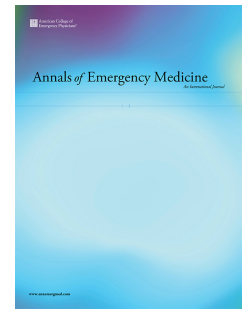


Journal Pre-proof



Accuracy of Emergency Department clinical findings for diagnostic of coronavirus disease-2019

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Final approval of manuscript: all authors

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Ethical Aproval:

The study was approved by the Institutional Review Board of the French Speaking society for respiratory medicine – Société de Pneumologie de Langue Française (number CEPRO 2020-014).

Abstract:

Objective: We sought to describe the medical history and clinical findings of patients attending the ED with suspected COVID-19 and estimate the diagnostic accuracy of patients' characteristics for predicting COVID-19.

Methods: We prospectively enrolled all patients tested for SARS-CoV-2 by RT-PCR in our ED from March 9, 2020 to April 4, 2020. We abstracted medical history, physical examination findings, and the clinical probability of COVID-19 ("low", "moderate", "high") rated by emergency physicians depending on their clinical judgment. We assessed diagnostic accuracy of these characteristics for COVID-19 by calculating positive and negative likelihood ratios (LR+/LR-).

Results: We included 391 patients of whom 225 tested positive for SARS-CoV-2. RT-PCR was more likely to be negative when the emergency physician thought that clinical probability was low, and more likely to be positive when she or he thought that clinical probability was high. Patient-reported anosmia and the presence of bilateral B-lines on lung ultrasound had the highest LR+ for the diagnosis of COVID-19 (7.58; 95% CI 2.36–24.36 and 7.09; 95% CI 2.77–18.12 respectively). The absence of a high clinical probability determined by the emergency physician and the absence of bilateral B-lines on lung ultrasound had the lowest LR- for the diagnosis of COVID-19 (0.33; 95% CI 0.25–0.43 and 0.26; 95% CI 0.15–0.45 respectively).

Conclusions: Anosmia, emergency physician estimate of high clinical probability and bilateral B-lines on lung ultrasound increased the likelihood of identifying COVID-19 in patients presenting to the ED.

Keywords:

Covid-19, SARS-CoV-2, Emergency Department, clinical findings, clinical probability, lung ultrasound

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Introduction:*Background*

The novel Coronavirus disease of 2019 (COVID-19) outbreak has led to major reorganizations of emergency departments (EDs) in order to face the dramatic increase of patients suspected to be infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The clinical description of hospitalized patients has been reported in the literature [2-6] but no study has focused on clinical and diagnostic findings in the ED setting.

Importance

Among patients attending EDs, rapid triage of those suspected of COVID-19 is mandatory to appropriately isolate them and avoid secondary transmissions. Clinical diagnosis can be challenging since the disease may present with non-specific symptoms such as myalgia, cough or fever [3,6]. Medical history and clinical presentations of COVID-19 patients attending EDs need to be precisely described to facilitate early recognition by emergency physicians and promptly trigger diagnostic procedures such as real-time reverse transcriptase polymerase chain reaction (RT-PCR).

Goals of this Investigation

The objectives of this study were to collect and describe the medical history and clinical findings of patients attending the ED with suspected COVID-19, and to assess utility of clinical parameters, physician gestalt (clinical judgment) and lung ultrasound (US) to accurately identify COVID-19 patients at the time of ED presentation.

Methods:*Study Design and Setting*

This prospective observational study was conducted in the ED of Saint-Louis University Hospital, Paris, France. Starting on March 9, 2020, we prospectively enrolled a cohort of all COVID-19 suspected adult patients that were tested for SARS-CoV-2. This study reports the results of patients enrolled until April 4, 2020. The study was approved by the Institutional Review Board of the French Speaking Society for Respiratory Medicine – Société de Pneumologie de Langue Française (number CEPRO 2020-014). Our study followed the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [7].

Selection of Participants and Measurements:

All adult patients (age ≥ 18 years) that were tested for SARS-CoV-2 in our ED were included after giving oral consent. Cases were identified and enrolled 24 hours per day and 7 days per week during the study period by the attending emergency physician or resident who was in charge of the patient. Testing for SARS-CoV-2 in COVID-19 suspected patients was left to the clinician's discretion but most of the time, patients were tested when they were dyspneic or reported shortness of breath; had comorbidities that put them at risk of severe infection such as immunosuppression, chronic respiratory insufficiency, cardiovascular diseases, and obesity; if they were over 70 years old; or if they were too weak to be discharged home. Some patients without clinical suspicion of COVID-19 but needing hospitalization in non-COVID areas were also tested. Patients under the age of 70, with no comorbidities, and with no respiratory symptoms were not tested. Prior to the outbreak, our department received approximately 110 to 120 patients per day and this number dropped to approximately 50 to 60 from the beginning of the pandemic in March. During the study period, we tested approximately 10 to 20 patients per day. If patients attended the ED more than once, only the last visit was included. There were no other exclusion criteria.

When testing for SARS-CoV-2, the attending emergency medicine attending or resident physician was asked to report in a dedicated form the patient's medical history; Eastern Cooperative Oncology Group Performance Status (ECOG PS), which is a scale that describes patients' ability to care for themselves and perform daily activities, ranging from 0 ("fully active") to 4 ("completely disabled"); physical examination; and chest X-ray and lung US findings when those were performed. Lung US was performed with a pocket-size device (VSCAN, GE Healthcare). After medical history, physical examination, US, and chest X-rays, attending physicians were asked to rate the clinical probability of COVID-19 based on both their clinical judgment and a predefined three-level scale ("low", "moderate", "high"). As anosmia was reported in Europe around the end of March, this clinical sign was added to the form on March 24, 2020.

All study data and variables with their categories were defined prior to the beginning of the study. Four residents who were previously trained in data abstraction completed the forms using a dedicated spreadsheet. Age, gender, vital signs at ED arrival and any data that was missing in the forms were abstracted retrospectively from the patients' ED medical files with the exception of clinical probability that could only be determined prospectively. An emergency physician with expertise in research periodically monitored data abstraction. When there was disagreement between abstractors or if data was ambiguous, this emergency physician, made the final decision. No assessment of inter-rater reliability was performed. The gold standard for diagnosis was the result of SARS-CoV-2 RT-PCR via nasal swab (Cobas® SARS-CoV-2 Test, Roche, Meylan, France). The patients who initially had a negative RT-PCR in the ED but were tested positive in the next 48 hours were considered positive (initial false negative).

Analysis

Continuous variables were reported as medians with their interquartile ranges (IQR). To assess the performances of each characteristic to accurately identify COVID-19, we calculated the sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LRs) and their 95% confidence intervals (CI). We also calculated PPVs and NPVs for each characteristic under a variety of prevalence assumptions (5%, 10%, 25%, 75%). We calculated post-test probabilities depending on both pre-test probabilities (5%, 10%, 25%, 50%, 75%) and the presence or absence of bilateral B-lines on lung US. Accuracy of the physician clinical probability in identifying patients with COVID-19 was assessed with a receiver operating characteristics (ROC) curve and by calculating the area under the curve (AUC) with its 95% CI. Data were analyzed with R 3.5.0 software (the R Foundation for Statistical Computing, Vienna, Austria).

Results:

Characteristics of Study Subjects

During the study period, 400 patients were tested for SARS-CoV-2. After excluding nine patients who were tested two times during two ED visits, we included 391 patients. Among those patients, 225 (57.6%) were tested positive for SARS-CoV-2 (including five initial false negatives). Median age was 62 [48–71] years and 150 (38.4%) were females. General characteristics of these COVID-19 suspected patients are presented in Table 1. Among patients with confirmed COVID-19, 67 (29.8%) were discharged home from the ED, 134 (59.5%) were hospitalized in wards, 22 (9.8%) were admitted to the ICU and 2 (0.9%) died in the ED.

Main Results

Patient-reported symptoms, physical examination, lung ultrasound and chest X-ray findings in patients with or without COVID-19 are summarized in Table 2. Among patients with confirmed COVID-19, 53 (23.6%) reported gastrointestinal symptoms such as vomiting, diarrhea or abdominal pain, 147 (65.6%) had a temperature below 38 °C and 97 (43.3%) had a temperature below 37.5 °C upon ED arrival (temperature was missing for one patient). When lung ultrasound was performed on 48 (21.4%) patients with COVID-19, bilateral B-lines were present in 36 (76.6%) of them.

Emergency physicians rated the clinical probability for 273 patients. Table 3 shows the proportion of patients with or without COVID-19 depending on the emergency physician's clinical probability. RT-PCR was more likely to be negative for SARS-CoV-2 when the emergency physician thought that clinical probability was low, and more likely to be positive when she or he thought that clinical probability was high. Figure 1 shows the accuracy of physician clinical judgment in identifying COVID-19 patients (AUC = 0.795; 95% CI: 0.743-0.848).

Table 4 shows the Se, Sp, PPV, NPV, LR+ and LR- for some of the patient-reported symptoms, clinical US and chest X-ray findings. Patient-reported anosmia and the presence of bilateral B-lines on lung US had the highest LR+ for the diagnosis of COVID-19 (7.58; 95% CI 2.36–24.36 and 7.09; 95% CI 2.77–18.12 respectively). The absence of a high clinical probability determined by the emergency physician and the absence of bilateral B-lines on lung US had the lowest LR- for the diagnosis of COVID-19 (0.33; 95% CI 0.25–0.43 and 0.26; 95% CI 0.15–0.45 respectively).

Supplemental Table shows the post-test probability depending on the pre-test probability (i.e. prevalence) and the results of lung US.

Limitations:

Our study has several limitations. First, not every patient was tested for SARS-CoV-2 and testing was left to the clinician's discretion. However, despite the absence of clear predefined inclusion criteria, testing was performed in the vast majority of cases in patients who had severe symptoms such as dyspnea, reported shortness of breath, presented with comorbidities (e.g., immunosuppression or chronic pulmonary or cardiovascular diseases), or were over 70 years old. Thus, our results may not be valid in other populations such as young people without comorbidities and those with very few symptoms. Also, as our results are issued from a single center in France, they may not be generalizable to other centers. Second, it is possible that patients did not systematically report their symptoms, and this might have lowered the estimates of their prevalence. Third, we may have underestimated anosmia because we only added this to the form on March 24, 2020. Fourth, lung ultrasound was not systematic and occurred in only 22.3% of the patients, which contributed to the large 95% CI observed. It is possible that emergency physicians performed lung US in the most severe cases and that the accuracy of this exam in predicting COVID-19 is likely to be lower in patients with fewer symptoms. Lastly, our gold-standard to diagnose COVID-19 was based on the RT-PCR which may have false-negatives. To address this, we also evaluated patients who were initially tested negative for SARS-CoV-2 but were then hospitalized and secondarily tested positive and considered them as positives.

Discussion:

To the best of our knowledge, this is the first prospective study that both described patient-reported symptoms and physical examination findings in a large cohort of COVID-19 suspected patients attending the ED and estimated the accuracy of clinical findings for the diagnosis of COVID-19.

At the beginning of the epidemic in France, knowledge of the COVID-19 clinical picture was mainly extrapolated from cases in Wuhan, China. Emergency physicians prepared to face an unknown disease and attend to patients with non-specific influenza-like symptoms with clinical signs of lung infection, or acute respiratory failure for the most severe cases [3,6]. Since then, studies have been published about the epidemiology [1], the risk factors for severe disease [4] and the description of critically ill patients [8-11] infected with SARS-CoV-2, but there is limited data regarding the accuracy of clinical findings in patients with suspected COVID-19. Moreover, most studies have focused on patients who were already hospitalized for the disease, which may differ from the ED population.

Prompt identification of possible cases is mandatory to avoid the spread of the virus by patients with mild or non-specific symptoms [12]. Therefore, emergency physicians need to be cautious when they evaluate such patients and be aware of some pitfalls. Whereas fever ($>37.3^{\circ}\text{C}$) was reported in more than 90% of the patients hospitalized with COVID-19 [4,6], we found that, even if 78.2% of the patients reported fever, only 34.4% of the patients had $\geq 38^{\circ}\text{C}$ and 56.7% had $\geq 37.5^{\circ}\text{C}$ at ED triage. It is possible that the temperature was initially lowered by antipyretics and subsequently rose during the ED stay. Nevertheless, temperature should not be used in isolation to exclude COVID-19 [13]. Consistent with other studies, we found that the most frequent reported symptoms were fever, cough, dyspnea and myalgia [2-6]. Gastrointestinal symptoms were present in 23.6% of our patients, whereas one small study of 18 patients found a rate of 17% [14], while larger cohorts have reported these symptoms in less than 10% [2-6]. Anosmia was reported by 13.8% of the patients in our cohort and was the

most specific sign of COVID-19. It is likely that we underestimated this sign, which was not initially described in the Chinese literature and was reported in Europe around the end of March [15-17].

Other findings like bilateral crackles on lung auscultation or the rapid need for high levels of oxygen delivery at ED arrival were highly suggestive of COVID-19, especially among middle-aged or older patients with comorbidities such as diabetes or cardiovascular diseases [18]. As this disease induces endotheliitis, leading to vascular derangements [19], it is very likely that new symptoms involving multiple organs such as neurological [20] or skin disorders [21] will emerge in the future.

Besides clinical signs, lung imaging and particularly CT-scans have shown to have a high sensitivity for the diagnosis of COVID-19, particularly in severe cases, and may be valuable in patients with high clinical probability but negative RT-PCR [22-24]. Another option might be to perform lung ultrasound, allowing rapid diagnosis and severity assessment at patient bedside for suspected COVID-19 [25, 26]. In our study, the presence or absence of bilateral B-lines with a pocket-size ultrasound device had the higher LR+ and a low LR-, respectively. In a study with 20 patients with COVID-19, Xing et al found that all patients showed pleural line abnormalities, and bilateral B-lines on lung US, regardless of the severity or stage of the disease [27]. In another retrospective study that included 30 patients with COVID-19, interstitial pulmonary edema was present on lung US in 90.0% of the cases [28]. Nonetheless, literature on this topic is scarce and more data is needed [29].

In the present study, we found that emergency physician clinical judgment was quite accurate and that only 19.4% of the patients with low clinical probability had COVID-19 while 15.6% of the patients with high clinical probability did not have it. The AUC of 0.795 appeared to us quite fair for a new disease with very few specific clinical signs. Emergency physician gestalt has been studied in predicting other diseases and performed equally well with an observed

AUC of 0.83 for appendicitis in children [30], 0.75 for acute coronary syndrome [31], 0.86 for acute heart failure syndrome [32] and 0.81 for pulmonary embolism [33].

In summary, in this large prospective cohort study of patients attending the ED with a suspicion of COVID-19, anosmia, emergency physician estimate of high clinical probability and bilateral B-lines on lung ultrasound increased the likelihood of identifying COVID-19 in patients presenting to the ED. Future studies should assess this in other emergency departments and the role of combining findings to develop clinical decision tools.

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Table 1. General characteristics of COVID-19 suspected patients.

Variable	Total (N=391)		Missing data, n (%)
Age (years), median [IQR]	62	[48–71]	0
Female gender, n (%)	150	(38.4)	0
ECOG PS, n (%)			104 (26.6)
0–2	257	(89.5)	
3–4	30	(10.5)	
Immunosuppression, n (%)	195	(50.5)	5 (1.3)
Diabetes mellitus	68	(17.6)	
Solid cancer	58	(15.0)	
Hematological malignancy	47	(12.2)	
Solid organ transplant	14	(3.6)	
HIV	23	(6.0)	
Long course corticosteroids	22	(5.7)	
Other	16	(4.1)	
Chronic lung disease, n (%)	85	(22.1)	6 (1.5)
COPD	24	(6.2)	
Asthma	22	(5.7)	
Lung cancer	8	(2.0)	
Bronchiectasis/emphysema	8	(2.0)	
Sarcoidosis/fibrosis	7	(1.8)	
Other	23	(6.0)	
Cardiovascular disease, n (%)	156	(40.4)	5 (1.3)
Hypertension	122	(31.6)	
Atrial fibrillation	29	(7.4)	
Coronary disease	22	(5.7)	
Chronic heart failure	16	(4.1)	
Other	5	(1.3)	
Obesity, n (%)	58	(15.2)	9 (2.3)
No comorbidity, n (%)	70	(18.1)	5 (1.3)

COPD chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *ECOG PS* Eastern Cooperative Oncology Group Performance Status

Table 2. Patient-reported symptoms, clinical and chest X-ray findings in patients with or without COVID-19

Variable	Total (N=391)		COVID-19 + (n=225)		COVID-19 - (n=166)		Missing data, n (%)
Patient-reported symptoms, (%)							1 (0.2)
Classic symptoms							
Fever	259	(66.4)	176	(78.2)	83	(50.3)	
Cough	239	(61.3)	158	(70.2)	81	(49.1)	
Dyspnea	197	(50.5)	131	(58.2)	66	(40.0)	
Myalgia	93	(23.8)	71	(31.6)	22	(13.3)	
Rhinitis/pharyngitis	45	(11.5)	19	(8.4)	26	(15.8)	
Anosmia	34	(8.7)	31	(13.8)	3	(1.8)	
None	41	(10.5)	10	(4.4)	31	(18.8)	
Less classic symptoms							
Headache	27	(6.9)	15	(6.7)	12	(7.3)	
Gastrointestinal symptoms	94	(24.1)	53	(23.6)	41	(24.8)	
Fatigue	55	(14.1)	34	(15.1)	21	(12.7)	
Chest pain	24	(6.2)	11	(4.9)	13	(7.9)	
Dizziness/syncope	21	(5.4)	8	(3.6)	13	(7.9)	
Hemoptysis	4	(1.0)	3	(1.3)	1	(0.6)	
Symptom duration (days), median [IQR]	5	[3–8]	7	[3–9]	4	[2–7]	37 (9.5)
Vital signs at ED arrival, median [IQR]							
SBP (mmHg)	130	[113–143]	129	[111–141]	131	[116–145]	6 (1.5)
DBP (mmHg)	75	[65–85]	75	[65–85]	75	[66–85]	7 (1.8)
HR (/min)	94	[84–109]	93	[85–106]	99	[82–110]	8 (2.0)
Temperature (°C)	37.3	[36.6–38.0]	37.6	[36.9–38.1]	36.9	[36.4–37.6]	6 (1.5)
RR (/min)	22	[19–28]	25	[20–30]	20	[17–24]	70 (17.9)
Oxygen saturation (%)	100	[96–100]	99	[96–100]	100	[97–100]	1 (0.2)
Need for oxygen therapy, n (%)	131	(34.0)	96	(43.0)	35	(21.6)	6 (1.5)
Oxygen delivery (L/min), median [IQR]	3	[2–5]	3	[2–6]	2	[2–3]	5 (3.8)
Physical examination							
Altered mental status, n (%)	28	(7.2)	15	(6.7)	13	(7.8)	1 (0.2)
Mottled skin, n (%)	34	(9.1)	23	(10.7)	11	(7.0)	19 (4.9)
Lung auscultation, n (%)							7 (1.8)
Normal	218	(56.8)	106	(48.4)	112	(67.9)	
Unilateral crackles	33	(8.6)	21	(9.6)	12	(7.3)	
Bilateral crackles	95	(24.7)	80	(36.5)	15	(9.1)	
Wheezing	17	(4.4)	4	(1.8)	13	(7.9)	
Lung ultrasound, n (%)							4 (1.0)
Not performed	303	(78.3)	176	(78.9)	127	(77.4)	
No bilateral B-lines	44	(11.4)	11	(4.9)	33	(20.1)	
Bilateral B-lines	40	(10.3)	36	(16.2)	4	(2.5)	
Chest X-ray, n (%)							0
Not performed	262	(67.0)	145	(64.4)	117	(70.5)	
Normal	48	(12.3)	19	(8.4)	29	(17.5)	

One lung involved	11 (2.8)	6 (2.7)	5 (3.0)
Both lungs involved	43 (11.0)	35 (15.6)	8 (4.8)
Other	27 (6.9)	20 (8.9)	7 (4.2)

DBP diastolic blood pressure, *ED* emergency department, *HR* heart rate, *RR* respiratory rate, *SBP* systolic blood pressure

Table 3. Proportion of COVID-19 positives or negatives depending on the emergency physician clinical probability

Clinical probability (N=273)	RT-PCR result for SARS-CoV-2	
	n (%; 95% CI)	
	Positive (n=167)	Negative (n=106)
Low	12 (19.4)	50 (80.6)
Moderate	31 (48.4)	33 (51.6)
High	124 (84.4)	23 (15.6)

RT-PCR real-time reverse transcriptase polymerase chain reaction.

Table 4. Clinical and chest X-ray findings accuracy for the diagnosis of COVID-19

	Se (95% CI)	Sp (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)
Patient-reported symptoms						
Fever	0.78 (0.72-0.83)	0.50 (0.42-0.58)	0.68 (0.62-0.74)	0.63 (0.54-0.71)	1.56 (1.32-1.84)	0.40 (0.32-0.50)
Dyspnea	0.58 (0.51-0.65)	0.60 (0.52-0.68)	0.66 (0.59-0.73)	0.51 (0.44-0.59)	1.46 (1.17-1.81)	0.40 (0.32-0.50)
Myalgia	0.32 (0.26-0.38)	0.87 (0.81-0.91)	0.76 (0.66-0.85)	0.48 (0.42-0.54)	2.37 (1.53-3.65)	0.10 (0.06-0.17)
Anosmia	0.14 (0.10-0.19)	0.98 (0.95-1.00)	0.91 (0.76-0.98)	0.46 (0.40-0.51)	7.58 (2.36-24.36)	0.02 (0.01-0.04)
Vital signs at ED arrival						
Temperature $\geq 38^{\circ}\text{C}$	0.34 (0.28-0.41)	0.83 (0.76-0.88)	0.73 (0.64-0.81)	0.47 (0.42-0.54)	1.98 (1.35-2.90)	0.30 (0.22-0.40)
Oxygen saturation $<95\%$	0.17 (0.12-0.22)	0.91 (0.85-0.95)	0.72 (0.58-0.83)	0.45 (0.39-0.50)	1.86 (1.06-3.26)	0.20 (0.13-0.30)
RR $>25/\text{min}$	0.47 (0.39-0.54)	0.78 (0.70-0.85)	0.76 (0.68-0.84)	0.49 (0.42-0.56)	2.13 (1.49-3.06)	0.30 (0.22-0.40)
Oxygen flow $\geq 6\text{ L/min}$	0.28 (0.19-0.38)	0.91 (0.75-0.98)	0.90 (0.73-0.98)	0.30 (0.21-0.40)	2.95 (0.96-9.09)	0.10 (0.06-0.17)
Physical exam						
Bilateral lung crackles	0.37 (0.30-0.43)	0.91 (0.85-0.95)	0.84 (0.75-0.91)	0.52 (0.46-0.58)	4.02 (2.41-6.71)	0.20 (0.13-0.30)
Lung US						
Bilateral B-lines	0.77 (0.62-0.88)	0.89 (0.75-0.97)	0.90 (0.76-0.97)	0.75 (0.60-0.87)	7.09 (2.77-18.12)	0.10 (0.06-0.17)
Chest X-ray						
Both lungs involved	0.16 (0.11-0.21)	0.96 (0.91-0.98)	0.83 (0.69-0.93)	0.45 (0.40-0.51)	3.67 (1.67-8.05)	0.10 (0.06-0.17)
High clinical probability	0.74 (0.67-0.81)	0.78 (0.69-0.86)	0.84 (0.77-0.90)	0.66 (0.57-0.74)	3.42 (2.36-4.97)	0.10 (0.06-0.17)

ED emergency department, *LR* likelihood ratio, *NPV* negative predictive value, *PPV* positive predictive value, *RR* respiratory rate, *Se* sensitivity, *Sp* specificity, *US* ultrasound

Figure 1. Receiver operating characteristics curve. Accuracy of the emergency physician clinical probability in identifying patients with COVID-19. *AUC* area under the curve.

