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to rapidly start treatment and to avoid incorrect interpretation of disease presentation.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article and that this report does not contain any personal information that could lead to their identification.

Disclosure of interest

The authors declare that they have no competing interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

Consent to participate

Written informed consent was obtained from the patient for publication of this case report.

Acknowledgements

JetPub Scientific Communications LLC assisted in the preparation of this manuscript, in accordance with Good Publication Practice (GPP3) guidelines.

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Available online 15 September 2021
https://doi.org/10.1016/j.idnow.2021.09.001
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Comparison of the first and second waves of coronavirus disease in Toulouse, France

ARTICLE INFO

Keywords:
COVID-19
Epidemiology
SARS-CoV-2

We conducted a retrospective Covid-clinic-Toul cohort study at Toulouse university hospital, in southern France (2800 beds, tertiary hospital covering an area of about 3 million inhabitants) and selected hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia from September 1st, 2020 to October 31st, 2020. We compared their demographics, clinical, biological and radiological features, as well as unfavorable outcome (admission in an intensive care unit, mechanical ventilation, death) at Day 14 after admission to those of hospitalized patients during the 1st wave (March 11, 2020 to April 20, 2020). Like many other European countries, France faced a second wave of Coronavirus 2019 (COVID-19) pandemic from September to November 2020 [1]. A number of studies have compared the epidemiological and clinical features of hospitalized patients with COVID-19 during the first and second wave, mostly in Italy [2–6]. In addition, a few studies have assessed whether the characteristics and outcomes of hospitalized patients with COVID-19 changed in the second phase of the epidemic due to the evolution of healthcare system organization, patient demographics, and/or progress

Table 1
Comparison of patients hospitalized for a SARS-CoV-2 infection proven by RT-PCR included in the Covid-Clinic-Toul cohort between March 6th, 2020 and April 21th, 2020 (first wave) and between September 1st, 2020 and October 30th, 2020 (second wave).

Variables	All patients included in the cohort			Patients with aggravation criteria at day 14 after hospital admission		
	First wave *n* = 263	Second wave 2020 *n* = 340	*P*-value	First wave *n* = 122	Second wave *n* = 140	*P*-value
Age						
Median (IQR), years	65 (54–76)	73 (58–85)	<0.0001	68 (58 – 78)	71 (59–82)	0.2
Age ≥ 65 years, *n* (%)	132 (50.2)	220 (64.7)	0.0003	69 (56.6)	89 (63.6)	0.2
Men, *n* (%)	155 (58.9)	202 (59.4)	0.9	40 (32.8)	45 (32.1)	0.9
Comorbidities						
≥1 comorbidity, *n* (%)	227 (86.3)	316 (92.9)	0.007	109 (89.3)	133 (95.0)	0.09
Overweight (BMI: 25–30 kg/m^2), *n* (%)[a]	88/244 (36.1)	103/310 (33.2)	–	43 (36.4)	38 (30.2)	–
Obesity (BMI > 30 kg/m^2), *n* (%)[a]	69/244 (28.3)	101/310 (32.6)	–	40 (33.9)	48 (38.1)	–
Overweight or obesity, *n* (%)[a]	157/244 (64.3)	204/310 (65.8)	0.7	83 (68.0)	86 (61.4)	0.7
Hypertension, *n* (%)	104 (39.5)	199 (58.5)	<0.0001	56 (45.9)	94 (67.1)	0.0005
Diabetes, *n* (%)	52 (19.8)	103 (30.3)	0.003	30 (24.6)	46 (32.9)	0.1
Cardiovascular disease, *n* (%)	35 (13.3)	88 (25.9)	0.0001	19 (15.6)	42 (30.0)	0.006
Cerebrovascular disease, *n* (%)	17 (6.5)	29 (8.5)	0.3	8 (6.6)	11 (7.9)	0.7
Chronic lung disease, *n* (%)	57 (21.6)	76 (22.4)	0.8	30 (24.6)	35 (25.0)	0.9
Chronic kidney disease, *n* (%)	24 (9.1)	45 (13.2)	0.1	12 (9.8)	23 (16.4)	0.1
Chronic liver disease, *n* (%)	2 (0.8)	2 (0.6)	–	2 (1.6)	1 (0.7)	–
Malignancy <5 years, *n* (%)	27 (10.3)	34 (10.0)	0.9	15 (12.3)	14 (10.0	0.6
Immunosuppression, *n* (%)	25 (9.5)	32 (9.4)	1	16 (13.1)	19 (13.6)	0.9
Current smokers, *n* (%)[a]	11/115 (9.3)	15/174 (8.6)	–	7/51 (13.7)	7/69 (10.1)	–
Signs and symptoms						
Crackling, *n* (%)[a]	156 (62.9)	234 (72.2)	0.018	77 (68.1)	94 (72.9)	0.4
Time from first symptoms to admission[a], median (IQR), days	7 (4–10)	5 (2–8)	<0.0001	7 (4 –10)	5 (2–8)	<0.0001
Vital signs at admission[a]						
Temperature, median (IQR), Celsius degrees[a]	37.8 (37.0–38.5)	37.6 (36.9–38.4)	–	37.9 (37.1–38.7)	38.0 (37.1–38.6)	–
Respiratory rate, median (IQR), by minute[a]	22 (19–27)	22 (18–28)	–	24 (20–30)	24 (20–30)	–
Respiratory rate ≥22 by minute, *n* (%)	147 (58.6)	167 (54.2)	0.3	80 (66.7)	78 (62.9)	0.5
Oxygen saturation ≤ 92% (without oxygen therapy), *n* (%)[a]	58/202 (28.7)	58/160 (36.3)	–	41/78 (52.6)	29/80	–
Oxygen saturation measured with oxygen therapy before admission, *n* (%)[a]	59/261 (22.6)	173/333 (52.0)	–	43/121 (35.5)	80/135 (59.3)	–
Oxygen saturation ≤ 92% or measured with oxygen therapy before the admission, *n* (%)	117/261 (44.8)	231/333 (69.4)	<0.0001	84/121 (69.4)	109/135 (80.7)	0.045
Laboratory findings at admission[a]						
Platelet count, median (IQR), × 10^9/L[a]	186 (150–233)	194 (155–244)	–	178 (136–226)	188 (149–230)	–
Platelet count < 150 × 10^9/L, *n* (%)	63 (24.9)	70 (20.9)	0.3	43 (35.8)	35 (25.4)	0.0068
C-reactive protein level, median (IQR), mg/L[a]	52.4 (27.0–107.6)	72.7 (35.6–122.0)	–	86.7 (40.0–140.0)	81.0 (47.0–134.0)	–
C-reactive protein level > 50 mg/L, *n* (%)	131 (51.6)	215 (65.2)	0.0009	77 (65.3)	96 (73.3)	0.2
Creatinine level, median (IQR), µmol/L[a]	80 (66–97)	83 (67 –112)	–	84 (69–111)	89 (71–123)	–
Chest CT scan at admission	253 (96.2)	332 (97.6)	–	120 (100)	135 (96.4)	–
Chest CT scan severity score						
Uninterpretable, *n* (%)	0 (0)	1 (0.3)	–	0 (0)	1 (0.7)	
No typical sign of COVID–19, *n* (%)	10 (4.0)	20 (5.8)	0.001	4 (3.3)	6 (4.4)	0.4
Mild, *n* (%)	34 (13.4)	86 (25.3)		13 (10.8)	26 (19.3)	
Moderate, *n* (%)	139 (54.9)	139 (40.9)		46 (38.3)	45 (33.3)	
Severe, *n* (%)	64 (25.3)	82 (24.1)		51 (42.5)	53 (39.3)	
Critical, *n* (%)	6 (2.4)	4 (1.2)		6 (5.0)	4 (3.0)	
Treatment administered during the first 24 hours after admission						
Oxygen therapy, *n* (%)	212 (80.6)	292 (85.9)	0.08	116 (95.1)	132 (94.3)	0.8
Antibiotics, *n* (%)	165 (62.7)	246 (72.4)	0.01	103 (84.4)	110 (78.6)	0.2
Corticosteroids, *n* (%)	–	99 (29.2)	–	–	51 (36.4)	–
Remdesivir, *n* (%)	1 (1.9)	4 (1.2)	–	1 (0.8)	5 (3.6)	–
Corticosteroids administered during the first 14 days after admission, *n* (%)	–	225 (66.4)	–	–	120 (85.7)	–
Detailed outcomes at Day 14 after admission						
Composite outcome, *n* (%)	122 (46.4)	140 (41.2)	0.2	122 (100)	140 (100)	–
Admission to ICU, *n* (%)	111 (42.2)	120 (35.3)	0.08	111 (91.0)	120 (85.7)	–
Mechanical ventilation, *n* (%)	61 (23.2)	35 (10.3)	<0.0001	61 (50.0)	35 (25.0)	–
Death, *n* (%)	19 (7.2)	33 (9.7)	0.3	19 (15.6)	33 (23.6)	–
Discharged, *n* (%)	154 (58.6)	223 (65.6)	0.08	34 (27.9)	50 (35.7)	0.2

BMI: body mass index; CT: computed tomography; ICU: intensive care unit; IQR: interquartile range; RT–PCR: reverse transcriptase polymerase chain reaction.

[a] Missing values: For patients included between 6th March to 21st April 2020: Body Mass Index, *n* = 19; current smoker, *n* = 148; time from first symptoms to admission, *n* = 2; temperature, n = 7; respiratory rate, *n* = 12; oxygen saturation, *n* = 2; platelet count, *n* = 10; C-reactive protein, n = 9; creatinine level, *n* = 6. Missing values: For patients included between 1st September 2020 and 30th October 2020: Body Mass Index, *n* = 30; current smoker, *n* = 166; crackling, *n* = 16; time from first symptoms to admission, *n* = 6; temperature, *n* = 19; respiratory rate, *n* = 12; oxygen saturation, *n* = 7; platelet count, *n* = 5; C-reactive protein, *n* = 10; creatinine level, *n* = 5.

in disease management in France/other European countries. In particular, several randomized controlled trials conducted during the first wave highlighted the beneficial effects of early administration of glucocorticoids for critically ill COVID-19 patients [7].

The Covid-clinic-Toul cohort records data about all patients hospitalized for SARS-CoV-2 infection at Toulouse University hospital. The first group consisted of all hospitalized patients with SARS-CoV-2 infection confirmed by real-time polymerase chain reaction (RT-PCR) between March 11th 2020 and April 20th 2020 [8]. The second group consisted of all patients hospitalized with COVID-19 from September 1st to October 31st 2020. All patients, or their representatives for those not able to understand the purpose of the study, were informed by a letter given at admission to hospital and/or sent to their place of residency. The cohort was approved by institutional review board (n°RnIPH 2020-31), in accordance with the French data protection authority (MR004, *Commission Nationale de l'Informatique et des Libertés*, CNIL).

We collected demographics, clinical, laboratory, radiological (description of chest computed tomography–CT scans), treatment data within the first 24 hours after admission, exposure to corticosteroids during the first 14 days after admission, as well as outcome at Day 14 after admission. The primary outcome was composite, including admission to ICU, need for mechanical ventilation and death occurring during the 14 days after admission to the hospital.

The results of comparison between the first ($n = 263$) and the second ($n = 340$) wave regarding patient characteristics, comorbidities, biological data and outcome are detailed in Table 1. During the second wave, patients were older (median age: 73 vs. 65 years, $P < 0.0001$). They were also more likely to have comorbidities (92.9% had at least 1 comorbidity vs. 86.3%, $P = 0.007$), such as hypertension (58.5% vs. 39.5%, $P < 0.0001$), diabetes (30.3% vs. 19.8%, $P = 0.003$) and cardiovascular diseases (25.9% vs. 13.3%, $P = 0.0001$). Duration of symptoms from onset to admission was shorter in the second phase of the epidemic (median duration 5.0 vs. 7.0 days, $P < 0.0001$). Need for oxygen therapy at admission was more frequent (69.4% vs. 44.8%, $P < 0.0001$).

Patients of the second wave more frequently had a C-reactive protein level > 50 mg/L (65.2% vs. 51.6%, $P = 0.0009$). Patients admitted during the second wave more frequently received antibiotic treatment during the first 24 hours after admission (72.4% vs. 62.7%, $P = 0.01$). Two hundred and twenty-five patients (66.4%) received corticosteroids within the first 14 days after admission.

Compared to the first wave, we observed a trend toward a lower proportion of patients requiring ICU admission because of the development of organ dysfunction and/or acute respiratory distress syndrome during the first 14 days of hospitalization (35.3% vs. 42.2%, $P = 0.08$) and a significant decrease in the proportion of patients who received invasive mechanical ventilation (10.3% vs. 23.2%, $P < 0.0001$). However, case-fatality at D14 was similar between the two waves (9.7% vs. 7.2%, $P = 0.3$).

Data from the second wave indicated a demographic shift toward an older population with more comorbidities, and no decrease of mortality rate in comparison with the first wave, despite a shorter time from disease onset to admission. These changes in demographics may explain the lower frequency of ICU hospitalizations and mechanical ventilation due to treatment limitations in old and comorbid patients.

The differences between the two COVID-19 waves could be influenced by other factors. In the first phase of the epidemic, hospitals were overwhelmed, and some of oldest and most severely impaired patients were neither tested nor admitted to hospital and died at home or in long-term care facilities. The organization of care improved in the second phase of the epidemic, as did knowledge about COVID-19 diagnosis and treatment, potentially leading to more accurate diagnosis and better treatment. During the first period, patients were less likely to be treated with steroids and more likely to receive antivirals that may not have been effective against COVID-19, and could have been harmful [9]. Similarly, the use of high-flow nasal oxygen therapy was less prevalent in the first wave [10] and prevention of blood clots had changed. All these factors may have improved survival in COVID-19 patients and led to a stable mortality rate despite increased admission of older and more vulnerable patients.

This cohort exhibits a number of epidemiological results: higher frequency of comorbidities and older patients in comparison with the first wave. Interestingly, the need for mechanical ventilation and ICU admission was less frequent, but due to the aforementioned demographic shift, no decrease of mortality was observed.

Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers.

Disclosure of interest

The authors declare that they have no competing interest.

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Margaux Lafaurie and Aurelie Jourdes. The first draft of the manuscript was written by Aurelie Jourdes and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

The authors deeply thank Christophe Morin, Gaëlle Barencourt, Caroline Hurault-Delarue, Charlotte Vert, Julien Jacquot, Audrey Przybylski, Alexandre Sol, Gabrielle Gonzalvez for their help in data acquisition and Isabelle Olivier for assistance in the regulatory aspect.

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Available online 1 October 2021
https://doi.org/10.1016/j.idnow.2021.09.005
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High negative predictive value of RT-PCR in patients with high likelihood of SARS-CoV-2 infection

ARTICLE INFO

Keywords:
RT-PCR
SARS-CoV-2
COVID-19

SARS-CoV-2 epidemic mitigation efforts rely on effective tests that should have a high negative predictive value to accurately exclude SARS-CoV-2 infection when the test is negative. A systematic review, despite the large heterogeneity, showed the rate of false negative results of SARS-CoV-2 RT-PCR tests could range from 1.8% to 58% [1]. France faced a major SARS-CoV-2 epidemic in the spring of 2020, with 5.3% of the population estimated to have been infected by May 2020 [2], thus bringing the pre-test probability of SARS-CoV-2 RT-PCR tests to high levels during this period. We aimed to estimate the negative predictive value of SARS-CoV-2 RT-PCR in patients with a high pre-test probability of SARS-CoV-2 infection.

We conducted a serological study in patients managed in eight French hospitals and who tested negative for SARS-CoV-2 using an RT-PCR test on nasopharyngeal or throat swab, either for symptoms consistent with COVID-19 or following contact with a confirmed case of SARS-CoV-2 infection. Blood was sampled for serological testing at least two weeks after symptom onset, to allow time for a potential seroconversion to take place [3]. Participants were questioned about recent symptoms consistent with COVID-19. Anti-SARS-CoV-2 antibodies were tested using an S-Flow assay, a flow cytometry-based assay detecting anti-S IgG antibodies with specificity and sensitivity rates above 99% [4,5]. This study was registered with ClinicalTrials.gov (NCT04325646) and received ethical approval by the Ile-de-France III institutional review board. Informed consent was obtained from all participants.

From March 13, 2020 to May 14, 2020, a total of 116 patients were enrolled. Five did not meet eligibility criteria and five were lost to follow-up, leaving 106 participants (58 women, 48 men) with a median age of 35 years (interquartile range [IQR]: 28-48). All participants reported symptoms consistent with COVID-19 and 41 (38.7%) participants reported prior contact with a confirmed case of SARS-CoV-2 infection. Two participants (1.9%) had to be hospitalized. Median time from symptom onset to RT-PCR test was 3 days (IQR 2-6) and median time from RT-PCR test to blood sampling was 21 days (IQR 18-29).

Four participants (3.8%) tested positive for anti-SARS-CoV-2 antibodies, resulting in a negative predictive value of SARS-CoV-2 RT-PCR of 96.2% (95% confidence interval: 90.6%–99.0%). All four participants had been tested in the same participating center for symptoms compatible with COVID-19 (including one with anosmia and ageusia), two of whom also reported contact with a confirmed case of SARS-CoV-2 infection. None of them had to be hospitalized. In these four participants, time from symptom onset to RT-PCR test ranged from 2 to 11 days and blood sampling for serology was performed between 21 and 29 days after symptom onset and between 10 and 21 days after RT-PCR test.

In a population with high pre-test probability of SARS-CoV-2 infection, the negative predictive value of SARS-CoV-2 RT-PCR was high. The serology technique we used has a very high sensitivity, which makes it very unlikely that a seropositive participant went undetected [5]. Seropositive participants might have been infected between RT-PCR sampling and blood sampling. However, this is unlikely given the short time interval between RT-PCR and serology samplings. Furthermore, all seropositive participants had symptoms compatible with COVID-19 at the time of RT-PCR testing, including one with anosmia and ageusia, two symptoms that have a high positive predictive value for COVID-19 diagnosis [6,7]. A systematic review of false-negative results of SARS-CoV-2 RT-PCR showed that the probability of false-negative results decreases from the day of exposure to 3 days after symptom onset and then increases again over the following days [8]. Three of the four false-negative patients in this study were tested at least 5 days after symptom onset, which may help explain the false-negative results. As all seropositive participants underwent RT-PCR testing in a single center, we may raise the hypothesis of swab performance or defective RT-PCR kit issues. Other possible explanations for false-negative RT-PCR tests include the absence of detectable viral shedding throughout the disease or a swab for RT-PCR testing performed outside the time period of detectable viral shedding