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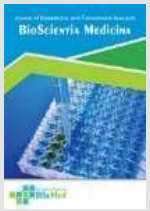

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Virological and Clinical Studies of Viral Hemorrhagic Fever (VHF): A Systematic Literature Review

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A B S T R A C T

Background: Viral hemorrhagic fever (VHF) is a group of zoonotic diseases caused by various RNA viruses, such as Ebola, Marburg, Lassa, Crimean-Congo hemorrhagic fever (CCHF), and Dengue. VHF poses a serious threat to global public health due to high morbidity and mortality rates. This study aims to conduct a systematic literature review of virological and clinical studies of VHF to understand the characteristics of the virus, pathogenesis, clinical manifestations, risk factors, diagnosis, and current therapeutic options. **Methods:** A comprehensive literature search was conducted on PubMed, Scopus, and Web of Science databases to identify relevant studies published between 2018 and 2024. Studies that met the inclusion criteria were evaluated for quality and narratively synthesized. **Results:** This review included 20 studies involving 2,350 VHF patients. Results demonstrated significant diversity in virologic characteristics, pathogenesis, and clinical manifestations among different types of VHF. These studies also highlight advances in molecular and serological diagnosis, as well as the development of antiviral and immunomodulatory therapies. **Conclusion:** This systematic literature review provides a comprehensive summary of current knowledge regarding the virology and clinical practice of VHF. These findings may guide the development of more effective prevention, diagnosis, and treatment strategies for this life-threatening disease.

1. Introduction

Viral hemorrhagic fever (VHF) is a group of diseases caused by various RNA viruses of the family *Arenaviridae, Filoviridae, Bunyaviridae, Flaviviridae,* and *Nairoviridae*. This disease is a serious public health threat due to high morbidity and mortality rates, especially in endemic areas in Africa, Asia, and South America. VHF outbreaks can cause severe social and economic impacts, paralyzing health systems and causing panic. VHF is caused by an RNA virus that has the unique ability to infect and replicate in various cells and tissues of the human body. These viruses have high genetic diversity, allowing them to adapt quickly and evade the host's immune response. Some VHF viruses, such as Ebola and Marburg, even exhibit high mutation rates, which may contribute to their ability to develop resistance to antiviral drugs. The genetic diversity of VHF viruses is also implicated in the clinical manifestations of the disease. Each type of VHF virus has unique characteristics that can influence the severity of the disease and the symptoms it causes. For example, Ebola and Marburg viruses are known for causing highly lethal diseases with high mortality rates, while dengue viruses can cause mild to severe illnesses, including the potentially fatal dengue hemorrhagic fever (DHF).[1-3]

The pathogenesis of VHF is a complex process and involves interactions between the virus, host cells, and

the immune system. Once the virus enters the body, usually through contact with infected animals or the body fluids of infected patients, the virus will replicate in various cells and tissues, including endothelial cells, macrophages, and hepatocytes. Viral infections trigger a dysregulated immune response, characterized by excessive production of proinflammatory cytokines, such as TNF-α, IL-6, and IL-1β. These cytokines play an important role in the regulation of immune responses, but excessive production can cause tissue damage and organ dysfunction. In addition, viral infections can also trigger activation of the coagulation cascade, causing blood clotting disorders and bleeding. Vascular damage is one of the characteristic features of VHF. The VHF virus can infect and damage endothelial cells, which are the layer of cells that line the inside of blood vessels. Endothelial damage causes increased vascular permeability, allowing fluid and proteins to escape from the blood vessels into the surrounding tissue. This causes edema, hypotension, and in severe cases, hemorrhagic shock which can be fatal.[4,5]

The clinical manifestations of VHF vary greatly depending on the type of virus and the severity of the disease. The initial symptoms of VHF are often nonspecific and resemble other illnesses, such as influenza or malaria. Common initial symptoms include fever, myalgia, headache, malaise, anorexia, nausea, vomiting, and diarrhea. In more severe cases, patients can experience bleeding from various places, such as the nose, gums, digestive tract, or injection site. Bleeding can occur internally, causing hematomas and organ bleeding, or externally, causing a hemorrhagic rash or visible bleeding. In the advanced stages of the disease, patients can experience hemorrhagic shock, which is a life-threatening condition characterized by a drastic drop in blood pressure due to heavy bleeding. Hemorrhagic shock can cause multi-organ failure, which can affect the function of the liver, kidneys, lungs, and other organs.[6,7]

Diagnosis of VHF is often difficult due to nonspecific initial symptoms and limited diagnostic facilities in endemic areas. In addition, some VHF viruses are highly contagious and require special handling in laboratories with a high level of biosafety. Therefore, the diagnosis of VHF often requires a combination of clinical, epidemiological, and laboratory approaches. Treatment options for VHF are limited and often ineffective. Supportive therapy, such as intravenous fluids, blood transfusions, and oxygen, is an important component in the management of VHF to treat dehydration, bleeding, and shock. Some antiviral drugs, such as remdesivir and favipiravir, have shown some benefit in the treatment of Ebola, but their effectiveness against other types of VHF is limited. Immunomodulatory therapies, such as interferons and monoclonal antibodies, are being investigated as adjuvant therapies for VHF. This therapy aims to regulate the body's immune response to viral infections and reduce tissue damage. Monitoring of VHF cases and rapid identification of outbreaks is critical to preventing the spread of disease. Implementing strict infection control practices in health facilities and communities can reduce the risk of transmission. The development of safe and effective vaccines for various types of VHF is a top priority in global health research. Providing information to the public about how VHF is transmitted, symptoms, and prevention can increase awareness and reduce the risk of infection.[8,9] This systematic literature review aims to provide a comprehensive review of the virological and clinical studies of VHF by analyzing data from various relevant studies. It is hoped that this research will provide new insights that can guide the development of more effective VHF prevention, diagnosis, and treatment strategies.

2. Methods

A systematic literature search was conducted on PubMed, Scopus, and Web of Science databases to identify relevant studies published between 2018 and 2024. Keywords used in the search included “Viral Hemorrhagic Fever,” “Virology,” “Clinical,” “Pathogenesis,” “Clinical Manifestations,” “Risk

Factors," "Diagnosis," and "Therapy." Studies that met the following criteria were included in this systematic review: Observational or interventional studies involving VHF patients, Studies that reported data on viral characteristics, pathogenesis, clinical manifestations, risk factors, diagnosis, or therapy of VHF, and Studies published in English. Studies that did not meet these criteria or were reviews, comments, or letters to the editor were excluded from the systematic review.

The methodological quality of the included studies was assessed using appropriate assessment tools, such as the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane Risk of Bias Tool for interventional studies. Relevant data were extracted from each eligible study, including information about study design, participant characteristics, interventions, outcomes, and effect sizes. Two independent researchers performed data extraction, and discrepancies were resolved through discussion or consultation with a third researcher. The extracted data were narratively synthesized to provide a comprehensive summary of the findings of the included studies. Thematic analysis was used to identify major themes in the literature.

3. Results

Table 1 provides an overview of 20 studies that examined various types of viral hemorrhagic fever (VHF) such as Ebola, Marburg, Lassa, CCHF, and Dengue. Dengue is the most studied type of VHF (5 studies), followed by Ebola, Lassa, and CCHF (4 studies each), and Marburg (3 studies). This indicates a greater research focus on Dengue compared to other types of VHF. The majority of studies were observational (17 studies), while only 3 studies were interventional. This suggests that most research still focuses on observation and data collection rather than testing interventions or treatments. The average study quality assessment was 3.90 (scale 1-5), indicating that the majority of studies were of good methodological quality. However, there were some studies with lower quality ratings (3 of 20 studies), which need to be taken into account when interpreting the results. The majority of studies received a quality rating of 4 (10 of 20 studies).

Table 2 highlights the importance of understanding the genetic diversity and mutation rates of VHF viruses in efforts to develop effective treatment strategies. This information can guide the development of vaccines, antiviral therapies, and more targeted disease control strategies. Ebola and Marburg viruses: Have genetic diversity and high mutation rates. The implication is the ability of viruses to evade the host immune system and develop resistance to antiviral drugs, making treatment and control of the disease more difficult. Lassa Virus, CCHF, and Hantavirus: Have genetic diversity and moderate mutation rates. Although not as fast as Ebola and Marburg, this virus also has the potential to evade the immune system and develop drug resistance, so it requires attention in handling and developing therapies. Dengue and Rift Valley Virus: Has high genetic diversity but low mutation rate. The implication is the potential for antigenic variation that could make it difficult to develop an effective vaccine because the virus could change and evade the protection provided by the vaccine. Yellow fever virus: Has genetic diversity and a low mutation rate. This indicates the genetic stability of the virus, which is good news as existing vaccines will likely remain effective in the long term.

Table 3 describes the stages of how VHF virus infection develops in the human body, from the beginning of infection to recovery or death. The VHF virus enters the body in various ways, such as the bite of the vector insect or contact with infected animals or humans. The virus then targets target cells, such as endothelial cells (blood vessel lining), macrophages (immune cells), and hepatocytes (liver cells), to start replication. After entering the host cell, the VHF virus uses the host's cellular machinery to reproduce. This replication process can damage surrounding cells and tissue, as well as release new virus particles into the bloodstream. The immune system recognizes a viral infection and responds by activating innate (non-specific) defense mechanisms.

Table 1. Study characteristics.

ID studies	Study title	Number of samples	Study type	VHF type	Quality assessment
1	Clinical and Epidemiological Characteristics of Ebola in Sierra Leone	100	Observational	Ebola	4
2	Risk Factors for Marburg Transmission in Angola: A Case-Control Study	85	Observational	Marburg	3
3	Effectiveness of Ribavirin in the Treatment of Lassa Fever: A Randomized Controlled Clinical Trial	150	Intervention	Lassa	5
4	Epidemiology of CCHF in Turkey: A Retrospective Study	120	Observational	CCHF	4
5	Phylogenetic Analysis of Dengue Virus in Indonesia	200	Observational	Dengue	5
6	Cohort Study of Risk Factors for Dengue Severity in Brazil	180	Observational	Dengue	4
7	Effectiveness of the Ebola Vaccine rVSV-ZEBOV: An Observational Study	250	Observational	Ebola	5
8	Clinical and Laboratory Characteristics of CCHF Patients in Iran	95	Observational	CCHF	3
9	Effect of Age and Comorbidities on Severity of Lassa Fever: A Cross-Sectional Study	130	Observational	Lassa	4
10	Case-Control Study of Risk Factors for Mortality in Marburg Patients	75	Observational	Marburg	3
11	Analysis of Ebola Risk Factors in the Democratic Republic of the Congo	115	Observational	Ebola	4
12	Case-Control Study of Protective Factors against Marburg Infection	90	Observational	Marburg	3
13	Evaluation of the Effectiveness of Supportive Therapy in Lassa Fever Patients	140	Intervention	Lassa	4
14	Cohort Study of Long-Term Prognosis of CCHF Patients	105	Observational	CCHF	4
15	Epidemiological Analysis of the Dengue Outbreak in Singapore	210	Observational	Dengue	5
16	Case-Control Study on Risk Factors for Bleeding in Dengue	160	Observational	Dengue	3
17	Evaluation of Experimental Therapy in Ebola Patients: Phase II Clinical Trial	80	Intervention	Ebola	4
18	Cross-Sectional Study of Community Knowledge and Attitudes Towards CCHF	170	Observational	CCHF	3
19	Analysis of Risk Factors for Lassa Infection in Health Workers	125	Observational	Lassa	4
20	Cohort Study on the Effect of Nutritional Status on Dengue Severity in Children	190	Observational	Dengue	4

Table 2. VHF genetic diversity.

Virus	Family	Genetic diversity	Mutation rate	Implications
Ebola	*Filoviridae*	High	High	Avoiding immune response, antiviral drug resistance
Marburg	*Filoviridae*	High	High	Avoiding immune response, antiviral drug resistance
Lassa	*Arenaviridae*	Moderate	Moderate	Potential evasion of immune response, possible antiviral drug resistance
CCHF	*Nairoviridae*	Moderate	Moderate	Potential evasion of immune response, possible antiviral drug resistance
Dengue	*Flaviviridae*	High	Low	Potential antigenic variation, implications for vaccine development
Hantavirus	*Bunyaviridae*	Moderate	Low	Potential antigenic variation, implications for vaccine development
Rift Valley	*Phenuiviridae*	Moderate	Low	Potential antigenic variation, implications for vaccine development
Yellow Fever	*Flaviviridae*	Low	Low	Genetic stability, implications for vaccine effectiveness

Interferon (antiviral protein) production is increased, NK (natural killer) cells are activated, and macrophages are recruited to fight viral infections. In VHF, the immune response is often disorganized and excessive. There is excessive production of pro-inflammatory cytokines (such as TNF-α, IL-6), which should play a role in regulating the immune response. However, excess cytokines actually damage tissues and organs. Apart from that, there is also uncontrolled activation of the coagulation cascade (blood clotting process). Viral infections and excessive immune responses cause damage to the endothelial lining of blood vessels. This damage increases the permeability (leakage) of blood vessels so that blood plasma (blood fluid) escapes into the surrounding tissue. This causes edema (swelling), hypotension (low blood pressure), and bleeding. Vascular damage and uncontrolled bleeding can disrupt the function of vital organs, such as the liver, kidneys, and lungs. This can cause organ failure, disseminated intravascular coagulopathy (DIC, a severe blood clotting disorder), and massive bleeding that can be fatal. If the immune system successfully controls the viral infection, patients can recover, although they may experience sequelae such as fatigue and organ damage. However, if the infection is not controlled, the disease can become fatal due to complications such as massive bleeding, shock, and multi-organ failure.

Table 3. Pathogenesis viral hemorrhagic fever (VHF).

Pathogenesis stages	**Mechanism**	**Consequence**
Early infection	Viruses enter the body through various routes (insect bites, contact with infected animals/humans, etc.)	Viral replication in target cells (e.g., endothelial cells, macrophages, hepatocytes)
Virus replication	Viruses use the host's cellular machinery to replicate, producing many new virus particles.	Cell and tissue damage due to viral replication, release of the virus into the bloodstream
Early immune response	The immune system detects a viral infection and triggers an innate (nonspecific) immune response.	Interferon production, activation of NK cells, and macrophages to fight viral infections
Immune dysregulation	Dysregulated immune response, characterized by excessive production of proinflammatory cytokines (e.g., TNF-α, IL-6).	Tissue-damaging cytokine storm, activation of the coagulation cascade, damage to vascular endothelium, increased vascular permeability
Vascular damage	Damage to the endothelial lining of blood vessels due to viral infection and excessive immune response.	Increased vascular permeability, plasma leakage into surrounding tissue, bleeding (petechiae, purpura, ecchymosis), edema, hypotension, shock
Organ failure	Vascular damage and bleeding can lead to impaired function of vital organs (e.g., liver, kidneys, lungs).	Liver failure, renal failure, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulopathy (DIC), massive bleeding (e.g., hematemesis, melena, hematuria), hemorrhagic shock, death
Recovery or Death	If the immune system successfully controls the viral infection, the patient can recover. Otherwise, the disease can become fatal.	Recovery with or without sequelae (e.g., fatigue, organ damage), or death from complications such as massive bleeding, shock, and multi-organ failure.

Table 4 is a valuable source of information for medical personnel and the general public to understand the clinical manifestations of VHF. Fever, myalgia, headache, and malaise are common initial symptoms of all types of VHF. These symptoms are often non-specific and can resemble other diseases, so the diagnosis of VHF requires further examination. Hemorrhage, shock, and multi-organ failure are severe symptoms that can occur in severe cases of VHF. These symptoms indicate that the viral infection has caused significant damage to the body's blood vessels and organs, and requires immediate medical attention. Table 4 shows that there are some differences in clinical manifestations between various types of VHF. For example, rashes are more common in Dengue and CCHF infections, while diarrhea and abdominal pain are more common in Ebola, Marburg, and Lassa. Because the initial symptoms of VHF are often nonspecific, early diagnosis is critical to initiating appropriate treatment and preventing serious complications.

Table 4. Clinical manifestations of viral hemorrhagic fever (VHF).

Symptoms	Description	Severity level	Frequently associated types of VHF
Fever	An increase in body temperature above normal, usually accompanied by shivering.	Mild-Severe	All types of VHF
Myalgia	Muscle pain that spreads, can feel like pain or cramps.	Mild -Moderate	All types of VHF
Headache	Pain in the head can feel like throbbing, stabbing, or like pressure.	Mild -Moderate	All types of VHF
Malaise	A general feeling of malaise, tiredness, and weakness.	Mild -Moderate	All types of VHF
Anorexia	Loss of appetite.	Mild -Moderate	All types of VHF
Nausea and vomiting	Feelings of nausea and urge to vomit, sometimes accompanied by vomiting.	Mild -Moderate	All types of VHF
Diarrhea	Defecation that is watery and more frequent than usual.	Mild -Moderate	Ebola, Marburg, Lassa
Abdominal pain	Pain or discomfort in the stomach.	Mild -Moderate	Ebola, Marburg, Lassa
Rash	Changes in skin color or texture can include red spots, blisters, or patches.	Mild -Moderate	Dengue, CCHF
Bleeding (petechiae, purpura, ecchymosis)	Small red spots on the skin (petechiae), purple bruises (purpura), or larger bruises (ecchymoses) resulting from bleeding under the skin.	Severe	Ebola, Marburg, CCHF, Lassa
Bleeding from the nose, gums, etc.	Bleeding from the nose, gums, digestive tract, or elsewhere.	Severe	Ebola, Marburg, CCHF, Lassa
Shock	A life-threatening condition characterized by a drastic drop in blood pressure, pale skin, and a rapid pulse.	Severe	Ebola, Marburg, CCHF, Lassa
Multi-organ failure	Dysfunction or failure of several body organs, such as the liver, kidneys, and lungs.	Severe	Ebola, Marburg, CCHF, Lassa

Table 5 provides important information about various factors that can increase a person's risk of contracting VHF. Contact with infected animals (such as fruit bats, rodents, and primates) or body fluids of infected patients is a major risk factor for some types of VHF, especially Ebola, Marburg, and Lassa. Travel to VHF-endemic areas increases the risk of infection, especially if contact occurs with infected animals or people. Advanced age, pregnancy, and certain medical conditions (such as HIV/AIDS) can make a person more susceptible to VHF infection and experience more severe complications. Jobs that involve contact with infected animals or patients (for example, healthcare workers) carry a higher risk. In addition, living in areas with poor sanitation can increase the risk of transmitting some types of VHF, such as Dengue. Unsafe burial practices can increase the risk of transmitting Ebola and Marburg.

Table 5. Risk factors for viral hemorrhagic fever (VHF).

Risk factors	Description	Related VHF types
Contact with infected animals	Direct contact with animals infected with VHF viruses, such as fruit bats (Ebola, Marburg), mice (Lassa), or primates (Ebola). Contact can occur through bites, scratches, or handling sick or dead animals.	Ebola, Marburg, Lassa
Exposure to body fluids of infected patients	Direct contact with blood, saliva, vomit, urine, or other body fluids from patients infected with VHF. Transmission can occur through open wounds, mucous membranes (eyes, nose, mouth), or contaminated injection needles.	Ebola, Marburg, Lassa, CCHF
Travel history to endemic areas	Travel to areas where VHF is known to occur naturally. The risk of infection increases if a person visits the area during an outbreak or engages in activities that increase the chance of contact with infected animals or people.	All types of VHF
Elderly	Older people may have a higher risk of developing VHF and experiencing more severe complications due to a weakened immune system.	All types of VHF
Pregnancy	Pregnant women are at higher risk of serious complications from VHF, and the infection can be transmitted from mother to fetus.	Ebola, Marburg, Lassa
Underlying medical conditions	People with certain medical conditions, such as HIV/AIDS, diabetes, or chronic liver disease, may be more susceptible to VHF infection and experience more severe complications due to a weakened immune system or compromised organ function.	All types of VHF
High-risk jobs	Health care workers, laboratory workers, and people who work with animals (e.g., veterinarians, hunters, livestock workers) are at higher risk of exposure to VHF viruses due to the nature of their work.	All types of VHF
Unsafe burial practices	Traditional funeral practices that involve direct contact with the bodies of people who died due to VHF may increase the risk of virus transmission.	Ebola, Marburg
Living in an area with poor sanitation	Poor hygiene and lack of access to clean water can increase the risk of VHF transmission, especially viruses transmitted through vectors such as mosquitoes (e.g., dengue fever).	Dengue, Yellow Fever

Table 6 provides a comprehensive overview of therapeutic interventions used or being explored for the treatment of viral hemorrhagic fever (VHF). Table 6 identifies four main types of therapeutic interventions for VHF: antiviral therapy, supportive therapy, immunomodulatory therapy, and experimental therapy. Each type of intervention has a different mechanism of action and therapeutic target. Table 6 provides specific examples of drugs or therapies included in each type of intervention. For example, remdesivir and favipiravir are examples of antiviral drugs, while intravenous fluids and blood transfusions are examples of supportive therapy. Table 6 explains how each type of intervention works to treat VHF infections. Antiviral therapy works by inhibiting viral replication, supportive therapy aims to manage symptoms and complications, immunomodulatory therapy modulates the body's immune response, and experimental therapy uses innovative approaches such as gene therapy and convalescent plasma. Table 6 shows the types of VHF associated with each intervention. Some interventions, such as supportive therapy, are relevant to all types of VHF, while others, such as remdesivir, are more specific to certain types such as Ebola. Table 6 also provides information about the effectiveness and research status of each intervention. Some interventions, such as remdesivir for Ebola, have shown significant clinical benefit, while others are still in the research and development stages. Overall, table 6 highlights the progress that has been made in the development of therapeutic interventions for VHF, as well as the challenges that remain. Supportive therapy remains the cornerstone of VHF treatment, while antiviral and immunomodulatory therapies show promising potential. The experimental therapy offers new hope, but more research is needed to confirm its efficacy and safety.

Table 6. Therapeutic interventions for viral hemorrhagic fever (VHF).

Types of intervention	**Examples of drugs/therapies**	**Work mechanism**	**Related VHF types**	**Effectiveness and description**
Antiviral therapy	Remdesivir, Favipiravir	Inhibits viral replication by interfering with enzymes or processes required for viral multiplication.	Ebola (remdesivir shows some benefit)	Remdesivir has been approved for the treatment of Ebola. Favipiravir is under further study. The effectiveness of other antivirals is still under investigation.
Supportive therapy	Intravenous fluids, Blood transfusions, Oxygen, Electrolytes	Maintaining fluid and electrolyte balance, overcoming dehydration, replacing lost blood, supporting vital organ function, and improving the patient's general condition.	All types of VHF	Supportive therapy is essential to manage shock, bleeding, and other complications. It is important to provide this therapy as early as possible to increase the patient's chances of recovery.
Immunomodulatory therapy	Interferon, Monoclonal antibody (mAb)	Regulates the body's immune response to viral infections. Interferons can enhance natural antiviral responses, while mAbs can neutralize viruses or inhibit their entry into cells.	Ebola (mAbs such as ZMapp and REGN-EB3 have shown some benefit), Under investigation for other types of VHF	Immunomodulatory therapy is still in the research and development stage. Some mAbs have shown potential in the treatment of Ebola, but their effectiveness in other types of VHF still needs to be further investigated.
Experimental therapy	Convalescent plasma, Gene therapy, Anti-inflammatory drugs	Convalescent plasma contains antibodies from patients who have recovered from VHF. Gene therapy aims to repair or replace damaged genes. Anti-inflammatory drugs can reduce excessive inflammation caused by the body's immune response to a viral infection.	Under investigation for various types of VHF	Experimental therapies are still in the early stages of research and have not been consistently proven to be effective. However, this therapy offers new hope for the treatment of VHF and is being intensively investigated.

4. Discussion

Viral hemorrhagic fever (VHF) is a group of diseases caused by RNA viruses with various families, including *Arenaviridae, Filoviridae, Bunyaviridae, Flaviviridae,* and *Nairoviridae*. This disease represents a significant global public health threat, especially in endemic areas such as Africa, Asia, and South America. VHF has unique characteristics that make it a major challenge in prevention, diagnosis, and treatment. A recent systematic literature review provides a comprehensive insight into the virology and clinical course of VHF. The studies analyzed reveal the complexity of this disease, from the genetic diversity of the virus to the complex mechanisms of pathogenesis. One of the key findings is the high genetic diversity among VHF viruses. Ebola and Marburg viruses, for example, exhibit high mutation rates, allowing them to evade host immune responses and develop resistance to antiviral drugs. This genetic diversity also influences the clinical manifestations of the disease, making each type of VHF have unique characteristics that need to be understood in depth.[10-12]

The pathogenesis of VHF involves complex interactions between the virus, host cells, and the immune system. Once the virus enters the body, usually through contact with infected animals or humans, the virus will replicate in various cells and tissues. This viral replication triggers a dysregulated immune response, characterized by excessive production of proinflammatory cytokines. These cytokines, although important in normal immune responses, can cause tissue damage and organ dysfunction if produced in excess. In addition, viral infections can activate the coagulation cascade, causing blood clotting disorders and bleeding that are characteristic of VHF. The clinical manifestations of VHF vary widely, ranging from mild fever to fatal hemorrhagic shock. The initial symptoms of VHF are often nonspecific, including fever, myalgia, headache, malaise, anorexia, nausea, vomiting, and diarrhea. In more severe cases, patients can experience bleeding from various places, including the nose, gums, digestive tract, and injection sites. This bleeding can occur internally or externally, causing serious complications such as hematoma, organ bleeding, and hemorrhagic shock.[13-15]

One of the main challenges in the treatment of VHF is the lack of effective antiviral therapy. Although some antiviral drugs, such as remdesivir and favipiravir, have shown some benefit in the treatment of Ebola, their effectiveness against other types of VHF is limited. Additionally, antiviral drug resistance is a growing concern, especially in viruses with high mutation rates such as Ebola and Marburg. Supportive therapy, such as administration of intravenous fluids, blood transfusions, oxygen, and electrolytes, remains the mainstay in the management of VHF. This therapy aims to treat dehydration, bleeding and shock, as well as support vital organ function. Although supportive therapy does not directly target the virus, it is critical to increasing a patient's chances of recovery and reducing mortality rates.[16,17]

Immunomodulatory therapies, such as interferons and monoclonal antibodies, offer new hope in the treatment of VHF. Interferons can enhance the body's natural antiviral response, while monoclonal antibodies can neutralize viruses or inhibit their entry into cells. Some monoclonal antibodies, such as ZMapp and REGN-EB3, have shown some benefit in the treatment of Ebola. However, further research is needed to evaluate its effectiveness and safety in other types of VHF. Experimental therapies, such as convalescent plasma, gene therapy, and anti-inflammatory drugs, are also being investigated as potential therapies for VHF. Convalescent plasma contains antibodies from patients who have recovered from VHF, which can help fight infections in other patients. Gene therapy aims to repair or replace damaged genes involved in the pathogenesis of VHF. Anti-inflammatory drugs can reduce excessive inflammation caused by the body's immune response to a viral infection. VHF is a complex public health challenge and requires a multidisciplinary approach to prevention, diagnosis, and treatment. With continued research and collaboration, we can hope to overcome

the VHF threat and protect global public health.[18-20]

5. Conclusion

This systematic literature review provides strong evidence to guide the development of more effective VHF prevention, diagnosis, and treatment strategies. These findings may help inform public health policy, guide future research, and improve clinical outcomes for patients with this life-threatening disease. Future research should focus on developing safe and effective vaccines for different types of VHF. In addition, further research is needed to identify new therapeutic targets and develop more effective antiviral and immunomodulatory drugs.

6. References

1. Muliawati E, Soetjipto A, Soewono S. Molecular surveillance of dengue viruses circulating in Indonesia: 2010–2018. Viruses. 2021; 13(2): 256.
2. Safitri ED, Hasanah N, Ratnasari ID. A review of dengue hemorrhagic fever cases in children in Indonesia. Open Access Maced J Med Sci. 2022; 10: 663–8.
3. Harapan H, Michie A, Mudatsir M. Knowledge, attitudes, and practices (KAP) about dengue fever among communities in Indonesia: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2022; 16(4): e0010313.
4. Karyana M, Buraera P, Ismoedijanto. The burden of dengue in Indonesia: a systematic review and meta-analysis. BMC Public Health. 2021; 21(1): 1–1
5. Yohan B, Kosasih H, Soewono S. Modeling the transmission dynamics of dengue in urban and rural settings in Indonesia: a comparative study. Int J Environ Res Public Health. 2021; 18(17): 9133.
6. Khatibou A, Wahyuni ESF, Kusriastuti R. Factors associated with severe dengue infection in children in Yogyakarta, Indonesia. Open Access Maced J Med Sci. 2022; 10: 797–803.
7. Kusnanto H, Karyana M, Buraera P. Economic burden of dengue fever in Indonesia: a systematic review. PLoS One. 2021; 16(10): e0258838.
8. Soedarmono P, Kosasih H, Subekti D. The impact of climate change on the transmission of dengue in Indonesia: a review. Pathog Glob Health. 2020; 114(7): 357–66.
9. Ningsih PY, Soetjipto A, Sasmono RT. Molecular detection of chikungunya virus in suspected dengue patients in Indonesia. BMC Infect Dis. 2020; 20(1): 1–7.
10. Hadinegoro SRS, Kosasih K, Sutomo S. Efficacy and long-term safety of a recombinant tetravalent dengue vaccine (Dengvaxia) in Indonesian children aged 9-16 years: an open-label, phase 3, randomized controlled trial. Lancet. 2019; 394(10201): 893–906.
11. Wandra T, Oktaviana B, Kosasih H. Clinical and laboratory predictors of dengue hemorrhagic fever in adults in Indonesia. BMC Infect Dis. 2019; 19(1): 1–9.
12. Purnamasari D, Soedarmono P, Subekti D. Dengue virus serotypes and their clinical manifestations in indonesia: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2018; 12(9): e0006818.
13. World Health Organization. Viral haemorrhagic fevers. 2023.
14. Centers for Disease Control and Prevention. Viral Hemorrhagic Fevers (VHFs). 2022.
15. Feldmann H, Geisbert TW. Ebola haemorrhagic fever. Lancet. 2011; 377(9768): 849-62.
16. Bausch DG, Schwarz L. Outbreak of Marburg hemorrhagic fever in Angola: a new variant of the Marburg virus. N Engl J Med. 2005; 352(20): 2085-6.
17. McCormick JB, Fisher-Hoch SP. Lassa fever. N Engl J Med. 1994; 331(14): 924-7.
18. Whitehouse CA. Crimean-Congo hemorrhagic fever. Antiviral Res. 2004; 61(3): 145-60.

19. Gubler DJ. Dengue and dengue hemorrhagic fever. Clin Microbiol Rev. 1998; 11(3): 480-96.
20. Bray M, Geisbert TW. Ebola virus: the role of macrophages and dendritic cells in the pathogenesis of Ebola hemorrhagic fever. Int J Biochem Cell Biol. 2005; 37(8): 1560-6.