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Clinical identification and severity in patients with COVID-19

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Abstract

The clinical evaluation of the patient with COVID-19 allows better care, application of safety criteria and preventive measures. The disease progresses from mild to severe and critical. In this work, is evaluated in patients with COVID-19 clinical format to identify moderate to severe stages of the disease. Following a cohort of male and female patients over 18 years of age admitted to the Infectology Service of the General Hospital of Mexico. Each patient is studied using the "COVID-19 Infectology" clinical format and in the first 24 hours of admission, a real-time RT-PCR molecular test is performed for SARS-CoV-2 infection. 65 patients classified as severe COVID-19 were studied, the RT-PCR was positive in 60 patients and negative in 5, clinical data did not differ from the positive ones and the 5 negative were considered false negative cases of the molecular test. There were no differences between positives and negatives with Fisher's test, and no difference in age, comorbidities, or prognostic evaluation with Student's t test. The conclusion is that the clinical format "COVID-19 Infectology" allows to recognize the cases and identify those that are in a severe evolution.

Keywords: *Clinical identification Covid-19. Identification severe Covid-19. Clinical evaluation Covid-19.*

Introduction

When dealing with patients with COVID-19, diagnosing the disease in time and providing early management, even if it isn´t etiological due to the fact we don´t have it, enables us to improve patient care and, to the extent possible, prevent progression to severe disease. As such, doctors in clinical practice faced with this disease need to refine their evaluation, as clinical evolution is extremely variable.

The incubation period for SARS-CoV-2 ranges from 2 to 14 days from contact with the infecting person. The signs appear as an acute disease that evolves from mild to severe or critical as follows: 80% of patients have mild to moderate disease, 14% severe, and 5% critical. Many patients develop a mild, uncomplicated, flu-like upper respiratory infection with non-specific symptoms such as moderate fever, dry cough, nasal congestion, fatigue, anorexia, general malaise, myalgia, dysphagia, and headaches; 90% of patients have more than one of these symptoms. Some patients also have gastrointestinal symptoms such as diarrhea, nausea, vomiting and abdominal pain[1,2].

The evolution of COVID-19 may also give rise to arthralgia, dyspnea, anosmia or dysosmia, dysgeusia or ageusia, hyporexia, sputum production, conjunctivitis, sore throat, mental confusion, dizziness, rhinorrhea, chest pain, hemoptysis, and skin disorders. There is so much clinical data available that we have grouped it into General, Algological (Table 1), Respiratory, Neurological

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Table 1. General clinical manifestations in different series of patients

General clinical manifestations	Algological manifestations
Fever	Myalgia
Shivering	Arthralgia
General malaise	Arthralgia in the fingers
Body pain	Lack of strength in the hands
Dizziness	Pain in:
Headache	Face
Drowsiness	Oral mucosa
Hemoptysis	Molars
Fatigue - Weariness	Neck
Lack of energy	Shoulders
Weakness	Arms
Hyporexia	Wrists
Facial edema	Hands
Tachycardia	Hips
Sweating	Knees
Head	Legs
Neck	Thighs
Forehead	Ankles
Head and neck	Feet
Feet	Heels
Middle body	Soles of the feet
Cold sweating	Testicular pain
Edema in the fingers	Renal fossa pain
	Intense pain throughout the body

(Table 2), Gastrointestinal, Ocular and Cutaneous (Table 3) clinical manifestations. In general, patients that develop moderate disease have respiratory symptoms such as a cough, dyspnea and tachypnea; unlike the more severe disease, with mild pneumonia with no signs of severity, but with oxygen saturation in ambient air of less than 90% and/or a respiratory rate greater than 30 breaths a minute, or severe pneumonia with acute respiratory distress syndrome. 5% of the latter patients may develop critical illness with cardiac injury, septic shock, or multi-organ dysfunction[3].

Table 2. Clinical respiratory and neurological manifestations

Respiratory	Neurological
Pharyngeal pain	Anosmia - Hyposmia - Hyperosmia
Pharyngeal burning	Ageusia - Dysgeusia
Dry throat	Facial itching
Sore throat, sensation of something stuck (obstruction)	Tinnitus
Pharynx sores	Numbness
Tickly throat	Hands
Mouth sores	Legs
Pimply tongue	Arms
Dysphonia	Sensation of edema in the feet
Coughing	Sometimes burning heat
Nasal congestion	Face
Sputum	Eyes
Dry nose	Ears
Rhinorrhea	Hands
Mucus with blood from the nose	Feet
Epistaxis	Knees
Sensation of fullness in the middle of the face	Calves
Otic fullness	Thighs
Ear pain	Legs
Tinnititus	Considerable heat with no fever
Sneezing	Sensation of inner heat in the torso, throat and feet
Dyspnea	Burning sensation in the back
Chest pain	Cold
Retrosternal pain	Chest
Burning sensation in the chest	Feet
Burning sensation in the chest when breathing in air	Soles of the feet
Chest congestion	General
A sensation of obstruction in the chest	Feeling cold when inhaling
Sensation of blocked phlegm	Burning
Back pain	Feet
Burning sensation in the back	Toes

(Continues)

Table 2. Clinical respiratory and neurological manifestations (*Continued*)

Respiratory	Neurological
Rales	Soles of the feet
Wheezing	Fine trembling of the hands
Tachypnea	Sweaty hands
	Insomnia
	Anguish
	Tingling
	Face
	Nose
	Hands
	Chest
	Abdomen
	Legs
	Pruritus
	Face
	Ears
	Body
	Feet
	Heaviness
	Head
	Feet
	Lack of strength
	Legs
	Wrists

(Continues)

Table 2. Clinical respiratory and neurological manifestations (*Continued*)

Respiratory	Neurological
	Hands
	Clumsy hands
	Bewilderment
	Confusion
	Disorientation
	Non-specific discomfort from the knees down
	Mouth sensation of rough lips and cheeks
	Cramp
	Feet
	Arms
	Tired feet
	Mild shaking
	Limbs
	Trembling voice, I feel shaky inside
	Stabbing pain in the chest and left armpit
	Numb fingers
	Numb hands
	Facial pain
	Scalp pain
	Numb tongue
	Numb legs
	Bewilderment
	Ringing in the ears

The evolution of patients is variable, and in some cases deterioration can occur in as little as 2 to 3 days, characterised by the presence of signs of pneumonia and ventilatory insufficiency, the patient has a grim appearance, worsens quickly and suffers from tachypnea. Signs of inspiratory crackles, rales, bronchial respiration, tachycardia, tachypnea and cyanosis should be looked out for and oxygen saturation is reduced. It should be pointed out that patients with COVID-19 can develop what has been called "silent hypoxia"; in these cases oxygen saturation drops to low levels and precipitates acute respiratory failure without the previous presence of data on ventilatory difficulties[3,4].

The measurement of oxygen saturation is essential and is interpreted as follows: between 95% and 99% normal; 91% to 94% mild hypoxia; 86% to 90% moderate hypoxia; and less than 86% severe hypoxia. This may vary slightly due to differences in the altitude above sea level where the person is.

The purpose of this work is to evaluate and identify patients with probable COVID-19 in need of in-hospital management using a clinical format.

Material and Method

The study is conducted on a cohort of patients of 18 years of age or older diagnosed with COVID-19, admitted to the Infectious Diseases Department of the "Eduardo Liceaga" General Hospital of Mexico. Each patient was evaluated as follows:

Anyone with suspected COVID-19 requesting an appointment was granted one in the external appointments area of the Infectious Diseases department. A detailed clinical evaluation was carried out using the Clinical Format known as "COVID-19 Infectology" for the evaluation of suspected cases of COVID-19 classified as moderate and severe. This format is based on the assessment of the following clinical data grouped into three sections: A.- Fever, cough, and headache. B.- Arthralgia, myalgia, odynophagia, rhinorrhea, conjunctivitis and chest pain. C.- Dyspnea and oxygen saturation less than 90%. The following severity criterion was then applied to identify the patients in need of hospitalization: at least two positive items from section A, at least one positive item from section B, and all positive items from section C.

Once the evaluation had been carried out and the clinical diagnosis and scores had been established, the patients identified with a moderate to severe probability of COVID-19 were offered a hospital bed in the Department; those who accepted were then required to complete the acceptance and informed consent forms. A sample of nasopharyngeal and oropharyngeal exudate was taken within the first 24 hours of the patient being admitted to perform a real-time RT-PCR molecular test for SARS-CoV-2 infection; the sample was submitted to the Molecular Biology laboratory for the respective tests.

The descriptive statistical analysis consisted of determining the measures of central tendency and dispersion for the quantitative variables and percentages for the qualitative variables. For the inferential statistical analysis, a Fisher exact test was conducted for qualitative variables and a Student t test for quantitative variables.

Results

65 patients were analysed, 39 (60.0%) of were male and 26 (40.0%) female. Table 4 illustrates the age breakdown of the 65 patients: less than 30 years of age: 3 (4.6%); 31 to 40 years of age: 7 (10.8%); 41 to 50 years of age: 16 (24.6%); 51 to 60 years of age: 20 (30.8%); 61 to 70 years of age: 16 (24.6%); and more than 70 years of age: 3 (4.6%). The highest number of cases (52 (80%) occurred in people in the fourth, fifth and sixth decades of life, with an average age of 52.6 ± 12.5 years and a range of 24 to 83 years of age (Table 4).

The clinical manifestations observed in patients upon admission were classified in 4 groups: systemic, respiratory system, digestive system and others (Table 5). With regard to general symptoms, fever was registered in 87.7% (57); headache in 66.2% (43); general deterioration 55.4% (36); shivering in 41.5% (27); and irritability in 30.8% (twenty). As can be seen, the three symptoms with a percentage of over 50% were: fever, headache and general deterioration. The respiratory system registered cough in 92.3% (60); dyspnea in 86.2% (56); rhinorrhea and odynophagia in 30.8% (20); chest pain in 27.7% (18); polypnea in 15.4% (10); and cyanosis in 6.2% (4). The main manifestations in relation to the respiratory system were undoubtedly coughing and dyspnea. The digestive system featured diarrhea in 16.9% (11); abdominal pain in 15.4% (10); and vomiting in 9.2% (6). Other symptoms were: arthralgia in 56.9% (37); myalgia in 55.4% (36); and conjunctivitis in 4.6% (3); (Table 5).

All the patients were evaluated using the Call Scale to predict risk progression, and it was found that 13 were low risk, 24 medium risk and 28 high risk (Table 6).

The results of the real-time polymerase chain molecular test for SARS-CoV-2 were positive in 60 patients (92.3%) and negative in 5 patients (7.7%); 4 of the latter being female and and 1 male.

43 (66.2%) of the 65 patients registered an improvement while they were in hospital and 22 (33.8%) died.

Discussion

Despite the fact that COVID-19 is a new disease, it is clear that clinical studies are essential to identifying it in the patient. The "COVID-19 Infectology" clinical format was used in this study to identify severe cases in the 65 patients admitted to the Department of Infectious Diseases, who were already hospitalised, and a detailed clinical study confirmed the presence of fever, coughing and headache, arthralgia, myalgia, odynophagia, rhinorrhea, conjunctivitis and chest pain, along with dyspnea and hypoxemia. Oxygen saturation of less than 90%, fever, headache, general deterioration, coughing, dyspnea, arthralgia and myalgia stood out as the most frequent data; Other authors have already

Table 3. Clinical gastrointestinal, ocular and cutaneous manifestations

Gastrointestinal	Ocular	Cutaneous
Dry mouth	Photophobia	Erythematous lesions on the fingers and soles of the feet
Scalded tongue	Ocular erythema	Intense peeling of the soles of the feet
	Eye pain	Ecchymosis
Abundant night sialorrhea	Itchy eyes	Legs
Discomfort when swallowing	Burning eyes	Buttocks
Belching	Periorbital edema	Hyperpigmentation of the genitals
Nausea	Tearing	Urticaria
Vomiting	Eye secretion	Gallbladder
Hiccups	Eyelid edema	Petechiae
Abdominal pain		Acroischemia
Epigastralgia		Rash
Transprandial fullness		Erythematous
Abdominal distension		Macular
Rumbling		Maculopapular
Flatulence		Perifollicular
Diarrhea		Purpuric
Constipation		Morbilliform
Rectal tenesmus		Erythema
Fetid stool		Multi-form
		Palmar
		Facial
		Enanthem
		Pityriasis rosea
		Necrotic lesions
		Rash on the face, back and chest
		Red spots in the mouth
		Pale skin
		Red and sweaty hands and feet
		Itchy penis with burning sensation, appearance of ulcers and significant dryness
		Dry calves
		Hand edema
		Dry lips

used evaluation models, also known as triage systems[5].

All the patients were evaluated using the Call Scale to predict risk progression, and it was found that 24 (36.9%) were medium risk and 28 (43.1%) high risk (Table 6). It should be pointed out that the patients´ outcomes were as follows: Discharge due to improvement 43 (66.2%) and death 22 (33.8%). When

Table 4. Breakdown of age of patients with COVID-19

Age	PCR+		PCR-		Total	
(years)	No.	%	No.	%	No.	%
< 30	3	5.0			3	4.6
31-40	6	10.0	1	20.0	7	10.8
41-50	13	21.7	3	60.0	16	24.6
51-60	20	33.3			20	30.8
61-70	15	25.0	1	20.0	16	24.6
> 70	3	5.0			3	4.6
Total	60	100.0	5	100.0	65	100.0

correlating the CALL scale results with evolution to death, it was found that most of the deaths involved patients from the high-risk group, illustrating that the CALL scale did predict the risk of progression in our patients and, as such, that this scale is quite useful, as other researchers have published[6] (Fig. 1).

As we have pointed out, the clinical manifestations of this disease are very varied and when reviewing the literature on the subject we found that other authors have published series of cases with reports on different clinical characteristics. We have compiled comparison tables to illustrate the consistency with the findings registered in our patients, whereby we suggest that special attention needs to be paid to researching and acknowledging all this clinical data when caring for patients with COVID-19[2,4,7-11] (Tables 7 and 8).

The real-time polymerase chain reaction test registered SARCoV2 infection in 60 of the 65 patients. It should be pointed out that the 5 negative cases involved four females and one male, and the main clinical manifestations were fever, headache, coughing and dyspnea; these being no different to the symptoms registered in the 60 positive cases to RT-PCR, which were fever and headache in systemic data and coughing and dyspnea in respiratory data (Table 5).

The definitive test for SARS-CoV-2 is the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test. It is regarded as highly specific, however the sensitivity of the test ranges from 60% to 97%, compared to specificity of 89%. The sensitivity varies in relation to the time elapsed since exposure to SARS-CoV-2, in such a way that there are 100% false negatives on the first day after exposure and 67% on the fourth day. The false negative rate remains at 38% and reaches its lowest point of 20% three days after the onset of symptoms. The false negative rate begins to rise again from this time on, reaching 66% on the 21st day after exposure. Hence, false negatives are a real clinical problem, and multiple negative tests may be required in a single case to be sure disease can be ruled out. We need to bear in mind that negative results in the SARS-CoV-2 RT-PCR test do not rule out the possibility of infection, particularly if the patient has highly suspicious clinical manifestations of COVID-19.

This test involves the use of biological products from the nasopharynx, oropharynx or saliva, and targets the following RNA genes: envelope (ENV), nucleocapsid (N), spike (S), RNA polymerase, RNA-dependent (RdRp) and ORF1. The identification of viral RNA is achieved at the threshold of the cycle (Ct is the number of replication cycles required to produce a fluorescent signal), which varies in the days of evolution and reaches its maximum point in the first week of the onset of symptoms; positivity decreases at week 3 and then becomes undetectable. It also varies in accordance with differences in Ct for the different genes in question. The biological product to be studied causes variations in the results of the test; positivity in bronchoalveolar lavage (93%), followed by sputum (72%), nasal swab (63%) and pharyngeal swab (32%)[5]. Moreover, false negative results occur due to unreliable sampling techniques, in particular nasopharyngeal swabs, and due to technical errors and the contamination of reagents[6,12-15]. Despite the fact that this technique features high sensitivity and specificity, its effectiveness depends on proper processing, as there are many factors that can affect the results of the test, including the effective collection of samples using a swab in the nasopharyngeal area, as this region in which the virus undergoes a higher rate of replication, in addition to transporting samples to the laboratory in the appropriate manner with no contamination[16]. Another factor we need to bear in mind is the RT-PCR technique, which needs to be carried out in the proper manner in order to guarantee the maximum performance of the test, which involves obtaining a good quality RNA, as this material is susceptible to degradation due to the action of ribonucleases (RNAs). To this end, this material needs to be kept in cold conditions during handling. Another relevant factor is the concentration of the PCR components, as the improper amount of reagents used to amplify samples inhibits the amplification of genes[17].

The main clinical symptoms included in the evaluation carried out in our study with the use of the

Table 5. Clinical data on patients with COVID-19

Patients with	PCR +		PCR -		Total		P
General symptoms	**No.**	**%**	**No.**	**%**	**No.**	**%**	
Fever	53	88.3	4	80.0	57	87.7	0.493
Headache	40	66.7	3	60	43	66.2	0.555
General deterioration	34	56.7	2	40.0	36	55.4	0.397
Shivering	26	43.3	1	20.0	27	41.5	0.302
Irritability	19	31.7	1	20.0	20	30.8	0.509
Gastrointestinal symptoms	**No.**	**%**	**No.**	**%**	**No.**	**%**	
Diarrhea	10	16.7	1	20.0	11	16.9	0.617
Abdominal pain	10	16.7	0	0	10	15.4	0.421
Vomiting	6	10.0	0	0	6	9.2	0.606
Other symptoms	**No.**	**%**	**No.**	**%**	**No.**	**%**	
Arthralgia	36	60	1	20	37	56.9	0.104
Myalgia	34	56.7	2	40	36	55.4	0.397
Conjunctivitis	3	5	0	0	3	4.6	0.783
Respiratory symptoms	**No.**	**%**	**No.**	**%**	**No.**	**%**	
Coughing	56	93.3	4	80.0	60	92.3	0.339
Dyspnea	52	86.7	4	80.0	56	86.2	0.538
Odynophagia	20	33.3	0	0	20	30.8	0.148
Rhinorrhea	18	30	2	40	20	30.8	0.491
Chest pain	16	26.7	2	40.0	18	27.7	0.426
Polypnea	10	16.7	0	0	10	15.4	0.421
Cyanosis	4	6.7	0	0	4	6.2	0.72

Table 6. CALL Score for patients with COVID-19

Call Total	PCR+		PCR-		Total	
	No.	**%**	**No.**	**%**	**No.**	**%**
4	2	3.3			2	3.1
5	4	6.7			4	6.2
6	7	11.7			7	10.8
7	8	13.3	2	40.0	10	15.4
8	8	13.3			8	12.3
9	5	8.3	1	20.0	6	9.2
10	10	16.7	1	20.0	11	16.9
11	10	16.7			10	15.4
12	4	6.7	1	20.0	5	7.7
13	2	3.3			2	3.1
Total	60	100	5	100	65	100

"COVID-19 Infectology" Clinical Format are fever, coughing and dyspnea, in addition to the other symptoms of headache, arthralgia, myalgia, chest pain, odynophagia, rhinorrhea and conjunctivitis, in addition to oxygen saturation of less than 90%. When analysing the negative PCR cases, we see that the 5 negative patients registered the same clinical data as the 60 positive cases, reason for which they were regarded as being in the false negative range for the molecular test. A statistical analysis was conducted of the two groups using the Fisher test and the results show that the negative cases are no different clinically to the positive cases. Moreover, the student t test shows that there is no difference in age, comorbidities or the Call scores[6,18].

In relation to the development of variants of the virus, the United States government´s Inter-Agency Group on SARS-CoV-2 has classified the genetic variants of the virus in 3 groups: Variants of interest, Variants of concern and Variants of high consequence. The first group includes the ETA variant, identified in the United Kingdom, the IOTA variant, identified in New York and the KAPPA variant, identified in India. The characteristics of these three variants are a possible reduction in

Table 7. Clinical respiratory manifestations in different series of patients

Symptoms	Lei P	Wang D	Guan W	Chen N	Huang Ch	Lechein JR	Chiesa-Estomba CM	Romero-Cabello R
No. of patients	204	138	1099	99	41	2579	542	65
Fever	92.23	98.6	43.8	83	98	42.1	35.4	87.7
Myalgia	14.56	34.8	14.9	11		53.5	62.7	55.4
Dyspnea		31.2	18.7	31	55	45.2	5.8	86.2
Expectoration		26.8	33.7		28	13	18.6	
Coughing			67.8	82	76	55.2	43.6	92.3
Headache		6.5	13.6	8	8	59.8	72.5	66.2
Rhinorrhea			4.8	4			7.4	30.8
Arthralgia						39.5	47	56.9
Chest pain				2		17.9		27.7

Table 8. Clinical gastrointestinal manifestations in different series of patients

Symptoms	Lei P	Wang D	Lechein JR	Chiesa Estomba CM	Romero-Cabello R
No of patients	204	138	2579	542	65
Loss of appetite	78.64	39.9	40.6	46.7	
Diarrhea	33.98	10.1	31		
Vomiting	3.88	3.6	17.5	19.9	16.9
Abdominal pain	1.94	2.2			15.4
Nausea		10.1			9.2

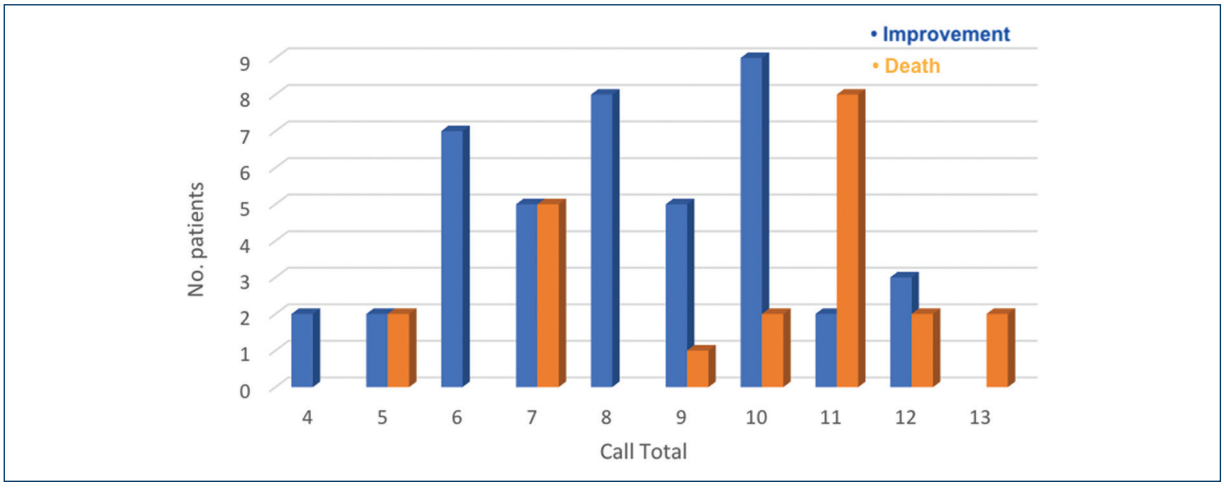

Figure 1. Call score and evolution of patients. Number of patients, improvement and death.

neutralisation with monoclonal antibodies and in neutralisation with convalescent sera and post-vaccination sera. This group also includes the LAMDA variant, identified in Peru, the EPSILON variant, identified in the United States, the THETA variant, identified in the Philippines and the ZETA variant, identified in Brazil. The

characteristics of the latter variants have still not been clarified, and the MU variant, identified in Colombia, could pose the risk of immune evasion or resistance to vaccines.

The Variants of Concern group includes the ALPHA Variant, identified in the United Kingdom, with increased levels of transmission and potential greater severity in hospitalisations and deaths. The BETA Variant, identified in South Africa, with increased levels of transmission, less susceptibility to monoclonal antibody treatment and less neutralisation with convalescent and post-vaccination sera, and the DELTA Variant, identified in India, with increased levels of transmission, potential reduction in neutralisation in some monoclonal antibody treatments and a reduction in neutralisation using post-vaccination sera, can cause symptoms two to three days faster, in addition to more severe disease and a reduction in the efficacy of vaccines and treatment. Finally, the GAMMA variant, identified in Japan and Brazil, with a considerable reduction in susceptibility to monoclonal antibody treatment and less neutralisation of convalescent and post-vaccination sera.

The variants of high consequence that have not yet been identified would cause problems in diagnostic tests, less efficacy with regard to vaccines, less response to treatment and generate more serious cases[19-21].

Conclusion

The clinical evaluation of patients with COVID-19 and the use of evaluation models such as the "COVID-19 Infectology" Clinical Format enable us to recognise cases and to identify those that are progressing to severity. Given that this pathology features a large number of manifestations, the clinical physician requires a comprehensive evaluation in professional practice. The pulse oximeter is now an instrument that every clinical physician should use in the evaluation of patients on a daily basis.

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Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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