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Development of a clinical scoring system to make a presumptive diagnosis of Kyasanur Forest Disease: a case-control study from South India

Nitin Gupta[1], Carl Boodman[2,3], Kavitha Saravu[1]

[1]Department of Infectious Diseases, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India;
[2]Division of Infectious Diseases, Department of Internal Medicine, University of Manitoba, Winnipeg, Canada;
[3]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

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SUMMARY

Introduction: Kyasanur Forest Disease (KFD) is a viral haemorrhagic fever endemic in South India. Based on clinical presentation alone, it is challenging to distinguish KFD from other febrile illnesses in the region. The study aimed to develop a clinical scoring system for early presumptive diagnosis of KFD.
Patients and methods: This retrospective case-control study included microbiologically diagnosed KFD patients (n=186) with other undifferentiated febrile illnesses as controls (n=203). The clinical and laboratory features between cases and controls were compared. A logistic regression analysis included those variables found to be significantly associated with KFD on univariate analysis. The adjusted odds ratio for the significant variables was calculated and converted into logarithmic scales. These numbers were rounded off to the nearest integer to find the score assigned to each variable. A receiver operating characteristics curve was created to find the best cut-off for the scoring system that predicted the diagnosis of KFD.
Results: A total of 186 anonymised cases and 203 anonymised controls were recruited from the records for this study. Myalgia, headache, lymphadenopathy, bleeding manifestations, Central Nervous System (CNS) involvement, raised haematocrit, leukopenia, and raised transaminases were more common in patients with KFD. Except for lymphadenopathy and raised transaminases, all the other variables were independent predictors of making a diagnosis of KFD. Since raised transaminases tended towards significance, it was included in the scoring system with other independent predictors. A scoring system was created with a maximum score of 12. The receiver operating characteristic curve showed an Area Under Curve of 0.912 (95%CI: 0.88-0.94). A score of 4 or more was found to have a sensitivity and specificity of 83% and 87%, respectively.
Conclusion: The presence of specific features should alert primary care physicians working in endemic areas about the possibility of KFD. This diagnostic scoring system can be used to make a presumptive diagnosis of KFD after undergoing a prospective validation study.

Keywords: Kyasanur Forest Disease, scoring system, case-control.

INTRODUCTION

Kyasanur Forest Disease (KFD) was first described in the namesake forest in Shimoga, Karnataka, India, in 1957 [1]. In that outbreak, several individuals with a history of visit to the forest presented with fever and haemorrhagic manifestations in the dry months of December to April [1]. The human cases were preceded by a

Corresponding author
Kavitha Saravu
E-mail: kavithasaravu@gmail.com

string of monkey deaths in forests [1]. It was later identified that KFD is caused by an RNA flavivirus transmitted by the bite of hard ticks, such as *Haemaphysalis spinigera* [1]. The nymphal forms of the ticks are responsible for transmission and are most active in the dry season [2]. Incidentally, this period is when people venture into the forest to retrieve wood or harvest, increasing transmission risk [3-5]. The disease was initially reported in Shimoga district but has gradually expanded to involve other districts of Karnataka, Tamil Nadu, Kerala, Maharashtra, and Goa [3, 6]. On average, 160 KFD patients are reported annually [6]. Due to the rurality of the disease and the fact that diagnostic testing is centralized in urban referral laboratories, the number of reported cases is likely the tip of the iceberg. While the disease is fatal in monkeys, cattle can act as a reservoir [2]. Cattle grazing in the forest is likely responsible for importing the ticks into the villages [2]. The treatment is primarily supportive; some patients may need critical care support. The areas endemic to KFD are also prone to outbreaks from other infections such as dengue, leptospirosis and scrub typhus [3]. There is a significant clinical overlap between these diseases [3, 7]. Very few studies have focussed on the clinical manifestations of KFD. Limited studies with extremely small sample sizes have focused on differentiating KFD from other causes of febrile illness. To the best of our knowledge, there are no scoring systems to diagnose KFD. The study, therefore, aimed to develop a scoring system based on simple clinical and laboratory parameters that can help in the early presumptive diagnosis of KFD.

PATIENTS AND METHODS

This retrospective case-control study was performed in a tertiary care hospital in South India, catering to patients referred from KFD endemic areas. The cases of KFD (diagnosed by polymerase chain reaction assay targeting the NS-5 gene) presenting in the first phase and admitted in 2018-2019 at our tertiary care hospital were recruited from the records. The controls were selected from a registry of admission records of patients with undifferentiated febrile illnesses (2020-2021) with either an alternative proven diagnosis or an exclusion of KFD. Ethical clearance was obtained to access the records and collect data (IEC/451/2019, 209/2020). No patient identifiers, including age, sex, occupation, and district of residence, were collected for this study.

An anonymised case record form was created to collect the following variables from cases and controls: final diagnosis, clinical features [myalgia, arthralgia, headache, lymphadenopathy, bleeding manifestations, hepatosplenomegaly, rash, conjunctival involvement, abdominal pain, diarrhoea, cough, lower respiratory tract (LRT) involvement, myocarditis and central nervous system (CNS) involvement] and laboratory features (raised haematocrit, leucocytosis, leukopenia, thrombocytopenia, raised transaminases, raised bilirubin and raised creatinine).

Conjunctival involvement was defined as hyperaemia, congestion, or oedema in bilateral conjunctiva. Lymphadenopathy was defined as palpable cervical lymph nodes on examination. Hepatosplenomegaly was defined as the liver or spleen enlargement as appreciated by clinical examination. Diarrhoea was defined as an increased frequency of loose stools (three or more per day). LRT involvement was defined as the presence of dyspnoea, the requirement of supplemental oxygen, or infiltration on chest X-ray. Myocarditis was defined as elevated troponin levels without an alternative explanation. CNS involvement was defined as the presence of altered sensorium or nuchal rigidity. Haematocrit of more than 40% was defined as raised. A total leucocyte count of more than 11,000/ cu mm was defined as leucocytosis and a count of less than 4,000/ cu mm was defined as leukopenia. Thrombocytopenia was defined as a platelet count of less than 150,000/ cu mm. Aspartate transaminase or alanine transaminase of more than five times the upper limit of normal (200 IU/l) was considered as raised transaminases. Bilirubin or creatinine levels of more than 3 mg/dL were defined as raised.

A univariate analysis was done to compare the case and controls. The cases were also compared with the most common aetiology identified in the controls. The categorical variables were expressed as proportions, and a chi-square test was performed to compare the proportions. The contingency table used Fisher's exact test when the frequency in any of the cells was less than 5. A p-value of less than 0.05 was considered as significant. Only significant variables more commonly seen in cases compared to controls were

used to perform a multivariable logistic regression analysis. Adjusted odds ratio was calculated for each of the variables used in the models. Those variables that were significant in the regression analysis were used for the development of the scoring system. The adjusted odds ratio for these significant variables was converted into logarithmic scales. These numbers were then rounded to the nearest integer to find the score assigned to each variable. Individual scores for each case and control were calculated using these scores. A receiver operating characteristics (ROC) curve was created to find the best cut-off for the scoring system that predicted the diagnosis of KFD. The sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (PLR) and negative likelihood ratio (NLR) were calculated.

RESULTS

A total of 186 anonymised cases and 203 anonymised controls were recruited from the records for the purpose of this study. A univariate analysis done to compare cases and controls showed that myalgia, headache, lymphadenopathy, bleeding manifestations, CNS involvement, raised haematocrit, leukopenia, and raised transaminases were more common in patients with KFD (Table 1). Hepatosplenomegaly, abdominal pain, LRT involvement, myocarditis, leucocytosis, elevated creatinine, and elevated bilirubin were more common

Table 1 - Baseline parameters comparing cases (patients with KFD) and controls (patients without KFD).

Parameters	*KFD (n=186)*		*No KFD (n=203)*		*p-value*
Myalgia	*97*	*(52.15%)*	*73*	*(35.96%)*	*0.001*
Arthralgia	27	(14.52%)	21	(10.34%)	0.211
Headache	*84*	*(45.16%)*	*44*	*(21.67%)*	*<0.001*
Lymphadenopathy	*13*	*(6.99%)*	*1*	*(0.49%)*	*0.001*
Bleeding manifestations	*45*	*(24.19%)*	*4*	*(1.97%)*	*<0.001*
Hepatosplenomegaly	*14*	*(7.53%)*	*73*	*(35.96%)*	*<0.001*
Rash	14	(7.53%)	10	(4.93%)	0.287
Conjunctival involvement	25	(13.44%)	26	(12.81%)	0.853
Abdominal pain	*30*	*(16.13%)*	*60*	*(29.56%)*	*0.002*
Diarrhoea	29	(15.59%)	35	(17.24%)	0.661
Cough	24	(12.90%)	36	(17.73%)	0.188
LRT involvement	*20*	*(10.75%)*	*42*	*(20.69%)*	*0.007*
Myocarditis	*11*	*(5.91%)*	*45*	*(22.17%)*	*<0.001*
CNS involvement	*22*	*(11.83%)*	*4*	*(1.97%)*	*<0.001*
Raised HCT	*88*	*(47.31%)*	*68*	*(33.50%)*	*0.005*
Leucocytosis	*1*	*(0.54%)*	*103*	*(50.74%)*	*<0.001*
Leukopenia	*153*	*(82.26%)*	*35*	*(17.24%)*	*<0.001*
Thrombocytopenia	137	(73.66%)	145	(71.43%)	0.623
Raised transaminases	*79*	*(42.47%)*	*39*	*(19.21%)*	*<0.001*
Raised Bilirubin	*5*	*(2.69%)*	*73*	*(35.96%)*	*<0.001*
Raised creatinine	*6*	*(3.23%)*	*51*	*(25.12%)*	*<0.001*

Notes: Conjunctival involvement (hyperaemia or congestion or oedema in bilateral conjunctiva), Lymphadenopathy (Cervical lymph nodes palpable on clinical examination), Hepatosplenomegaly (enlarged liver or spleen on clinical examination), LRT involvement- Lower respiratory tract involvement (presence of dyspnoea, the requirement of supplemental oxygen or infiltrate on Chest X-ray), myocarditis (clinical suspicion along with elevated troponin), CNS involvement- Central nervous system involvement (altered sensorium or neck signs), Raised HCT- Raised Haematocrit (more than 40), Leucocytosis (Total leucocyte count more than 11,000/ cu.mm), Leukopenia (Total leucocyte count of less than 4,000/ cu. mm), Thrombocytopenia (platelet count of less than 150,000/ cu.mm), Raised transaminases (Aspartate transaminase or alanine transaminase more than 200 IU/l), Raised Bilirubin (>3 mg/dl) or creatinine levels (>3 mg/ dl).

Table 2 - Logistic regression analysis to calculate adjusted Odd's ratio for variables predicting KFD on univariate analysis and score assigned to the variables.

Clinical/Laboratory parameters	*Adjusted Odds ratio*	*Adjusted Log Odds ratio*	*Score assigned*	*p-value*
Myalgia	2 (1.1-3.7)	0.68	1	0.032
Headache	2.3 (1.2-4.4)	0.83	1	0.011
Lymphadenopathy	4.7 (0.2-8.6)	1.5	0	0.298
Bleed	20.7 (6-70)	3	3	<0.001
CNS involvement	7.4 (1.7-31.6)	2	2	0.007
Raised HCT	2.1 (1.1-4)	0.75	1	0.021
Leukopenia	24.9 (13.1-47.4)	3.2	3	<0.001
Raised transaminases	1.9 (0.97-3.8)	0.648	1	0.063

Notes: Lymphadenopathy (cervical lymph nodes palpable on clinical examination), CNS involvement- Central nervous system involvement (altered sensorium or neck signs), Raised HCT- Raised Haematocrit (more than 40), Leukopenia (Total leucocyte count of less than 4,000/ cu. mm), Raised transaminases (Aspartate transaminase or alanine transaminase more than 200 IU/l).

in patients without KFD.

A binary logistic regression analysis was conducted to predict a diagnosis of KFD. The model included variables identified by univariate analysis as listed above (Table 2). Except for lymphadenopathy and raised transaminases, all the other variables were independent predictors of making a diagnosis of KFD. Since raised transaminases tended towards significance, they were included in the scoring system with other significant variables.

Based on the methods described before, a scoring system was created with a maximum value of 12. The ROC curve was constructed to find the optimal cut-off for the scoring system (Figure 1). It was found to have an Area Under Curve of 0.912 (95%CI: 0.88-0.94) with a p-value of less than 0.001. A score of 4 or more was found to have a sensitivity and specificity of 83% and 87%, respectively. A score of 6 or more was found to have a sensitivity and specificity of 43% and 97%, respectively.

The sensitivity, specificity, PPV, NPV, PLR, and NLR were calculated for the significant variables on univariate analysis. Leukopenia was found to have high sensitivity (82%), specificity (83%), PPV (81%) and NPV (84%) (Supplementary Table 1). Lymphadenitis, bleeding, and CNS manifestations were found to have high specificities and PPV. Leukopenia had the lowest negative likelihood ratio as well.

Amongst the controls, after excluding co-infections, the most identified aetiologies of interest were leptospirosis (n=47), scrub typhus (n=14), and dengue (n=14). Features of KFD were compared with leptospirosis, the most predominant cause of undifferentiated febrile illness (Table 3). The comparison of KFD with scrub typhus and dengue has been added in Supplementary Table 2. Although myalgia was common in both leptospirosis and KFD, headache was commoner in KFD. Lymphadenopathy was infrequently present in KFD but not in leptospirosis. This difference was, however, not significant. Bleeding manifestations and CNS involvement were significantly more common in patients with KFD. Hepatosplenomegaly, pain in the abdomen, and myocarditis were more common in leptospirosis. Raised haematocrit, leukopenia and elevated transaminases

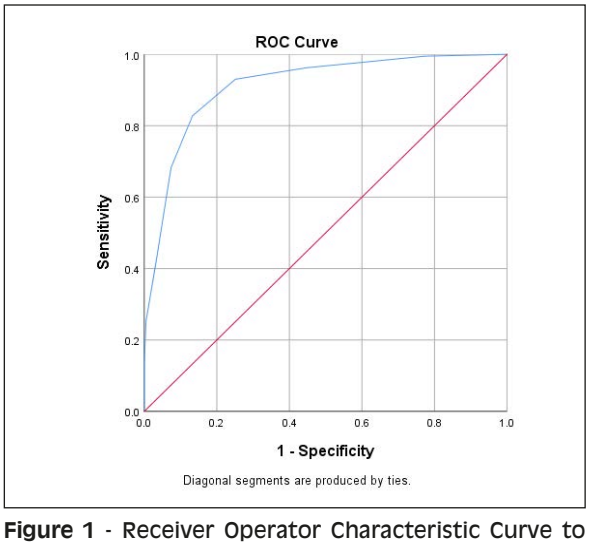

Figure 1 - Receiver Operator Characteristic Curve to calculate the most accurate cut-off for the scoring system.

were significantly more common in KFD patients. Leucocytosis, elevated bilirubin, and elevated creatinine were more common in patients with leptospirosis.

DISCUSSION

In this case-control study, myalgia, headache, bleeding manifestations, CNS involvement, raised haematocrit, and leukopenia were independent predictors of making a diagnosis of KFD. The scoring system created using these manifestations showed a significant AUC of 0.9. A score of 4 or more had excellent sensitivity and specificity in predicting KFD. Leukopenia had the highest sensitivity individually, while lymphadenitis, bleeding, and CNS manifestations were highly specific in diagnosing KFD. Headache, bleeding manifestation, leukopenia, elevated HCT and elevated transaminases were more common in KFD when compared to leptospirosis.

Myalgia and headache were found to be independent predictors of making a diagnosis of KFD. Although myalgia is a non-specific feature of many febrile illnesses, it was consistently observed in patients with KFD. In a previous study by Webb et al., myalgia was seen in 92% of KFD-positive cases, while it was seen in only 54% of the KFD-negative cases [8]. In the study by Iyer et al., the virus was identified in the skeletal muscles of dead monkeys [9]. The myalgia is severe in KFD, as evidenced by high creatine phosphokinase levels in a previous study [10]. Bleeding in KFD was another differentiating factor. It is due to a combination of factors such as thrombocytopenia, impaired coagulation and activation of endothelial cells. In the study by Webb et al., bleeding was seen in 43% of KFD cases compared to 31% in cases without KFD [8]. In a previous study, APTT levels were consistently high in patients with KFD [10]. CNS involvement was also significantly common in KFD compared to other febrile illnesses. This is similar to previous studies that showed CNS involvement in the form of encephalitis or encephalopathy to be a common finding in patients with the first phase of KFD [11, 12]. Conjunc-

Table 3 - Comparison of clinical and laboratory features between Kyasanur Forest Disease and leptospirosis cases.

Variable	*KFD (n=186)*	*Leptospirosis (n=47)*	*p-value*
Myalgia	97 (52%)	28 (60%)	0.415
Headache	84 (45%)	12 (25%)	*0.02*
Lymphadenopathy	13 (7%)	0	0.076
Bleeding manifestation	45 (24%)	1 (2%)	*<0.001*
Hepatosplenomegaly	14 (8%)	16 (34%)	*<0.001*
Pain abdomen	30 (16%)	19 (40%)	*0.001*
LRT involvement	20 (11%)	9 (19%)	0.138
Myocarditis	11 (6%)	15 (32%)	*<0.001*
CNS involvement	22 (12%)	1 (2%)	0.054
Increased HCT	88 (47%)	9 (19%)	*<0.001*
Leukopenia	153 (82%)	3 (6%)	*<0.001*
Leucocytosis	1 (1%)	30 (64%)	*<0.001*
Thrombocytopenia	137 (74%)	39 (83%)	0.254
Raised transaminases	79 (42%)	6 (13%)	*<0.001*
Increased bilirubin	5 (3%)	28 (60%)	*<0.001*
Increased creatinine	6 (3%)	25 (53%)	*<0.001*

Notes: KFD- Kyasanur Forest Disease, Lymphadenopathy (Cervical lymph nodes palpable on clinical examination), Hepatosplenomegaly (enlarged liver or spleen on clinical examination), LRT involvement- Lower respiratory tract involvement (presence of dyspnoea, requirement of supplemental oxygen or infiltrate on Chest X-ray), myocarditis (clinical suspicion along with elevated troponin), CNS involvement- Central nervous system involvement (altered sensorium or neck signs), Raised HCT- Raised Haematocrit (more than 40), Leucocytosis (Total leucocyte count more than 11,000/ cu.mm), Leukopenia (Total leucocyte count of less than 4,000/ cu. mm), Thrombocytopenia (platelet count of less than 150,000/ cu.mm), Raised transaminases (Aspartate transaminase or alanine transaminase more than 200 IU/l), Raised Bilirubin (>3 mg/dl) or creatinine levels (>3 mg/ dl).

tival involvement, described by some authors as pathognomic for KFD, was not significantly different between cases and controls [8]. This was possibly due to leptospirosis being the commonest cause of febrile illness among the controls. Lymphadenopathy was not an independent predictor for diagnosing KFD but was found to be specific for patients with KFD.

Leukopenia is a valuable marker to differentiate KFD from other bacterial infections, such as leptospirosis, where leucocytosis is more common. Leukopenia was identified as one of the most sensitive markers in diagnosing KFD. In previously published studies, it has been seen as a constant feature in patients with KFD [8, 13, 14]. In an animal study by Webb and Burston on monkeys infected with KFD, nuclear materials were identified in the lymph nodes, suggesting the destruction of leucocytes [15]. The authors hypothesised that the KFD virus may predominantly reside in the white blood cells [15]. In another study, Chatterjea et al. hypothesised that leukopenia results from antibodies against leucocytes [13]. In a study by Sirmarova et al., KFD was found to infect and activate human vascular endothelial cells [16]. The activation of these cells leads to increased capillary leakage, explaining the commonly seen raised haematocrit in patients with KFD. This is a helpful finding to differentiate it from febrile illnesses other than dengue. It is also essential to identify increased haematocrit as this signifies the need for oral or intravenous fluid supplementation. Raised transaminases (more than five times the upper limit of normal) were more commonly seen in KFD compared to other diseases. This was, however, not found to be an independent predictor. Post-mortem biopsy of affected patients shows areas of necrosis in the liver [17]. In a previous study, transaminases were commonly elevated to more than five times the upper limit of normal [18].

Molecular tests diagnose the disease in the early part of the illness and serology in the late part [19]. Previous studies have shown that most patients are managed at the primary care level with poor laboratory support. In a study from Goa, 73% of the patients with KFD were managed at community health centres [5]. No point-of-care (POC) tests are available to diagnose KFD. There is an urgent need to invest in their development. In their absence, it is important to develop a scoring system to identify and differentiate KFD from other infections. The pooled mortality rate with KFD was found to be 2.5%, according to an analysis [6]. The number is higher during outbreaks [16]. Scoring systems like ours can help in the early diagnosis of KFD and can help in avoiding empiric antimicrobial prescriptions for bacterial illnesses with similar presentations. In a study on undifferentiated febrile illness, an average of 2.5 different antibiotics were prescribed to the included patients [20]. Reducing antimicrobial consumption will not only help decrease the problem of antimicrobial resistance prevalent in these areas but also help to decrease hospital costs [21, 22]. Since 10-15% of KFD patients present with aseptic meningitis-like presentation later, making a provisional diagnosis of KFD in the first phase will be helpful for primary care physicians to be mindful of what can come later [3]. Also, in regions where laboratory-based surveillance is difficult, scoring systems such as these will be helpful for the surveillance of probable KFD cases. The reports of these probable cases can alert public health officials to take appropriate measures to investigate and control the outbreak.

The study had several limitations. The data on patients with KFD were collected from clinical records, which might not reflect the true picture. Some of the subtle clinical findings, such as conjunctival congestion, palatal petechiae and cervical lymphadenopathy, weren't explicitly mentioned for all patients in the clinical records. These features have been believed to be commoner in KFD than in other febrile illnesses. The true prevalence of those symptoms might have been underestimated owing to the study's retrospective nature. Biochemical abnormalities such as activated partial thromboplastin time and creatinine phosphokinase, reported to be higher in KFD, could not be evaluated for the scoring system as their values were unavailable for the controls. A prospective study, where these features are particularly sought, is required to address the concerns of our study. It must be noted that except for the higher prevalence of leukopenia in KFD, there wasn't much difference between the presenting features of KFD and dengue. Although it is difficult to draw conclusions when dengue cases are so low, the scoring system should be cautiously used in high dengue-endemic areas. The time period of controls varied from the cases. It must also be noted that the va-

lidity of the scoring system is limited to endemic areas and should be cautiously interpreted in areas not known to be endemic to KFD. This tool also requires prospective validation in a different cohort before being used routinely. Despite these limitations, this is the largest study that has compared KFD and other febrile illnesses. The diagnostic scoring system, although not perfect, is the first attempt at creating a simple decision support tool for making an early and presumptive diagnosis of KFD.

The presence of certain features such as myalgia, headache, bleeding manifestations, CNS involvement, raised haematocrit, and leukopenia should alert primary care physicians working in endemic areas about the possibility of KFD. After prospective validation of the diagnostic scoring system built using these features, this tool can be used to make a presumptive diagnosis of KFD in high-endemic areas.

Conflict of interest
None to declare.

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Supplementary Table 1 - Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Positive Likelihood ratio, Negative likelihood ratio, Confirming and Exclusion power of clinical and laboratory parameters for diagnosing KFD.

Parameters	*Sensitivity*	*Specificity*	*PPV*	*NPV*	*+LR*	*-LR*
Myalgia	52.1%	64%	57.1%	59.4%	1.45	0.75
Headache	45.2%	78.3%	65.6%	60.9%	2.08	0.7
LN	7%	99.5%	92.9%	53.9%	14.19	0.93
Bleeding	24.2%	98%	91.8%	58.5%	12.28	0.77
CNS	11.8%	98%	84.6%	54.8%	6	0.90
Raised transaminases	42.5%	80.8%	66.9%	60.5%	2.21	0.71
Raised HCT	47.3%	66.5%	56.4%	57.9%	1.41	0.79
Leukopenia	82.3%	82.8%	81.4%	83.6%	4.8	0.21
Leucocytosis	0.54%	49.3%	0.96%	35.1%	0.01	2.02

Notes: PPV- Positive predictive value, NPV- Negative predictive value, +LR- Positive likelihood ratio, -LR- Negative likelihood ratio, LN-Lymphadenopathy (Cervical lymph nodes palpable on clinical examination), CNS involvement- Central nervous system involvement (altered sensorium or neck signs), Raised HCT- Raised Haematocrit (more than 40), Leukopenia (Total leucocyte count of less than 4,000/cu. mm), Raised transaminases (Aspartate transaminase or alanine transaminase more than 200 IU/l).

Supplementary Table 2 - Differentiating KFD from diagnosed cases of other febrile illnesses (excluding coinfections).

Variable	*KFD (n=186)*	*Scrub (n=14)*	*KFD vs scrub p-value*	*Lepto (n=47)*	*KFD vs Lepto*	*Dengue (n=14)*	*KFD vs dengue*	*Overall p-value*
Myalgia	97 (52%)	5 (36%)	0.276	28 (60%)	0.415	4 (29%)	0.103	0.138
Headache	84 (45%)	2 (14%)	*0.026*	12 (25%)	*0.02*	6 (43%)	0.547	0.016
Lnpathy	13 (7%)	0	0.605	0	0.076	0	0.605	0.180
Eschar	0	5 (36%)	*<0.001*	0		0		<0.001
Bleeding	45 (24%)	1 (7%)	0.197	1 (2%)	*<0.001*	1 (7%)	0.197	0.001
Hepatosplenomegaly	14 (8%)	9 (64%)	*<0.001*	16 (34%)	*<0.001*	2 (14%)	0.310	<0.001
Abdomen pain	30 (16%)	4 (29%)	0.264	19 (40%)	*0.001*	4 (29%)	0.264	0.003
LRT involvement	20 (11%)	5 (36%)	*0.019*	9 (19%)	0.138	1 (7%)	1	0.03
Myocarditis	11 (6%)	3 (21%)	0.063	15 (32%)	*<0.001*	1 (7%)	0.592	<0.001
CNS involvement	22 (12%)	0	0.373	1 (2%)	0.054	0	0.373	0.091
Increased HCT	88 (47%)	2 (14%)	*0.023*	9 (19%)	*<0.001*	8 (57%)	0.583	<0.001
Leukopenia	153 (82%)	2 (14%)	*<0.001*	3 (6%)	*<0.001*	4 (29%)	*<0.001*	<0.001
Leucocytosis	1 (1%)	4 (29%)	*<0.001*	30 (64%)	*<0.001*	5 (36%)	*<0.001*	<0.001
Thrombocytopenia	137 (74%)	12 (86%)	0.525	39 (83%)	0.254	13 (93%)	0.196	0.238
Raised transaminases	79 (42%)	6 (43%)	1	6 (13%)	*<0.001*	3 (21%)	0.162	<0.001
Increased bilirubin	5 (3%)	4 (29%)	*0.002*	28 (60%)	*<0.001*	2 (14%)	0.078	<0.001
Increased creatinine	6 (3%)	2 (14%)	0.101	25 (53%)	*<0.001*	2 (14%)	0.101	<0.001

KFD- Kyasanur Forest Disease, Scrub- scrub typhus, lepto- leptospirosis, LNpathy- Lymphadenopathy (Cervical lymph nodes palpable on clinical examination), Hepatosplenomegaly (enlarged liver or spleen on clinical examination), LRT involvement- Lower respiratory tract involvement (presence of dyspnoea, requirement of supplemental oxygen or infiltrate on Chest X-ray), myocarditis (clinical suspicion along with elevated troponin), CNS involvement- Central nervous system involvement (altered sensorium or neck signs), Raised HCT- Raised Haematocrit (more than 40), Leucocytosis (Total leucocyte count more than 11,000/ cu.mm), Leukopenia (Total leucocyte count of less than 4,000/ cu. mm), Thrombocytopenia (platelet count of less than 150,000/cu.mm), Raised transaminases (Aspartate transaminase or alanine transaminase more than 200 IU/l), Raised Bilirubin (>3 mg/dl) or creatinine levels (>3 mg/dl).