Original Article

Restructuring the Modified Faine's Criteria for the Diagnosis of Leptospirosis in Monsoon: A Study from South Gujarat

U. C. Samudyatha, Vipul Chaudhari, Naresh Chauhan, Rahul Damor, J. K. Kosambiya, Rikita Munshi

Department of Community Medicine, Government Medical College, Surat, Gujarat, India

Abstract

Context: Clinical and epidemiological variables in the modified Faine's criteria offered low validity in our study setting. **Aims:** Restructuring and validating modified Faine's criteria for leptospirosis to better suit health scenario of south Gujarat. **Subjects and Methods:** Clinical, epidemiological, and laboratory features of derivation cohort (1216 suspected leptospirosis cases) admitted at a tertiary care hospital of south Gujarat (2007–2015) that significantly correlated with confirmed leptospirosis were used in binary logistic regression to derive scoring models and receiver operating characteristic to determine cutoff values. Validity and net reclassification improvement (NRI) were estimated in validation cohort (82 cases, 2016–2017) and algorithm for diagnosis was prepared. **Results:** Screening model consisted of the presence of conjunctival suffusion, calf tenderness, raised serum creatinine, headache with conjunctival suffusion and/or jaundice, and dyspnea/meningism. Area under curve (AUC) for screening model was 0.590 (standard error [SE] ±0.017) and cutoff score ≥9 gave sensitivity 79.16%, specificity 50%. The confirmatory model consisted of laboratory parameters, namely polymerase chain reaction, immunoglobulin M ELISA, and microscopic agglutination test and gave AUC 0.998 (SE ± 0.001), sensitivity 89.58%, specificity 85.29%, positive predictive value 89.58%, and negative predictive value 85.29% at cutoff score ≥100. Net sensitivity of algorithm was 98.27% at the point of screening (screening model and rapid test) and net specificity 87.89% at the point of confirmation (screening followed by confirmatory model) in validation cohort. **Conclusions:** Simultaneous use of screening model and rapid test gave NRI 81.25% and sequential use of confirmatory test gave NRI 47.18% compared to corresponding parts of the modified Faine's criteria.

Keywords: Microscopic agglutination test, modified Faine's criteria, net reclassification improvement, polymerase chain reaction

Introduction

Leptospirosis is an anthropozoonosis, endemic in several parts of the world, including south Gujarat, India. It has a strong association with annual rainfall in the given region.[1,2] The clinical features of leptospirosis are highly variable and are broadly classified into four categories:[3,4]

i. A mild, infectious-like illness
ii. Weil's syndrome, characterized by jaundice, renal failure, hemorrhage, and myocarditis
iii. Meningitis/meningioencephalitis
iv. Pulmonary hemorrhage with respiratory failure.

However, the pattern and combinations of these clinical features can be varied.[3] Moreover, these clinical features are common to a number of other common diseases such as dengue, malaria, typhoid, tuberculosis, scrub typhus, influenza, pneumonia, urinary tract infections, sepsis, and viral hepatitis.[5] This makes the early diagnosis of leptospirosis a challenge, especially in a season like monsoon.[6]

While the laboratory diagnosis of leptospirosis is relatively conclusive with the advent of advanced microbiological tests like polymerase chain reaction (PCR) and microscopic agglutination test (MAT), these are not used as the first line of investigations in resource-poor settings.[7] Moreover, these tests require time to yield results.[7] All these, together, lead to delay in the initiation of specific management in these cases. Furthermore, different case definitions[3,5,8-10]

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Address for correspondence: Dr. U. C. Samudyatha, Department of Community Medicine, Government Medical College, Surat, Gujarat, India.
E-mail: ucsamudyatha@gmail.com

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have further made the confirmation of leptospirosis nonuniform.

To ease the diagnosis of leptospirosis, the WHO introduced the Faine's criteria. This was later modified as per the Indian scenario[5] [Table 1]. However, our experience and some studies[11] showed that modified Faine's criteria had positive predictive value (PPV) of 21%–25%. Hence, we conceptualized this study with following aim and objectives:

Aim

Restructuring the modified Faine's criteria to improve its utility as both screening tool and confirmatory tool.

Objectives

1. Identify the variables that are associated with the diagnosis of leptospirosis and restructure modified Faine's criteria
2. To develop a diagnostic algorithm to make the practical use of these screening and confirmatory models for the diagnosis of leptospirosis.

Subjects and Methods

This diagnostic study was conducted in a tertiary care hospital in south Gujarat, India, where leptospirosis is endemic, and the Department of Community Medicine is nodal agency for routine leptospirosis surveillance. A prestructured format predominantly including variables in the modified Faine's criteria [Table 1] was prepared to compile the data required for the study from this leptospirosis control program data (2007–2017). The data compilation and analysis were carried out in October–December 2017.

The following case definitions were used in this study:

- Suspected case of leptospirosis was defined as a case of febrile illness presenting with the clinical symptoms of leptospirosis as mentioned.[3] Patients who had clear cut diagnostic features of other diseases at the time of admission were excluded from the study.

Several studies[12,13] have used the definition given by the WHO for suspected leptospirosis, which includes the presence of acute febrile illness with headache, myalgia, and prostration associated with any other clinical signs. However, in this study, these were taken as additional symptoms and not as case defining symptoms, to decrease the false negatives.

- Confirmed case of leptospirosis (Leptospirosis Burden Epidemiology Reference Group [LERG-2] criteria)[9] was defined as a suspected case of leptospirosis with any of the following:
  i. Four-fold rise in MAT titer in acute and convalescent serum samples
  ii. MAT titer ≥1:400 in single or paired serum samples
  iii. Isolation of pathogenic leptospira in the clinical sample
  iv. Detection of leptospira species in the clinical sample
  v. Pathogenic leptospira species DNA detected by PCR.

In the first phase, data of 46 cases of suspected leptospirosis patients who were admitted in 2017 were collected to evaluate the accuracy of different existing diagnostic criteria of leptospirosis (modified Faine's criteria, immunoglobulin M ELISA, MAT, and PCR) with LERG-2 criteria as the reference standard.

In the second phase, data of all cases of suspected leptospirosis admitted between 2007 and 2017 were included in the study. This being a diagnostic study, we were required to have a derivation cohort consisting of a large data set or participants. The features (variables) of these participants and the final diagnosis had to be correlated. The significantly correlated variables could be used as predictors in binary logistic regression equation for the final diagnosis and the prediction model could be developed. To check the validity of the prediction model, the model had to be applied to a smaller, new set of participants known as validation cohort. In this study, the cases from 2007 to 2015 (1216 cases) were included in the derivation cohort and cases from 2016 to 17 (82 cases) in the validation cohort. All cases which had confirmatory diagnosis of nonleptospirosis fever on admission were excluded from the study.

The screening model was developed by including those features that could be assessed in the peripheral health centers such as clinical features, epidemiological features, and minimal laboratory investigations. The confirmatory model

Table 1: Modified Faine's criteria (2012) (scores) for the diagnosis of leptospirosis in cases of acute febrile illness

Part A: Clinical data	Part B: Epidemiological factors	Part C: Bacteriological and laboratory findings
Headache (2)	Rainfall (5)	Isolation of leptospira in culture - diagnosis certain
Fever (2)	Contact with contaminated environment (4)	PCR (25)
Temperature >39°C (2)		ELISA IgM positive
Conjunctival suffusion (4)	Animal contact (1)	OR
Meningism (4)		SAT positive OR
Myalgia (4)		MAT-single positive in high titer (15)
Conjunctival suffusion + meningism + myalgia (10)		MAT-rising titre (25)
Jaundice (1)		Other rapid tests (15)
Albuminuria (2)		
Hemoptysis/dyspnea (2)		

A score of 26 or more in parts A + B or a score 25 or more in parts A + B + C is considered diagnostic of leptospirosis. OR: Odds ratio, PCR: Polymerase chain reaction, IgM: Immunoglobulin M, MAT: Microscopic agglutination test, SAT: Slide agglutination test

included microbiological tests done at tertiary care hospitals. The features were correlated with confirmed diagnosis of leptospirosis. The features that positively and significantly correlated with the diagnosis of leptospirosis were used in binary logistic regression models (enter method). The b-coefficients of these variables were rounded off to the nearest integer and multiplied by a common factor of 10, which was designated as the score of the variable. Regression was done to derive the scores, and hence, the positively correlated variables that had clinical significance were included in the final models, even if the odds ratio was insignificant. Apart from these, "presence of Dyspnea or Meningism" was included as a variable in screening model to account for the transition in clinical manifestations of the disease over the past 10 years. The sensitivity, specificity, predictive values, and area under curve (AUC) were obtained from the derivation cohort. The models were validated in the validation cohort.

An algorithm for screening and confirming leptospirosis was prepared using results.

To know the benefit of the new algorithm over the existing modified Faine's criteria, net reclassification improvement (NRI)[14] was calculated using the formula:

NRI = (up|confirmed leptospirosis) − (down|confirmed leptospirosis) +

(down|nonleptospirosis fever) − (up|nonleptospirosis fever).

where (up | confirmed Leptospirosis fever) referred to the proportion of confirmed cases that were previously considered as nonleptospirosis using modified Faine's criteria but reclassified as cases of leptospirosis using the models derived in the study. The other terms were defined similarly. The data were entered in Microsoft Excel 2007 (Microsoft Corp., Washington, USA) and analyzed using IBM SPSS Statistics for Windows, Version 23 (IBM Corp., Armonk, N.Y., USA)

The study was approved by the Institutional Review Board.

Results

The existing diagnostic criteria and tools for leptospirosis can be divided into those that can be assessed in peripheral health centers (clinical, epidemiological, and minimal laboratory) and those that can be assessed in tertiary care hospitals (microbiological). Table 2 shows that those existing criteria that can be used at peripheral health centers offer either low sensitivity or low predictive values. Similarly, the criteria that can be used at tertiary care (which must be confirmatory) offer low specificity.

The age–sex distribution and proportion of confirmed cases in the derivation and validation cohorts were similar ($P > 0.05$).

In the derivation cohort, correlation of various signs, symptoms, and laboratory investigations with leptospirosis and nonleptospirosis fever was done. Along with the variables in the modified Faine's criteria, the presence of some of these symptoms in combination was also considered [Table 3].

Conjunctival suffusion, myalgia, raised serum creatinine, the presence of headache with conjunctival suffusion or jaundice or both were found to be significantly and positively correlated to leptospirosis, and they were included in the screening model [Table 3].

The receiver operating characteristic (ROC) of the screening model is denoted by curve C in Figure 1.

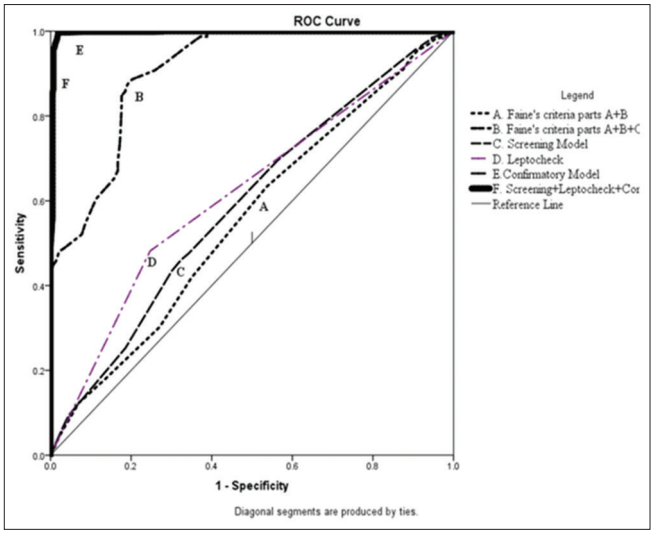

Figure 1: Receiver operating characteristic curve of different models

Table 2: Validity of different diagnostic criteria of leptospirosis (with Leptospirosis Burden Epidemiology Reference Group-2 criteria as reference standard)

Criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Criteria that can be used at peripheral health centers				
Modified Faine's criteria (parts A + B)	5.0	88.0	25.0	57.0
Rapid test (leptocheck)	73.7	7.4	35.9	28.6
Criteria that can be assessed at tertiary care hospital				
Modified Faine's criteria (parts A + B + C)	100.0	14.8	45.2	100.0
IgM ELISA	78.9	29.6	44.1	66.6
MAT	68.4	51.8	50.0	70.0
PCR	36.8	100.0	100.0	69.2

PPV: Positive predictive value, NPV: Negative predictive value, PCR: Polymerase chain reaction, MAT: Microscopic agglutination test, IgM: Immunoglobulin M

The AUC of ROC of the screening model was 0.590 (standard error [SE] ±0.017). The cutoff score value was determined to be ≥9.

A score of 10 was given for a positive rapid test (b coefficient 1.047).

The confirmatory model was developed by including the microbiological tests [Table 3].

The ROC for the confirmatory model is depicted by curve E in Figure 1.

The AUC of the confirmatory model was 0.998 (SE ± 0.001). To get higher specificity, the cutoff value was set at 100.

Validation of the screening model, leptospirosis rapid test, and confirmation model in derivation and validation cohorts was done [Table 4].

It was found that the addition of scores of screening model, leptospirosis rapid test, and confirmatory model yielded higher sensitivity and similar specificity when compared to the use of confirmatory model alone in the derivation cohort. To derive higher sensitivity at the point of screening and higher specificity at the point of confirmation, we developed an algorithm [Figure 2].

The net sensitivity of simultaneous use[15] of screening model and leptospirosis rapid test was calculated as 84.92% in the derivation cohort and 98.27% in the validation cohort. The specificity reduced to 31% and 17%, respectively. However, the sequential use of screening model and leptospirosis rapid test followed by confirmatory model gave net sensitivity 80% and 88% and net specificity of 99.5% and 87.89% in derivation and validation cohorts, respectively.

The NRI of screening model over the modified Faine's criteria parts A + B was 43.99% and 41.79% when the rapid test was used. When both screening model and rapid test were used simultaneously, the NRI was 81.25% [Table 5].

The simultaneous use of the screening model and rapid test with sequential use of confirmatory test has an NRI of 47.18% over the modified Faine's criteria parts A, B, and C.

Table 3: Screening and confirmatory models: Variables and scores

Variable	Correlation coefficient (*P*)	B coefficient	SE	Exp (B) (95% CI)	Score
Screening model					
Conjunctival suffusion	0.057 (0.047)*	0.15	0.17	1.16 (0.83-1.62)	2
Calf tenderness with or without myalgia	0.093 (0.001)**	0.78	0.24	2.19 (1.38-3.50)	8
Raised serum creatinine	0.122 (0.000)**	0.51	0.13	1.67 (1.30-2.14)	5
Consider one of the 3					
Headache with conjunctival suffusion OR	0.064 (0.026)*	0.05	0.27	1.05 (0.61-1.79)	1
Headache with jaundice OR	0.059 (0.041)*	0.14	0.14	1.15 (0.88-1.50)	1
Headache with both conjunctival suffusion and jaundice	0.076 (0.008)**	0.39	0.38	1.47 (0.70-3.08)	4
Dyspnea or meningism	0.020 (0.489)				1
Total					22
Confirmatory model					
PCR	0.629 (0.000)**	12.01	1.35	164410 (11734-2303452)	120
IgM ELISA	0.298 (0.000)**	2.37	0.71	10.73 (2.69-42.84)	20
MAT	0.594 (0.000)**	8.84	8.84	6905.85 (1255.99-37970.62)	90
Total					230

*Significant at *P*<0.05, **Significant at *P*<0.001. SE: Standard error, CI: Confidence interval, OR: Odds ratio, PCR: Polymerase chain reaction, MAT: Microscopic agglutination test, IgM: Immunoglobulin M

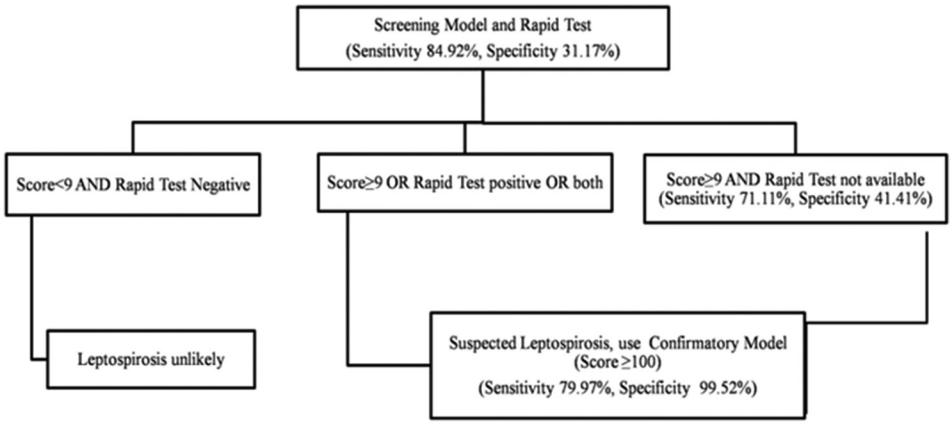

Figure 2: Algorithm for diagnosis of leptospirosis

Table 4: Validity of the models with Leptospirosis Burden Epidemiology Reference Group-2 as reference standard in derivation and validation cohorts

	Screening model		Leptospirosis rapid test		Confirmatory model		Added scores of screening, leptospirosis rapid test and confirmatory models	
	Derivation cohort	Validation cohort	Derivation cohort	Validation cohort	Derivation cohort	Validation cohort	Derivation cohort	Validation cohort
Sensitivity (%)	71.18 (67.92-74.22)	79.16 (65.74-88.27)	48.16 (44.7-51.65)	91.66 (80.45-96.71)	94.18 (92.33-95.61)	89.58 (77.83-95.47)	95.20 (93.62-96.59)	89.58 (77.83-95.47)
Specificity (%)	42.35 (37.74-47.1)	50.00 (34.07-65.93)	75.29 (70.98-79.16)	35.29 (21.49-52.09)	99.29 (97.95-99.76)	85.29 (69.87-93.55)	99.29 (97.95-99.76)	85.29 (69.87-93.55)
PPV (%)	69.67 (66.42-72.75)	69.09 (55.97-79.72)	78.39 (74.52-81.82)	66.66 (54.66-76.84)	99.59 (98.83-99.86)	89.58 (77.83-95.47)	99.60 (98.84-99.87)	89.58 (77.83-95.47)
NPV (%)	43.56 (39.38-48.97)	62.96 (56.34-76.28)	43.83 (40.28-47.46)	75.00 (50.5-89.82)	90.17 (87.14-92.55)	85.29 (69.87-93.55)	91.94 (89.09-94.1)	85.29 (69.87-93.55)

PPV: Positive predictive value, NPV: Negative predictive value

Discussion

South Gujarat is located in the western part of the Indian peninsula. Leptospirosis is endemic in this region.[16] It is an established fact that the Leptospirosis is a zoonotic disease and the transmission occurs through a variety of animal contact or contact with the contaminated environment[17] such as in rainy season (monsoon)[3,8] and during floods.[18] However when dealing with patients with fever from one geographical area who have all been exposed to rainfall/flood and history of animal contact is often vague, not recollected or unnoticed, the exposure to epidemiological factors (part B of modified Faine's criteria) cannot be used in a scoring system to distinguish leptospirosis from nonleptospirosis fever in monsoon.

We found that restructuring modified Faine's criteria by changing some variables and assigning new weights (scores) to features (variables) helped to improve diagnostic accuracy and its usefulness as screening and confirmatory tool. The algorithm we have developed based on this study provides a net sensitivity of 84.92% at the point of screening (using screening model and leptospirosis rapid test). Thus, more patients were correctly diagnosed at the point of screening when compared to modified Faine's criteria (part A + B), with NRI of 81.25%. At the point of confirmation, net specificity of 99.52% at the point of confirmation (sequential use of screening followed by confirmatory model) was achieved with NRI of 47.18% over modified Faine's criteria (part A + B + C).

Both the screening and confirmatory models have obtained higher accuracy when compared to modified Faine's criteria. Rajpakse *et al*.[12] carried out a prospective study and developed a model that included a history of exposure to contaminated source and laboratory investigations such as serum creatinine, neutrophil differential percentage, serum bilirubin, and platelet count. They achieved a sensitivity of 80.3%, specificity 60.2%, PPV 54%, and NPV 84%. Similarly, THAI-LEPTO score[19] used hypotension, jaundice, muscle pain, AKI, low hemoglobin, and hypokalemia with hyponatremia and neutrophilia and obtained a sensitivity 78%, specificity 73%, PPV 87%, and NPV 58%. Both these studies obtained higher validity than the screening model of the present study and similar sensitivity as the simultaneous use of screening models and leptospirosis rapid test. Screening tests are most useful if they can be readily used when the patient reaches the health-care center. To incorporate this attribute to the screening model, the first set of symptoms noted by the patient and the first reported laboratory findings were used to build the model. In this study, we have also aimed at minimizing laboratory investigations in the screening tool to facilitate the utilization of the models in primary health-care settings. Hence we recommend the use of the algorithm to screen the patients of suspected leptospirosis by defining the leptospirosis probable case during monsoon as a patient with acute febrile illness with a screening model score ≥9 or a positive leptospirosis rapid test or both at primary health care setting.

Table 5: Net reclassification improvement following the use of algorithm compared to modified Faine's criteria in validation cohort

Screening model and rapid test for leptospirosis, compared with parts A+B of modified Faine's criteria			
Proportion	**Screening model (%)**	**Rapid test for leptospirosis (%)**	**Simultaneous use of screening model and rapid test (%)**
Up|confirmed leptospirosis	33 (68.75)	37 (77.08)	39 (81.25)
Down|confirmed leptospirosis	2 (4.16)	0 (0.00)	0 (0.00)
Down|nonleptospirosis	5 (14.7)	2 (5.88)	0 (0.00)
Up|nonleptospirosis	12 (35.2)	14 (41.11)	0 (0.00)
NRI	43.99	41.79	81.25

Screening model and rapid test for leptospirosis followed by confirmatory test, compared with parts A+B + C of modified Faine's criteria	
Proportion	**Screening model and rapid test for leptospirosis followed by confirmatory test (%)**
Up|confirmed leptospirosis	0 (0.00)
Down|confirmed leptospirosis	7 (14.58)
Down|nonleptospirosis	22 (64.71)
Up|nonleptospirosis	1 (2.94)
NRI	47.18

NRI: Net reclassification improvement

However, at tertiary care hospitals where microbiological tests are available, the addition of scores of screening model, leptospirosis rapid test, and confirmatory model with a cutoff value of 110 can provide higher accuracy, as given in Table 4.

The limitation of this study is that some studies have shown that the sensitivity of rapid test kits available for leptospirosis is in a range of 78.7%[20] – 93.81%[21] in acute phase and 87.87% in convalescent phase. Most of the rapid kits procured by the government hospitals for leptospirosis in India claim a sensitivity and specificity of about 90%.[22] However, in this study, the validity of rapid test differed in derivation and validation cohort, probably because the change of commercial kits over 10 years. Hence, the actual sensitivity and specificity of the algorithm could be higher than calculated as seen in the validation cohort.

Conclusions

The changing serovars of leptospira can alter the symptoms and hence the scores. This being a hospital-based study is nonrepresentative of the whole population. However, this model is capable and feasible for the early diagnosis of leptospirosis in this part of the country, especially in primary health-care settings. Hence, its utility needs to be expanded to peripheral centers of this region. This would help in the early diagnosis and prompt treatment of leptospirosis. We plan to determine the external validity of these models and algorithms in the hospitals and villages of south Gujarat and improve it accordingly.

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Conflicts of interest

There are no conflicts of interest.

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