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Marburg Virus Disease: A Narrative Review

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ABSTRACT

Background and Aims: Given the recent deadly outbreaks of the Marburg virus (MARV), in early 2023 in Tanzania and Equatorial Guinea, and the most recent one in Rwanda in 2024, there has been renewed attention across Africa on the threat posed by the re-emergence of MARV as a growing concern for public health. Therefore, it needs to provide a comprehensive overview of the virus and its related infections, encompassing virus classification, historical outbreaks, transmission dynamics, the intricate interface between the virus and its hosts, the methods of diagnosis, core prevention strategies, and current therapeutic options, to better understand the virus and the disease characteristics in responding to future outbreaks.

Methods: For this review, four scientific online databases, including PubMed, Google Scholar, Scopus, and Web of Science were thoroughly searched for peer-reviewed journal papers (original, case reports/series, and review studies) published in English language using the following keywords: Filovirus, Marburg virus, Marburg Haemorrhagic Fever, Marburg virus disease, and Marburg virus outbreak.

Results: MARV shares similarities with its close cousin —the Ebola virus [EBOV]—in terms of viral characteristics and most clinical features. These two viruses are of animal origin and primarily spread to humans through infected bats (both direct and indirect close contact), which serve as the common natural host reservoirs. The potential for interhuman transmission, coupled with the ability to cross borders of endemic regions combined with the absence of a licensed vaccine and effective treatment, have made MARV a significant threat to human health. This virus is clinically characterized by a range of symptoms and organ dysfunctions. The disease is often fatal in a significant proportion of infected individuals. This viral infection is diagnosed by various diagnostic tools, prevented mainly through personal protective measures, and treated usually with clinical management and supportive care.

Conclusion: The outbreaks of MARV are continuously threaten public health; therefore, the world must be alert and well-prepared. For MVD, taking precautions along with investing in research and preparedness at regional, national, and global levels is of crucial importance and should be prioritized.

1 | Introduction

In recent years, the world has experienced a significant surge in the number of emerging and re-emerging viral diseases with Influenza A (H1N1) virus [1], Ebola Virus [EBOV] [2], Zika virus [ZIKV] [3], Severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] [4], Monkeypox virus [MPXV] [5], and most recently Marburg virus [MARV] among the most remarkable epidemic-causing viruses

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with zoonotic connection and potential to interhuman transmission.

The epidemics caused by the Marburg virus, often recognized as MARV, have remained a major threat to global public health since its identification and characterization in 1967. Over the past few decades, several outbreaks of MARV have been declared, primarily in Africa with the Democratic Republic of Congo (DCR) (128 deaths in 2000) and Angola (227 deaths in 2004) being the most severely affected countries, and continue to pose a global health concern with new regions remains to be at risk of first-ever outbreaks as the disease disregards geographical boundaries [6]. A recently declared outbreak in Rwanda, with 66 confirmed cases, 15 deaths [case fatality ratio (CFR) of 23%], and 51 recoveries as of 19 December 2024, has sparked an alarm and global fear, highlighting immediate public health interventions at both national and regional levels to contain the cross-border spread of the outbreak (www.cdc.gov). MARV is a zoonotic virus of particular concern for both humans and nonhuman primates that causes a deadly disease (referred to as Marburg Virus Disease [MVD]), with symptoms of hemorrhagic fever (HF) after 3–21 days of incubation period [7]. HF, which is characterized by a rise in body temperature above the normal average and unexplained bleeding can be usually caused primarily by mainly four families of viruses (i.e., Arenaviridae, Bunyaviridae, Filoviridae, and Flaviviridae), all of important zoonotic viruses relevant to human infections [8]. MARV shares similarities with the Ebola virus (EBOV) and is classified as one of the most virulent viruses that account for a fatal infection (Case Fatality Ratio [CFR] ~ 90%) [9]. Like the Ebola virus, MARV initially transmits to humans from animal sources (e.g., cave-dwelling fruit bats), however, other routes of transmission (i.e., direct contact with infected humans [e.g., through close contact with the corpse of the deceased] or contaminated material) have also been identified [10, 11]. The potential for infectivity, high transmissibility, and a high death toll have made this virus a major concern for public health at both national and international levels [12]. Therefore, the virus needs to be monitored with an enhanced surveillance system to timely respond to future outbreaks [13]. Given its high transmissibility, pathogenicity, and lack of licensed vaccines and effective treatments, MARV must be studied in high-containment biological laboratories. Since its first identification and characterization in 1967, several minors and major outbreaks of the virus have been reported predominantly in Africa [9]. The National Institute of Allergy and Infectious Diseases (NIAID) and the Centers for Disease Control and Prevention (CDC) both have listed MARV as Category A, the former as a priority pathogen and the latter as a bioterrorism agent, respectively [14]. The World Health Organization (WHO), in 2018, declared MARV as one of the priority pathogens that will likely cause the next pandemic, requiring urgent research owing to its potential risk to public health [15].

In this review, we summarize information from the virus classification to the management and treatment, to provide an overview of the main features of MARV and its associated diseases.

2 | MARV Classification

MARV belongs to the Mononegavirales order and the family Filoviridae [16]. The order includes viral families with a single-stranded negative-sense genome (i.e., Paramyxoviridae, Bornaviridae, and Rhabdoviridae together with Filoviridae) [17]. The family of Filoviridae consists of five known genera (with the proposal of Dianlovirus as the sixth genus), which includes Ebolavirus, Marburgvirus, Cuevavirus, Striavirus, and Thamnovirus, of which two closely related genera (Ebolavirus and Marburgvirus) considered to be the most pathogenic members, causing disease in humans and outbreaks worldwide [18]. The genus Ebolavirus is the only genus with more than one species (Zaire, Sudan, Reston, Tai Forest, Bombali, and Bundibugyo) [18]. There are only one species in the Marburgvirus genus known as Marburg marburgvirus (previously referred to as Lake Victoria marburgvirus) with two viruses (having genetically ~20% nucleotide divergence) recognized as the Ravn virus (RAVV) and Marburg virus (MARV) with different variants (i.e., Musoke and Angola) [16, 19].

3 | Virion Structure, Genome, and Proteins

MARV is a pleomorphic virus characterized by a spiked host-derived membrane layer, appearing with a range of morphologies (e.g., filamentous [the most commonly seen shape], rod-like, ring-like, and U-like), with various lengths and dimensions [11, 20]. This virus is frequently observed with a uniform diameter of 80 nanometers width and an average length of 790 nm for highly infective virions, which are decorated by several glycosylated spike-like protrusions measuring approximately 5–10 nm in length [7, 21] (Figure 1A).

As illustrated in Figure 1B, the MARV virion contains a non-segmented and negative-strand ribonucleic acid (RNA) with an approximate length of 19.1 kilobases (Kb) [22]. The genome exhibits a nearly identical organization to its cousin—i.e., Ebola Virus — and consists of seven monocistronic genes arranged tandemly as 3'- Nucleoprotein (NP)- Viral protein 35 (VP35)-VP40- Glycoprotein (GP)-VP30-VP24- Large Protein (L)-5' flanked by two untranslated regions (3' and 5' UTRs) [22]. The cis-acting elements located in the noncoding regions contribute to play roles in viral genome replication, transcription, and packaging. EBOV possesses an additional protein called the non-structural soluble GP (sGP), which is secreted from infected cells [23]. These genes are essential for virus replication, transcription, and pathogenicity [9]. The genes contain of highly conserved transcription signals at both their beginnings and ends [22]. There are intergenic regions with a variety in lengths (ranging from 4 to 97 nucleotides) and differences in their nucleotide composition, harboring initiation and termination signals [22, 24, 25]. The RNA of the virus is neither polyadenylated at the 3′ end nor does it have a 5′ cap or any linked protein encapsulated in the nucleocapsid complex which is a complex of four structural proteins (NP, VP35, VP30, and L) [24, 26]. As the main nucleocapsid protein, NP is associated with cellular inclusion bodies forming a tubular structure with helical symmetry which subsequently interacts with VP35 and L protein known as a component of the RNP complex [26, 27]. The VP35, while involved in a role in nucleocapsid formation, plays roles in viral RNA synthesis (known as RNA-dependent RNA polymerase cofactor) and inhibition of host immune responses [9, 28]. VP40 is recognized as the matrix component and a species-specific virulence factor participating in different functions involved in virus transcription/replication, assembly, and release as well as immune

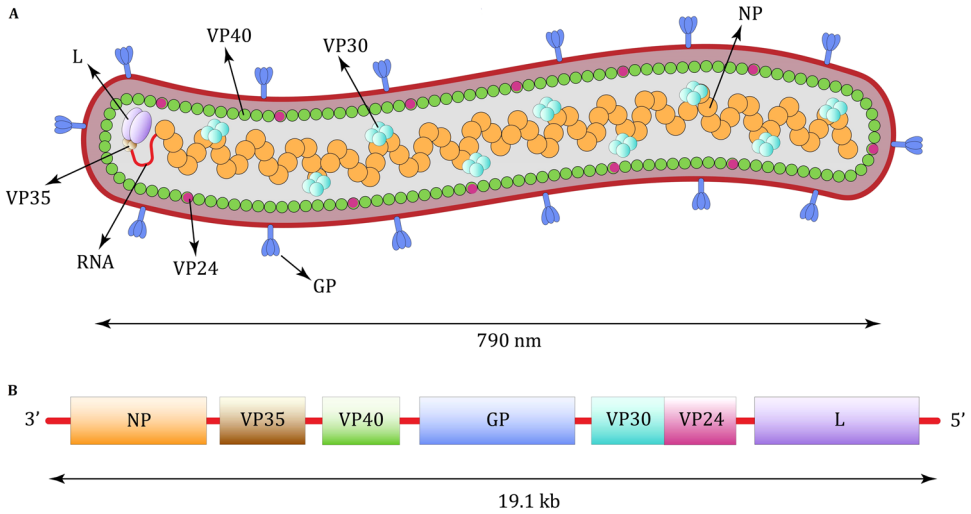

FIGURE 1 | Virion structure (A) and genome organization (B) of Marburg Virus. (GP, Glycoprotein; L, Large Protein; NP, Nucleoprotein; VP, Viral Protein; RNA, Ribonucleic Acid).

suppression [29, 30]. Glycoprotein (GP), the virus transmembrane protein with two covalently linked subunits, GP1 and GP2, is involved in the determination of cell and tissue tropism and is essential in the early stages of the viral life cycle for virus attachment and entry targeted for the development of anti-MARV vaccines and therapeutics [9, 28]. Another protein is VP30. While many questions remained open regarding the role of VP30, it appears that this protein is important in viral transcription and/or replication [31]. The VP24, one of four proteins in the nucleocapsid complex, is likely essential for viral transcription and replication and also for budding, but likely not immune suppression [7, 32]. The L gene is a key component of the virus polymerase complex, featuring a high molecular weight and functioning as the catalytic domain of viral RNA-dependent RNA polymerase [7].

4 | MVD Epidemiology

MARV has a long history of epidemics, primarily in sub-Saharan African countries. The first lethal outbreak of MARV dates back to 1967 in Germany when a group of scientists and laboratory technicians were conducting research on tissues taken from an old-world monkey (chlorocebus aethiops) had been imported from Uganda for the development of a tissue culture-derived poliomyelitis vaccine [12]. In the same year, a veterinarian working with grivet monkeys, and his wife, who attended to him during his illness, were both diagnosed in Yugoslavia (Serbia) [7]. These two outbreaks collectively encompassed a total of 31 infected individuals of which seven cases succumbed at the end as a result of the sickness with an overall mortality rate of 23% [9]. Since the first identification, multiple outbreaks have been declared across different years and locations where the disease had not previously been reported, with Africa being the most affected global region.

In 1975, the first recognized MVD outbreak in Africa occurred in the city of Johannesburg, involving three cases (a 20-year-old Australian man who had traveled to Zimbabwe, his travel companion, and a nurse), with the man being fatal [33]. Five years later, in 1980, two additional cases of MVD were diagnosed in Kenya with one death and one recovered during the third documented viral outbreak. This outbreak is believed to have originated in Kitum Cave, Mount Elgon National Park [34]. In 1987, a 15-year-old boy who died of the disease was diagnosed in the country of Kenya with a history of visiting Kitum Cave inhabited by infected fruit bats [35]. From 1988 to 1995, Russia (predominantly Koltsovo) experienced four outbreaks (two of which were fatal). These outbreaks all occurred through unexpected events in laboratory settings [6]. A large outbreak occurred during 1998–2000 in the Democratic Republic of the Congo (DRC) with a total of 154 cases and tragically 128 deaths with an 83% case fatality rate. It has been reported that multiple viral genetic lineages were identified in this outbreak [36]. Four years later, from October 2004 to July 2005, the largest historical outbreak of MVD, with an unknown mode of transmission (likely involving a hospital employee) took place in Uige province, Angola. This outbreak resulted in 252 reported cases and 227 deaths with a mortality rate of 90% [9, 37]. In 2007, Africa experienced another epidemic of MVD this time among Ibanda district workers at the Kitaka mine, likely caused by direct contact with bats or bat excretions. In this outbreak, four cases became ill and one died [9, 38]. A year later, in January 2008, a non-fatal, imported case of infection was described in a 44-year-old woman in the United States (US). This patient reportedly visited the python cave in the southern part of Queen Elizabeth National Park [39]. A few months later, in July 2008, MVD was diagnosed in a middle-aged woman in the Netherlands. This patient, who, died had also visited the python cave [40]. The next outbreaks occurred in Uganda (in 2012 [with 4 fatalities and a total of 15 infected cases], in 2014 [with one fatal case who was a health care worker in Kampala], and in 2017 [with 3 deaths]) [6]. Guinea experienced its most recent outbreak in 2021 with a single case who subsequently passed away [9].

A year later, an outbreak was recorded in Ghana in 2022 (with 2 fatal out of 3 confirmed cases) [41]. In 2023, the most recent outbreaks of MVD emerged in both Equatorial Guinea (40 cases and 35 deaths) and Tanzania (8 cases and 5 deaths, highly relevant to the Kagera region), where the local authorities reported their first-ever cases of the disease [41, 42]. On September 27, 2024, the Ministry of Health of the Republic of Rwanda declared the country's first-ever MVD outbreak [43]. In

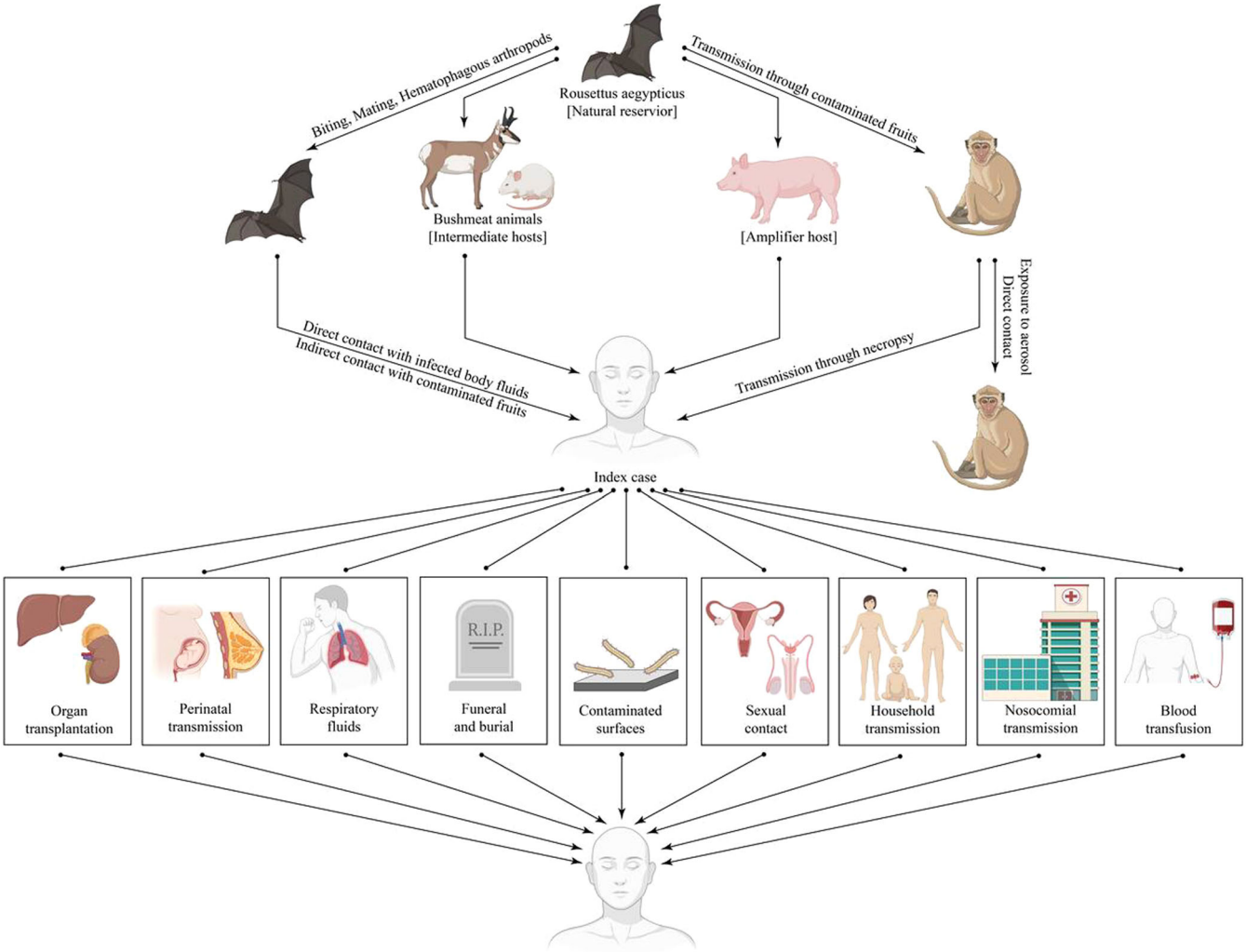

FIGURE 2 | A schematic representation of Marburg Virus transmission (Created with the help of BioRender. com).

this region, as of 24 October 2024, a cumulative number of 64 cases were diagnosed with the disease and the case fatality ratio (CFR) is estimated to be 23.4%. The most recent suspected fatal outbreak was declared [on January 14, 2025] by the World Health Organization (WHO) in Tanzania's Kagera Region—notably in the Biharamulo and Muleba districts highlighting the continued threat posed by MVD to human public health.

5 | MARV Transmission

MARV has a highly infectious nature, with an estimated basic reproduction number of 1.59 based on the 2005 outbreak in Angola [44]. As shown in Figure 2, infection in humans is known to be associated with animal contact; however; debates exist regarding the origin of MARV with some scientists proposing that the virus is of bat origin, while others consider other animal species (e.g., nonhuman primates) as the main sources of MARV transmission to in close contact humans [19]. The Cave-dwelling bats, particularly the Egyptian fruit bat (Rousettus aegyptiacus), are believed to harbor MARV and are ecologically and experimentally thought to be the natural reservoir. However, other bat species (i.e., long-fingered bats [Miniopterus inflatus] and eloquent horseshoe bats [Rhinolophus eloquens]) may also contribute to further virus cross-species spread [45]. Inter-species transmission may vertically or horizontally occur between bats [12]. These flying mammals may become infected through other modes of transmission [12]. For a successful transmission, nonhuman vertebrates (e.g., African green monkeys [AGMs], chimpanzees, forest antelopes, and pigs) play a role in virus spread [12]. Additionally, while animal-to-human transmission is considered the primary route, especially in endemic areas, human-to-human contact can also lead to viral spread. Infection in humans primarily begins after unprotected close contact (injured skin or mucous membranes) with those who are diagnosed with the disease and their infected body fluids (i.e., urine, saliva, breast milk, amniotic fluid, and genital fluids) [9]. Patients with hemorrhagic syndrome and a high level of viremia may pass the virus to others, likely through infectious respiratory fluids [46]. MARV can also be transmitted via transfusion and transplantation as the virus has been detected in blood and has tropism to solid organs [9]. MARV has the potential to persist in immune-privileged sites of body organs [47]. The presence of the virus has been detected in semen, and its persistence has been reported to be established in seminiferous tubules and Sertoli cells of nonhuman primate's testes, raising concerns about the virus spread through engaging in sexual activities [48]. Children may acquire the infection from their female parent as a result of vertical transmission [49]. Feeding with breast milk by infected mothers

could be hypothesized as an alternative route for virus transmission in early childhood [49]. Based on case report studies, hematogenous transplacental transmission is regarded as a major source of fetal infection and loss [50]. The detection of MARV in human body fluids sparked debate regarding the potential sources of infection through human-to-human transmission. Human dead bodies if inappropriately touched or prepared for burial may also increase the risk of viral spread [51]. Thus, traditional funeral and burial rituals should be held with a minimum number of attendees because of safety concerns. MARV can also spread through nosocomial transmission, especially in countries with poor medical education, resources, and services; therefore, standard precautions need to be undertaken by healthcare workers [52]. As an indirect transmission mode, fomite-mediated transmission has also been considered for filoviruses as these viruses have been shown to survive in liquids and on solid surfaces for long periods [53].

6 | MARV Life Cycle

The high infectiousness and lethality of filoviruses have limited the study of the mechanisms by which they replicate by the use of cell machinery. The life cycle of filoviruses is a multi-step process that begins by binding the carbohydrate structure of virus glycoprotein (GP), primarily GP1 subunits, to cell surface proteins (i.e., C-type lectin receptors [CLRs] and the TAM family of receptor tyrosine kinases [RTKs]) [54]. Virus attachment is followed by acid PH-dependent endocytic pathways that allow cell-bound viruses to enter host cells [55]. In addition to cell-associated attachment factors, there are several cell surface receptors (T-cell immunoglobulin and mucin domain 1 [TIM-1]) and endosomal receptors (Niemann-Pick C1 [NPC1]) that mediate filoviral entry enhancement [56]. For MARV specifically, much remains unknown in knowledge about the cell types targeted by the virus and the mechanisms involved in viral entry necessitating further studies. Once virions are internalized, endosomal cleavage of GP occurs through a process that is essential for an efficient entry and is likely mediated most likely by cathepsins [57]. Releasing viral nucleocapsid into the cytoplasm is mediated by the fusion of the virus and endosomal membrane through a PH-dependent mechanism, followed by genetic processes that are necessary for decoding virus genetic information and generating new viral genomes [7]. The virus replicates within the cytoplasmic inclusion bodies (IBS) and is characterized by a synthesizing process of negative-strand RNA from antigenomic ribonucleoprotein complexes synthesized from incoming genomes [58]. Once assembled, newly synthesized viral components are transported in association with the actin cytoskeleton, aided by the contribution of viral matrix protein to the plasma membrane where virion assembly and budding occur to complete the replication cycle in the presence of host proteins (e.g., ESCRT and its associated proteins) that promote the process of viral release [59, 60].

7 | Pathogenesis and Clinical Features

Little is known about the underlying mechanisms utilized by MARV to cause disease and death. Nonhuman primates (NHPs), in particular rhesus and cynomolgus macaques, are one the most common laboratory animal models used to study the pathogenesis of filoviruses including MARV. These animals often show fatal infections and have clinical features similar to those of human infections [9]. As mentioned earlier, MARV enters the body via direct or indirect contact with an infected animal or human. Once inside the body, the virus predominantly targets cells of the immune system (i.e., macrophages and dendritic cells) which play a central role in antivirus innate immunity. MARV enters these cells and begins to replicate, ultimately leading to dysfunction of the host immune system [61]. In addition to immune cells, liver parenchymal cells, adrenocortical cells, and lymphoid tissues are also considered the main sites targeted by the virus [9]. MARV often causes severe infection and a deadly disease within the first week of symptomatic infection (or even longer) likely at the peak of viremia [44]. The severity of illness greatly varies from mild to critical infection [62]. Patients with MVD are almost always symptomatic with no asymptomatic infection yet described [19] (Figure 3). The level of viremia is likely correlated with the disease severity being 100- to 1000-fold higher in non-survivors compared to survivors [63]. Several factors (e.g., host susceptibility, the ability of the viral strain to cause tissue damage, and medical care) may determine the clinical course of the disease [64]. The clinical characteristics are closely resemble to those of its close cousins—EBOV disease. There is an agreement that typically 5–10 days postexposure, infection with MARV abruptly begins with sudden nonspecific, and usually flu-like symptoms [19]. The viral infectious dose and the route of infection may alter the incubation period [7]. During the early phase, patients are febrile with a high degree of body temperature peaked on the third and fourth days, showing a number of general symptoms such as weight loss, sore throat, joint pain, extreme malaise, and a subset of gastrointestinal symptoms (e.g., loss of appetite, abdominal pain, dysphagia, nausea, vomiting, and watery diarrhea) in the early days [6, 9]. Patients may also experience sunken eyes (also known as enophthalmos) and suffer from conjunctivitis [9]. The cardiovascular system may be involved and the symptoms of bradycardia and tachycardia and signs of myocardial injuries may be diagnosed as a result of the disease [6, 65]. MARV can infect the reproductive organs of both males and females and shed in genital fluids suggesting a potential risk of sexual transmission [47]. MARV can cause orchitis (inflammation of one or both testicles) and result in testicular pain, also known as scrotal pain, in the male gender and vaginal bleeding in women who are sick due to the infection [6, 9]. In affected genders, necrosis of the testicles and ovaries has been observed [6]. MARV can also affect the respiratory system, causing lung hemorrhage and diffuse congestion, suppurative pneumonia, pharyngitis, and shortness of breath (also known as dyspnea) [6]. Lymphopenia, indicative of immunosuppression, and thrombocytopenia (low platelet count) are two hematological abnormalities that typically appear in the first week after the onset of symptoms [66]. An endothelial cell infection can lead to altered in blood vessel permeability and cause abnormal blood clotting throughout the body's blood vessels [9]. As the virus disseminates, the liver, spleen, and lymph nodes become affected, displaying the most severe necrotic lesions [9]. At the organ level, the liver and adrenal glands are both regarded as the primary targets for the virus [9]. The liver serves as a major metabolic site that functions as the site of detoxification, metabolism, and the production of proteins necessary for blood clotting [67]. When the

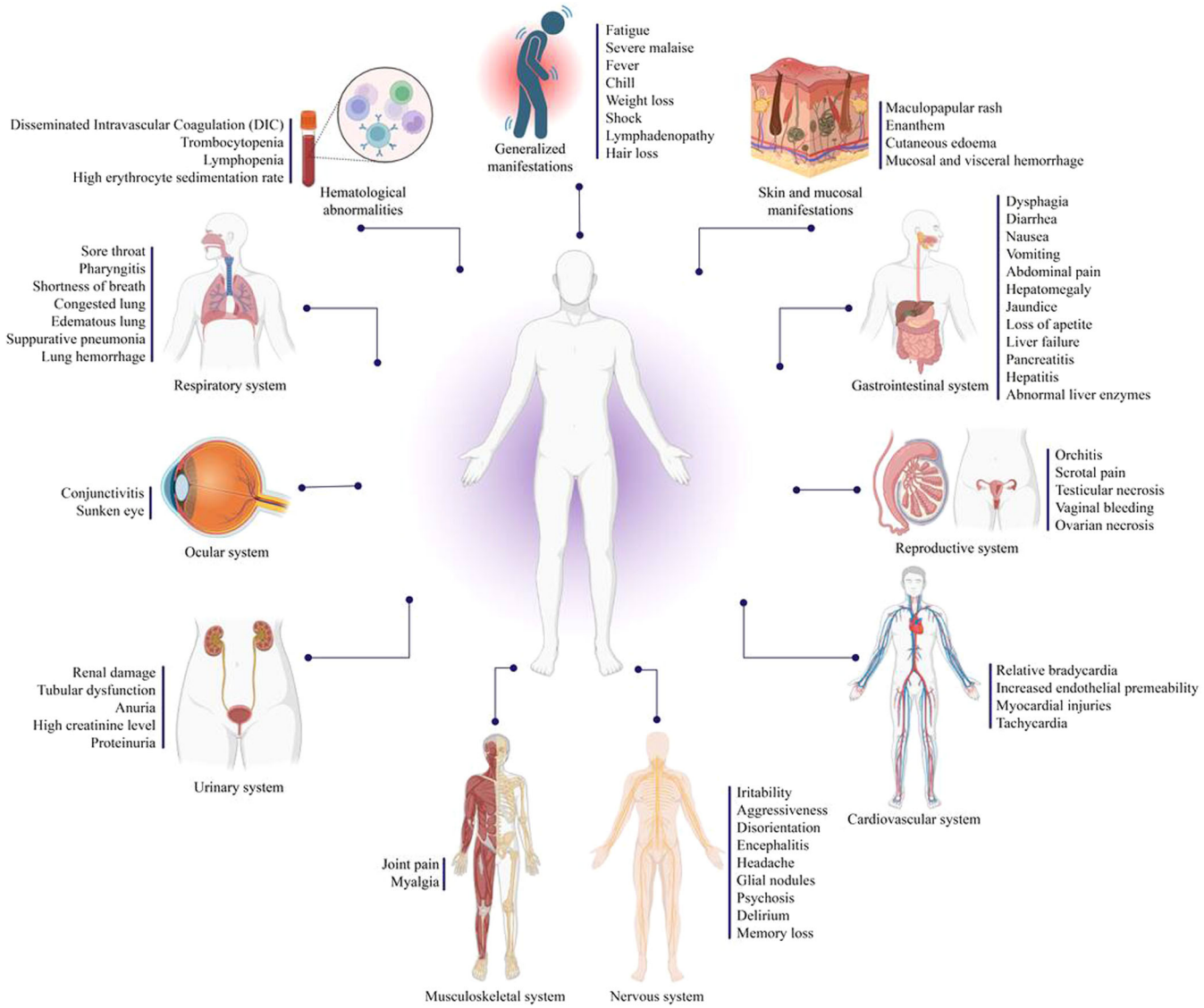

FIGURE 3 | Clinical features and complications of Marburg Virus Disease (Created with the help of BioRender. com).

liver is damaged, these functions are impaired and symptoms of jaundice, mild to moderate steatosis, hepatomegaly, and abnormal liver enzymes can develop [6, 68]. A common feature that is attributed to the course of MVD is cutaneous involvement. The skin of patients (firstly face and buttocks and then trunk and extremities) may be covered by nonspecific maculopapular rashes with small and dark red spots that are around the hair follicles presenting between days 5th and 8th of the infection [62, 66]. In most symptomatic cases exhibiting with external rashes, lesions on the mucous membranes can also be clinically diagnosed [62]. As the disease progresses, bleeding may develop with signs of mucosal and visceral hemorrhage [64]. Infection with MARV may cause damage to the lymph nodes. The lymph nodes are small, bean-shaped structures located throughout the body, which contain immune cells that can detect and respond to infectious viruses [69]. In severe cases of MVD, the damage to the lymph nodes can lead to lymphadenopathy, which is a condition characterized by the enlargement and hardening of the lymph nodes. This can occur due to the accumulation of immune cells and other inflammatory cells in response to the viral infection [70]. Complications of lymph node damage in MARV infection can include impaired immune function, which can increase the risk of secondary infections. Filoviruses share similarities in histopathological features triggering necrosis in different internal body organs [71]. The lungs of patients with MVD are likely to be congested and edematous [72]. In the kidney, there are signs of renal failure (characterized by proteinuria) and tubular necrosis [9, 19, 72]. Acute metabolic anomalies can result in urine output of fewer than its normal milliliters per day (referred to as Anuria) [9]. In the bone marrow, the virus leaves nonspecific morphological changes [71]. In the spleen, perifollicular congestion, pyknosis, and karyorrhexis may also occur [72]. MARV leaves glial nodules and causes perivascular lymphocytic infiltration in the central nervous system [71]. The involvement of the nervous system may cause symptoms of headache, irritability, violence, disorientation, encephalitis, memory loss, and delirium [6, 9]. As previously noted, MARV causes a lethal infection with death usually occurring between days 8th and 16th after the onset of the symptoms as the result of shock and multiorgan failure [7]. Patients diagnosed with MVD returned to their normal health status 2–3 weeks after the

onset of the disease [62]. Patients who survive MVD may suffer from myalgia, arthralgia, fatigue, hepatitis, ocular discomfort, psychosis, memory and hair loss, and other sequels for a long period after the infection is resolved [19, 64].

8 | Host Immune Responses

Even though MARV was discovered decades ago, the complexities of the host immune response to this viral infection have not been thoroughly characterized. During infection, MARV infects monocytes, macrophages, and dendritic cells [DCs] [9]. As a result, the release of inflammatory mediators by these cells leads to disrupts the integrity of the vascular endothelium [73]. Furthermore, the infected migratory cells of the immune system allow MARV to disseminate within the host, moving from the initial site of infection to lymph nodes through the lymphatic system and further via the bloodstream to tissues of the liver and spleen, where the virus can infect additional cells [23]. MARV can also infect and activate natural killer (NK) cells, which favor tissue inflammation [61]. In addition to NK cells, other immune-component cells such as CD1d-restricted iNKT cells and IFN-producing killer DCs (IKDCs) are likely to be triggered in response to the virus infection [61]. The virus-cell interaction occurs via the use of DC-SIGN, TIM-1, Axl, and Tyro32 [56, 74]. This interaction activates the immune system, leading to the activation of both innate and cell-mediated immunity. However, MARV evades and dysregulates both innate and adaptive immune systems [61]. In initial responses to MARV infections, IFNs are key contributors; nevertheless,the virus can counteract this type of immunity and inhibit the activation of transcription factors such as IRF-3, IRF-7, and NF-KB, which are essential for the expression of IFN-stimulated genes (ISGs) [75]. The ISGs include immune mediators essential for the recruitment of immune cells and promoting inflammation, thereby contributing to antiviral defenses and various processes at the cell level [76]. MARV can inhibit JAK/STAT phosphorylation, block the nuclear translocation of STAT1/2, and avert the RIG-I-like receptors (RLRs) -mediated recognition of the virus by targeting cellular components and factors [21]. The innate immune responses mediated by IFN are likely to be more detrimental than beneficial, as it might impair adaptive immunity by inducing the contraction and death of T-cell populations [77]. In addition to innate immunity, MARV undermines the adaptive immune response by affecting the function and survival of DCs and lymphocytes. DCs are essential for antigen presentation and the activation of T and B cells [78, 79]. However, MARV-infected DCs do not mature properly and fail to express costimulatory molecules, such as CD80, CD86, and CD40 [61, 80]. Lymphocytes are also targeted by MARV. The virus induces apoptosis in T and B cells by activating caspases and disrupting mitochondrial membrane potential [6]. The virus also triggers a co-inhibitory pathway involving PD-1 and its ligands PD-L1 and PD-L2 on the surface T cells and antigen-presenting cells (APCs), respectively. This pathway leads to T-cell exhaustion and dysfunction [81–83]. The cumulative effects of MARV infection result in a profound immunosuppression and a dysregulated inflammatory response. The latter is characterized by a “cytokine storm”, which is a massive release of pro-inflammatory mediators, such as TNF-α, IL-6, IL-8, MCP-1, MIP-1α, MIP-1β, RANTES, IP-10, and IFN-γ. These cytokines cause systemic damage to the vascular system, resulting in hemorrhage, edema, shock, organ failure, and death [84–86]. The immune response against MARV is not entirely ineffective or absent. Some studies have shown that survivors of MARV infection develop specific antibodies and T-cell responses that can confer protection against reinfection [61]. However, the factors that determine the outcome of viral infection are not fully understood. It is likely that the timing, magnitude, quality, and balance of the immunity play a crucial role in determining survival or death.

9 | MVD Diagnosis

As the similarity of symptoms has made it difficult to clinically discriminate MARV from other viral infections (e.g., coronavirus disease-2019 [COVID-19], Influenza, and Ebola [EBOV]) as well as non-viral infections (e.g., malaria, typhoid fever, leptospirosis, and rickettsia), confirmatory tests are crucial to minimize any misdiagnosis [10]. Filoviruses are initially diagnosed through a clinical assessments, which include measuring body temperature, blood pressure, heart and respiratory rates, and looking for signs of hemorrhage, as well as considering general discomforts [19, 68, 87]. Clinicians need to be aware of the incubation period, which typically ranging from 5 to 10 days after initial contact with the source of infection (based on the infectious dose and route of infection), to make appropriate diagnostic decisions regarding whether the signs and symptoms presented by patients are associated with MVD [88]. However, uncertainty regarding the incubation time in some cases has led to controversies over how to identify them and contain the further spread of MARV within human populations.

A collection of detailed travel history and any close contact with individuals suspected or confirmed to be infected is also recommended. Patients with MVD, in addition to clinical features, exhibit abnormalities in their laboratory findings characterized by hematological abnormalities (e.g., relatively high erythrocyte sedimentation rate, leukopenia, thrombocytopenia, lymphocytosis, increase in the count of immature megakaryocytes of the bone marrow) and abnormalities in the level of liver-associated enzymes (e.g., an increase of serum transaminases and bilirubin as well as creatinine, a decrease of the total serum protein) [62].

Over the last few years, multiple efforts have been made to develop faster and more accurate diagnostic tests, particularly in the early stages of the disease [89]. Developing reliable tests minimizes the risk of false positive and negative results, for accurate patient diagnoses and appropriate management. Furthermore, these tests reduce the likelihood of interhuman transmission by tracking infected individuals and isolating patients promptly during a natural outbreak. Multiple diagnostic modalities are used for the diagnosis of filovirus diseases. Given that MARV is highly pathogenic, all detections must be carried out under maximum biological containment conditions [90]. Serological assays, particularly antibody detection systems, are available for epidemiological studies to assess infections by detection of specific antigens or antiviral antibodies [91]. The enzyme-linked immunosorbent assay (ELISA), one of the primary diagnostic assays, possesses high sensitivity and can be used to test whole blood, serum, or plasma during the viremic stage of infection to diagnose specific MARV antibodies (anti-GP and anti-VP40 antibodies) in a relatively late stage of the disease [92–94]. The production of anti-MARV IgM antibodies occurs within the first week of illness (as early as 2–4 days post

onset of symptoms), peaks in the second week, and is later replaced by IgG antibodies around 8–10 days after the symptom onset, remaining detectable for a couple of years following the infection onset [68, 91]. There is an agreement that the appearance of IgM signifies early infection, while IgG indicates past infection. Immunohistochemical analysis is another available test to identify viral antigens, particularly in post-mortem examinations [89]. An alternative approach for the detection of viruses like MARV involves by molecular diagnostic methods that are designed to confirm virus infection in epidemic setting by measuring the amount of viral nucleic acid-targeting NP, L, and GP viral genes in a given specimen [95]. As the most widely used laboratory tool, the real-time PCR molecular test identifies viral RNA in blood (e.g., whole blood, serum, or plasma) is collected in non-heparinized tubes, using a minimum volume of 5 mL, or of suspected individuals [89, 92]. This method of detection used well in past filovirus outbreaks and typically confirms virus infection on the day of the disease onset [96, 97]. It is useful for the quantification of the level of viremia to predict disease outcomes and is valuable for disease management. In survivors the infection, viremia levels are usually low compared to fatal infections lasting no more than 2 weeks in nonfatal cases [68]. According to available guidelines, the temperature required for blood storage depends on the time of testing ranging from room temperature (for short storage within a day) to −20° or −70° centigrade (for long storage of more than 1 week) [98]. For structural studies, electron microscope (EM) can be employed to observe viral particles [89]. Cell culture techniques may also be employed to isolate the MARV, although this method is time-consuming and requires complementary tests [89]. Two commonly utilized cell lines for MARV isolation include Vero cells and their derivative, Vero E6 cells MARV isolation [93]. Given the high risk of viral transmission and the lack of definitive treatment for viruses like EBOLA and MARV, sampling from patients for diagnostic testing requires handling at biosafety level (BSL)- III as well as virus isolation and identification to a BLS-IV laboratory due to the propensity for person-to-person transmission [99].

10 | Inactivation OF MARV

There are several methods of inactivation that are employed against filovirus infectivity before handling and working with virus-containing samples in diagnostic and research laboratories. MARV can be inactivated by gamma irradiation in a dose-dependent manner [100]. Ultraviolet light exposure for 2 min can also reduce the infectivity of the virus [101]. Additionally, agents such as diethyl ether and sodium deoxycholate, formaldehyde, paraformaldehyde, and 1% sodium hypochlorite solutions can also be used for virus inactivation. For clinical laboratory analyses, thermal methods [heating serum (60°C for 1 h)] and chemical approaches [3% acetic acid for blood dilution] are among the effective strategies employed to eliminate MARV infectivity [101, 102]. MARV remains stable at room temperature [101]. For instruments contaminated with MARV, as recommended for EBOV, applying a heat deactivation protocol (10 min at 100°C or 5 min at 120°C) may reduce the titer of the virus, thereby ensuring the safety of laboratory procedures and the working environment [103]. For the feeding of infants born to infected mothers, it is recommended to treat breast milk at low temperatures for extended periods to minimize the risk of mother-to-child transmission [104].

11 | Prevention and Control Measures

During viral epidemics, healthcare authorities need to provide care services for those affected by the outbreaks. This, if no licensed prophylaxis is available for any potential exposures, can put community members, especially front-line healthcare providers, at a heightened risk of infection. Therefore, irrespective of the signs and symptoms that patients show, appropriate measures and standard precautions must be taken and followed carefully due to the high biohazard risk. Housing patients who are suspected of or diagnosed with the disease in spacious and well-equipped isolation units with dedicated services is essential to reduce the risk of community exposure and contain the outbreak, especially in the presence of inadequate resources [105]. There is a consensus on the strict adherence to hand hygiene, either by washing or using alcohol-based hand rubs, to minimize the risk of cross-transmission of filoviruses, which are representatives of enveloped viruses [106, 107]. In addition, workers are always encouraged to use personal protective equipment (commonly known as “PPE”), the material covering exposed body parts, to increase the confidence for the establishment of safe contact with infected persons and their body fluids [108]. In this regard, wearing well-sized double gloves (preferably nitrile gloves), single-use gown or disposable coverall, waterproof boots and apron for limiting virus spread and translocation from the neck down to the mucus membranes of the neck up, fluid-resistant medical/surgical mask or good breathability respirator to protect nose and mouth, and eyewear such as fog and scratch resistant goggles or face shield for protection of eyes against virus-containing droplets or contaminated hands are recommended for miners, caverns, and researchers as well as those who care patients before entering the isolation rooms [12, 109–111]. While using appropriate PPE is essential to limit virus spread and reduce the likelihood of self-contamination, some problems such as overheating especially in tropical regions with high risk of filovirus outbreak should be addressed as can pose adverse mental and physical effects on the wearers [110]. After using the PPE and before leaving the isolated units, such equipment should be carefully disposed of in special waste containers. Also, after using needles, syringes, and sharp instruments such as surgical knives, throwing them with care in puncture-resistant containers is needed [109]. In outbreak settings, raw or undercooked meat should not be consumed until inadequately cooked [12]. In addition, activities like hunting and bush meat trading, grazing, mining, and eating contaminated fruits and meat from monkeys that have been in close contact with bats are not recommended especially during the time of virus outbreak [112, 113]. There is an encouragement for men to abstain from having sex (vaginal, oral, and anal intercourse) for at least 12 months to minimize the risk of viral transmission through sexual contact [11, 24]. There is also a need for identifying potential reservoirs, early recognition, and contact tracing, strengthening surveillance systems and public health infrastructure, raising public awareness, and staying committed to standard infection control measurements to limit virus spread, contain the disease, and mitigate further outbreaks [114].

For filoviruses, vaccines are likely to focus on the viral surface proteins as the most utilized antigen targets [99]. The strategies used for vaccine design and development include inactivated or

destroyed viruses, live-attenuated strains of the virus, and vector or protein-based vaccines [9]. For MVD, no approved vaccine is available to protect against infection; however, efforts are underway, and multiple candidates are undergoing assessment and development, with some exhibiting efficacy for use in human clinical trials after displaying promising results in preclinical research. The vaccine development platforms for MVD include live-attenuated virus strain, adenoviral vector-based vaccine, protein-based vaccines, formalin-inactivated virus, modified vaccinia Ankara vector vaccine, vesicular stomatitis virus (VSV)-based vaccine, virus-like particles (VLP), and DNA plasmid vaccine), along with other additional platforms with different efficacies [9, 19, 64]. With the recent advancement of using immunoinformatics approaches, a multi-epitope vaccine based on the viral proteins (structural ones) promising in silico result has recently been designed and formulated [115]. Given the low incidence rate, some experts suggest prioritizing funding resources, particularly in resource-limited settings, as there is uncertainty about the necessity of investing in vaccine research and distribution for preventing the spread of this virus compared to more common infectious diseases with higher transmissibility and infectious rates. Investing in developing therapies has also received such controversies.

To date, several approaches have been employed and different platforms assessed in animal models (predominantly nonhuman primate models) with relatively low (Intact MV, RAVV [50% survival rate], MV GP [67% survival rate]) to high protectiveness (100% survival rate [Virus like particles + RIBI (Vaccine adjuvant)], [Cad Vax-Pan Filo], [EBOV GP + SUDV GP + MV GP + RAVV GP], [rAD5 (vector) + MV GP + DNA MV GP], and [VSV + MV]) [9]. There is a lack of trials evaluating the safety and immunogenicity of MVD vaccines in humans. For instance, In a trial by Kibuuka et al., a DNA-based vaccine encoding virus glycoprotein used for immunization was well-tolerated with the potential to activate both humoral and cellular immunity in 31% and 52% of vaccine receivers, respectively [116]. This platform is stable in exposure to temperature fluctuations and can be manufactured relatively in a short duration time [117]. Through another approach in a first-in-human trial, the chimpanzee adenovirus type 3-vectored Marburg virus vaccine was used for the immunization of healthy adults against virus infection in the US. This vaccine reportedly encodes a wild-type Marburg Angola glycoprotein. Ninety-five percent of single-dose vaccine receivers exhibited detectable long-lasting (for over 48 weeks in 70% of participants) antibody responses specific for the virus post-vaccination with no safety concerns [118]. However, pre-existing immunity in the public has restricted the use of adenovirus as a vector in vaccine research [119]. Recently, leveraging bioinformatics and computational approaches, two constructed vaccine candidates (multiepitope subunit vaccine (MSV) and mRNA vaccine (MRV)) have shown a capacity to activate the host's immune system aim to protect against hemorrhagic fever caused by the MARV, suggesting these candidates could be a choice for further validation and consideration [120]. In one study, using reverse vaccinology and immunoinformatics approach, the recombinant multi-epitope vaccine construct MarVax was designed and showed stability, and antigenicity, however, in vitro and in vivo validation is needed through further investigations [121]. The side effects of MARV vaccination in human trials are reported to be mild to moderate which may include pain at the injection site, malaise, headache, and muscle aches [118]. However, in some cases, vaccines can cause more severe reactions requiring vaccine discontinuation [15]. This suggests that precautions should always be considered.

12 | Management and Treatment

Although MVD was first described over 50 years ago, no specific treatment has yet to be developed. The symptoms are primarily treated by both palliative management and supportive care. Therapeutic approaches include pain and fever management by taking acetaminophen, fluid supplementation, using unspecified antimicrobial (e.g., antimalarials and antibiotics), psychosocial treatment [to reduce of anxiety and agitation], replacement therapy by using electrolyte solutions (e.g., high dose calcium), maintenance of oxygen levels via mechanical ventilation for respiratory failure, transfusion of fresh blood platelet concentrates, and dialysis [for renal dysfunctions] [122]. Additionally, antiemetics, antacids, heparins [to prevent disseminated intravascular coagulation (DIC)], and steroids [likely for eye inflammation or to manage immune-mediated reactions] have also been administered to patients in past outbreaks [35, 123]. The use of albumin [for the reversal of hypoproteinemia], is an option for post-exposure treatment, although its efficacy in humans is questionable.

Efforts are underway to discover promising therapeutic agents aimed at treating MVD. One approach involves directly targeting the virus. This may include virus neutralization (e.g., convalescent plasma therapy), antibody-mediated complement lysis (e.g., immunotherapy by monoclonal antibodies (mAbs)), blocking viral mRNA translation (e.g., using phosphorodiamidate morpholino oligomer-plus), viral interference (e.g., by the use of vesicular stomatitis virus -MARV GP), increasing virus mutation rate (e.g., antiviral treatment by ribavirin), and inhibition of viral gene expression (e.g., lipid-encapsulated small interfering RNA (siRNA)-based therapy) [64, 124]. Besides to direct targeting, suppressing deleterious host responses may also serve as effective therapeutic approach against filovirus infections including MVD. In this regard, the inhibition of cytokine synthetizes, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), with antibodies and receptor antagonists has yielded beneficial outcomes [64]. Furthermore, ridostin, prednisone, and interferon which contribute to interferon induction, suppression of aberrant inflammation, and antiviral responses have demonstrated efficacy in animal studies, respectively [64]. Efficacious management benefits from the results of recent studies that assessed the efficacy of Remdesivir (GS-5734), Cholesterol-conjugated fusion inhibitors, 4-(aminomethyl) benzamide, Aloperine, Favipiravir (T-705), BCX4430, FC -10696, FGI-103, and AVI-7288 whether in vitro or in vivo [125–131]. In recent advancements through a computational investigation, natural Fisetin and its derivatives were identified to be potential inhibitor and alternative approaches for the treatment of both viral infections (e.g., Monkeypox and Marburg disease) and noninfectious diseases (e.g., breast cancer) [132].

13 | Future Direction and Conclusion

In recent years, global public health has been threatened by numerous infectious viral diseases, many of which have originated

from animals (zoonotic diseases) [2, 133, 134]. The recent MVD has served as a wake-up call to the world, particularly impacting Africa, as a heavily affected region, reminding us of the necessity of preparedness, vigilance, and taking appropriate measures in response to the outbreaks caused by MARV. MVD is recognized as a neglected infectious disease that pose a threat to health security if underestimated. Therefore, having a comprehensive understanding of key aspects of this virus and its associated diseases is of great importance to minimize the risk of virus spread on a large scale and better manage future outbreaks of the infectious disease. To mitigate the future risk of MVD outbreaks and contain them in their inception and their impact on public health, strengthening or establishing robust surveillance and reporting systems, especially importantly in previously affected regions, is important for the early identification and tracking of the virus distribution patterns [135, 136]. This largely depends on developing reliable and rapid diagnostic tools to timely respond to any increase in case numbers before the prominent signs of outbreaks and tracing contacts aiming to contain interhuman transmission in the future [137]. Furthermore, enhancing public awareness about preventive measures and promoting healthy behavior practices through communications campaigns, along with collaborations at a local and a global scale close work with healthcare organizations and international organizations needs significant improvement to be improved and enhanced [42]. At the first sign of outbreaks, strict infection control measures such as implementing travel restrictions, establishing quarantine protocols, and isolating those suspected of the disease must be enforced to contain further spread of the virus and disease transmission [137]. Investment in the development and testing of vaccines and therapeutics is essential before the next outbreak occurs [136, 137]. Availability of and accessibility to personal protective equipment should be ensured before the outbreak hits the healthcare systems [138]. The biology and behavior of the virus and its transmission dynamic also need to be thoroughly researched to better contain the virus transmission. In addition to primary prevention, pre-exposure prophylaxis by the development of an effective vaccine ensures a small-scale outbreak from evolving into an uncontrollable health crisis.

Author Contributions

Arash Letafati: investigation, data curation, writing – original draft. **Somayeh Sadat Hosseini Fakhr:** investigation, writing – original draft, data curation. **Ali Qaraee Najafabadi:** visualization. **Negin Karami:** writing – original draft. **Hassan Karami:** conceptualization, writing – original draft, writing – review and editing, supervision, investigation, data curation.

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Ethics Statement

It is an analysis of online available aggregate data. No ethical approval was needed.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Transparency Statement

The lead author Hassan Karami affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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