ORIGINAL ARTICLE

Kyasanur Forest Disease: Clinical profile, diagnostic approaches, and management protocol

Rima R Sahay[1], Deepak Y Patil[2], Tushar Chiplunkar[3], Jagdish Patil[4], Anita M Shete[5], Manoj Murhekar[6], Nivedita Gupta[7], Kavitha Saravu[8], Pragya D Yadav[9]

[1]Indian Council of Medical Research-National Institute of Virology, Pune, Maharashtra, India
[2]National Institute of One Health, Seminary Hills, Nagpur, Maharashtra, India
[3]Primary Health Centre, Talkat, Dodamarg, Sindhudurg, Maharashtra, India
[4]Primary Health Centre, Banda, Sawantwadi Maharashtra, India
[5]Indian Council of Medical Research-National Institute of Epidemiology, Chennai, Tamil Nadu, India
[6]Indian Council of Medical Research, Ansari nagar, New Delhi, India
[7]Department of Infectious Diseases, Kasturba Medical College Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India

CORRESPONDING AUTHOR
Dr Pragya D. Yadav, Indian Council of Medical Research-National Institute of Virology, Pune, Maharashtra, India
Email: hellopragya22@gmail.com

CITATION
Sahay RR, Patil DY, Chiplunkar T, Patil J, Shete AM, Murhekar M, Gupta N, Saravu K, Yadav PD. Kyasanur Forest Disease: Clinical profile, diagnostic approaches, and management protocol. Journal of the Epidemiology Foundation of India. 2026;4(2):189-200.
DOI: https://doi.org/10.56450/JEFI.2026.v4i02.008
ARTICLE CYCLE
Received: 29/05/2026; Accepted: 11/06/2026; Published: 30/06/2026
COPYRIGHT
© The Author(s), [2026]. Published by the Journal of the Epidemiology Foundation of India (JEFI) under a Creative Commons Attribution 4.0 International License (CC BY 4.0).

Abstract

Background: Kyasanur Forest Disease (KFD) is an emerging tick-borne flavivirus first identified in 1957 in Karnataka, India. Since 2012, the disease has expanded to four other states, posing an increasing public health threat. **Aims:** To develop a standardized protocol for clinical characterization, diagnostic approaches, and management of KFD to assist clinicians and public health specialists. **Methods:** This protocol was developed through multidisciplinary expert consultations and synthesis of experiential learnings from managing KFD cases across multiple endemic states. **Results:** KFD poses a significant public health challenge with mortality rates of 2-10%, with higher fatality in non-endemic regions. Typical presentation includes abrupt fever, severe headache, myalgia, and prostration, with 10-18% progressing to a biphasic course. Haemorrhagic and neurological complications, including altered sensorium, seizures, and meningitis, may occur and are linked to increased mortality and multi-organ dysfunction. Diagnosis relies on molecular methods (RT-PCR, real-time RT-PCR) and serological assays (IgM/IgG ELISA). No specific antiviral treatment is available; management is primarily supportive, focusing on symptom control, fluid balance, and complications. **Conclusion:** This manuscript consolidates knowledge on epidemiology, clinical characteristics, differential diagnosis, laboratory investigations, and management strategies for KFD for clinicians and public health specialists. It highlights the need for early diagnosis, robust surveillance, and improved supportive care to reduce morbidity and mortality.

KEYWORDS
Kyasanur Forest Disease; clinical management; diagnosis; protocol; India

INTRODUCTION

Kyasanur Forest Disease (KFD), commonly known as "monkey fever," is a zoonotic disease caused by KFDV, a pathogenic arbovirus belonging to the family *Flaviviridae* [1]. First identified in 1957 following monkey deaths in Kyasanur forest, Karnataka, the virus is maintained in *Haemaphysalis* ticks, mammals, and birds. Humans acquire infection primarily through tick nymph bites, while monkey deaths indicate active transmission zones [1].

Transmission occurs seasonally from October to May during tick questing activity. High-risk populations include tribal communities, farmers, forest workers, cashew/areca nut cultivators, and animal grazers with occupational forest exposure. Case fatality rates range from 2-10% and are reportedly higher in non-endemic areas [1]. With 400-500 annual cases, KFD remains a persistent public health concern in Karnataka. Since 2012, the disease has expanded to Tamil Nadu, Kerala, Goa, and Maharashtra [1-10], driven by deforestation, land-use changes, and increased human-wildlife-tick contact [11].

The formalin-inactivated KFDV vaccine was discontinued in October 2022 due to poor efficacy and manufacturing issues [12-14], leaving personal protection and vector control as primary prevention strategies. Accurate diagnosis using molecular and serological assays (RT-PCR, IgM/IgG ELISA) is critical for effective clinical management and disease surveillance.

Aims & Objectives:

1. To provide a systematic, evidence-based, and experiential review of clinical presentations of KFD
2. To establish standardized diagnostic algorithms for KFD detection
3. To develop comprehensive management protocols for symptomatic KFD cases across different healthcare levels
4. To inform clinicians and public health professionals about the expanding epidemiology and changing clinical presentation of KFD

MATERIAL & METHODS

Study type & design

This study presents a protocol developed through expert consensus and synthesis of existing evidence. The methodology involved systematic review of published literature, analysis of experiential learnings from clinicians managing KFD cases, and multidisciplinary expert consultations.

Study setting

The protocol was developed through consultations with experts from endemic states including Karnataka, and Maharashtra, where the KFDV cases were managed actively, representing both established and new protocols that were followed in clinical management at primary health centres as well as tertiary care hospitals.

Study population

The protocol is designed for application across all age groups presenting with suspected KFD infection, with particular emphasis on high-risk populations including forest workers, tribal populations, and agricultural workers in endemic areas.

Study duration

Expert consultations and protocol refinement were conducted during January 2025 to July 2025.

Inclusion criteria for protocol development

- Published peer-reviewed literature on KFD epidemiology, clinical presentation, diagnosis, and management
- National and WHO guidelines on arboviral disease management
- Experiential learnings from clinicians with direct patient management experience in KFD-endemic areas both at primary health centers as well as tertiary care hospital.
- Laboratory diagnostic data and field epidemiology experiences from ICMR-National Institute of Virology (NIV), Pune and ICMR-National Institute of Epidemiology (NIE), Chennai

Strategy for data collection

Data were synthesized from:

- Systematic literature search using PubMed, Scopus, and Google Scholar for studies published between 2010-2025
- Review of national guidelines including the Operational Manual for KFD (Directorate of Health and Family Welfare Services, Government of Karnataka) and WHO guidelines for clinical management of arboviral diseases
- Expert consultations through structured meetings and Delphi methodology for consensus building

Working definitions: Case definitions for suspected, probable, and confirmed KFD cases were established based on modifications of existing definitions from the Directorate of Health and Family Welfare Services (Government of Karnataka), with adaptations to increase sensitivity for outbreak detection in new foci [1].

Ethical statement: This manuscript presents a clinical and management protocol developed through expert consensus and synthesis of existing evidence and experiential learnings from clinicians involved in the management of Kyasanur Forest Disease cases. It does not involve primary research on human participants, human samples, or identifiable data; therefore, institutional ethical approval and informed consent were not required.

Data Analysis: Data synthesis was performed through thematic analysis of clinical presentations, diagnostic approaches, and management strategies. Consensus was achieved through iterative expert discussions and review.

RESULTS

Integrating the insights from multidisciplinary experts with established clinical evidence, the following sections present the standardized framework for KFD management, ranging from initial clinical characterization to specific treatment protocols

Clinical characterization

Incubation period: The incubation period of KFD in humans is estimated to be 2 to 7 days after tick bites or exposure [1,11]. In up to 18% of cases, the disease follows a biphasic course, with a second phase often occurring after a 1 to 2-week afebrile period [15].

Signs and symptoms: KFD is a biphasic illness. The onset of the first phase is abrupt, beginning with chills and progressing to a severe frontal headache. Fever can escalate to as high as 104°F (40°C) and persists for about 3-9 days (mean 6.3 ±3 days) [13]. Severe myalgia, often likened to dengue fever, is a prominent feature, with body aches particularly pronounced in the nape of the neck, lumbar region, and calf muscles.

The clinical features are different in two phases of illness. The first phase presents with fever, myalgia, headache (40%) and other constitutional symptoms. Patients may have arthralgia, abdominal pain, vomiting, or diarrhoea. Diarrhoea and vomiting may develop by the third or fourth day of illness [15].

During the initial phase of illness, physical examinations reveal a febrile patient with severe prostration. Conjunctival suffusion is common. The cervical lymph nodes may be palpable [16]. A frequent feature is the appearance of macular or maculopapular lesions on the soft palate (enanthem), and diffuse maculo-papular rashes on the body. Petechiae, ecchymosis may be seen in patients with coagulopathy. Hypotension is observed in a proportion of patients at hospital presentation. Abdominal examination may reveal hepatosplenomegaly. Patients developing complications may also show hepatic dysfunction with jaundice and decreased urine output. Haemorrhagic manifestations, such as bleeding from the nose (epistaxis), gums, and intestines, can occur as early as the third day. However, the majority of cases resolve without significant haemorrhagic symptoms. Patient may present with vomiting of blood (haematemesis), a sign of upper gastrointestinal (GI) bleeding or fresh blood in the stools, (haematochezia), which indicates lower GI bleeding. Some patients may experience a persistent cough with blood-tinged sputum, and, rarely, significant haemoptysis (coughing up blood). Other sites of bleeding are oral cavity bleeding, intracranial haemorrhage and in women, vaginal bleeding or polymonorrhagia.

Haemorrhagic manifestations are seen in 8% of patients with KFD [15,16].

In the first phase of the illness, up to 10% of hospitalized patients may experience significant neurological complications such as altered sensorium, seizures, and coma, which have been linked to increased mortality [15,17]. With the exception of intracranial haemorrhage, focal neurological deficits are uncommon in the first phase.

KFD complications include pneumonitis, which can progress to acute respiratory distress syndrome (ARDS). Other reported complications are myocarditis, pancreatitis, and hepatitis, which can sometimes advance to fulminant hepatitis and hepatic encephalopathy. Acute kidney injury is also a possible complication [17]. The second phase of the illness, if it occurs, may be characterised by a resurgence of headache (100%), fever (neurological abnormalities such as aseptic meningitis, asthenia (weakness), tremors, delirium, convulsions, and focal neurological deficits such as cerebellar signs. Haemorrhagic manifestations can rarely be reported in the second phase. While the neurological manifestation in the first phase is due to encephalopathy or encephalitis, in the second phase it is usually due to meningitis, meningoencephalitis and cerebellar dysfunction.

The two phases show distinct laboratory features. The first phase is associated normal or elevated haemoglobin because of haemoconcentration or anemia because of bleeding or underlying nutritional cause. Characteristically there will be leucopenia and thrombocytopenia in the first phase whereas in the second phase there will be normal white blood cells or leucocytosis, and thrombocytopenia is rare. Similarly, elevated bilirubin, liver enzymes, creatine kinase, are observed in the first phase, they are primarily normal during the second phase [15,17]. In the first phase, activated partial thromboplastin time (aPTT) is elevated, while prothrombin time (PT) remains normal; however, in the second phase, both coagulation parameters are normal. In the first phase, severe cases might have disseminated intravascular coagulation, indicated by high prothrombin time (PT), aPTT, and low fibrinogen levels. The CSF analysis during the second phase reveals aseptic meningitis with lymphocytic predominance, elevated proteins and normal glucose.

The reported deaths are commonly observed during the first phase of the illness in about 2-10% of hospitalized patients. Causes of death can be refractory shock, myocarditis, ARDS, diffuse alveolar haemorrhage, gastrointestinal haemorrhage, fulminant hepatic failure, multi organ dysfunction and secondary bacterial sepsis. In a tertiary care retrospective study of hospitalized patients, independent predictors of mortality in the first phase included lower Cycle threshold (Ct) values, older age, lower respiratory tract involvement, altered sensorium, and elevated white blood cell counts [18]. Death is very rare in the second phase. The people who survive usually recover without neurological deficits. The convalescent phase of KFD is often prolonged with persistent generalized weakness, and reduce appetite.

Differential diagnosis: The clinical similarity of KFD to other endemic infections requires the exclusion of the common co-circulating pathogens, particularly those common in the Western Ghats area. Differential diagnoses should be classified by clinical syndrome:

- **Acute Undifferentiated Febrile Illness:** Chikungunya, Malaria, Typhoid fever.
- **Hemorrhagic Fevers:** Dengue, Crimean-Congo Hemorrhagic Fever (CCHF), Leptospirosis, Scrub Typhus, Omsk haemorrhagic fever (OHF)
- **Neurological Infections:** Japanese Encephalitis, West Nile Virus, Zika virus disease, Tick-borne encephalitis (TBE), Lyme disease, Bacterial Meningitis.

The clinical overlap necessitates careful consideration of the patient's epidemiological history and timely laboratory confirmation to distinguish KFD from these other conditions.

Case definition: Given the variability in clinical illness associated with KFD infection and the scarcity of definitive clinical diagnostic criteria, laboratory testing is paramount for accurate case ascertainment. The following case definitions are proposed with modifications in earlier available case definition The case definitions used following are according to the

guidelines of the Directorate of Health and Family Welfare Services (Government of Karnataka), and have been changed to provide greater sensitivity to outbreak detection in new foci [1]:

Suspected Case: A person of any age presenting with acute onset of fever with any of the following: headache, myalgia, prostration, generalized weakness, nausea, vomiting, diarrhoea, and occasionally neurological or haemorrhagic manifestations. AND associated with any of the following risk factors:

- Lives in the forests of an endemic area.
- Recent visit to an endemic area* during the past 2 weeks.
- Recent visit to an area with unexplained monkey deaths.
- History of occupational engagement in forests of an endemic area during the past 2 weeks.

*Endemic area: An area which has reported positivity in human or monkey viscera or tick pools in the last 5 years.

Probable Case: A clinically similar presentation that does not meet the criteria for a confirmed definition but has one of the following features:

- Epidemiological link to a documented exposure to a KFD-affected area (one or more of the following exposures within 2 weeks before onset of symptoms).
- Positive result on immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) testing of clinical serum specimens.

Confirmed Case: A confirmed case of KFD is defined as a case that meets the criteria for a probable KFD case and, in addition, should cover any of the following:

- Detection of KFDV-specific genetic sequence by reverse transcription-polymerase chain reaction (RT-PCR) or real-time RT-PCR from blood or tissues.
- Isolation of KFDV in cell culture or in a mouse model, from blood or tissues.

Screening of the suspected cases: Serological or molecular testing is necessary to exclude other differential diagnoses, as detailed in the "Differential Diagnosis" section.

Diagnostic workflow at different healthcare levels: To ensure early detection and systematic management, a stratified diagnostic approach is implemented across the healthcare hierarchy, guiding clinicians from initial screening to advanced critical care interventions

At Primary/Community health centers

Patients presenting at primary or community health centers should undergo an initial screening and basic investigations to detect hematological abnormalities. The following steps are recommended [Figure-1]:

- Complete Blood Count (CBC): Includes Total Leukocyte Count (TLC), Differential Leukocyte Count (DLC), Hemoglobin (Hb), and Platelet count. This helps in identifying leukopenia, thrombocytopenia, and reduced hemoglobin (Hb) levels.
- If abnormalities are detected (leukopenia, thrombocytopenia, or reduced Hb):
  - Liver Function Test (LFT): Assesses hepatic involvement.
  - Coagulation Profile: Evaluates blood coagulation status.
  - Renal Function Test (RFT): Assesses renal involvement.

At tertiary care centers

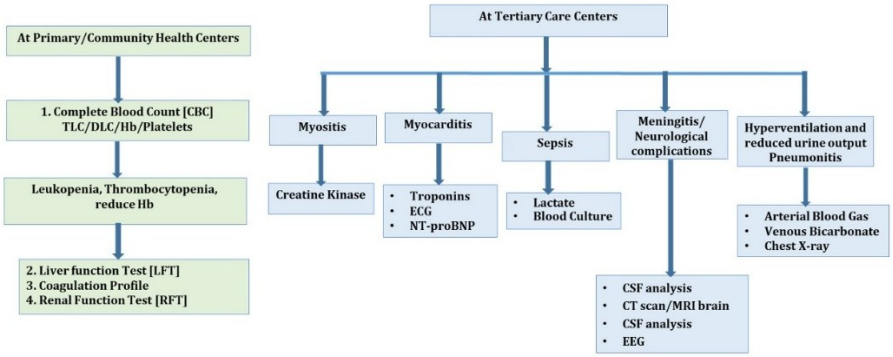
Patients requiring comprehensive evaluation or those with severe symptoms or complications are referred to tertiary care centers, where advanced investigations are performed, depending on the clinical presentation [Figure-1]:

- Myositis:
  - Creatine Kinase: measured to assess muscle involvement and diagnose myositis.
- Myocarditis:
  - Troponins: indicates myocardial injury
  - Electrocardiogram (ECG): Evaluates cardiac rhythm and detects myocarditis
  - NT-proBNP: assesses heart failure.
- Sepsis:
  - Lactate: Indicates tissue hypoperfusion and metabolic stress.
  - Blood Culture: Identifies the causative organism and blood samples to be collected prior to antibiotic administration.
- Meningitis/Neurological Complications:
  - Cerebrospinal Fluid (CSF) Analysis: to identify infectious or inflammatory causes

- CT Scan/MRI Brain: to detect structural or inflammatory brain involvement.
- Electroencephalogram (EEG): to evaluate functional brain abnormalities.

- Hyperventilation, Reduced Urine Output, Pneumonitis:
  - Arterial Blood Gas (ABG): Assesses respiratory function and acid-base balance.
  - Venous Bicarbonate: Evaluates metabolic status,
  - Chest X-ray: Detects pulmonary involvement.

This stepwise approach ensures systematic evaluation of patients based on the level of healthcare facility and clinical presentation, allowing for timely detection and management of hematologic, hepatic, renal, muscular, sepsis, cardiac, neurological, and respiratory complications.



Laboratory diagnosis:

- **Real-time RT-PCR:** This is the first-line test for KFD, recommended during the acute stage of infection (1-24 days) from human blood/serum [16]. KFD RT-PCR is also utilized for testing dead infected monkey blood and viscera, or tick tissues during surveillance activities [19-21].
- **IgM ELISA:** The IgM ELISA test can be used to identify KFD antibodies starting from the fourth day of illness, which is a sign of a recent infection [19].
- **IgG ELISA/ Neutralization Tests:** These are applied to the diagnosis of past infections (paired sera) and in serosurveillance when it is necessary to determine whether a previously naïve area has any infected individuals.

Table 1 summarizes the major differences in clinical and laboratory features of the two phases to make easier reference.

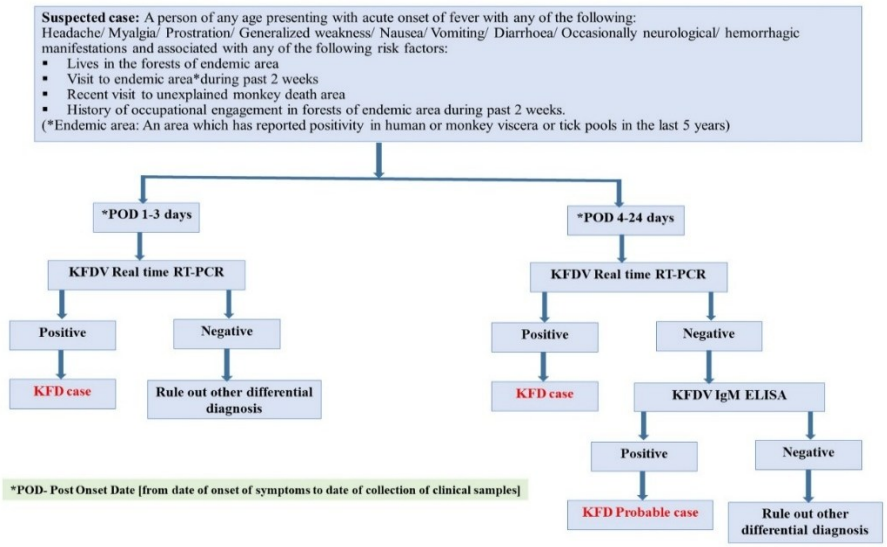
Table 1: Comparison of Clinical and Laboratory Features in KFD Phases

Feature	First Phase (Days 1-8)	Second Phase (Weeks 3-4)
Clinical Symptoms	Sudden high fever, severe headache, myalgia, prostration, hemorrhagic manifestations (in severe cases).	Recurrence of fever, severe headache, meningeal signs, tremors, mental status changes.
Pathophysiology	Viremia, cytokine storm.	Immune-mediated / Inflammatory response.
Hematology	Leukopenia, Thrombocytopenia.	Normal WBC (or leukocytosis), Normal Platelets.
Diagnostic Test	RT-PCR Positive.	IgM and IgG antibodies Positive.

Biosafety, specimen handling, and transport

During sample collection and processing, strict compliance with the biosafety measure is obligatory. Handling of all specimens should be done in accordance with risk group-2 equivalent precautions [22]. The staff should use the right personal protective equipment (PPE) such as N95 masks, gloves, and gowns. Any biological waste produced during the sampling process should undergo decontamination and should be disposed of in accordance with the biomedical waste

management regulations [22]. The detailed standard operating procedures (SOPs) must be rigorously followed at each hospital ward and laboratory to ensure proper specimen collection. The Blood samples should be collected by the treating physician or a trained phlebotomist via venipuncture using an aseptic technique from the hand or antecubital fossa. 5-6 ml of blood samples should be collected and distributed into EDTA, SSGT (Serum Separator Gel Tube), Citrate, and Heparin tubes as per the desired serological and hematological tests. Transportation of clinical samples should comply with the WHO/ International Air Transport Association recommendations on the transport of Infectious Substances (Category B) [23]. The samples must be transported under cold chain (2–8°C) using triple layer packaging system. The transit time to the testing laboratory must be no longer than 24-48 hours. The diagnostic algorithm to be followed for testing of suspected KFDV cases [Figure-2].



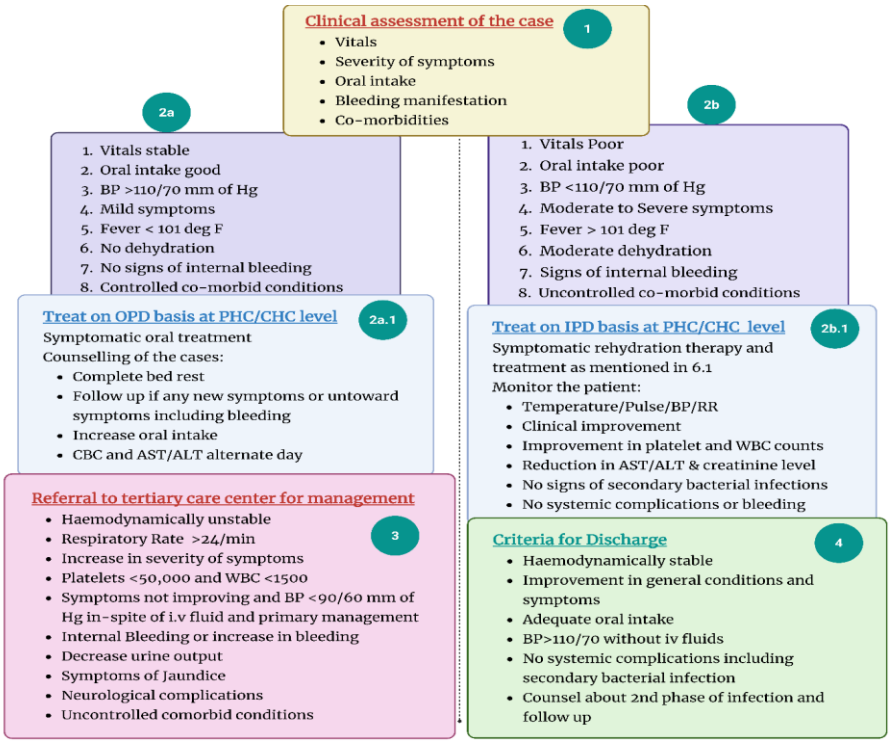
Surveillance and reporting workflow

Proper surveillance requires a well-organized reporting process. The positive laboratory results of KFD are to be reported to the District Surveillance Unit (DSU). The data is then channeled to the State Surveillance Unit (SSU) where the information is updated in Integrated Health Information Portal (IHIP) under the Integrated Disease Surveillance Programme (IDSP) of the National Centre for Disease Control (NCDC). This will guarantee real time, thorough surveillance loop in response to outbreaks.

Clinical management of KFD cases

The management of KFD is purely supportive because no specific antiviral treatment is currently available. This involves managing symptoms, maintaining hydration, and using standard precautions for patients who have bleeding disorders. At the Primary Health Centre (PHC) level and Community Health Center (CHC) level- including Rural Hospital (RH) and Sub-district hospital (SDH), the clinical management of KFD cases is stratified based on the patient's presenting signs, symptoms, and potential complications. Initial assessment encompasses vital signs, symptom severity, oral intake status, evidence of bleeding, and co-morbidities. Patients presenting with stable vitals, adequate oral intake, mild symptoms, and no overt signs of dehydration or internal bleeding are typically managed on an outpatient department (OPD) basis, focusing on symptomatic relief, bed rest, and close monitoring with follow-up complete blood count (CBC) and liver function tests. Conversely, individuals exhibiting clinical deterioration, characterized by poor vitals, compromised oral intake, moderate to severe symptoms, dehydration, or signs of internal bleeding, necessitate inpatient department (IPD) care at the PHC. This involves intensive symptomatic rehydration therapy and meticulous monitoring of physiological parameters and laboratory markers. Critically, any patient displaying hemodynamic

instability, progressive symptom severity, significant thrombocytopenia or leucopenia, refractory hypotension despite intensive fluid resuscitation, persistent bleeding, neurological sequelae, or uncontrolled co-morbidities mandates immediate referral to a higher-level facility for advanced medical intervention. This tiered approach optimizes resource utilization at the PHC while ensuring timely escalation of care for complicated KFD presentations [Figure-3].



Recommended treatment symptomatic KFD cases:

As KFD is a viral illness, its management is primarily supportive, focusing on the alleviation of symptoms, correction of physiological derangements, and prevention/treatment of secondary complications. This document outlines a structured approach to the symptomatic management of KFD cases, based on common clinical presentations.

Fever, headache, severe myalgia, malaise [24]:

- Paracetamol (Acetaminophen): 0.5–1g every 4–6 hourly, with a maximum of 4g daily, until symptoms abate. Dosage should be adjusted based on patient weight and age. Caution is advised in patients with liver abnormalities or altered liver enzymes.
- Tramadol: 50-100 mg every 8 hourly for severe myalgia. (Oral/Intravenous)
- Tepid sponging: To help reduce fever.
- Non-steroidal anti-inflammatory medications NSAIDS should be avoided.

Nausea and vomiting:

- Antiiemetics such as
  - Metoclopramide: 5–10 mg intravenously (IV) single dose.
  - Domperidone: 10 mg orally three times daily (tid) half an hour before meals.
  - Ondansetron: 8 mg IV twice daily (bd).
- Stress ulcer prophylaxis/gastritis
  - Pantoprazole: 40 mg orally once daily (od), may be given IV
  - Ranitidine 150 mg twice daily oral or IV
- Intravenous fluids: Administer if the patient has prostration or dehydration and is unable to take oral fluids.

Secondary infections:

- Broad-spectrum antibiotics is indicated if super-added bacterial infection is suspected, particularly in hemodynamically unstable patients. Examples include Inj Ceftriaxone 1g IV od or Piperacillin Tazobactam 4.5g IV tid or

other antibiotics based on local antibiogram. Blood cultures are to be requested before starting antibiotics.

Haemorrhagic diathesis:

- Vitamin K: 10mg/day IV for 3 days.
- Tranexamic acid: 500mg orally or IV three times daily for 5-7 days if active bleeding is present.
- Prophylactic platelet transfusions are not definitively recommended for patients with a platelet count of <50,000 platelets/microlitre who have no active bleeding [20]. Such transfusions are only suggested for non-bleeding patients with a platelet count <10,000/µL, or for invasive procedures.

Altered sensorium, irritability, and seizures:

- Mannitol 20%: Administer every 8 hourly (age-wise dosage based on body weight is recommended) for cerebral oedema. Mannitol should be avoided in cases of decreased urine output or renal failure. In such scenarios, 3% NaCl or Furosemide (Lasix) 20 mg can be considered.
- Levetiracetam: 20-60 mg/kg IV at 2-5 mg/kg/min if the patient experiences seizures. Dose modification is required in renal failure.
- Lorazepam/Diazepam: Can be used to terminate active seizures.

Electrolyte imbalance/Hyponatraemia and acidosis:

- Intravenous fluids: Administration of Sodium chloride or Ringer Lactate depending on the degree of dehydration and the patient's general condition.
- Metabolic acidosis: If present, it needs to be evaluated and treated, particularly if the pH is less than 7.1.

Fluid refractory hypotension/Shock [25]:

- Norepinephrine: 0.2 to 1.5 µg/kg/min (5-30 µg/min).
- Vasopressin: Up to 0.03-0.04 units/min, or Epinephrine: 0.01 to 0.5 µg/kg/min in adults (5-15 µg/min), may be considered as second-line agents if norepinephrine is insufficient.

Referral of the patient to a higher centre:

If the patient presented with any of the following signs or symptoms, it should be immediately taken o tertiary care centre:

- Refractory Shock: Hemodynamic instability despite initial fluid resuscitation.
- Severe Thrombocytopenia: Platelet count <50,000/µL with or without active bleeding.
- Neurological Manifestations: Altered sensorium (Glasgow Coma Scale < 13), seizures, or focal neurological signs.
- Multi-Organ Dysfunction: Evidence of acute kidney injury (oliguria/anuria) or severe liver dysfunction.
- Co-morbidities: Uncontrolled pre-existing conditions (e.g., severe diabetes) complicating management.
- Blood pressure (BP) less than 90/60 mm of Hg (even after IV fluids)
- Persistent heart rate >100/min, Irregular pulse
- Respiratory rate greater than 24 breaths/min
- Altered sensorium
- Significant bleeding manifestations
- Decreased urine output
- Jaundice
- Severe dehydration
- Uncontrolled co-morbid conditions
- White blood cell count less than 1500/µL

Note: The administration, dosage, and duration of medicines/drugs are determined by the patient's clinical condition. The treating physician or specialist retains the authority to make decisions regarding the course of treatment and management.

Discussion

KFDV remains a significant public health challenge in India, with its expanding geographical footprint and potential for severe outcomes. The lack of specific antiviral treatment underscores the critical importance of early diagnosis, aggressive supportive care, and robust surveillance. It is crucial for clinicians in both endemic and newly affected areas to consider the possibility of KFD in patients who present with an acute fever and a history of relevant exposure. Non-specific febrile illness may however be more common in children requiring a high index of suspicion in endemic countries in order to avoid delays in diagnosis and worse prognoses. While comprehensive data on pediatric KFD is

limited, available literature shows that the clinical course of infection among children is similar to that among adults. [26]. Standardized case definitions, timely laboratory confirmation through molecular and serological assays, and comprehensive supportive clinical management are crucial for better patient outcomes. Clinicians should also be alert to co-infections (e.g. KFD with malaria or leptospirosis or typhoid fever) especially during the post-monsoon seasons when there is overlapping of vectors. The co-infection also may modify the course and severity of the clinical presentation, which makes it harder to diagnose and provide supportive treatment.

Mitigating the burden of KFD and preventing future outbreaks requires key actions such as further research into antiviral treatments, newer vaccine development, and enhancing preparedness strategies. This protocol is designed for healthcare providers who are responsible for identifying and treating patients with KFDV infections, and it can be used at all levels of the healthcare system. The protocol will also be used as a resource by policymakers, health managers, and health facility administrators to help develop national, regional, and local guidelines for clinical management. In conclusion, this protocol provides a gap in the current literature as it synthesizes multi-centers experience learning and recent epidemiological changes- namely the extension to Maharashtra, Goa and Kerala. It also offers a standardized, up-to-date method of diagnosis and management in both established and newer endemic areas that has a significant gap in existing clinical guidelines.

Conclusion

This protocol fills a significant gap in the current literature by synthesizing multi-center experiential learning and recent epidemiological changes, namely the extension to Maharashtra, Goa, and Kerala. It offers a standardized, up-to-date approach to diagnosis and management in both established and newer endemic areas, which has been lacking in existing clinical guidelines. The comprehensive algorithms presented provide practical guidance for healthcare providers at all levels of the healthcare system, from primary centers to tertiary care facilities.

Recommendation

This protocol may be used as a resource for healthcare providers responsible for identifying and treating patients with KFDV infections and can be used at all levels of the healthcare system. It will also be useful for policymakers, health managers, and health facility administrators to develop national, regional, and local guidelines for clinical management.

Limitation of The Study

This protocol has few limitations that should be considered when interpreting and applying its recommendations. First, the clinical presentation and outcomes may vary across different geographic regions due to differences in host genetics, and healthcare access, which may not be fully captured in this consolidated protocol. Additionally, the rapid geographic expansion of KFD to new states and districts may outpace the current understanding of disease patterns and risk factors, potentially limiting the generalizability of certain recommendations to newly affected areas. Limited published data on paediatric KFD cases constrains the ability to provide age-specific management recommendations, and clinicians must therefore exercise caution when applying adult-derived protocols to children. Furthermore, the absence of specific antiviral therapies means that all management recommendations are supportive, and evidence for some interventions is extrapolated from other viral haemorrhagic fevers rather than derived from KFD-specific clinical trials. Finally, the discontinuation of the formalin-inactivated KFD vaccine in October 2022 has created a significant gap in prevention strategies, and this protocol cannot address this deficiency pending the development and deployment of new-generation vaccines with improved efficacy and safety profiles.

Authors Contribution

RRS, DYP, KS, TC, JP, MM, AMS, NG, PDY contributed to protocol writing, data

interpretation, and critical review. All authors contributed to the critical review and finalization of the paper. The authors' extensive clinical experience in managing patients with Kyasanur Forest Disease in India, alongside their active involvement in the establishment and validation of laboratory diagnostic methods, underpin the development of this comprehensive clinical protocol.

Rima R Sahay and Deepak Y Patil have contributed equally and are equal first authors. Tushar Chiplunkar and Jagdish Patil have contributed equally and are equal second authors. Pragya D Yadav and Kavitha Saravu are co-corresponding authors.

Financial Support and Sponsorship

The PM-ABHIM intramural grant was provided from Indian Council of Medical Research, New Delhi for conducting this study under the project "Country-wide sero and tick surveys, host susceptibility, immune correlates of protection, development of diagnostics and vaccine, and prediction and prevention models for Kyasanur Forest Disease" [MCE2408].

Conflict of Interest

There are no conflicts of interest.

Acknowledgement

Authors are grateful for the administrative support from Dr. Naveen Kumar, Director, ICMR-National Institute of Virology, Pune.

Declaration Of Generative AI And AI Assisted Technologies In The Writing Process

During the preparation of this work, the authors used AI-assisted tools (including grammar and language refinement tools) for the purpose of improving clarity, consistency, and readability of the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

1. Operational Manual Kyasanur Forest Disease. Directorate of Health and Family Welfare Services Government of Karnataka 2020. Available from https://monkeyfeverrisk.ceh.ac.uk/sites/default/files/2022-05/Operational-Manual-Kyasanur-Forest-Disease-DHFWS-2020-compressed.pdf (Accessed on 25/06/2026)
2. Awate, P., Yadav, P., Patil, D., Shete, A., Kumar, V., Kore, P., & Mourya, D. T. (2016). Outbreak of Kyasanur forest disease (monkey fever) in Sindhudurg, Maharashtra State, India, 2016. Journal of Infection, 72(6), 759-761.
3. Chakraborty S, Andrade FC, Ghosh S, Uelmen J, Ruiz MO. Historical expansion of Kyasanur forest disease in India from 1957 to 2017: a retrospective analysis. GeoHealth. 2019 Feb;3(2):44-55.
4. Kasabi GS, Murhekar MV, Yadav PD, Raghunandan R, Kiran SK, Sandhya VK, Channabasappa GH, Mishra AC, Mourya DT, Mehendale SM. Kyasanur forest disease, India, 2011–2012. Emerging infectious diseases. 2013 Feb;19(2):278.
5. Mehla R, Kumar SR, Yadav P, Barde PV, Yergolkar PN, Erickson BR, Carroll SA, Mishra AC, Nichol ST, Mourya DT. Recent ancestry of Kyasanur Forest disease virus. Emerging infectious diseases. 2009 Sep;15(9):1431.
6. Mourya DT, Yadav PD, Patil DY, Sahay RR, Rahi M. Experiences of Indian Council of Medical Research with tick-borne zoonotic infections: Kyasanur Forest disease & Crimean-Congo haemorrhagic fever in India with One Health focus. Indian Journal of Medical Research. 2021 Mar 1;153(3):339-47.
7. Munivenkatappa A, Sahay RR, Yadav PD, Viswanathan R, Mourya DT. Clinical & epidemiological significance of Kyasanur forest disease. Indian Journal of Medical Research. 2018 Aug 1;148(2):145-50.
8. Tandale BV, Balakrishnan A, Yadav PD, Marja N, Mourya DT. New focus of Kyasanur Forest disease virus activity in a tribal area in Kerala, India, 2014. Infectious diseases of poverty. 2015 Mar 5;4(1):12.
9. Work TH, Trapido H. Summary of preliminary report of investigations of the Virus Research Centre on an epidemic disease affecting forest villagers and wild monkeys of Shimoga District, Mysore. Indian J Med Sci. 1957.
10. Munivenkatappa A, Yadav PD, Sahay RR, Sk K, Shete AM, Patil DY, et al. Clinical, epidemiological, and molecular investigation of Kyasanur forest disease from Karnataka state, India during 2018-2019. Infect Dis (Lond). 2024;56(2):145-156. doi: https://doi.org/10.1080/23744235.2023.2282042

11. Paladan S, Kumbar B, Govindasamy D, Patil S, Kumar HC, Yogisharadhya R, Yadav P, Vivian TJ, Gaekwad SS, Kumar N, Gulati BR. Unravelling ecological factors influencing phylodynamics of Kyasanur Forest Disease in India. Infection, Genetics and Evolution. 2025:105831. https://doi.org/10.1016/j.meegid.2025.105831
12. Dandawate CN, Desai GB, Achar TR, Banerjee K. Field evaluation of formalin inactivated Kyasanur forest disease virus tissue culture vaccine in three districts of Karnataka state. Indian J Med Res. 1994; 99:152-8.
13. Oliveira A, Selvaraj K, Tripathy JP, Betodkar U, Cacodcar J, Wadkar A. Kyasanur Forest Disease vaccination coverage and its perceived barriers in Goa, India—A mixed methods operational research. Plos one. 2019 Dec 31;14(12): e0226141
14. Bohra B, Srivastava KS, Raj A, Pal N, Shukla R. Kyasanur Forest disease virus: epidemiological insights, pathogenesis, therapeutic strategies, and advances in vaccines and diagnostics. Viruses. 2025;17(8):1022.
15. Gupta N, Varma M, Saravu K. Difference in clinical presentation between the first and second phases of Kyasanur Forest disease: an experience from a teaching hospital in South India. *Infez Med*. 2020;28(4):597-602.
16. Gupta N, Chunduru K, Safeer K M, Saravu K. Clinical and laboratory profile of patients with Kyasanur forest disease: A single-centre study of 192 patients from Karnataka, India. *J Clin Virol*. 2021; 135:104735. https://doi.org/10.1016/j.jcv.2021.104735
17. Gupta N, Nallapati VT, Chunduru K, Vithivattical AR, Kadavigere R, Saravu K. Neurological manifestations of Kyasanur Forest disease: a retrospective cohort study from South India. Transactions of The Royal Society of Tropical Medicine and Hygiene. 2022 Oct;116(10):944-8 https://doi.org/10.1093/trstmh/trac018
18. Gupta N, Tirlangi PK, N S, Swathi Kiran PV, Varma M, Mukhopadhyay C. Role of cycle threshold values in predicting poor outcomes in patients with Kyasanur Forest disease: a retrospective cohort study. Ann Med. 2025;57(1):2532857. https://doi.org/10.1080/07853890.2025.2532857
19. Yadav PD, Gurav YK, Shete AM, Jain R, Nyayanit DA, Pardeshi PG, et al. Kinetics of viral RNA, immunoglobulin-M & G antibodies in Kyasanur forest disease. Indian J Med Res. 2019;150(2):186-193. https://doi.org/10.4103/ijmr.IJMR_1929_17 .
20. Mourya, D. T., Yadav, P. D., Mehla, R., Barde, P. V., Yergolkar, P. N., Kumar, S. R., ... & Mishra, A. C. (2012). Diagnosis of Kyasanur forest disease by nested RT-PCR, real-time RT-PCR and IgM capture ELISA. Journal of virological methods. 2012;186(1-2), 49-54.
21. Mourya DT, Munivenkatappa A, Kulkarni R, Yadav PD, Gupta N, Rahi M. Re-assessing the biosafety level requirement & defining surveillance need for Kyasanur forest disease virus: Changed paradigm. Indian J Med Res. 2021;154(6):776-780. https://doi.org/10.4103/ijmr.IJMR_1757_19
22. World Health Organization (2020). Laboratory biosafety manual. 4th edition.
23. World Health Organization (2021). Guidance on regulations for the transport of infectious substances 2021-2022. World Health Organization. Available online at: https://iris.who.int/server/api/core/bitstreams/bebbc361-e2f7-40d0-9e8f-6e4660869b64/content (Accessed on 25-06-2026)
24. WHO guidelines for clinical management of arboviral diseases: dengue, chikungunya, Zika and yellow fever [Internet]. Geneva: World Health Organization; 2025–. PMID: 40690567. Available from https://www.who.int/publications/i/item/9789240111110 Accessed on 25-06-2026
25. Oczkowski S, Alshamsi F, Belley-Cote E, Centofanti JE, Hylander Møller M, Nunnaly et al. Surviving Sepsis Campaign Guidelines 2021: highlights for the practicing clinician. Pol Arch Intern Med. 2022;132(7-8):16290. https://doi.org/10.20452/pamw.16290 .
26. Chakraborty S, Sander W, Allan BF, Andrade FCD. Sociodemographic factors associated with Kyasanur forest disease in India - a retrospective study. IJID Reg. 2024;10:219-227. https://doi.org/10.1016/j.ijregi.2024.02.002