BRIEF REPORT

COVID-19 or not COVID-19? Compared characteristics of patients hospitalized for suspected COVID-19

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Abstract
During an epidemic period, we compared patients hospitalized for initial suspicion of COVID-19 but for whom an alternative diagnosis was finally retained ($n = 152$) with those who had COVID-19 ($n = 222$). Most common diagnoses were another infectious disease and heart failure. COVID-19-negative patients were more often active smokers had less often cough, fever, and digestive symptoms, as compared to the 222 COVID-19-positive patients. They had higher median neutrophil and lymphocyte counts and lower CRP level. In multivariate analysis, no current smoking, neurocognitive disorder, myalgia, and fibrinogen ≥4g/L were independently associated with a final diagnosis of COVID-19.

Keywords COVID-19, · SARS-CoV2, · Differential diagnosis, · Tobacco

Introduction

Since December 2019, the world is facing a pandemic situation, Coronavirus Disease 2019 (COVID-19), a manifestation of infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [1]. COVID-19 clinical manifestations are mainly respiratory. Almost 5% of patients develop severe pneumonia with acute respiratory distress syndrome (ARDS), with a mortality rate as high as 50% [2–4].

In the literature, there are many studies on patients suffering from COVID-19. By contrast, we lack data on the patients who were initially suspected of suffering from COVID-19, but for whom the diagnosis was finally ruled out. This is of particular interest at the collective level since hospitalization flows and wards need to be reorganized because of the epidemic, and to avoid overloading the system by suspicions which will finally turn out wrong. It is also of particular interest at the individual level, since the isolation to avoid contamination and the potential delay in clinical biological and radiological diagnostic procedures may be associated with lost opportunities for patients suffering from diseases other than COVID-19.

Thus, the aim of this study was to describe and compare the population of patients hospitalized for a suspicion of COVID-19 in an epidemic context in the University Hospital of Dijon, France.

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Patients and methods

Study design and patient selection

Patients hospitalized with suspected COVID-19 in the COVID-19 diagnostic unit and the Infectious Diseases (ID) department of the University Hospital of Dijon between February 23, 2020, and April 28, 2020, were retrospectively included. This period corresponded to the first wave of COVID-19 in Burgundy (France), a massive SARS-CoV-2 outbreak.

Patients were considered as COVID-19 positive if at least one RT-PCR assay was positive on a respiratory sample during the hospitalization. Patients were considered as COVID-19-negative if all RT-PCRs assays were negative, without any other strong argument for COVID-19 at the end of the hospitalization. Patients with negative real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays but with suggestive chest CT and without an alternate diagnosis were considered indeterminate and were not included. Patients with negative RT-PCRs assay but with suggestive chest computed tomography (CT) and alternate diagnosis were considered as COVID-19 negative. At the beginning of the epidemics, all patients suspected of COVID-19 were hospitalized in the ID department. Then, from the 18th of March, such patients were first admitted in a COVID-19 unit of diagnosis, whose functions were to sort out patients based on the results of RT-PCR and chest-CT. From that date on, the ID department only received patients with confirmed COVID-19. Patients initially admitted in intensive care unit were not included.

Variables of interest and data collection

Demographic data were collected, as well as the major comorbidities. Clinical data reviewed were the worst characteristics during the first 24 h of the stay. Biological parameters were determined from the first blood sampling during the first 48 hours of the hospitalization. The RT-PCR assay was performed on nasopharyngeal secretions and/or another respiratory sample. Chest CT findings were classified into evocative or not of COVID-19, according to the radiologist's interpretation. The severity of the impairment was classified according to the recommendations of the French Society of Radiology as: slight (including minimal), moderate or severe (including critical) [5, 6].

Statistical analysis

Continuous variables were expressed as means +/- SDs or medians and inter-quartile ranges (IQRs). Categorical variables were described by frequencies and percentages. Univariate analysis consisted of comparisons between variables, according to COVID-19 status, performed using the chi-square test (or Fisher's exact test) for percentages, Student's test for means and Wilcoxon Mann-Whitney test for medians and IQRs. The discriminant thresholds of the quantitative variables were determined using ROC curves. The statistically significant variables with $p < 0.2$ in univariate analysis were then used in a multivariate step-down model to determine a predictive model for the diagnosis of COVID-19. To limit classification bias, a sensitivity analysis was performed by classifying patients with moderate or severe impairment on chest CT as COVID-19 positive. Statistical significance was defined as a p-value <0.05. Statistical analyses were performed with Epi Info 7.2 and XLSTAT software 2020.

Results

As depicted in the flowchart (Fig. 1), among the 304 patients hospitalized in the ID department and the 379 patients

Fig. 1 Flowchart
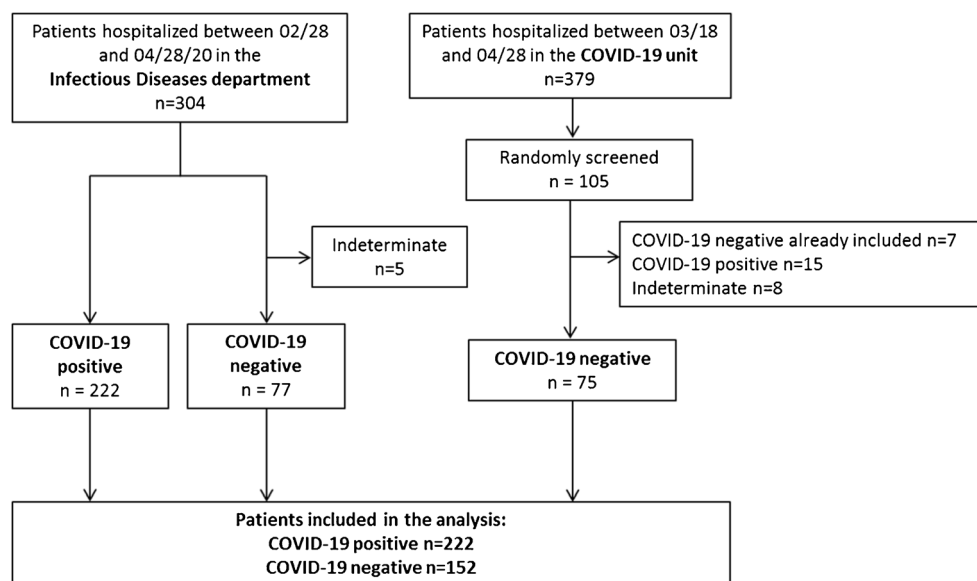
hospitalized in the COVID-19 diagnostic unit, 374 patients (152 COVID-19 negative and 222 COVID-19 patients) were included and compared.

Characteristics of COVID-19-negative patients were depicted in Table 1. More than 75% were over 50 years old. Seventy-eight (51.3%) had fever and dyspnea. Chest CT was not suggestive of COVID-19 in more than 75% of patients. Main final diagnoses were another infectious disease for 68 (44.7%) patients (pneumonia for 31 (20.4%) patients, bacteremia for 12 (7.9%) patients), heart failure for 13 (8.6%) patients, and exacerbation of a chronic pulmonary disease for 12 (7.9%) patients (Table 2).

In multivariate analysis, four variables were independently associated with a final diagnosis of COVID-19: neurocognitive disorder, no current smoking, myalgia, and a fibrinogen level greater than 4 g/L.

Among COVID-19-negative patients, two had a delay in surgical management (one spinal cord hematoma and one appendicular peritonitis). In addition, 5 patients with bacteremia had not been given antibiotics on admission to hospital. Finally, a late diagnosis of pneumocystis pneumonia leading to HIV infection at the AIDS stage was made in a patient with an interstitial syndrome and several negative RT-PCRs.

Discussion

Herein we present what is, to our knowledge, the first study of patients hospitalized with a suspicion of COVID-19 but a final alternative diagnosis. Among the 404 patients hospitalized with an initial suspicion of COVID-19, 154 (nearly 40%) were negative and considered with an alternative diagnosis.

First, we showed that about 40% ($n = 68$) of patients initially suspected as COVID-19 patients, in fact had another infectious disease, especially a bacteremia for 12 (7.9%) patients and a urinary tract infection for 7 (4.6%) patients, highlighting the importance of widespread blood cultures and cytobacteriological testing of urine. Furthermore, almost one tenth of the patients had acute heart failure and more than 50% had NT-pro-BNP > 1000pg/mL, highlighting that heart failure is therefore a differential diagnosis of COVID-19 infection, especially in elderly patients, even though heart failure is also a common condition associated with higher risk of in-hospital mortality among COVID-19 hospitalized patients [7–9].

In the context of a pandemic, it seems important to have simple ways to sort COVID-19-infected patients from uninfected ones. This could allow us to avoid overloading the health care system and avoid significant loss of opportunity in uninfected patients. Accordingly, 8 patients out of the 152 COVID-19-negative had a delay in management even though no death was reported due to this misdiagnosis. COVID-19-negative patients appear to have been symptomatic for a shorter period of time before being hospitalized, and to have less fever, digestive symptoms and myalgia, which has been reported previously [10]. Also, it is interesting to point out that COVID-19-negative patients had a higher neutrophil and lymphocyte count, which has also been mentioned [10, 11].

Up to now, screening patients with suspected COVID-19 have relied on nasopharyngeal RT-PCR and chest CT. When the results of RT-PCR and chest CT are combined, a sensitivity of 88% and a specificity of 100% may be achieved [11]. However, chest CT is a radiation procedure and its use for screening purposes during a pandemic may result in a longer time frame for other patients. Other means of screening need to be evaluated. In our multivariate analysis, we showed that in the context of pandemic, not smoking, neurocognitive disorder, having a fibrinogen ≥ 4g/L, and/or myalgia largely increased the probability of COVID-19.

In our study, whereas the prevalence of active smokers in hospitalized COVID-19-negative patients was close to that reported in the whole population in France (24.0%) [12], there were nearly 5-times fewer active smokers in patients hospitalized with COVID-19. Whether active smoking could prevent COVID-19 is still debated [13]. On the one hand, cigarette smoking seems to induce up-regulation of the natural SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2) in human cells [14, 15]. On the other hand, ACE2 allows the conversion of angiotensin II into angiotensin 1-7 (Ang1-7), a peptide with anti-inflammatory properties [16, 17]. Thus, smokers could have at a greater risk of infection but at lower risk of developing a severe form of the disease [18, 19].

Our study has several limitations. First, our findings are themselves the reflection of specific epidemiological and organizational conditions. The suspicion of COVID-19 was not standardized, but was dependent on physician in charge of patients, who referred the patients to the hospital. In addition, the study was conducted when the epidemic peaked in France, and results would be different with circulation of other respiratory viruses (e.g., influenza, respiratory syncytial virus) responsible for flu syndrome. Moreover, 21 (13.8%) COVID-19-negative patients had no radiological examination; chest CT was not performed in 35.5% and 22 (22.4%) had evocative impairment on the chest CT. Nevertheless, sensitivity analysis confirmed our results. In addition, the higher frequency of cognitive disorders in COVID-19 patients might be explained by the admission of older patients from nursing homes. However, we did not find any association with these two variables, possibly by a lack of power of the study. Patients with neurocognitive disorders also have less ability to comply with preventive measures, which could explain their propensity to get COVID-19. This association may also reflect a frailty which leads to an increased risk of COVID-19

Table 1 Comparison between patients with (COVID-19 +) and without (COVID-19 -) COVID-19

Characteristics	COVID-19 +	COVID-19 -	p
Number	222	152	NA
Demographic data			
Sex F* (n, %)**	99 (44.6)	82 (53.4)	0.09
Age at admission (mean, sd)	70.2 (17.0)	67.8 (20.0)	0.46
Current smoking status (n, %)**	8 (4.4)	28 (27.2)	<0.001
Cardiovascular disease (n, %)**	133 (59.9)	75 (49.3)	0.04
Obesity (n, %)	34 (16.0)	17 (11.2)	0.22
Cirrhosis (n, %)	1 (0.5)	8 (5.3)	0.003
Chronic kidney disease (n, %)	18 (8.1)	12 (7.9)	1
Immunodeficiency (n, %)	19 (8.6)	9 (5.9)	0.43
Chronic pulmonary disease (n, %)**	30 (13.5)	32 (21.1)	0.05
Neurocognitive disorders (n, %)**	48 (21.6)	13 (8.6)	<0.001
Clinical and paraclinical data			
Clinical			
Number of days between admission and symptoms onset (median, IQR)**	6 (3–9)	3 (0–7)	<0.001
Myalgia (n, %)**	82 (36.9)	21 (14.0)	<0.001
Confusion (n, %)	37 (16.7)	18 (11.8)	0.23
Cough (n, %)**	146 (65.8)	76 (50.0)	0.003
Fever (n, %)**	169 (76.1)	78 (51.3)	<0.001
Dyspnea (n, %)**	137 (61.7)	78 (51.3)	0.06
Digestive symptoms (diarrhea and/or vomiting) (n, %)**	66 (29.7)	18 (11.8)	<0.001
NEWS2* at admission (median, IQR)	5 (3–8)	5 (3–8)	0.87
qSOFA* at admission (median, IQR)**	0 (0–1)	1 (0–1)	0.049
CRB65* at admission (median, IQR)	1 (1–1)	1 (0–2)	0.47
RT-PCR (mean, sd)	MD	1.3 (0.7)	
Site (n, %)			
- Nasopharyngeal	MD	134 (88.2)	NA
- Depth	MD	4 (2.6)	NA
- ≥ 2 sites	MD	14 (9.2)	NA
Biological (median, IQR)			
Neutrophil (G/L)**	4.7 (3.3–6.6)	7.6 (5.1–10.5)	<0.001
Lymphocyte (G/L)**	0.9 (0.6–1.4)	1.1 (0.7–1.7)	0.02
Fibrinogen (g/L)**	6.0 (5.3–6.8)	5.3 (4–6.5)	<0.001
Urea (mmol/L)	6.6 (4.8–10.4)	7 (4.8–11.4)	0.30
Creatinine (μmol/L)	76 (60–100)	77 (61–100)	0.45
CRP* (mg/L)**	83.7 (37.7–127)	57.3 (13–126)	0.008
ALAT* ≥ 3N (n, %)	12 (7.1)	10 (8.3)	0.82
Radiological data (n, %)			
No radiological examinations performed	MD	21 (13.8)	NA
Chest radiograph	MD	39 (27.7)	NA
- Non-evocative	MD	25 (64.1)	NA
- Lobar pneumonia	MD	7 (17.9)	NA
- Potentially compatible with COVID-19	MD	7 (17.9)	NA
Chest CT*	164 (73.9)	98 (64.5)	0.07
- Non evocative	17 (10.4)	76 (77.6)	<0.001
- Evocative			
- Slight	19 (11.6)	10 (10.2)	0.84
- Moderate	53 (32.3)	10 (10.2)	<0.001
- Severe	75 (45.7)	2 (2.0)	<0.001
Evolution			
Length of hospital stay (median, IQR)	6 (3–9.5)	4 (2–10)	0.06
In-hospital mortality or transfer to intensive care unit (n, %)	64 (28.8)	14 (9.2)	<0.001

*F female; NEWS National Early Warning Score; qSOFA quick sepsis-related organ failure assessment; CRB confusion respiratory blood; CRP C-reactive-protein; ALAT alanine aminotransferase; CT computed tomography; MD missing data

**Variables included in multivariate model

requiring hospitalization. Thus, 13 patients (3% of the included population) were excluded due to an indeterminate status (negative PCR but chest CT-scan suggestive of COVID-19). Accordingly, this may lead to a bias that could have been avoided if serology or multiplex PCR had been available.

Finally, anosmia and loss of taste were not collected though they were described as highly predictive of the presence of the virus [20]. Indeed, these data were not often collected from the sickest patients; many other patients were unable to describe these symptoms because of their age or altered brain function.

Table 2 Final diagnosis for COVID-19-negative patients

Infectious disease (n,%)	68 (44.7)
- Pneumonia	31 (20.4)
- Bacteremia	12 (7.9)
- Urinary tract infection	7 (4.6)
- Upper respiratory tract viral infection	7 (4.6)
- Digestive viral infection	3 (2.0)
- Diverticulitis	3 (2.0)
- Other	5 (3.2)
Cardiovascular or respiratory disease (n,%)	33 (21.7)
- Heart failure	13 (8.6)
- Exacerbation of chronic pulmonary disease	12 (7.9)
- Other	5 (3.2)
- Pulmonary embolism	3 (2.0)
Unlabelled diagnosis (n,%)	18 (11.8)
Other (n,%)	33 (21.7)
- Neurological disease	10 (6.7)
- Cancer or hematologic malignancy discovery or complications	7 (4.6)
- Inflammatory disease	2 (1.3)
- Cirrhosis complication	3 (2.0)
- Abdominal disease	2 (1.3)
- Locomotor disease	2 (1.3)
- Endocrinological disease	1 (0.7)
- Psychiatric disease	2 (1.3)
- Urological disease	1 (0.7)
- Social	3 (2.0)

Conclusion

Since the patients who turned out to be COVID negative were initially suspected on the same basis as those who turned out to be positive, the differences observed highlight the relative utility of some characteristics in helping to distinguish genuine COVID-19 cases from other diseases. Since it can be advocated that rapid diagnosis (or diagnosis exclusion) of COVID-19 enables a better orientation of patients and avoids missed opportunities for uninfected patients, keeping in mind that these differences may help to better manage patients when/where very rapid diagnostic procedures are not yet available yet or not available all the time. This study also highlights the need for systematic heart function evaluation, as well as systematically looking for infections other than COVID-19. Last, it once again raises the question of the potential role of tobacco smoking in preventing COVID-19, which may still have to be further explored.

Declarations

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