# Clinical features of Marburg virus disease: a review of all reported patients since 1967



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### Summary

Background Marburg virus disease (MVD) is a severe and often fatal illness caused by the Marburg or Ravn virus. Given the remote areas affected and the infrequency of the disease, the MVD presenting syndromes are unclear, and this may limit timely recognition.

Methods We conducted 333 a literature review of published case reports and outbreak investigations from January 1st, 1967 to October 30th, 2024, to describe the prevalence of MVD-associated symptoms and syndromes.

Findings 722 cases of MVD occurred across 18 outbreaks, with detailed clinical data available for 325 cases. Common symptoms include fever, headache, fatigue, and myalgia; gastrointestinal symptoms are also frequently reported. Haemorrhagic symptoms, mainly hematemesis and bloody diarrhoea, are more specific but less frequent. The overall lethality rate is 72% (95% CI: 68.8-75.0%), dropping to 44% (95% CI: 37.1-50.9%) among PCR-confirmed cases.

Interpretation Variability in prevalent symptoms across different outbreaks complicates early recognition. The lower lethality observed in PCR-confirmed cases may reflect earlier access to appropriate care once Marburg virus disease was recognized, as well as potential misclassification of non-MVD febrile illnesses among unconfirmed cases.

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Keywords: Marburg viral disease; Clinical presentation; Syndromic presentation; Early recognition

# Introduction

Marburg virus disease (MVD) is a severe and often fatal disease caused by Marburg virus (MARV) or Ravn virus (RAVV), a non-segmented, negative-sense RNA viruses belonging to the order Mononegavirales, family Filoviridae<sup>1,2</sup> MARVwas firstly identified in 1967, following two concomitant outbreaksamong laboratory workers in Germany and Serbia, linked to importation of infected monkeys from Uganda.3 Since then, 18outbreakshave occurred in different African countries, as well as 3 cases imported in high-income countries.3 The natural reservoir of MARVis the Egyptian fruit bat

(Rousettus aegyptiacus). Most index cases of MVD outbreaks have been associated with prolonged exposure to mines or caves inhabited by bats, such as in cave visitors and mine workers. Following the spillover event, human-to-human transmission primarily occurs through direct contact with infected body fluids and contaminated fomites.4

Due to the rarity of outbreaks, limited healthcare access in affected areas and the challenges of data collection in emergency response settings, clinical descriptions of MVD cases are often limited in number or incomplete. According to available data, initial nonspecific prodrome may include general malaise, high fever, severe headache, nausea, vomiting, diarrhea and abdominal pain. At later stages, severe hemorrhagic symptoms affecting different systems may appear,

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### Research in context

### Evidence before this study

We searched PubMed, Web of Science, Embase, and African Journals Online (AJOL) from 1967 to October 30, 2024, using free-text terms such as "Marburg virus", "Marburg virus disease", and "Human Marburg disease", in combination with specific country names and outbreak years (e.g., "Marburg virus AND Uganda AND 2004-2005"). Only English-language publications were included. We included case reports, case series, and outbreak investigations including clinical details of confirmed or suspected MVD cases. Data were extracted independently by two reviewers, with discrepancies resolved by consensus. No formal quality assessment or risk of bias tool was applied, given the observational nature and heterogeneity of the included studies. No prior systematic meta-analysis of clinical symptoms across MVD outbreaks was identified. Our review includes clinical data from 325 patients across 16 of 18 known outbreaks.

### Added value of this study

This is the most comprehensive synthesis to date of clinical features of Marburg virus disease, aggregating patient data from over five decades of outbreak reports. It provides detailed frequencies of symptoms, grouped by syndromic categories, and estimates lethality among both confirmed and suspected cases. Our study highlights the predominance of general and gastrointestinal symptoms in early stages, the limited frequency and late appearance of hemorrhagic signs, and the variability in clinical presentations across outbreaks. The finding of lower case-fatality among PCR-confirmed cases underscores the potential impact of early diagnosis and care access.

### Implications of all the available evidence

The findings emphasize that MVD often presents with nonspecific symptoms, making early recognition and diagnosis challenging for clinicians. Hemorrhagic signs, while more specific, appear late and are not present in all patients. In the context of an active outbreak, known high-risk exposure or an unexplained rise in case-fatality, early suspicion of Marburg virus disease should be raised in patients presenting with febrile illness and gastrointestinal symptoms.

leading to hypovolemic shock, multiorgan dysfunction and death.<sup>5,6</sup> Given the non-specific nature of the initial symptoms, timely recognition of early cases is challenging, potentially leading to late provision of care and further spread of the disease.

The aim of our review is to provide a comprehensive description of the natural history of MVD and identify most common presenting symptoms and syndromes, to assist clinicians in timely recognition, and to estimate the overall lethality.

# Methods

This literature review was conducted to describe the clinical presentation and estimate the lethality of MVD, based on published reports of human cases since the first documented outbreak in 1967. We searched four databases: PubMed, Web of Science, African Journals Online (AJOL), and Embase, using free-text terms including "Marburg virus," "Marburg virus disease," and "Human Marburg disease." These terms were combined with the names of countries or outbreak locations and the corresponding years (e.g., "Marburg virus" AND "Uganda" AND "2004-2005"). The search was limited to articles published in English and was completed on October 30, 2024. Additional studies were identified by manually reviewing the references of relevant articles. Grey literature and unpublished reports were not included.

We included original studies, single case reports, case series, and outbreak reports that described clinical features or outcomes of confirmed or suspected human cases of MVD. Studies without clinical data, animal studies, and commentaries were excluded. In cases where multiple publications reported on the same outbreak, we selected the source with the most comprehensive clinical data for each symptom, to avoid duplication. Flow chart of article selection process is included as Fig. 1.

Data extraction was performed independently by two authors (RP and FMF), and discrepancies were resolved through discussion. Extracted variables included symptoms and signs at any stage of the disease, which were then categorized into four syndromic groups: systemic, gastrointestinal, respiratory, and hemorrhagic. Additional variables included outbreak context and case fatality rates when reported. Given the heterogeneity of data sources and the frequent use of aggregated clinical data in outbreak reports, results were summarized descriptively. In some cases, clinical details were presented as aggregated data for both microbiologically PCR-confirmed and probable cases. Probable cases were classified according to WHO criteria,8 as any clinically evaluated suspected case or any deceased suspected case epidemiologically linked to a confirmed case when timely specimens for laboratory confirmation could not be obtained. If specimens were collected in due time, these cases were reclassified as laboratoryconfirmed or non-cases. To preserve valuable outbreak data in remote settings with limited molecular diagnostics, we therefore included WHO-defined probable cases alongside confirmed cases in our analyses. In instances where multiple sources reported clinical descriptions from the same outbreak with partial overlap of patients, we selected, for each symptom, the source

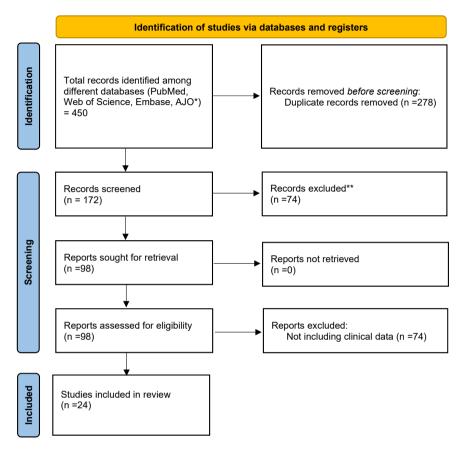


Fig. 1: Flow chart for study identification, screening and inclusion, according to PRISMA statement. \*African Journals Online. For more information, visit: http://www.prisma-statement.org/.

providing the most comprehensive dataset. Summary frequencies are presented with sample-size weighting of studies, i.e. based on unweighted pooled analysis of the individuals within studies.

Differences in proportions were evaluated using Chi-square test or Fisher's exact test, as appropriate. A two-tailed p-value <0.05 was considered statistically significant. Statistical analyses were performed using R version 4.3.2.

# Role of funding sources

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### Results

Since 1967, 18 MVD outbreakshave occurred, including imported cases in Western countries, accounting for a

total of 722 cases. After screening, 21 papers covering 16 of these outbreaks and providing detailed clinical descriptions of 325 cases (45% of all reported cases) were included in the review (Fig. 2).<sup>9-29</sup>

All included articles are observational studies describing specific outbreaks. Each study provides either patient-specific or aggregated descriptions of symptoms, and in some cases, information on patient outcomes.

There is substantial heterogeneity among the selected studies. They differ significantly in the time of data collection, spanning from 1967 to 2024; in geographical setting, including various African countries and high-income countries; and in context, ranging from large outbreaks in resource-limited settings to isolated imported cases.

The overall frequency of symptoms is summarized in Fig. 3. General systemic symptoms were the most commonly reported. Fever was the most frequent symptom, occurring in 296 cases (91.1%), followed by fatigue (74.8%), headache (64%), and myalgia (47.1%). Rash was observed in 11.7% of cases and conjunctivitis in 27.1%.

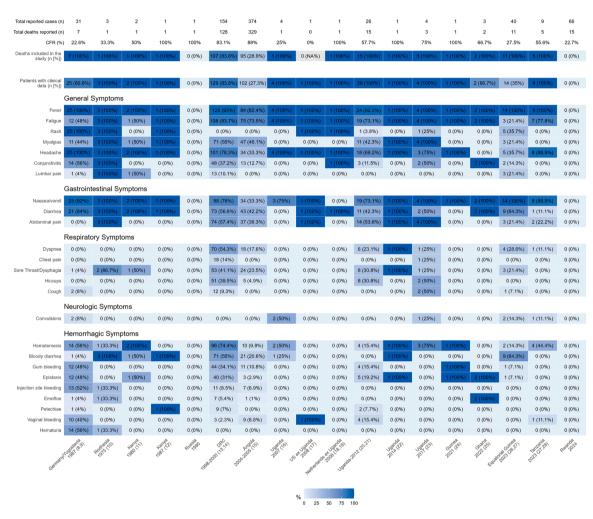


Fig. 2: Heat map of relative frequencies of MVD symptoms from 325 cases in 16 outbreaks.

Gastrointestinal symptoms were also prominent, with nausea or vomiting reported in 65.8% of cases, diarrhea in 52.6%, and abdominal pain in 42.8%. These symptoms were among the most consistent across different outbreaks and often presented early in the disease course.

Respiratory symptoms were variably reported. Dyspnea was present in 31.1% of cases, sore throat or dysphagia in 28.9%, and hiccups in 20.3%. Cough and chest pain were reported less frequently, in 5.2% and 5.8% of cases, respectively.

Hemorrhagic manifestations, while less common than general or gastrointestinal symptoms, were nonetheless clinically significant. Hematemesis was the most frequently reported hemorrhagic sign (43.1%), followed by bloody diarrhea (33.5%), gum bleeding (22.5%), epistaxis (20.3%), and injection site bleeding (9.8%). Less frequent bleeding manifestations included vaginal bleeding (8.6%), hematuria (4.6%), petechiae (4.0%), and subconjunctival hemorrhage (3.7%).

Neurologic symptoms were rare, with convulsions reported in only 2.5% of cases.

The overall case fatality rate (CFR) across all 722 reported cases was 72% (95% CI: 68.8–75.0%). Among the subset of 325 cases with available clinical data, the CFR was slightly higher at 77%, although this difference was not statistically significant (p = 0.86). Among PCR-confirmed cases alone (n = 200), 88 deaths were reported, resulting in a CFR of 44% (95% CI: 37.1–50.9%), which was significantly lower than the CFR among not-confirmed cases (83%, p < 0.001).

# Discussion

The review of clinical descriptions from 18 outbreaks confirms that MVD most often begins with general, non-specific symptoms that are difficult to distinguish from other endemic febrile illnesses. Given the nonspecific nature of its initial presentation, early

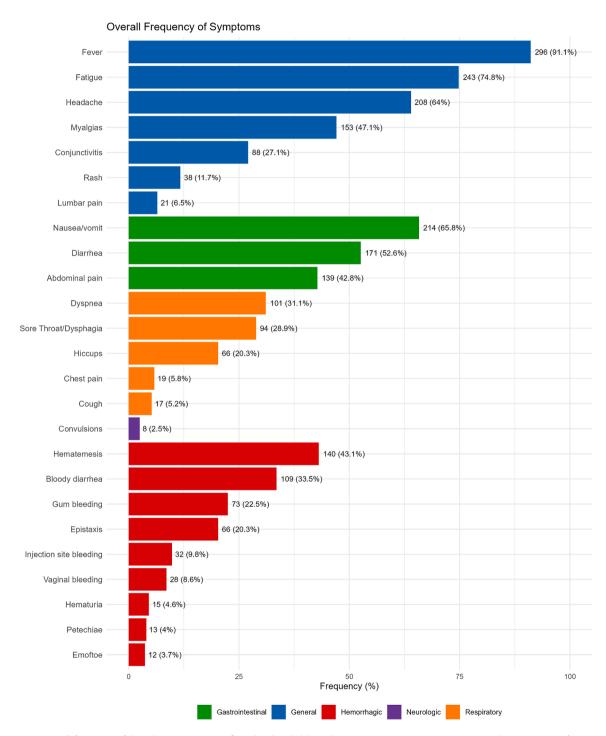


Fig. 3: Overall frequency of clinical symptoms in confirmed and probable Marburg Virus Disease cases. Bars represent the percentage of WHO-defined confirmed and probable cases reporting each symptom, with labels indicating absolute count and percentage. Symptoms are organized into five clinical categories, General (blue), Gastrointestinal (green), Respiratory (orange), Neurologic (purple) and Hemorrhagic (red), and ordered in descending frequency within each category. Only confirmed and probable cases (per WHO criteria; see Methods) were included in these summaries.

recognition and diagnosis are inherently challenging, especially in remote and resource-limited settings.<sup>30–33</sup>

The most frequently reported symptoms were general systemic signs such as fever, fatigue, headache, and myalgia, occurring in over half of the reported cases. Pever was present in over 90% of patients, making it a consistent feature of the disease, although not a discriminating one. These early symptoms closely resemble those of other common diseases in endemic areas, including malaria, typhoid fever, and various arboviral infections. As a result, reliance on general symptoms alone is unlikely to be sufficient for the timely identification of MVD, especially during the early stages of an outbreak or in the absence of known epidemiological links.

Gastrointestinal symptoms were the most prevalent syndromic presentation, with nausea or vomiting and diarrhea reported in more than half of patients. Abdominal pain was also common. 9-29 These symptoms are often present early in the disease course and may precede more specific signs, such as hemorrhagic manifestations. Importantly, gastrointestinal involvement has been observed consistently across most outbreaks, though notable variation was seen. For example, during the 2004-2005 outbreak in Angola, gastrointestinal symptoms were reported in only about one-third of patients, a finding that may reflect differences in data collection, disease evolution, or access to care. The high prevalence of gastrointestinal symptoms highlights the importance of considering MVD in patients presenting with febrile illness and significant digestive involvement, particularly in outbreak-prone areas or among exposed individuals.

Hemorrhagic symptoms, while not present in the majority of patients, remain critical indicators due to their greater specificity. Hematemesis and bloody diarrhea were the most common bleeding manifestations, each occurring in approximately one-third to one-half of cases. Other bleeding signs, such as gum bleeding, epistaxis, and bleeding from injection sites, were also documented. These symptoms tend to occur later in the disease course and are associated with more severe disease progression. Their absence in the early phase of illness should not be interpreted as an indication to rule out MVD. However, their presence should always prompt immediate consideration of viral hemorrhagic fevers, especially in the appropriate epidemiologic context.

Respiratory symptoms were variably reported, with dyspnea and sore throat/dysphagia being the most common. These findings challenge the traditional view that respiratory involvement is rare in MVD and suggest that these symptoms may be underrecognized or underreported. Notably, in the 1998–2000 Democratic Republic of the Congo outbreak, respiratory symptoms were present in nearly half of the reported cases. 14,15 The reasons for this discrepancy remain unclear and may be

related to differences in clinical practices, environmental factors, or virus-host interactions.

Neurologic symptoms were infrequent, with convulsions documented in only a small fraction of cases. 9.10.17.24.27.29 Similarly, skin manifestations such as rash and petechiae were not commonly reported. It is noteworthy that rash was more frequently described in Caucasian patients during early European outbreaks and was rarely reported in African patients. 9.10,13,21 This discrepancy may not reflect true biological differences but rather challenges in detecting and reporting cutaneous signs on darker skin tones.

The overall case fatality rate (CFR) observed across all outbreaks remains high, exceeding 70%.9-29 The higher CFR occurred during outbreak in Angola, in 2004-2005, reaching 88%.16 This finding may be partially explained by a more virulent, specific strain, as suggested by epidemiological and experimental studies.35,36 However, among the overall PCR-confirmed cases, the CFR was significantly lower at 44%. This difference is likely multifactorial. Confirmed cases are typically identified later in the outbreak, once laboratory diagnostics are available and response measures are in place. These patients are also more likely to benefit from earlier clinical recognition and access to supportive care. Conversely, cases from the initial phase of an outbreak, which are often not confirmed by laboratory testing, may include those with more severe disease or delayed presentation. The lower lethality among PCR-confirmed cases may therefore reflect both a temporal and access-to-care bias, rather than a difference in underlying disease severity.

These findings have important implications for clinical practice and outbreak response. The variability in symptom prevalence and syndromic presentation across different outbreaks underscores the need for flexible and context-adapted clinical case definitions. While hemorrhagic signs should always prompt urgent investigation, they occur too late in the disease course to be relied upon for early detection. Instead, clinicians should maintain a high index of suspicion for MVD in patients with fever and gastrointestinal symptoms, particularly in the setting of known exposure or ongoing transmission. The lack of reliable diagnostic capabilities, at least during the initial phases of epidemics, represents a significant limitation for appropriate clinical management, too. The displacement of mobile BSL-4 laboratories directly to areas with bat reservoirs or where prior spillovers have occurred may represent a viable strategic solution. Such units can rapidly bring high-containment diagnostic capabilities in remote or resource-limited settings. Mobile labs can significantly reduce sample transport delays, enabling faster pathogen detection, contact tracing, and outbreak containment, as successfully applied during past Ebola outbreaks in West Africa.37,38

This review is subject to several constraints that limit the interpretability of its findings. First, the majority of source reports provide only aggregated clinical summaries without patient-level data or clear differentiation between survivors and fatalities, thereby precluding robust correlations between symptomatology and outcome. Second, clinical observations were seldom tied to defined timepoints in the disease trajectory, and laboratory parameters (including hematological and biochemical measures) were rarely reported at standardized intervals, obscuring the temporal evolution and staging of Marburg virus disease. Third, variability in case definitions and diagnostic criteria, ranging from polymerase chain reaction confirmation to clinical or serological diagnosis, introduces misclassification bias, which may distort estimates of symptom prevalence and impede comparability across cohorts. Fourth, we reported symptom frequencies without weighting by study size or quality, because the included reports vary substantially in design, case definitions, data-collection methods and reporting completeness. Applying inverse-variance or sample-size weights under such heterogeneity would violate the assumptions required for valid meta-analysis and risk overrepresenting context-specific findings from larger cohorts while under-valuing important observations from smaller series. Fifth, by aggregating data spanning from the 1960s to the present, this analysis does not account for substantial advances in supportive care, such as fluid resuscitation protocols and critical-care availability, that have materially reduced case-fatality rates over time. Finally, the exclusion of non-English language publications may have omitted relevant data, although major Marburg virus disease outbreaks are documented in the English-language typically literature.

In summary, Marburg virus disease remains a highly lethal illness with a broad and evolving clinical spectrum. Early clinical presentation is dominated by general and gastrointestinal signs such as fever, myalgia, fatigue and diarrhea. These features overlap with those of many endemic infections and therefore complicate prompt recognition. Bleeding manifestations, which are more specific to Marburg virus disease, typically arise later in the course and are observed in only a minority of patients. To enhance early detection, development and validation of clinical algorithms tailored to local epidemiology must be accompanied by strengthened surveillance and rapid diagnostic testing at the point of care.

Looking ahead, outbreak research must adopt a prospective and standardized approach from first case detection. Response teams should deploy uniform case report instruments that capture detailed demographic, epidemiologic and symptom data at prespecified time points such as days 1, 3, 5 and 7 after symptom onset, together with serial laboratory measures including

hematology and biochemistry. Universal testing by polymerase chain reaction and serology for all suspected cases will secure accurate denominators for symptom prevalence and outcome analyses. Primary evaluations should be confined to laboratory confirmed cohorts, with probable or unconfirmed cases retained only for sensitivity assessments. When synthesizing data across sites or time periods, formal meta analytical methods using inverse variance weighting and predefined quality criteria are essential to address interstudy heterogeneity. Equally critical is comprehensive documentation of supportive care interventions, fluid administration volumes, blood transfusion practices and availability of intensive care, so that case fatality rates and patterns of symptom progression can be stratified by treatment context rather than era. Finally, the adoption of shared data platforms and common data elements, such as the WHO Global Clinical Platform forms to support the case management of viral haemorrhagic fever, will enable real-time collaboration, accelerate evidence generation during outbreaks, and inform adaptive clinical guidance to improve patient outcomes in future epidemics.39

#### Contributors

RP and FMF contributed to conceptualization, data sourcing and analysis, methodology, writing of orginal draft; RP and FMF verified the underlying data: LS contributed to data review and analysis, methodology, review and editing of initial draft; LF and EN contributed to conceptualization, data review and analysis, methodology, review and editing of initial draft, supervision of the whole process. All authors read and approved the final version of the manuscript.

# Data sharing statement

The complete database including clinical data of MVD symptoms derived from literature review, presented in a collective form, is available for those researchers who wish to access the data. Similarly, search strategy protocols is available. This data will be accessible soon after the publication, for any purposes, with no time limitation.

# Declaration of interests

All authors declare that no relevant conflicts of interest exist for the current paper. Details are included in the attached ICMJE form.

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# Review

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