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# Histopathology of Organ Tissues in Dengue Fever Patients: A Narrative Review

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**KEYWORDS**
Histopathology; Dengue hemorrhagic fever; organ tissues

**ABSTRACT**
Dengue hemorrhagic fever is one of the tropical diseases that remains a global public health problem. This is closely related to the environmental conditions that support the life cycle of the *Aedes* species mosquito, which is the vector of its spread. Laboratory testing to support diagnosis is generally performed by examining viral or serological components. The technique is limited to the acute phase, so the role of histopathological aspects that explain changes in tissue structure in organs is significant. The histopathology reports of dengue hemorrhagic fever patients in this literature review will be summarized so that they can be used as a reference source for medical laboratory technology students, strengthening understanding of the tissue pathology of dengue virus infection. A total of ±126 million academic articles were initially found, which were reduced to the 50 papers most relevant to the research question. Seven articles met the criteria. Post-infectious organ tissue in dengue hemorrhagic fever patients shows various conditions such as necrosis, edema, hemorrhage, vascular congestion in various organs; infiltration of inflammatory cells; viral replication characterized by the expression of dengue virus antigens in various cells; as well as the expression of chemokines and cytokines.



## Introduction

Dengue Hemorrhagic Fever (DHF) is one of the tropical diseases that remains a common global public health problem. This is closely related to the environmental conditions that support the life cycle of *Aedes* mosquitoes, which are the vectors of its spread (Bhatt et al., 2013) (Oliveira et al., 2022). Histopathological analysis reports on various organs are essential to narrow the gap in understanding tissue structure in various organs due to infection. Dengue is caused by dengue virus infection (DENV), which is an RNA-positive virus belonging to the *Flavivirus* family. DENV encases a spherical virion with surface proteins arranged in icosahedral symmetry (Guzman et al., 2016 ; Tuiskunen Bäck et al, 2013). DENV has a genome that is about 11 kb long, synthesizing three structural proteins consisting of the capsid, membrane, and envelope that make up the viral particle part, as well as seven non-structural proteins consisting of NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 that aid in replication (Perera and Kuhn, 2008 ; Sinha et al., 2024). Based on the

type of amino acid, there are four different DENV serotypes, including DENV1, DENV2, DENV3, and DENV4, which have been reported (Thomas et al, 2014 ; Dhole et al., 2024).

Laboratory testing to support the diagnosis of dengue is generally done by direct examination to detect viral components, such as NS1, or indirectly by serology to detect specific antibodies to DENV. The technique is considered effective in the acute phase but limited in the advanced phase. Here, the role of histopathological aspects that explain changes in tissue structure in organs becomes significant, especially in post-mortem studies (Thomas et al., 2025 ; Huits et al., 2017). The variation in tissue damage caused by the virus that causes dengue is the basis for the importance of a literature review on the histopathological picture of dengue patients. The histopathology report of dengue patients will be summarized so that it can be used as a reference source for medical laboratory technology students, strengthen understanding of tropical infectious tissue pathology, and support the development of procedures in post-analytical laboratories.

This narrative study presents novelty by synthesizing histopathological findings from various organs of dengue patients, including the liver, lungs, spleen, kidneys, heart, and brain, and explores the role of inflammatory markers such as cytokines and chemokines in mediating tissue damage. The goal is to identify patterns of organ damage, strengthen understanding of the pathology of DENV infection, and evaluate potential histopathological markers as support for diagnosis and prognosis. The benefits of this research include improved diagnostic accuracy, the development of more precise therapeutic strategies, as well as the provision of comprehensive references for students, researchers, and practitioners in the fields of pathology and tropical medicine. Thus, this review is expected to contribute significantly to the handling and research of dengue in the future.

## Materials and Methods

This literature review was conducted by filtering published scientific articles based on several screening criteria: laboratory confirmation and histopathology—whether the study included laboratory-confirmed dengue cases and tissue histopathological examinations; human tissue sources—whether the study examined human tissue samples (post-mortem or biopsy); research design—whether the study was original research (case report, case series, observational study) or a systematic review/meta-analysis; microscopic examination—whether the study included microscopic tissue examination beyond blood transfusions; research subject—whether human subjects were examined (excluding animal or tissue culture studies); and type of analysis—whether histopathological examination was performed (not limited to clinical symptoms or molecular/genetic analysis).

The article search used the research question: "What is the histopathology of the organ tissues of dengue hemorrhagic fever patients in the tropics from 2014 to 2024?" Semantic Scholar initially yielded approximately 126 million academic articles, which were narrowed down to the 50 most relevant papers. Seven articles met the inclusion criteria and were extracted for analysis based on study design, sample characteristics, organ-specific histopathological changes, viral replication and detection, and markers of inflammation and cellular response.

The analysis was qualitative, synthesizing findings to identify patterns of organ damage and their relationship with the immune response. Data were presented using comparison tables (Tables 1, 2, and 3) and diagrams (Figure 1) for ease of interpretation. Limitations included the small number of studies and methodological variations, which may affect the generalizability of the results.

## Results and Discussions

**Examination of the patient's organ tissue**

The diagnosis of dengue is generally supported by serological tests and *real Time-Polymerase Chain Reaction* (RT-PCR) tests using blood samples. However, under certain conditions tissue samples are required to confirm a case of dengue, especially in dengue samples *post-mortem*. Autopsy procedures sometimes become mandatory to classify diagnoses that may have epidemiological consequences. In addition, detecting the presence of viral antigens in tissue lesions through immunohistochemistry is also the right choice when biomolecular examination with RT-PCR is inadequate (Kanamura et al., 2022). Based on the results of the extraction of relevant publication data, information on the examination of tissue samples from various organs with different percentages was obtained (Figure 1). The percentage of tissue sample examination in order from the most commonly used organs, namely the liver, lungs and spleen, kidneys, heart, and brain.

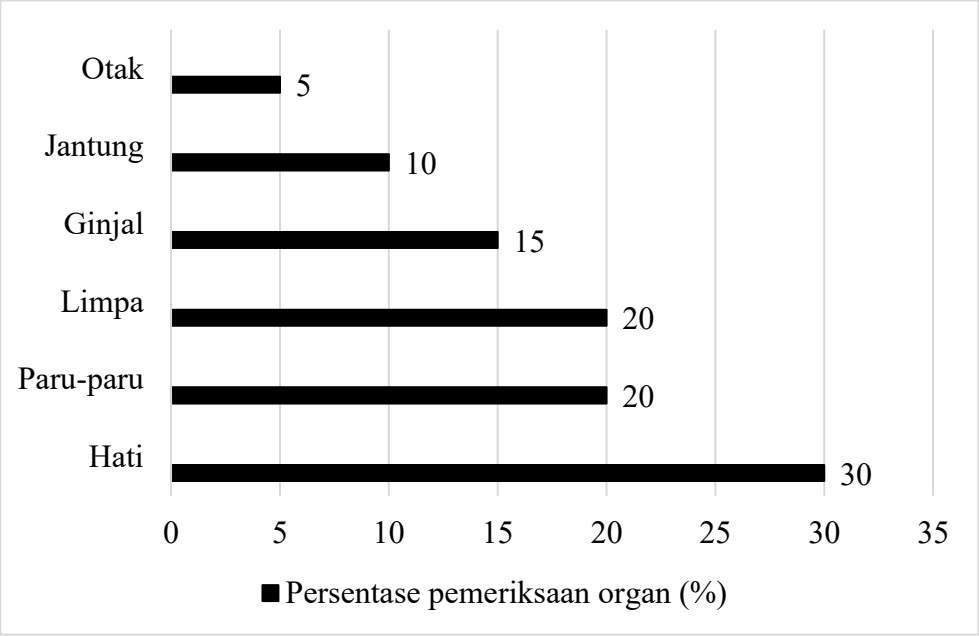


**Figure 1. Examination of the patient's organ tissue**

Source: Data compiled from the study Rivera et al. (2023), Oliveira et al. (2022), Kanamura et al. (2022), Póvoa et al. (2014, 2016), dan Aye et al. (2014)

Addressing concerns about the gap in understanding of structural changes due to DENV infection, this literature review also summarizes information on studies reporting the results of tissue sample examination of various organs (Fig. 1). Liver damage is one of the main symptoms of severe dengue fever cases. The report shows (Fig. 2) that DENV infection can cause significant damage to liver cells (Aye et al., 2014). Further, fatal cases of dengue have shown signs of liver damage, such as mononuclear cell infiltration and mitochondrial swelling, the presence of DENV antigens in hepatocytes and surrounding necrotic areas (Zellweger et al., 2010) (Póvoa et al., 2014) (Póvoa et al., 2016) (Rivera et al., 2023)(Dhole et al., 2024), the condition is accompanied by impaired liver architecture and extravasation of red blood cells conjugated with reticular damage (Kularatne et al., 2014). So it is not surprising that in our tracing it was found that liver tissue is commonly used to confirm the screening of dengue.

Published scientific studies have also tried to reveal the presence of DENV in various organs. DENV infectious virions can even be isolated from various cells derived from the kidneys, lungs, heart, spleen and brain (Balsitis et al., 2009) (Dhole et al., 2024) (Kanamura et al., 2022) (Aye et al., 2014) (L. de L. S. Oliveira et al., 2022) (Fig. 2). Based on our findings, it is known that the tissue condition of the lung organs after DENV infection is loss of alveolar septa integrity, necrosis, edema, hemorrhage, hyaluronic membrane formation, mononuclear cell infiltration, and alveolar macrophage hyperplasia (Póvoa et al., 2014)(Póvoa et al., 2016) (Rivera et al., 2023)(E. R. A. Oliveira et al., 2017). In addition, several publications also report on the condition of spleen organ tissue after DENV infection with lymphoid hyperplasia, lymphoid follicle atrophy, central germ damage, lymphoplasmic infiltration, conesti, varcular, and perifollicular reactivity, as well as severe parenchymal and circulatory dysfunction (Rivera et al., 2023) (Kanamura et al., 2022) (Póvoa et al., 2014) (Aye et al., 2014) (Table 2).

**Table 1. Data based on study design and sample characteristics**

| Studies | Study Design | Geographic location of the sample | Sample | Organs examined |
|---|---|---|---|---|
| Rivera *et al.,* (2023) | Autopsy/*Post-mortem*, histopathology, immunohistochemistry, RT-PCR | Unspecified (tropical) | 97 cases of dengue fever | Liver, spleen, kidneys, lungs, brain, heart |
| Oliveira *et al.,* (2022) | Otopsi/*Post-mortem*, histopatologi, imunohistokimia | Unspecified (tropical) | 3 cases of dengue fever in children | Kidney |
| Kanamura *et al.,* (2022) | Otopsi/*Post-mortem*, histopatologi, imunohistokimia | Brazil | 33 cases of dengue fever (20 liver samples, 13 spleen samples) | Liver, spleen |
| Oliveira *et al.,* (2017) | Otopsi/*Post-mortem*, histopatologi, imunohistokimia, Hybridization *in Situ* | Brazil | Not specified | Liver, lungs, heart |
| Povoa *et al.,* (2016) | Otopsi/*Post-mortem*, histopatologi, imunohistokimia, hibridisasi *in situ* | Brazil | 4 cases of dengue fever, 4 controls | Liver, lungs, kidneys |
| Povoa *et al.,* (2014) | Otopsi/*Post-mortem*, histopatologi, imunohistokimia, hibridisasi *in situ* | Brazil | 4 cases of dengue fever, 4 controls | Liver, lungs, heart, kidneys, spleen |
| Aye *et al.,* (2014) | Autopsy/*Post-mortem*, histopathology | Myanmar | 13 cases of dengue fever in children | Liver, spleen |

*Source: Data Processed*

Publications on changes in the tissue structure of organs such as kidneys, heart, and brain after DENV infection have also been reported, including tubule cell necrosis, interstitial nephritis, thrombotic microangiopathy, vascular congestion, edema in the medulla vacuolar degeneration, as well as infiltration of inflammatory cells in the cortical and medulla regions in renal organ samples (Rivera et al., 2023) (L. de L. S. Oliveira et al., 2022) (Póvoa et al., 2014) (Póvoa et al., 2016). Changes in parenchyma and circulation, myocarditis with degradation of heart fibers, loss of striation and nucleus, interstitial edema, apoptosis of heart fibers, pericardial hemorrhage, and infiltration of inflammatory cells in samples of heart organs (Rivera et al., 2023) (E. R. A. Oliveira et al., 2017)(Póvoa et al., 2014). Meanwhile, in brain samples, edema and signs of hypoxia were found (Rivera et al., 2023) (Table 2).

**Table 2. Histopathological data of dengue patients' organs**

| Studies | Liver | Lungs | Spleen | Kidney | Heart | Brain |
|---|---|---|---|---|---|---|
| Rivera *et al.,* (2023) | Hepatocyte necrosis, macro and microvascular stetosis in hepatocytes, hemorrhage, mononuclear infiltrates in the portal area, Kupffer cell hyperplasia | Edema, hemorrhagia, membran hyalin | Lymphoid hyperplasia, lymphoplasmastic infiltrate, vascular congestion | Tubule cell necrosis, Interstitial nephritis, thrombotic microangiopathy | Pericardial hemorrhages, inflammatory infiltrate | Oedema, hypoxia |
| Oliveira *et al.,* (2022) | Unresearched | Unresearched | Unresearched | Tissue necrosis, inflammatory infiltrate, vascular congestion, edema in the medulla, vacuolar degeneration | Unresearched | Unresearched |
| Kanamura *et al.,* (2022) | Nekrosis ringan, apoptosis hepatosit | Unresearched | Perifollicular reactivity | Unresearched | Unresearched | Unresearched |
| Oliveira *et al.,* (2017) | Necrosis of the sinusoid area, swollen hepatocytes, changes in Kupffer cells | Loss of alveolar septa integrity, necrosis, changes in alveolar macrophages | Unresearched | Unresearched | Destruction of cardiomyocytes, lymphocytes/ macrophages infiltrates | Unresearched |
| Povoa *et al.,* (2016) | Mononuclear infilrats that spread around the portal space | Bleeding, edema, mononuclear infiltration | Unresearched | Mononuclear infiltrates in the cortical and medulla regions | Unresearched | Unresearched |

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| Studies | Liver | Lungs | Spleen | Kidney | Heart | Brain |
|---|---|---|---|---|---|---|
| Povoa *et al.,* (2014) | Circulatory and parenchyma damage, diffuse macro/micro steatosis, mononuclear infiltrates | Thickening of the septum, mononuclear infiltrate, alveolar macrophage hyperplasia, formation of hyaline membranes | Severe dysfunction of the parenchyma and circulation, atrophy of lymphoid follicles, central germinal damage | Damage to the parenchyma and circulation, acute tubular necrosis | Changes in the parenchyma and circulation, myocarditis with degradation of heart fibers, loss of striation and nucleus, interstitial edema, apoptosis of heart fibers | Unresearched |
| Aye *et al.,* (2014) | DENV infection in hepatocytes and Kupffer cells, complement deposition | Unresearched | A noticeable reduction in the number of lymphocytes replaced by eosinophilic deposits | Unresearched | Unresearched | Unresearched |

*Source: Synthesis of findings*

**Cellular activity and markers of inflammation**

Multiorgan pathologies due to dengue infection are inevitable. Most morphological changes are related to vascular disorders (Rivera et al., 2023) (L. de L. S. Oliveira et al., 2022) (E. R. A. Oliveira et al., 2017) (Póvoa et al., 2014), which is a typical characteristic of the disease as a result of increased vascular permeability after DENV infection (Póvoa et al., 2016), However, it should be emphasized that there is no relationship between the tissue changes that occur or the findings of viral antigens in the organ and the location of the virus, nor the serotype that infects, as well as the process of replication. Dengue is considered a disease involving many organs, the results of which are not related to the serotype of the virus that infects (Rivera et al., 2023).

DENV antigens are important to be traced for as an indication of DENV replication (Swarbrick et al., 2017). Latest report by Rivera *et al.,* (2023) suggested that DENV antigens are detected in various cells in infected organ tissues such as in sinusoidal cells in the liver; white pulp cells in the spleen; proximal and distal contorted tubules and glomerulus in the kidneys; infiltrate cells, alveolar septum in the lungs; heart muscle fibers; as well as vascular cells and cerebral cortex (Rivera et al., 2023). Meanwhile, a few years ago, it was also specifically reported by Povoa *et al.,* (2014) that DENV3 antigen was observed in hepatocytes and Kupffer cells in the liver; alveolar macrophages, type II pneumocytes, and endothelium in the lungs; myocardial fibers in the perinucleus region, monocytes/macrophages and endothelium in the heart; macrophages and monocytes circulate in the blood vessels in the kidneys; and circulating macrophages located in the red pulp of the spleen (Póvoa et al., 2014).

Oliveira Report *et al.,* (2022) stated that after DENV infection, infitrat cells characterized by antigen expression high levels of macrophages, CD68-positive T cells, CD8-positive T cells, and CD56-Positive cells detected in the kidneys. At the same time, the expression of NS3 DENV protein was also observed in mesangial cells in the cortex region, and endothelial cells and monocytes/macrophages in the medulla region. While, Express *interferon gamma* (INF-γ) dan *tumor necrosis factor alpha* (TNF-α) as a cytokine that plays an important role in the induction and

modulation of immune responses, both are detected in the vicinity of the collection tubules in the medulla region and in macrophages in the cortex region respectively (L. de L. S. Oliveira et al., 2022) (Póvoa et al., 2016). Kanamura *et al.,* (2022) has also investigated the expression of anti-protein NS1 DENV in some cells such as Kupffer cells, cells near vascular endothelial in the liver; Perifollicular lymphoid and macrophage cells in the spleen (Kanamura et al., 2022).

Povoa Research *et al.,* (2016) reported that in the examination of organ samples of fatal dengue cases infected with Brazilian DENV3, it was found that there was an increase in the number of CCL5-producing cells. CCL5 or known as RANTES is a chemokine that is closely related to viral infections. Excessive secretion of CCL5 can cause plasma leakage and trigger infitrates to various feriferous organs, thus potentially mediating the occurrence of an inflammatory response (Póvoa et al., 2016) (Glass et al., 2003). The activity of cytokines and chemokines will increase vascular permeability around the area of infection so that the infiltration of inflammatory cells increases which can further aggravate injury to the feriferous organs.

Oliveira Research *et al.,* (2017) stated that in fatal cases of dengue infection, cytokine expression such as *Protein high-mobility group box 1* (HMGB1) excessive cytoplasm of several monocytes found in vascular and organ tissues such as in the lungs and heart; edges of heart fibers; Kupffer cells in the liver; and macrophage vesicles of various organs. Of course, this indicates an activity that allows the release of HMGB1 into the extracellular environment (E. R. A. Oliveira et al., 2017). HMGB1 serves as *damage-associated molecular patterns* (DAMPs) when they are outside the cell which plays a role in the process of inducing inflammation (Lu et al., 2014)(Kang et al., 2014). Inflammation triggered by HMGB1 activity is alleged to have contributed to increased organ damage (E. R. A. Oliveira et al., 2017).

**Table 3. Cellular and cytokine expression**

| Study | Mobile expression | Virus replication | Cytokines |
|---|---|---|---|
| Rivera *et al.,* (2023) | DENV antigen is detected in sinusoidal cells in the liver; white pulp cells in the spleen; proximal and distal contortus tubules and glomerulus in the kidneys; infiltrate cells; alveolar septum in the lungs; heart muscle fibers; and vascular cells and cerebral cortex | Not mentioned | Not mentioned |
| Oliveira *et al.,* (2022) | High expression of macrophages; CD68-positive T cells; CD8-positive T cells; CD56-Positive cells | The expression of the NS3 DENV protein is detected in mesangial cells in the cortex region as well as in endothelial cells; monocytes/macrophages in the medullary region of the kidneys | INF-γ expression is detected around the collection tubules in the medulla region; TNF-α detected in macrophages in cortex regions |
| Kanamura *et al.,* (2022) | Not mentioned | The anti-protein expression of NS1 DENV was detected in Kupffer cells; cells near vascular endothelial; cytoplasm of reactive lymphoid cells and perifollicular macrophages | Not mentioned |

| Study | Mobile expression | Virus replication | Cytokines |
|---|---|---|---|
| Oliveira *et al.,* (2017) | Not mentioned | Not mentioned | Expression of HMGB1 in the cytoplasm of some monocytes present in the vascular; edges of heart fibers; Kupffer cells in the liver; vesicles of macrophages and monocytes in the lungs |
| Povoa *et al.,* (2016) | Not mentioned | Not mentioned | INF-γ expression; TNF-α; increased number of CCL5 or RANTES producing cells |
| Povoa *et al.,* (2014) | DENV3 antigens are detected in hepatocytes and Kupffer cells in the liver; alveolar macrophages; type II pneumocytes and endothelium in the lungs; myocardial fibers in the perinucleus region; monocytes/macrophages and endothelium in the heart; macrophages and monocytes circulate in the blood vessels in the kidneys; circulating macrophages located in the red pulp of the spleen | Expression of the NS3 DENV protein is detected in hepatocytes and Kupffer cells and endothelials in the liver; alveolar macrophages, type II pneumocytes, and endothelium in the lungs; endothelium and heart fibers; circulating macrophages located in the red pulp of the spleen | Not mentioned |
| Aye *et al.,* (2014) | Not mentioned | Not mentioned | Not mentioned |

*Source: Data analysis*

## Conclusion

Post-DENV infection organ tissues in dengue patients, particularly in fatal cases, exhibit a range of pathological conditions including necrosis, edema, hemorrhage, and vascular congestion across multiple organs, alongside infiltration of inflammatory cells and viral replication marked by the presence of DENV antigens in various cells, as well as elevated expression of inflammatory chemokines and cytokines. This literature review synthesizes these multiorgan tissue changes, cellular activities, and inflammatory marker expressions, providing a valuable reference to enhance understanding of the tissue pathology of DENV infection. Future research should focus on longitudinal studies correlating specific histopathological changes with clinical outcomes to better inform prognosis and targeted therapeutic strategies.

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