengue patients. For example, the combination of thrombocytopenia and an elevated hematocrit is used as an indicator of a patient entering the critical phase and forms the basis for determining fluid management. Meanwhile, leukopenia and relative lymphocytosis are typical signs of ongoing viral infection. Furthermore, hematology tests can also help assess a patient's prognosis. A rapid decrease in platelets and a sharp increase in hematocrit are often associated with a high risk of dengue shock. Conversely, a rebound in platelets and a normalization of hematocrit indicate the recovery phase (Lancet et al., 2022). Thus, hematology

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tests serve not only for diagnosis but also as a tool for monitoring disease dynamics and the effectiveness of therapy. Therefore, serial monitoring of platelet, hematocrit, and leukocyte values every 24 hours is highly recommended during the treatment period of DHF patients, especially in regional hospitals with basic laboratory facilities (Sabottke & Spieler, 2020).

Serological and Molecular Testing

Serological and molecular testing play a crucial role in the diagnosis of Dengue Hemorrhagic Fever (DHF) because they can detect the presence of the dengue virus and the body's immune response to infection with a high degree of accuracy. Given that the clinical symptoms of DHF are often non-specific and resemble other viral infections such as chikungunya, Zika, or typhus, laboratory detection is key to establishing an accurate diagnosis. Serological testing aims to detect antibodies or antigens produced by the body in response to dengue virus infection, while molecular testing focuses on directly identifying the virus's genetic material using nucleic acid-based technology such as RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction) (Lancet et al., 2022).

1. Serological Testing

Serological testing is a commonly used method in the diagnosis of DHF because it can detect the presence of IgM and IgG antibodies to the dengue virus, as well as viral antigens such as NS1. This test can be performed in various healthcare facilities with relatively simple equipment. Serology plays a significant role in confirming the diagnosis, especially during the secondary infection phase, when specific antibodies to dengue have already developed.

a. Detection of IgM and IgG Antibodies

IgM and IgG antibody tests are performed to assess the body's immune response to dengue virus infection. IgM antibodies typically appear in the blood 3–5 days after symptom onset and peak in the second week, then disappear after 2–3 months. Meanwhile, IgG antibodies begin to be detected on the 7th day and can persist for years (Hunsperger et al., 2020). The presence of IgM indicates an acute or primary infection, while high IgG levels indicate a secondary infection or prior exposure to the dengue virus.

According to (Cristina, 2021), interpreting serology results is crucial for determining the phase of infection. If only IgM is detected, this indicates a primary infection; if both IgM and IgG are present, it indicates a secondary infection. In a clinical context, secondary infections carry a higher risk of complications such as plasma leakage and dengue shock syndrome due to cross-immune reactions (antibody-dependent enhancement). Although IgM/IgG testing is relatively easy and inexpensive, this method has limitations, particularly in the early stages of infection when antibodies have not yet developed significantly. False-negative results often occur if samples are taken before day 3 after symptom onset. Furthermore, cross-reactivity between dengue virus and other flaviviruses, such as Zika and West Nile, can lead to false-positive results (Madere et al., 2025). Therefore, serological testing is often combined with NS1 antigen testing or RT-PCR to improve diagnostic accuracy.

b. NS1 Antigen Detection

NS1 antigen (Nonstructural Protein 1) is a protein produced by the dengue virus during replication in the host. This protein is released into the bloodstream from the first day of infection and can be detected up to day 9 (Datta & Mukherjee, 2023). Therefore, NS1 testing is a valuable early detection tool, especially during the viremia phase, before IgM antibodies are formed. NS1 testing is typically performed using an Enzyme-Linked Immunosorbent Assay (ELISA) or rapid diagnostic test (RDT). According to research by (Luh et al., 2022), the sensitivity of NS1 testing reaches 80–90% in the first 3 days after symptom onset, decreasing as antibodies begin to form immune complexes with the NS1 antigen.

The NS1 test also has the advantage of being able to differentiate dengue infection from other diseases with similar symptoms. However, the NS1 test also has limitations. In secondary infections, NS1 antigen levels are often lower due to the more rapid formation of antigen-antibody complexes, thus reducing the test's sensitivity (Raafat et al., 2019).

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Therefore, the (Lancet et al., 2022) recommends a combination of NS1 testing and IgM/IgG antibody detection for optimal diagnostic results in both primary and secondary infections.

2. Molecular Testing

Molecular testing is the most sensitive and specific method for diagnosing dengue fever because it can directly detect dengue virus RNA. This method not only confirms the presence of the virus but also allows for serotype identification (DEN-1 to DEN-4), which is important for epidemiological monitoring and vaccine development.

a. Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR)

RT-PCR is a molecular diagnostic method used to detect dengue virus RNA in the early stages of infection, even before antibodies are formed. The basic principle of RT-PCR is to convert viral RNA into complementary DNA (cDNA) using the reverse transcriptase enzyme, then amplify it through a PCR reaction for detection (Valeria, 2020). The advantage of RT-PCR lies in its high sensitivity and ability to differentiate between the four dengue virus serotypes. This is crucial because serotype variation affects disease severity and the risk of secondary infections. A study by (Sabottke & Spieler, 2020) showed that RT-PCR can detect viral RNA up to 1–2 days after infection, with an accuracy of over 95%. However, the main obstacles to this method are its high cost, the need for sophisticated equipment, and trained laboratory personnel. Therefore, its implementation is limited to reference laboratories and research centers. Furthermore, viral RNA has low stability, requiring careful storage and transportation of samples to avoid compromising the accuracy of the results (Kabir, 2025).

b. Real-Time RT-PCR (qRT-PCR) and Isothermal Amplification

- Advances in molecular technology have given rise to real-time RT-PCR (qRT-PCR) methods that allow for rapid quantification of viral RNA. Using fluorescent dyes, qRT-PCR not only detects the presence of the virus but also quantifies the viral load in a patient's blood. This information is crucial in assessing the severity of the infection and the risk of complications (Tj et al., 2020).
- Furthermore, isothermal amplification methods such as Loop-Mediated Isothermal Amplification (LAMP) are being developed as an alternative to RT-PCR because they do not require expensive equipment and can be performed in healthcare facilities with limited resources. A study by Chen et al. (2022) showed that the LAMP method has sensitivity close to that of RT-PCR and a shorter test time (around 30–60 minutes).

3. Combination of Serological and Molecular Testing

To obtain comprehensive diagnostic results, the (Sabottke & Spieler, 2020) recommends a combined approach between serological (IgM/IgG or NS1) and molecular (RT-PCR) testing. This combination offers diagnostic advantages across various disease phases—NS1 and RT-PCR for the acute phase (days 1–5) and IgM/IgG for the convalescent phase (day 6 and above). For example, in a study by Santiago et al. (2021), the sensitivity of the combination of NS1 and RT-PCR reached 97%, significantly higher than using either method alone. Furthermore, the combination of methods helps reduce the risk of false-negative results due to inappropriate sampling timing.

Clinical and Epidemiological Implications

Serological and molecular testing serve not only in clinical diagnosis but also in monitoring disease spread in the community. Serotype identification through RT-PCR helps health authorities determine endemic areas and the patterns of transmission between different serotypes. This is important because secondary infections with different serotypes often lead to more severe forms of dengue fever due to the phenomenon of antibody-dependent enhancement (ADE) (Valeria, 2020). Furthermore, the use of molecular testing in surveillance also plays a role in vaccine development and evaluating the effectiveness of prevention programs. For example, early detection of the dominant serotype in a region can help local governments prioritize public health interventions.

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Clinical Implications of Dengue Hemorrhagic Fever Laboratory Tests

Laboratory tests in Dengue Hemorrhagic Fever (DHF) patients are crucial clinically, not only for establishing a diagnosis but also for determining prognosis, monitoring disease progression, and guiding appropriate therapeutic decisions. Because the clinical manifestations of DHF can vary from mild to severe, laboratory test results serve as objective indicators that assist medical personnel in assessing the severity of the infection, the stage of the disease, and the potential for complications such as plasma leakage, severe bleeding, and dengue shock syndrome (DSS) (Version, 2022).

One of the most clinically significant tests is the platelet count. Thrombocytopenia, a decrease in the platelet count below 100,000/µL, is a key characteristic in DHF patients. This condition generally begins to appear on days 3 to 7 after fever onset and is an indicator of bleeding risk (Datu, 2023). A decrease in platelet count below 50,000/µL indicates a critical phase and requires intensive monitoring to prevent spontaneous bleeding, especially in the gastrointestinal tract or vital organs. Therefore, regular platelet counts are crucial for determining the need for hospitalization and evaluating the success of supportive therapy.

In addition to platelets, hematocrit (Hct) measurements also have high prognostic value. A hematocrit increase of ≥20% from baseline indicates plasma leakage, a hallmark of severe dengue fever that can lead to hypovolemia and shock (Perez et al., 2021). Daily hematocrit monitoring helps medical personnel accurately determine the need for intravenous fluids. An increase in hematocrit accompanied by a decrease in platelets is a powerful diagnostic combination for detecting the critical phase of dengue fever (Lancet et al., 2022). Conversely, a sudden decrease in hematocrit levels may indicate massive bleeding that requires immediate intervention, such as a blood transfusion.

Leukocyte count and leukocyte differential also provide important information regarding the disease phase. In dengue fever, leukopenia (leukocyte count <5,000/µL) is a typical finding reflecting bone marrow suppression by the dengue virus (Singh et al., 2020). The proportion of lymphocytes is relatively increased, and peripheral blood smears often reveal atypical lymphocytes (reactive lymphocytes), which are an immune response to viral infection. These changes can help differentiate dengue fever from bacterial infections such as typhus or leptospirosis, which typically exhibit leukocytosis. Therefore, a leukocyte count plays a role in a more accurate differential diagnosis.

In addition to hematological parameters, blood biochemical tests also have important clinical implications. Elevated levels of liver enzymes such as AST (aspartate aminotransferase) and ALT (alanine aminotransferase) indicate liver involvement due to dengue virus infection (Suwarto, 2023). A higher AST elevation than ALT is often found, reflecting damage to muscle tissue in addition to the liver. Elevated albumin levels and decreased total protein can be signs of severe plasma leakage. On the other hand, Erythrocyte Sedimentation Rate (ESR) testing is usually not significantly elevated in dengue fever, unlike bacterial infections, and therefore can aid in clinical differential diagnosis (Kusumawati et al., n.d.).

Laboratory test results also have direct implications for the management of dengue patients. Decreased platelets and increased hematocrit are important guidelines for administering intravenous fluids to prevent hypovolemic shock. Leukocyte monitoring helps avoid unnecessary antibiotic use, while biochemical results, such as elevated liver enzymes, can provide a basis for monitoring organ function during treatment. In clinical practice, the combination of laboratory results and clinical assessment provides a comprehensive picture of the patient's status, minimizes the risk of complications, and increases the effectiveness of therapy (Luh et al., 2022).

CONCLUSION

The diagnosis of dengue hemorrhagic fever (DHF) relies heavily on accurate laboratory tests, including the detection of antigens, antibodies, and viral genetic material. Tests such as NS1 antigen, IgM/IgG serology, and RT-PCR play a crucial role at every stage of the disease, with

combinations of methods proven to increase diagnostic sensitivity and specificity. However, challenges such as limited resources, time, cost, and varying laboratory capabilities remain barriers to optimal implementation at various levels of health care. Strengthening laboratory capacity, standardizing methods, and implementing combination tests are key to improving the accuracy of dengue diagnosis in Indonesia. This approach allows for more effective and efficient early detection, management, and control of dengue outbreaks, thus positively impacting morbidity and mortality from the disease.

AUTHOR'S DECLARATION

Authors' contributions and responsibilities

PRS: Initial conceptualization and general supervision of the manuscript.
MPP: Literature search, article selection, drafting of the main manuscript, content analysis, and final revision and editing.
MNN: Technical support and preparation of the methodology section.
IRA: Collection of supporting literature.
KAM: Additional supervision and drafting of the introduction section.
SAZ: Preparation of additional theoretical review sections

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Availability of data and materials

All data and supporting materials for this study are available and can be requested directly from the corresponding author.

Competing interests

The authors declare no competing interests.

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