

Differentiating coronavirus disease 2019 (COVID-19) from influenza and dengue

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Abstract

Background: The novel coronavirus disease 2019 (COVID-19) presents with non-specific clinical features. This may result in misdiagnosis or delayed diagnosis, and lead to further transmission in the community. We aimed to derive early predictors to differentiate COVID-19 from influenza and dengue.

Methods: The study comprised 126 patients with COVID-19, 171 with influenza and 180 with dengue, who presented within 5 days of symptom onset. All cases were confirmed by reverse transcriptase polymerase chain reaction tests. We used logistic regression models to identify clinical characteristics and laboratory markers in classifying COVID-19 versus influenza, and COVID-19 versus dengue. The performance of the models were evaluated using receiver operating characteristic curves (ROC).

Results: Shortness of breath was the strongest predictor in the models for differentiating between COVID-19 and influenza, followed by diarrhoea. Higher lymphocyte count was predictive of COVID-19 versus influenza and versus dengue. In the model for differentiating between COVID-19 and dengue, patients with cough and higher platelet count were at increased odds of COVID-19, while headache, joint pain, skin rash and vomiting/nausea were indicative of dengue. The area under the ROC was 0.92 for flu model and 0.99 for dengue model.

Conclusion: Models based on clinical features and simple laboratory markers for differentiating COVID-19 from influenza and dengue, which possess good predictive performance, can serve as a useful tool for primary care physicians to determine if further investigations or referrals would be required.

Introduction

A cluster of cases of pneumonia with unknown cause was detected in Wuhan in December 2019^[1]. Caused by a novel human coronavirus now named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it has since spread rapidly on a global scale. On 11 March 2020, the World Health Organization (WHO) declared the novel coronavirus disease (COVID-19) as a pandemic, and expressed deep concern about the alarming levels of spread and severity^[2]. Confirmation of acute SARS-CoV-2 infection requires detection of the virus in respiratory samples by reverse transcriptase polymerase chain reaction (RT-PCR) test. Clinical presentation of COVID-19 patients ranges from asymptomatic to mild non-specific acute symptoms such as fever, dry cough and fatigue^[3]. Close to 20% of COVID-19 cases may be severe^[4].

Influenza is prevalent globally and remains an important cause of morbidity and mortality from respiratory viral infections^[5] while dengue is prevalent in tropical countries with geographic expansion^[6]. Dengue is also known as not only the leading cause of fever in returning travelers in non-endemic countries, but also the main source for triggering autochthonous transmissions^{[7],[8]}. Since clinical presentations of these common viral infections are non-specific, it is difficult for primary care physicians to differentiate COVID-19 from influenza and dengue. This may result in misdiagnosis or delayed

diagnosis, and lead to further transmission in the community. As the COVID-19 pandemic progresses, doctors in both dengue endemic^{[9],[10],[11]} and non-endemic countries where influenza may be the most relevant differential diagnosis for COVID-19^{5,[12]}, should maintain a high level of suspicion and be provided with effective tools to differentiate these three infections.

Singapore is a tropical city state with several endemic viral infections. Influenza circulates year round with bimodal peaks typically observed in April-July and November-January^[13]. Dengue epidemics of increasing magnitude have occurred in a five- to six-year cycle affecting more adults than children^[14]. As of 15 Jun 2020, a total of 40,818 cases of the COVID-19 including 26 deaths have been reported in Singapore^[15]. It is of concern that two local cases of COVID-19 with false positive dengue serology were reported in Singapore without travel or contact history^[16].

In this study, we compared clinical presentations and laboratory parameters of patients with COVID-19, influenza and dengue. We constructed predictive models using logistic regression with the aim to assist doctors in differentiating COVID-19 from influenza and dengue based on clinical features and simple laboratory investigations.

Methods

Cohort description

Our study population comprised laboratory confirmed COVID-19 from an ongoing prospective cohort, and influenza and dengue patients from previous studies. Briefly, prospective recruitment of COVID-19 patients took place from January to April 2020 at the National Centre for Infectious Diseases (NCID), Singapore³. Influenza patients were selected from a retrospective study of those who presented at Tan Tock Seng Hospital (TTSH), the primary centre for screening, treatment and isolation of H1N1(pdm09) cases from April to June 2009 in Singapore^[17]. Dengue patients were selected from a prospective cohort study where adult patients presented with acute undifferentiated febrile illness to TTSH from January 2010 to September 2012^[18].

At first presentation to the hospital, demographic data, symptoms and signs were collected. Full blood count, renal and liver function tests were performed. SARS-CoV-2, influenza and dengue viruses were detected in respiratory samples or venous blood by RT-PCR tests^{3,17,18}. Data of 215 patients with COVID-19, 200 with H1N1(pdm09) or seasonal influenza, and 300 with dengue (predominantly dengue virus serotype 2) were extracted. As our objective was to derive early predictors to differentiate COVID-19 from influenza and dengue, we analysed only symptomatic patients who presented to hospital within 5 days after symptom onset.

Ethics

Data for COVID-19 cohort was collected with waiver of informed consent granted by Ministry of Health, Singapore, under the Infectious Diseases Act as part of COVID-19 outbreak investigation. Research samples and data for the prospective COVID-19 and dengue cohort studies were collected with written informed consent approved by the Domain Specific Review Board (DSRB) of the National Healthcare Group, Singapore (DSRB/ E/12/917 and DSRB/E/09/432). Waiver of informed consent was approved for the retrospective study for influenza patients by the same review board (DSRB/E/09/344).

Statistical analysis

Fisher's exact test was used to compare categorical variables and Mann-Whitney U test to compare continuous variables between any two groups. All statistical tests were two-sided, and statistical significance was taken as $P < 0.05$.

We used multivariable logistic regression models as predictive tools to differentiate between COVID-19 and influenza, and COVID-19 and dengue. We followed the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) 2015 guideline^[19].

Two multivariable models were fitted for differentiating COVID-19 versus influenza (flu models 1 and 2) and COVID-19 versus dengue (dengue models 1 and 2): flu model 1 and dengue model 1 contained demographics and symptoms, whereas flu model 2 and dengue model 2 included laboratory parameters in addition to demographics and symptoms.

For the analysis on COVID-19 versus influenza, the proportion of missing data for laboratory parameters ranged from 3.4% (10 out of total 297 observations) for WBC count, haemoglobin, platelet, neutrophil count and lymphocyte count, to 28.3% (84 observations) for albumin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The variables for flu models 1 and 2 were selected through stepwise use of Akaike's information criterion. Multicollinearity was then checked using variance inflation factor (VIF) for the final predictor variables included in these 2 multivariable models, which ranged from 1.01 to 1.25.

For the analysis on COVID-19 versus dengue, the proportion of missing data for laboratory parameters ranged from 3.3% (10 out of total 306 observations) for WBC count, haemoglobin, haematocrit, platelet, neutrophil count and lymphocyte count, to 9.2% (28 observations) for AST. As the data for differentiating COVID-19 versus dengue exhibited separation, finite estimates of adjusted odds ratios (aOR) and Wald confidence intervals (CI) could not be obtained. Hence, we applied Firth's modified score procedure to estimate OR and derived CI using the profile-penalized likelihood function^[20]. The variables in dengue models 1 and 2 were selected by backward stepwise approach using penalized likelihood ratio tests. The VIF for the final predictor variables ranged from 1.01 to 1.23 for dengue model 1, and it ranged from 1.31 to 3.67 in dengue model 2 when laboratory parameters were included.

We assessed the predictive performance of the multivariable logistic regression models using receiver operating characteristic (ROC) curves and the corresponding area under the ROC (AUC).

Results

This study comprised 126 patients with COVID-19, 171 with influenza and 180 with dengue, who presented within 5 days after symptom onset. The demographic characteristics of the patients are shown in Table 1. The age of COVID-19 patients was older compared with influenza and dengue patients. A lower proportion of COVID-19 patients were male compared with dengue patients. The proportion of COVID-19 patients having comorbidities was higher compared with dengue patients but not with influenza patients.

The clinical features of patients with COVID-19, influenza and dengue at presentation are shown in Table 2. Shortness of breath and diarrhoea were more common in COVID-19 patients than in influenza patients, while fever, cough, running nose and sore throat were less common. Cough, shortness of breath, running nose and sore throat were more common in COVID-19 patients than in dengue patients. A lower proportion of COVID-19 patients had fever, diarrhoea, muscle aches, fatigue/malaise, abdominal pain, bleeding, conjunctivitis, headache, joint pain, skin rash and vomiting/nausea compared with dengue patients. We also provided an infographic of percentage of COVID-19, influenza and dengue patients with each symptom at presentation. It can be seen that COVID-19 and influenza patients have similar symptoms, while dengue patients present with symptoms that are significantly different from the other two groups (See Supplementary Table S1).

The vital signs and laboratory parameters of patients with COVID-19, influenza and dengue are shown in Table 3. COVID-19 patients had lower white blood cell (WBC) count, neutrophil count and creatinine compared with influenza patients whereas their lymphocyte count and alanine aminotransferase (ALT) were higher. WBC, platelet, neutrophil and lymphocyte counts and albumin were higher in COVID-19 patients than dengue patients. The haemoglobin, haematocrit, aspartate aminotransferase (AST) and creatinine were lower in COVID-19 patients than dengue patients.

The multivariable logistic regressions differentiating COVID-19 from influenza are shown in Table 4. In flu model 1 containing demographics and symptoms, older age (aOR 1.09; 95% CI: 1.07–1.12), shortness of breath (aOR 18.29; 95% CI: 2.28–411.81) and diarrhoea (aOR 13.70; 95% CI: 2.33–128.89) increased the odds that the patient had COVID-19, while fever, cough, running nose and vomiting/nauseas were indicative of influenza. In flu model 2 containing demographics, symptoms and laboratory parameters, older age (aOR 1.10; 95% CI: 1.07–1.13), shortness of breath (aOR 50.66; 95% CI: 3.09–1391.20), diarrhoea ((aOR 8.59; 95% CI: 1.67–67.62) and higher lymphocyte count (aOR 1.93; 95% CI: 1.09–3.46) were predictive of COVID-19, while cough, running nose and lower neutrophil count were indicative of influenza.

Table 5 shows the multivariable logistic regression analysis differentiating COVID-19 versus dengue. In dengue model 1 containing demographics and symptoms, older age (aOR 1.06; 95% CI: 1.01–1.12) increased the odds that the patient had COVID-19, while fever, headache, joint pain, skin rash, vomiting/nauseas and bleeding were indicative of dengue. In dengue model 2 containing demographics, symptoms and laboratory parameters, patients who had cough (aOR 51.48; 95% CI: 4.47–4,662.18),

higher platelet count (aOR 1.04; 95% CI: 1.01–1.09) and higher lymphocyte count (aOR 213.28; 95% CI: 9.65–98867.53) were at increased odds of COVID-19, while cough, headache, joint pain, skin rash and vomiting/nauseas were indicative of dengue.

The AUC of flu model 1 containing demographics and symptoms was 0.893 (95% CI 0.856–0.931), and the AUC of flu model 2 which included laboratory parameters in differentiating COVID-19 versus influenza was 0.920 (95% CI 0.888–0.953) (Figure 1). The AUC of dengue model 1 without laboratory parameters and of dengue model 2 which included laboratory parameters for differentiating COVID-19 versus dengue were 0.995 (95% CI 0.992–1.000) and 0.999 (95% CI 0.999–1.000) respectively (Figure 2).

Discussion

Early identification of COVID-19 suspected cases is critical for effective surveillance and successful containment of disease spread. Cases who are not diagnosed correctly and in a timely manner may lead to further transmission of the virus^[21]. However, rapid, sensitive, and affordable point-of-care screening tests are yet to be available^[22]. To ensure that suspected cases are detected as early as possible, primary care physicians who serve as the first point of contact in the healthcare system need a reliable predictive tool to differentiate COVID-19 from other viral infections such as influenza and dengue at the first presentation.

In this study, we built logistic regression models using clinical features and simple laboratory investigations to differentiate COVID-19 from influenza and dengue (Tables 4 and 5). In view of the lower sensitivity of flu model 1 when only symptoms were considered for differentiation of COVID-19 from influenza (Figure 1), it is important to consider full blood count for further assessment where appropriate.

Decision algorithms for differentiating dengue, influenza and other febrile illnesses have been reported before^[23]. There were a few studies on prediction models for diagnosis of COVID-19, however, these included measurement of cytokines, computed tomography scan or genome sequencing^[24]. Recently, Sun et al has come up with algorithms for estimating the risk of COVID-19 among all patients who presented at NCID, which comprised a smaller number of the same cohort of COVID-19 cases in our study, but the duration of symptom onset was not taken into consideration and controls included all SARS-CoV-2 negative patients regardless of final diagnosis^[25]. Sun et al found that the AUC of the logistic regression model that predicted COVID-19 was 0.65 when only demographics and clinical variables were considered. When laboratory and exposure-risk variables were included, the models had higher AUCs of 0.88 to 0.91²⁵.

As our study relied on simple parameters to differentiate COVID-19 from influenza and dengue, the predictors identified from the multivariable logistic regression models may guide primary care physicians, who serve as the first point of contact with the healthcare system, in deciding who should be tested with RT-PCR especially in the absence of travel history to high-risk countries and epidemiological links¹⁶. In countries and remote regions where confirmatory diagnostic capabilities are limited^[26], clinical features

and simple laboratory parameters identified in this study may be used as one of the criteria for isolation of suspected cases to prevent further transmission arising from prolonged delay from symptom onset to isolation^[27].

There are a few limitations in our study. We included patients who presented to hospital within 5 days of symptom onset, hence the findings may not be applicable to those presented late for medical care. Patients who were not suspected or sufficiently ill to be referred to hospitals were excluded. There may be differences in clinical and laboratory parameters among dengue patients by virus serotypes, and influenza patients by the circulating virus strains. Two COVID-19 cases co-infected with dengue were reported thus far; one in Singapore and one in Thailand^{[28],[29]}. Case series of pneumonia patients co-infected with COVID-19 and influenza was also reported in China^[30]. There is a need for separate studies to assess such cases, as it would be more challenging to identify co-infections based on their presenting symptoms and simple laboratory markers.

In conclusion, we have shown that multivariable models based on clinical features and simple laboratory markers for differentiating COVID-19 from influenza and dengue, which possess good predictive performance can serve as a useful tool for primary care physicians to determine if further investigations or referrals would be required. The findings from our study would need to be further validated, so as to address the knowledge gaps of the ongoing COVID-19 pandemic.

Declarations

Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

Y.S.L. and D.C.L. designed the study. T.L.T. and L.W.A. reviewed literature. T.L.T., B.Y. and M.I.C. extracted data. L.W.A. analysed data. T.L.T., L.W.A., M.I.C., Y.S.L. and D.C.L. interpreted the data. T.L.T. and L.W.A. wrote the drafts of the manuscript. B.Y., M.I.C., Y.S.L. and D.C.L. commented on and helped revise the manuscript. All authors read and approved the final manuscript.

Competing interest

Dr. Young reports personal fees from Sanofi and Roche, outside the submitted work. All other authors have no potential competing interest.

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Tables

Table 1. Demographics of COVID-19, influenza and dengue patients

	COVID-19 (N=126)	Influenza (N=171)	P-value	Dengue (N=180)	P-value
Age, median (IQR)	52 (37-62)	30 (22-40)	<0.0005	36 (29-43)	<0.0005
Male, n (%)	74 (58.7)	98 (57.3)	0.813	153 (85.0)	<0.0005
Co-morbidity, n (%)					
Diabetes	15 (11.9)	1 (0.6)	<0.0005	1 (0.6)	<0.0005
Chronic obstructive pulmonary disease (COPD)/Asthma	4 (3.2)	8 (4.7)	0.569	0 (0.0)	0.027
Myocardial infarction	7 (5.6)	-	-	1 (0.6)	0.009
Malignancies	2 (1.6)	-	-	0 (0.0)	0.167
Chronic liver disease	1 (0.8)	-	-	0 (0.0)	0.410
Chronic renal disease	1 (0.8)	-	-	0 (0.0)	0.410

IQR, interquartile range, ‘-’ indicates data is not available.

All P values shown are for comparison with COVID-19, based on Fisher’s exact test for categorical variables and Mann-Whitney U test for continuous variables.

^None of the COVID-19 and dengue patients had congestive heart failure, peripheral vascular disease, stroke or dementia, while these comorbid conditions were not recorded for influenza patients.

Table 2. Clinical features at presentation of COVID-19, influenza and dengue patients

Clinical feature, n (%)	COVID-19 (N=126)	Influenza (N=171)	<i>P</i> -value	Dengue (N=180)	<i>P</i> -value
Fever	86 (68.3)	155 (90.6)	<0.0005	180 (100.0)	<0.0005
Cough	82 (65.1)	139 (81.3)	0.002	44 (24.4)	<0.0005
Shortness of breath	17 (13.5)	1 (0.6)	<0.0005	8 (4.4)	0.005
Running nose	30 (23.8)	97 (56.7)	<0.0005	14 (7.8)	<0.0005
Sore throat	48 (38.1)	97 (56.7)	0.002	39 (21.7)	0.002
Diarrhoea	16 (12.7)	2 (1.2)	<0.0005	68 (37.8)	<0.0005
Muscle aches	26 (20.6)	31 (18.1)	0.655	137 (76.1)	<0.0005
Fatigue/malaise	12 (9.5)	8 (4.7)	0.107	161 (89.4)	<0.0005
Abdominal pain	1 (0.8)	3 (1.8)	0.64	32 (17.8)	<0.0005
Bleeding	0 (0.0)	-	-	56 (31.1)	<0.0005
Chest pain	2 (1.6)	-	-	10 (5.6)	0.132
Conjunctivitis	0 (0.0)	-	-	8 (4.4)	0.023
Headache	13 (10.3)	29 (17.0)	0.129	153 (85.0)	<0.0005
Joint pain	1 (0.8)	-	-	111 (61.7)	<0.0005
Skin rash	0 (0.0)	-	-	54 (30.0)	<0.0005
Vomiting/nausea	5 (4.0)	8 (4.7)	1.000	130 (72.2)	<0.0005

OR, odds ratio; CI, confidence interval, '-' indicates data is not available.

All *P* values shown are for comparison with coronavirus disease 2019 (COVID-19), based on Fisher's exact test.

Table 3. Vital signs and laboratory parameters of COVID-19, influenza and dengue patients

Value, median (IQR)	COVID-19 (N=126)	Influenza (N=171)	<i>P</i> -value	Dengue (N=180)	<i>P</i> -value
Vital signs at presentation					
Temperature, °C	37.7 (37.1–38.1)	38.2 (37.6–38.7)	<0.0005	37.5 (37.0–38.1)	0.547
Heart rate, beats per minute	89.0 (80.0–99.8)	103 (95–115)	<0.0005	75 (66–84)	<0.0005
Respiratory rate, breaths per minute	18.0 (17.0–19.0)	-	-	18 (18–18)	0.715
Systolic blood pressure (mmHg)	133.0 (121.0–146.0)	111 (103–123)	<0.0005	119 (110–128)	<0.0005
Diastolic blood pressure (mmHg)	80.0 (73.0–88.0)	68 (60–75)	<0.0005	72 (65–80)	<0.0005
Pulse oximeter O ₂ saturation (%)	98.0 (97.0–99.0)	-	-	99 (98–100)	<0.0005
Baseline laboratory investigations					
WBC count, x 10 ⁹ /L	4.7 (3.9–5.9)	6.8 (5.6–8.0)	<0.0005	2.5 (2.0–3.2)	<0.0005
Haemoglobin, g/dL	14.2 (13.0–15.1)	14.0 (13.0–14.9)	0.342	15.1 (14.1–15.9)	<0.0005
Haematocrit, %	42.1 (38.7–44.4)	-	-	44.0 (41.4–46.6)	<0.0005
Platelet count, x 10 ⁹ /L	200.5 (168.5–237.5)	210.0 (171.0–260.0)	0.066	97.5 (73.0–119.0)	<0.0005
Neutrophil count, x 10 ⁹ /L	2.7 (2.0–4.1)	5.0 (3.5–6.3)	<0.0005	1.5 (1.1–2.0)	<0.0005
Lymphocyte count, x 10 ⁹ /L	1.2 (0.9–1.5)	0.9 (0.7–1.3)	<0.0005	0.6 (0.4–0.8)	<0.0005
Albumin, g/L	41.0 (38.0–43.0)	40.0 (38.0–42.0)	0.463	39.0 (37.0–42.0)	0.044
ALT, U/L	28.0 (19.0–44.8)	20.0 (15.0–32.5)	<0.0005	31.0 (22.0–52.0)	0.062
AST, U/L	26.5 (19.0–36.3)	24.0 (20.0–30.0)	0.271	47.0 (32.0–77.8)	<0.0005
Creatinine, µmol/L	70.0 (59.0–89.0)	82.0 (67.3–98.0)	<0.0005	76.0 (68.0–88.8)	0.011

IQR, interquartile range; ALT, alanine aminotransferase; AST, aspartate aminotransferase, WBC, white blood cell

‘-’ indicates data is not available.

All *P* values shown are for comparison with coronavirus disease 2019 (COVID-19), based on Mann-Whitney U test for continuous variables.

Table 4. Final covariates in multivariable logistic regression models for differentiating COVID-19 versus influenza

Variable	Flu model 1			Flu model 2		
	aOR	(95% CI)	P-value	aOR	(95% CI)	P-value
Age	1.09	(1.07-1.12)	<0.0005	1.10	(1.07-1.13)	<0.0005
Fever	0.22	(0.09-0.48)	<0.0005	0.44	(0.18-1.05)	0.067
Cough	0.31	(0.15-0.63)	0.001	0.32	(0.14-0.72)	0.007
Shortness of breath	18.29	(2.28-411.81)	0.018	50.66	(3.09-1,391.20)	0.007
Running nose	0.30	(0.15-0.56)	<0.0005	0.31	(0.15-0.62)	0.001
Diarrhoea	13.70	(2.33-128.89)	0.009	8.59	(1.67-67.62)	0.018
Vomiting/nausea	0.11	(0.01-0.73)	0.031	0.19	(0.02-1.29)	0.120
Neutrophil count, x 10 ⁹ /L				0.69	(0.57-0.82)	<0.0005
Lymphocyte count, x 10 ⁹ /L				1.93	(1.09-3.46)	0.025

aOR, adjusted odds ratio shown as odds of having COVID-19, CI, confidence interval

Table 5. Final covariates in multivariable logistic regression models for differentiating COVID-19 versus dengue

Variable	Dengue model 1			Dengue model 2		
	aOR	(95% CI)	P-value	aOR	(95% CI)	P-value
Age	1.06	(1.01-1.12)	0.017			
Fever	0.09	(0.00-0.86)	0.034			
Headache	0.04	(0.007-0.15)	0.000	0.01	(0.00002-0.09)	<0.0005
Cough				51.48	(4.47-4662.18)	<0.0005
Joint pain	0.01	(0.001-0.11)	<0.0005	0.02	(0.0001-0.26)	0.001
Skin rash	0.02	(0.0001-0.38)	0.007	0.01	(0.00001-0.22)	0.002
Vomiting/nausea	0.02	(0.002-0.11)	0.000	0.001	(0.0000001-0.08)	<0.0005
Bleeding	0.01	(0.0001-0.21)	0.002			
Platelet count, x 10 ⁹ /L				1.04	(1.01-1.09)	0.001
Lymphocyte count, x 10 ⁹ /L				213.28	(9.65-98,867.53)	<0.0005

aOR, adjusted odds ratio shown as odds of having COVID-19, CI, confidence interval

Figures

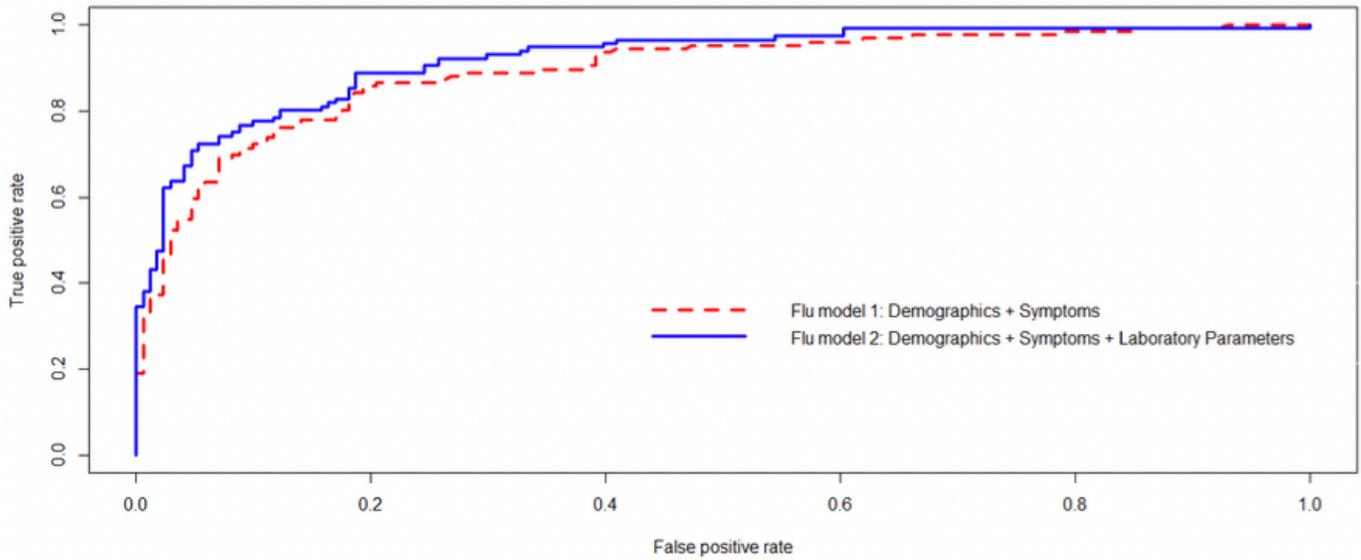


Figure 1

Receiver operating characteristic curves for flu model 1 (demographics and symptoms) and model 2 (demographics, symptoms and laboratory parameters) for differentiating COVID-19 versus influenza

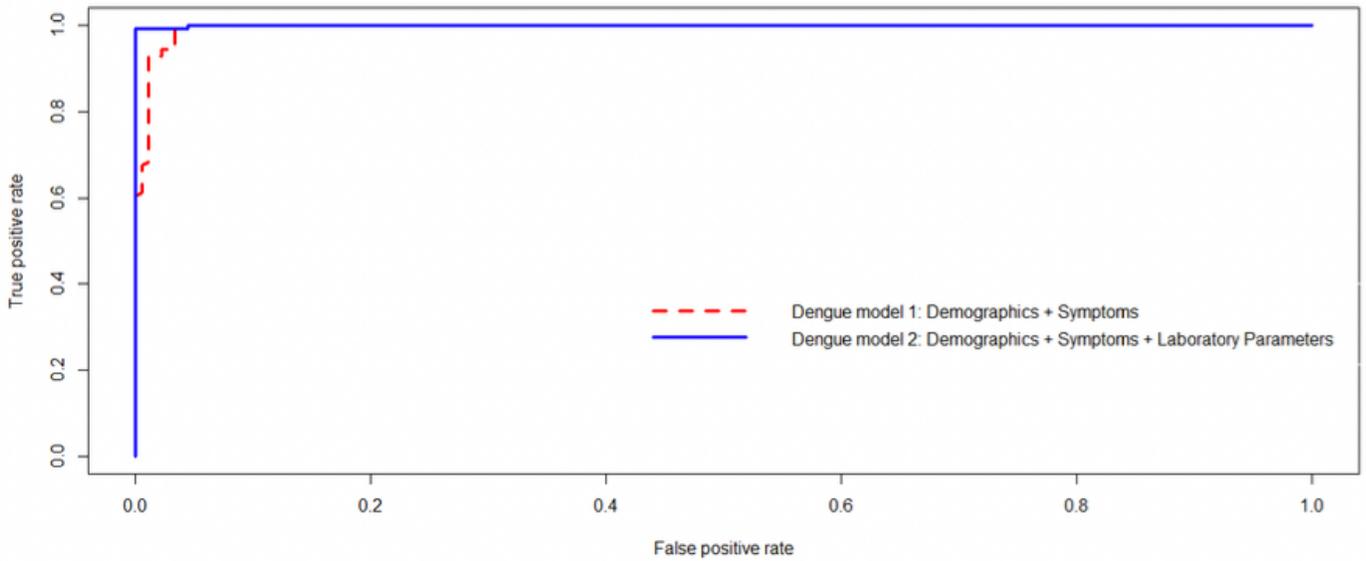


Figure 2

Receiver operating characteristic curves for dengue model 1 (demographics and symptoms) and model 2 (demographics, symptoms and laboratory parameters) for differentiating COVID-19 versus dengue

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [COVID19influenzaanddengueSupplementarytable.docx](#)