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COMMISSIONED ARTICLE

# Kyasanur forest disease: a state-of-the-art review

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**Summary**: Kyasanur forest disease (KFD) virus is a flavivirus that can be transmitted to humans from monkeys or other mammals through hard ticks (*Haemaphysalis spinigera*). The disease is endemic to 16 districts in 5 states of Southern India and is reported in the dry season, most commonly in humans travelling to the forests in these areas. The aim of this systematic review is to raise awareness of the clinical and laboratory manifestation of KFD among physicians and travel medicine practitioners. A total of 153 articles were screened of which 16 articles that met the inclusion and exclusion criteria were included for qualitative analysis. KFD is an acute haemorrhagic fever with a biphasic component in some individuals. The second phase is usually marked by neurological symptoms. Leucopoenia, thrombocytopenia and elevated transaminases are the hallmarks of the first phase of KFD. The diagnostic modality of choice in the first few days of illness is polymerase chain reaction assay, whereas serology is used in the late phase. In the absence of a specific antiviral treatment, the clinical management of patients is limited to supportive care. Avoidance of exposure and vaccination is recommended to prevent this infection.

## Introduction

Kyasanur forest disease (KFD) is named after a namesake forest area in the district of Shimoga in Karnataka, where it was first identified.[1] In 1957, this region reported a spate in deaths of the black-faced langur (*Presbytus entellus*) and the red-faced bonnet monkey (*Macaca radiata*).[1] This coincided with reports of febrile illness in humans, giving rise to the colloquial term of 'monkey disease'.[1,2] One of the first cases of KFD was described in a young male who climbed up a tree to collect what he thought was honey with a swarm of bees. It, however, turned out to be a dead monkey on a branch with flies all around.[1] It is now known that the infected hard tick, *Haemaphysalis spinigera* from the dead monkeys latch on to the humans and the bite results in the transmission of KFD virus (genus *Flavivirus*).[1,3–5] Other small mammals (rodents and shrews) and cattle are known to be reservoirs as well.[5] The disease is now endemic in five states of Southern India that is not only home for a large population but also attracts tourists from all over the world. Although several cases of KFD are reported between December and May every year, there are scarce reports on clinical and laboratory features of KFD. The

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aim of this review was to summarize the clinical and laboratory manifestations of KFD for the physicians working in the endemic areas and international travel medicine practitioners.

## Methodology

We first searched for any existing systematic review (SR) on clinical and laboratory manifestations of KFD. Although narrative reviews were present, no SR was identified. We conducted a comprehensive search of the English medical literature between January 1950 and June 2020 via the Medline/PubMed and SCOPUS database. We used (Kyasanur forest disease OR KFD OR KFDV OR Haemaphysalis) AND (India OR Karnataka OR Maharashtra OR Kerala OR Goa OR Bombay OR Madras OR Shimoga) AND (Clinical features OR Clinical findings OR Clinical study OR Clinical Observations OR Clinical epidemiology OR Symptoms OR Sign OR Haemorrhagic OR Neurological OR Laboratory features OR Laboratory findings OR Laboratory study OR Laboratory Observations OR Laboratory epidemiology) as the search terms. All case studies and case series (prospective or retrospective), where patient data were available were included. The references of included articles were screened for other articles that may satisfy the inclusion and exclusion criteria (snowball search). Articles not containing any of the following parameters were excluded: patient's age and sex, clinical and laboratory features of confirmed cases of KFD. The titles and abstracts of the 153 articles were reviewed independently by 2 of the authors (N.G. and W.W.) to find studies with clinical and/or laboratory manifestations of KFD (Figure 1). In case of any disagreement on study selection between the two authors, the third author (K.S.) was consulted. A total of 37 articles were included for full-text review, and a total of 16 articles were used for the final analysis (Table 1).[1–16] A total of 1429 confirmed cases were identified in these studies. The following study and

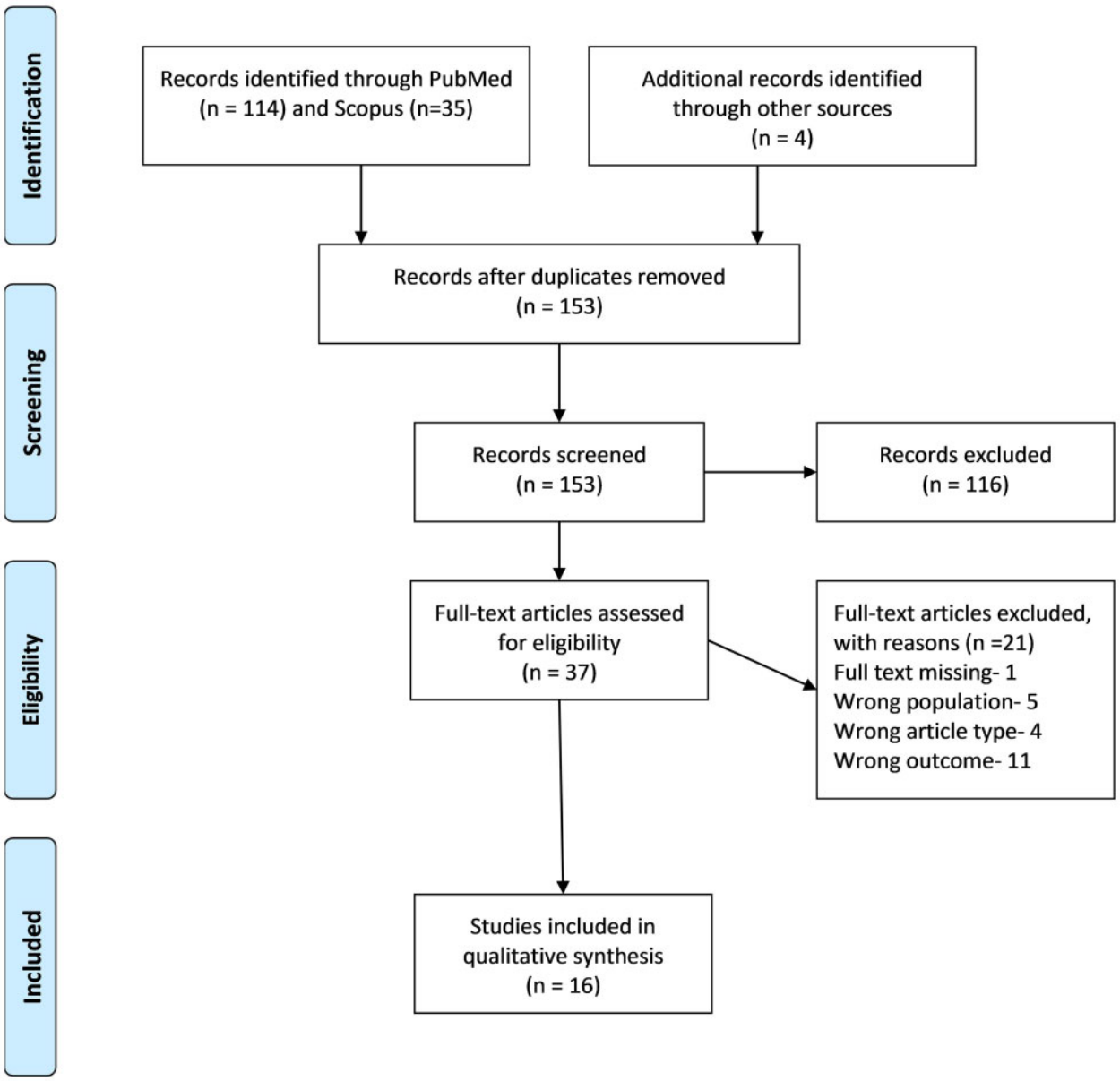


**Figure 1.** PRISMA flow diagram showing selection of articles reporting clinical and laboratory manifestations of KFD.

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**Table 1.** Summary of the studies on clinical and laboratory manifestations of KFD included in the SR

| S.no. | Author and year of publication | Study period | Study location | Number of suspected cases | Number of confirmed cases | Study methodology |
|---|---|---|---|---|---|---|
| 1 | Work *et al.*, 1957[1] | April–May, 1957 | Shimoga, Karnataka | | 9 | Case series |
| 2 | Iyer *et al.*, 1959[2] | April–June, 1959 | Shimoga, Karnataka | | 3 | Case series (details of only two cases retrieved) |
| 3 | Webb and Rao, 1961[3] | 3 weeks of March–April | Shimoga, Karnataka | 28 | 13 | Case series |
| 4 | Chatterjea *et al.*, 1963[4] | May–July, 1958 | Shimoga, Karnataka | 26 | 10 | Case series |
| 5 | Upadhyaya *et al.*, 1975[5] | 1959–66 | Shimoga, Karnataka | | 323 | Case series |
| 6 | Wadia *et al.*, 1975[6] | 1975 | Pune, Maharashtra | | 2 | Case series |
| 7 | Adhikari *et al.*, 1993[7] | 1984–85 | South Kanara, Karnataka | 100 | 54 | Case series (analysis was done for all 100 clinically suspected cases) |
| 8 | Kasabi *et al.*, 2013[8] | 2005–10 | 5 districts of Karnataka | | 168 | Analysis of KFD vaccination and surveillance data |
| 9 | Kasabi *et al.*, 2013[9] | December 2011 to March 2012 | Shimoga, Karnataka | 215 | 61 | Outbreak investigation, matched case-control study |
| 10 | Tandale *et al.*, 2015[10] | May, 2014 | Mamallapuram, Kerala | 32 | 4 | Outbreak investigation with details of index case |
| 11 | Shiji *et al.* 2016[11] | | Wayanad, Kerala | | 1 | Case report |
| 12 | Awate *et al.*, 2016[12] | January 2016 | Sindhudurg, Maharashtra | 54 | 29 | Outbreak investigation |
| 13 | Sadanandane *et al.*, 2017[13] | May 2015 | Wayanad and Malappuram, Kerala | 211 | 102 | Outbreak investigation |
| 14 | Gurav *et al.*, 2018[14] | December 2015 to July 2016 | Sindhudurg, Maharashtra | 488 | 130 | Outbreak investigation |
| 15 | Yadav *et al.*, 2019[15] | January 2016 to May 2017 | Sindhudurg, Maharashtra | 1046 | 72 | Prospective follow-up study |
| 16 | Oliveira *et al.*, 2020[16] | 2015–18 | Goa | | 448 | Hospital-based surveillance |

patient characteristics were extracted on a pre-designed spreadsheet: age, sex, clinical and laboratory manifestations of KFD. Continuous data were presented as mean ± SD (for normally distributed variables) or median and interquartile range when SD was more than 50% of the mean (extremes of data). The frequency of categorical variables was expressed in numbers and percentage. All analyses were done using STATA version 13. The SR was registered with PROSPERO (Registration ID: CRD42020198287).

## Epidemiology

The first outbreak of KFD was reported in the 1950s from the densely forested regions of Shimoga, Karnataka.[1] The people involved in the outbreak were the villagers who frequent the forests for cutting wood, raising cattle and other agriculture-related activities (Table 2).[1] In the early reports, the disease manifestations were also described in insect collectors who went to investigate the outbreaks.[1] The manifestations of KFD have also been reported in laboratory technicians working with viral cultures of KFD.[6] The initial reports of KFD were all localized in the region of Shimoga.[1–5] Since then, the disease has spread to the adjoining districts such as Chikamagalur, Uttar Kannada, Dakshina Kannada and Udupi.[7,8] With increasing deforestation, use of forest lands for agricultural purposes (cashew nut and areca nut) and subsequent displacement of lands and animals, the disease has now spread to the states of Maharashtra, Kerala, Tamil Nadu and Goa as well.[10–16] In an analysis, more than 9000 cases have occurred between 1957 and 2017.[17]

The profile of patients has also changed from villagers to farmworkers (cashew and areca nut plantation) and agriculturists.[14,16] The disease is transmitted by tick bite when an individual visits the forest. A total of 80–100% of the patients gave a history of visiting forests (Table 2). In some cases occurring in nearby villages, a history of visiting the forest may be absent as infected ticks have been found in such villages.[13] A history of tick bite has been reported in 38–72% of the cases (Table 2).[3,13,14] In the localities where KFD cases have been reported, concomitantly observed monkey deaths are reported in 31–65% of cases.[3,13] In some tribes residing in Kerala who hunt monkeys for meat, a high incidence of KFD has been reported.[13] In a case-control study by Kasabi *et al.*,[9] handling of cattle, a visit to the forest and the presence of piled-up dry leaves in the house were independent factors associated with KFD. No evidence of human-to-human transmission of KFD has been reported.[5,18]

Most of the patients presented between the months of December and May (Table 2).[5,13,14,16] In the western Ghats, this is the season with least amount of rainfall. The nymphal form (responsible for transmission) of the ticks is most active during this period. Also, the exposure of humans to the ticks is further increased as the villagers prefer to visit the forest in this dry season to collect wood.[1] In certain regions like Goa, this period also coincides with the cashew harvesting season increasing the risk of KFD in farm workers.[16] The incubation period ranges from 3 to 8 days.[19]

The mean age group of the affected patients ranges from 19.2 to 41.6 years as this age group is linked to outdoor forest-related work (Table 2).[5,9,15,16] In one of the studies, most of the patients were above the age of 40 years.[14] Initial studies suggested gender predilection to males, but later studies reported more KFD in females (Table 2).[1–5,8–10,12–16] Gender predilection is

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**Table 2.** Summary of demographic details, season, exposure risk and vaccination status of patients with confirmed KFD

| Study | Number of cases | Age (years) | Sex | Occupation | Season of infection | History of visit/ travel to forest | History of tick bite(s) | History of concomitantly observed local monkey deaths | History of vaccination against KFD (at least once) |
|---|---|---|---|---|---|---|---|---|---|
| Work *et al.*[1] | 9 | Mean: 31 | 100% male | Farmers, Insect collectors | April–May | 100% | | 100% | 0% |
| Iyer *et al.*[2] | 2 | 35 and 40 | 100% male | | April–June | 100% | | 100% | 0% |
| Webb *et al.*[3] | 13 | Mean: 38.2 | 77% male | | March–April | 100% | 69% | 31% | 54% |
| Chatterjea *et al.*[4] | 10 | | | | | | | | 0% |
| Upadhyaya *et al.*[5] | 323 | Young adults | 66% male | Predominantly farmers | 93% of cases January to May- | Most patients | | Reported in two-third of localities | |
| Wadia[6] | 2 | 25 and 44 | 100% male | Laboratory technicians | | NA | NA | | |
| Adhikari *et al.*[7] | 100 | 57% between 10 and 30 | 24% male | | December–May | 100% | | | |
| Kasabi *et al.*[8] | 168 | | | | | | | | 20% |
| Kasabi *et al.*[9] | 61 | 36% between 30 and 44 | 70% male | 80% labourers | Peaked in first two weeks of February | 80% | | | 36% |
| Tandale *et al.*[10] | 4 | | Female | | | Yes | | | |
| Shiji *et al.*[11] | 1 | 18 | Male | | | Yes | Yes | Yes | No |
| Awate *et al.*[12] | 29 | Majority of cases 14–50 | 41% male | Predominantly farmers | January | | | | 0% |
| Sadanandane *et al.*[13] | 102 | 91% above 15 | 42% male | 58% labourer | Started in January and peaked in February–March | 85% | 38% | 65% | |
| Gurav *et al.*[14] | 130 | 61% between 40 and 59 | 45% male | 93% farmers (cashew nut, betel nut, coconut) | December–July | 93% | 72% | | 0% |
| Yadav *et al.*[15] | 72 | Mean: 19.2 | 34.8% male | | | | | | |
| Oliveira *et al.*[16] | 448 | Mean : 41.6 | 48% male | 40% home-maker, 15% cashew plucker | Peak from January to April | 94% | | | 10.3% |

NA, not applicable.

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linked to the traditional roles of gender in relation to forest-related work. The traditional gender roles vary between the communities and have also evolved with time as is evident from the reports. Also, since the disease has spread to villages adjoining the forest, women involved in routine domestic activities are also exposed to the ticks.

## Clinical features

The clinical manifestations of KFD patients have been traditionally described as biphasic, but most reviewed studies do not classify clinical features into phases. Subclinical infection is not commonly described in KFD, but a study by Gurav *et al.*[14] reported asymptomatic individuals with IgM positivity. It is, however, difficult to exclude false-positive IgM cases. There is a need for further research to explore the entity of asymptomatic KFD through large-scale serosurveillance studies. The acute first phase of the illness usually begins with abrupt onset of high-grade fever associated with chills. The fever is present uniformly in all the patients and is usually continuous, with no diurnal variation and may last for 6–11 days (Table 3).[9,12–14] A study by Sadanandane *et al.*[13] reported that chills and rigours were significantly more common in confirmed KFD cases when compared with suspected KFD cases. Constitutional features such as myalgia (53–100%) and headache (69–93%) are commonly seen (Table 3).[9,14] The myalgia is severe and involves mainly the neck, back and calf.[1,3] Gastrointestinal manifestations such as abdominal pain (11–50%) and diarrhoea (21–92%) are common and usually appear by the third or fourth day of illness (Table 3).[7,13,14,19] Loss of hair as a symptom of KFD was reported by Sadanandane *et al.*[13] KFD is known to activate human vascular endothelial cells leading to haemorrhagic manifestations and increased intravascular permeability.[20] The haemorrhagic manifestations (8–63%) can vary from epistaxis or gum bleeds to haematemesis or melaena.[7,9,13,14] On physical examination, conjunctival congestion (>50%) and papulovesicular lesion on the soft palate (>20%) are signs which are considered pathognomonic in endemic areas (Table 3).[1,3,7] Signs of dehydration and hypotension on the first presentation have often been described.[7,19] Lymphadenopathy (often subcentimetric), usually cervical or axillary, has been described consistently in some series.[1,19] Hepatosplenomegaly can also be seen in some patients indicating possible lymphoreticular involvement.[1,3,7]

The second phase can be seen in 12–18% of the patients after an inter-current period of 1 to 3 weeks (Table 3).[7,12–14] Of note is a small prospective study conducted by Webb *et al.*[3] in which a second phase was reported in 46% of the cases. The second phase usually begins with fever and headache. In some individuals, features of meningoencephalitis (neck stiffness, Kernig's sign) and/or cerebellitis (giddiness, coarse tremors) can be seen.[7,13] Although meningoencephalitis has traditionally been described in the second phase, altered sensorium has been described in the first phase as well. This has been attributed to metabolic encephalopathy, most commonly due to liver dysfunction. Most studies, however, do not differentiate between neurological manifestations of the first and second phase. The following neurological manifestations have been described: altered sensorium (2–45%), seizure (2–22%) and meningitis (10.8–35%; Table 3).[7,12–14] In autopsy studies, although some of the monkey brains demonstrated histological changes of encephalitis, the same could not be demonstrated in humans.[2,7] Adhikari *et al.*,[7] however, demonstrated cerebral oedema

**Table 3.** Summary of clinical features of patients with confirmed KFD

| Study | *n* | Fever | Myalgia | Oral ulcers | Conjunctival congestion | Bleeding | Abdominal pain | Diarrhoea | Headache | Occurrence of a second fever episode | Altered sensorium | Seizure | Meningitis | Mortality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Work *et al.*[1] | 9 | 100% | 67% | 44% | 89% | 44% | 22% | 56% | 67% | 33% | 44% | | 33% | 22% |
| Iyer *et al.*[2] | 2 | 100% | 100% | 100% | 50% | 50% | 50% | 100% | 100% | | 50% | 0% | 0% | 100% |
| Webb *et al.*[3] | 13 | 100% | 92% | 23% | 69% | 46% | 31% | 0% | 46% | 46% | 31% | | 15% | |
| Chatterjea *et al.*[4] | 10 | | | | | | | | | | | | | |
| Upadhyaya *et al.*[5] | 323 | | | | | | | | | | | | | 4% |
| Wadia[6] | 2 | 100% | 100% | | 100% | | | 50% | 100% | 100% | | 0% | 100% | 0% |
| Adhikari *et al.*[7] | 100 | 99% | 53% | | 54% | 54% | | 22% | 69% | 14% | 45% | 22% | 35% | 33% |
| Kasabi *et al.*[8] | 168 | | | | | | | | | | | | | |
| Kasabi *et al.*[9] | 61 | 100% | 100% | | | 63% | | | | | | | | 0.5% |
| Tandale *et al.*[10] | 4 | Yes | Yes | | | Yes | | | | | | | | Recovered |
| Shiji *et al.*[11] | 1 | Yes | | Yes | Yes | Yes | – | Yes | Yes | Yes | Yes | | | Recovered |
| Awate *et al.*[12] | 29 | 76% | 59% | | | 0% | | | 72% | 18% | | 3% | | |
| Sadanandane *et al.*[13] | 102 | 100% | 62% | | | 8% | 50% | 92% | | 12% | | 8% | 10.8% | |
| Gurav *et al.*[14] | 130 | 100% | 83% | | | 29% | 11% | 21% | 93% | 17% | 2% | 2% | | 2.3% |
| Yadav *et al.*[15] | 72 | | | | | | | | | | | | | |
| Oliveira *et al.*[16] | 448 | | | | | | | | | | | | | 0.9% |

*n*, number of confirmed cases.

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in post-mortem examination. This cerebral oedema has again been attributed to metabolic encephalopathy.[7] In a study by Wadia *et al.*,[6] the cerebrospinal fluid (CSF) examination was normal in the first phase but showed pleocytosis in the second phase. The virus could be isolated from the CSF in some human cases, but that may not be conclusive proof of direct cerebral involvement by the virus.[1,2]

## Laboratory manifestations

The first phase is marked by thrombocytopenia and leucopoenia, with a reduction in neutrophil count (Table 4).[4,7,13,14] Chatterjea *et al.*[4] reported a decrease in lymphocyte and eosinophil count as well. They also reported leucopoenia and thrombocytopenia as a result of antibodies against leucocytes and platelets. The peripheral blood smear shows the presence of atypical lymphocytes with irregular nuclei and atypical monocytes with vacuolated cytoplasm.[1,3] Bone marrow cellularity is found to be normal in most cases.[4] All the haematological abnormalities return to the baseline at the time of discharge.[4] Biochemical tests show an elevation of liver enzymes in 40–81% of the patients (Table 4).[7,13,14] The initial autopsy reports suggested that the virus causes biliary stasis and focal necrosis in the liver.[1] The elevation of aspartate transaminase (AST) is more prominent than alanine transaminase.[21] This is because AST has multiple sources such as muscle and myocardium that may also be inflamed in patients with KFD.[21] Bleeding and clotting time are also prolonged in some patients.[3,4,7]

## Diagnostic methods

In the early days, molecular tests were not available, and animal inoculation tests were the diagnostic method of choice (Table 4).[1,2,4,6] Since the advent of molecular tests, polymerase chain reaction (PCR) assays have become the diagnostic modality of choice in the early first phase of the illness (Table 4). The NS-5 gene is the most common target of diagnostic PCR assays.[22] Both, real-time and nested PCR assays, have shown to have adequate diagnostic accuracy.[22] Since viraemia persists only in the early

**Table 4.** Summary of diagnostic modalities used for confirmation of and reported laboratory abnormalities related to KFD

| Study | Number of cases | Animal inoculation[a] | PCR[a] assay | IgM ELISA[a] | Laboratory parameters | Biochemical parameters |
|---|---|---|---|---|---|---|
| Work *et al.*[1] | 9 | Yes | | | Leucopoenia: 67% | |
| Iyer *et al.*[2] | 2 | Yes | | | Normal leucocyte count | |
| Webb *et al.*[3] | 13 | Yes | | | First phase: leucopoenia; second phase: leucocytosis | |
| Chatterjea *et al.*[4] | 10 | Yes | | | Leucopoenia (90%), thrombocytopenia (80%) Raised Bleeding and coagulation time | |
| Upadhyaya *et al.*[5] | 323 | Yes (100%) followed by serology (60%) | | | | |
| Wadia[6] | 2 | Yes | | | Leucopoenia (50%) | |
| Adhikari *et al.*[7] | 100 | | | Yes | Neutropenia (50%), thrombocytopenia (8%) | Raised transaminases (40%) |
| Kasabi *et al.*[8] | 168 | Yes | Yes | | | |
| Kasabi *et al.*[9] | 61 | Yes (7%) | Yes (93%) | | | |
| Tandale *et al.*[10] | 4 | | Yes (25%) | Yes (75%) | | |
| Shiji *et al.*[11] | 1 | | Yes | | Leucopoenia, thrombocytopenia | Raised transaminases |
| Awate *et al.*[12] | 29 | | Yes (55%) | Yes (59%) | | |
| Sadanandane *et al.*[13] | 102 | | Yes | | | |
| Gurav *et al.*[14] | 130 | | Yes (49%) | Yes (Days 4 to >14): 51% | Leukocytosis (39%), thrombocytopenia (42%) | Raised transaminases (81%) |
| Yadav *et al.*[15] | 72 | | Yes (PCR positivity D 0–4: 100%; D 5–10: 52%; D 11–20: 14%. | Yes (IgM ELISA positivity D 0–4: 4%; D 5–10: 59%; D 11–20: 93%. | | |
| Oliveira *et al.*[16] | 448 | | Yes | | | |

D, day of illness.

[a]Percentage of patients in which the particular assay was done.

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part of the illness, diagnosis in the latter half of the first phase or in the second phase is made by serological techniques. In a study by Yadav *et al.*,[15] PCR is uniformly positive in the first four days of illness. Although PCR can be positive up to 18 days of illness, the positivity decreases to <20% after 10 days of illness.[15] After 10 days of illness, an IgM enzyme-linked immunosorbent assay is most useful as it is positive in almost all cases.[15] Therefore, the diagnostic methods that can be recommended according to the day of illness are as follows: Days 1–4: PCR, Days 5–10: PCR and IgM-enzyme-linked immunosorbent assay (ELISA) and >Day 10: IgM-ELISA.

## Management

KFD is a potentially fatal disease with reported mortality that ranges from 0.9% to 33%.[7,14,16] The management of KFD is primarily supportive but higher levels of care may be required in certain cases to prevent mortality. In a study by Gurav *et al.*,[14] only 52% of the laboratory-confirmed patients of KFD could be managed in primary health care centres. Since most of the patients are managed in primary care centres, there is a need for studies determining predictors of mortality in patients with KFD. The patients in the first phase may be dehydrated and may require intravenous fluids.[3] Those individuals with bleeding manifestations may require blood products. Those patients presenting in the second phase with fever and headache require supportive management like analgesics. Those patients presenting with seizures may require anti-epileptics and anti-oedema measures.[7]

## Prevention

Potentially exposed local villagers, as well as travellers visiting endemic areas, must be advised regarding the use of anti-tick measures before going to the forest (i.e. wearing full-length clothes, the use of insect repellents on unprotected skin, the impregnation of clothes with e.g. permethrin) and to check their clothes and bodies for ticks after having to be outdoors.[9] The villagers living in the vicinity may use measures such as avoidance of cattle grazing in deep forests, avoidance of sleeping on floors outside the house and weekly washing and removal of ticks from cattle. Indigenously developed vaccines have been used in areas endemic to KFD, but the coverage has been low. In our review, 10.3–54% of the patients received atleast one dose of the vaccine (Table 2).[8,9,16] The recommended schedule for the formolized virus vaccine is two doses given 1 month apart followed by boosters.[8] The vaccine has been reported to be less effective (62% effectiveness for two doses) by some authors.[8] In a case-control study by Kasabi *et al.*,[9] vaccination did not alter the odds of developing KFD.

## Conclusion

KFD is a potentially fatal tick-borne disease that primarily affects individuals (residents/travellers) who visit endemic forests in the months of December and May. It is a biphasic febrile illness with haemorrhagic manifestations, bi-cytopenia and elevated liver enzymes in the first phase and neurological manifestations in the second phase. Physicians working in endemic areas and travel medicine specialists should suspect this disease in individuals with relevant exposure history and clinical manifestations. To the best of our knowledge, this is the first SR on clinical and laboratory manifestations of KFD. There is a need for further research on subclinical infection, pathogenesis behind coagulation abnormalities, evaluation of factors that predict the second phase and predictors of mortality.

*Conflict of interest*. None declared.

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