# The Daily COVID-19 Literature Surveillance Summary

## March 23, 2021

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# LEVEL OF EVIDENCE

**Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence**

| Question | Step 1 (Level 1*) | Step 2 (Level 2*) | Step 3 (Level 3*) | Step 4 (Level 4*) | Step 5 (Level 5) |
|---|---|---|---|---|---|
| **How common is the problem?** | Local and current random sample surveys (or censuses) | Systematic review of surveys that allow matching to local circumstances** | Local non-random sample** | Case-series** | n/a |
| **Is this diagnostic or monitoring test accurate?** (Diagnosis) | Systematic review of cross sectional studies with consistently applied reference standard and blinding | Individual cross sectional studies with consistently applied reference standard and blinding | Non-consecutive studies, or studies without consistently applied reference standards** | Case-control studies, or "poor or non-independent reference standard** | Mechanism-based reasoning |
| **What will happen if we do not add a therapy?** (Prognosis) | Systematic review of inception cohort studies | Inception cohort studies | Cohort study or control arm of randomized trial* | Case-series or case-control studies, or poor quality prognostic cohort study** | n/a |
| **Does this intervention help?** (Treatment Benefits) | Systematic review of randomized trials or *n*-of-1 trials | Randomized trial or observational study with dramatic effect | Non-randomized controlled cohort/follow-up study** | Case-series, case-control studies, or historically controlled studies** | Mechanism-based reasoning |
| **What are the COMMON harms?** (Treatment Harms) | Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect | Individual randomized trial or (exceptionally) observational study with dramatic effect | Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)** | Case-series, case-control, or historically controlled studies** | Mechanism-based reasoning |
| **What are the RARE harms?** (Treatment Harms) | Systematic review of randomized trials or *n*-of-1 trial | Randomized trial or (exceptionally) observational study with dramatic effect | | | |
| **Is this (early detection) test worthwhile?** (Screening) | Systematic review of randomized trials | Randomized trial | Non -randomized controlled cohort/follow-up study** | Case-series, case-control, or historically controlled studies** | Mechanism-based reasoning |

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

**How to cite the Levels of Evidence Table**

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

# EXECUTIVE SUMMARY

**Epidemiology**

- Some COVID-19 patients continued to have at least one symptom post hospitalization. The Université Paris-Saclay Writing Committee for the COMEBAC Study Group conducted a prospective uncontrolled cohort study at Hôpital de Bicêtre involving follow-up assessments of patients 4 months after hospitalization for COVID-19 infection. Analysis found the presence of at least one new symptom compared to pre-COVID infection; most commonly fatigue, cognitive symptoms, and dyspnea. CT scan abnormalities in the lungs were present in 108/171 (63.2%) patients and 172/177 patients had positive serology for anti-SARS-CoV-2, however persistent cardiac dysfunction and kidney failure were less common. These findings are limited given no control group or pre-COVID-19 infection assessments of these patients. However, further research is indicated to better understand the longer-term outcomes of COVID-19 infection.

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# ORAL CANDIDIASIS OF COVID-19 PATIENTS: CASE REPORT AND REVIEW OF EVIDENCE

Riad A, Gomaa E, Hockova B, Klugar M.. J Cosmet Dermatol. 2021 Mar 13. doi: 10.1111/jocd.14066. Online ahead of print.
Level of Evidence: 4 - Case-series

## BLUF

A 3-patient case series and literature review conducted by a group of dentists in the Czech Republic assessed oral candidiasis in COVID-19 patients. Some key results are that the three COVID-19 patients studied in the case series showed typical presentations of oral candidiasis and additionally the literature review netted evidence of 63 cases of reported candidiasis in COVID-19 patients (Table 1, Figure 1). The implication being that COVID-19 infection appears to help facilitate growth of this opportunistic infection.

## ABSTRACT

The immune dysregulation triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been hypothesised as a causal pathway for the increasingly reported oral manifestations associated with coronavirus diseases (COVID-19) especially the ones of fungal origin.1-3 As a result of this, we aim to report according to the CARE guidelines, three COVID-19 cases who sought teleconsultations from our private practice (Cairo, Egypt) from July to September 2020. In addition, we have performed a literature search in Ovid MEDLINE , EMBASE, Cochrane Library, and Epistemonikos from inception until November 30th , 2020 with a combination of keywords (COVID-19 OR SARS-CoV-2) AND oral candidiasis.

## FIGURES

| Study, Location | Number | Gender | Age | Medical History | Confirmation | COVID-19 Treatment | Onset | Description | Treatment |
|---|---|---|---|---|---|---|---|---|---|
| Amorim dos Santos et al. 2020; Brasilia (Brazil) | 1 | Male | 67 | Coronary disease, systemic hypertension, kidney disease, and kidney transplant which led him to take immunosuppressants and pharmacological prophylaxis. | Confirmed by PCR | ICU admission, and orotracheal intubation. *Hydroxychloroquine sulfate (HCQ), ceftriaxone sodium,* and *azithromycin.* | 24 days after hospital admission. | Persistent white plaque on the tongue dorsum. | Intravenous *fluconazole* and oral *nystatin.* |
| Baraboutis et al. 2020; Athens (Greece) | 2 | N/A | N/A | No risk factors like known immunosuppression or recent antimicrobial use. | Confirmed by PCR | N/A | 7-10 days after symptoms emergence. | Unexpected 'oral candidiasis'. One of them resembled oesophageal candidiasis. | N/A |
| Cantini et al. 2020; Tuscany (Italy) | 1 | N/A | > 50 | N/A | Confirmed by PCR | *Baricitinib* | N/A | Oral candidiasis was recorded as an adverse event for *Baricitinib* as COVID-19 medication. | N/A |
| Corchuelo et al. 2020; Cali (Colombia) | 1 | Female | 40 | Lymphadenopathy managed by *azithromycin*. Headache managed by *ibuprofen*. | Confirmed by serological test (+IgG) | N/A | N/A | Mild oral candidiasis infection at the level of the posterior tongue. | Oral *nystatin* |
| Díaz Rodríguez et al. 2020; Madrid (Spain) | 1 | Female | 78 | N/A | Confirmed by PCR. | N/A | N/A | Lesions on the tongue, palate, and commissure compatible with pseudomembranous candidiasis and angular cheilitis were observed. | Oral *nystatin* |
| Dima et al. 2020; Timisoara (Romania) | 3 | 1 Female, 2 Male | 0 (neonates) | Previously healthy | Confirmed by PCR. | Vitamin D | During hospitalization | Oral candidiasis was accompanied by diaper erythema. | *Nystatin* |
| Riad et al. 2020; Gharbia (Egypt) | 1 | Female | 47 | Mild hypothyroidism managed by *levothyroxine.* | Confirmed by PCR | *Azithromycin, linezolid,* and *ceftriaxone* | A few days after anosmia & amblygeustia. | Multiple medium- sized pseudomembranous structures were detected with white plaques scattered over the dorsal surface of the tongue. | N/A |
| Salehi et al. 2020; Tehran (Iran) | 53 | 30 Female, 23 Male | 11 (< 50 y), 42 (≥ 50 y) | 28 cardiovascular diseases, 20 diabetes mellitus, 11 chronic kidney diseases, 5 haematological malignancies. | Confirmed by PCR | 49 broad-spectrum antibiotics, 25 corticosteroids, 26 ICU admission, 16 mechanical ventilation | Mean interval between COVID-19 diagnosis and candidiasis emergence was 8 days (range 1-30 days). | In total, 65 *Candida* isolates causing OPC were recovered from 53 patients. C *albicans* (46/65; 70.7%) was the most prevalent yeast species. | 21 (*fluconazole* 17 (*fluconazole* *nystatin*), 13 (*nystatin*), 1 (*caspofungin*) |
| Total | 63 | 34 Female, 26 Male, 3 Missed | Mean age: 59.5 years (3 missed). | 56 comorbidities, 5 previously healthy, 2 missed. | 62 confirmed by PCR, 1 confirmed by serological test. | The majority are hospitalized and treated by *HCQ*, antibiotics, corticosteroids. | Within one month since COVID-19 symptoms emergence. | Pseudomembranous oral candidiasis related to tongue and oral mucosa, and oropharyngeal candidiasis. | 39 *fluconazole*, 36 *nystatin*, 1 *caspofungin*, 4 missed. |

N/A = not reported by the investigators

Table 1: Characteristics of COVID-19 Patients with Oral Candidiasis; Reported January-November 2020

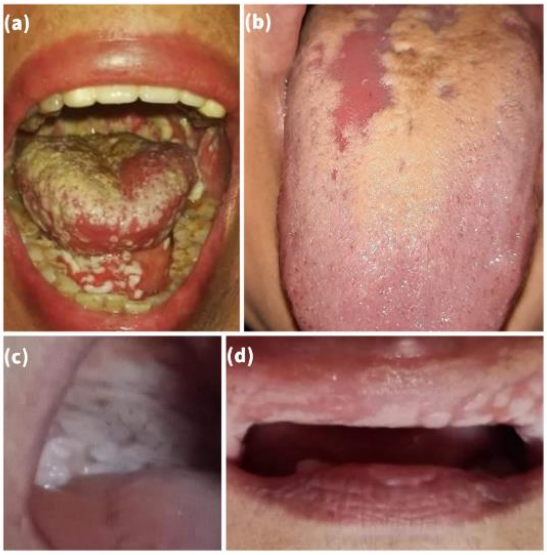


Figure 1

# ADULTS

## FOUR-MONTH CLINICAL STATUS OF A COHORT OF PATIENTS AFTER HOSPITALIZATION FOR COVID-19

Writing Committee for the COMEBAC Study Group, Morin L, Savale L, Pham T, Colle R, Figueiredo S, Harrois A, Gasnier M, Lecoq AL, Meyrignac O, Noel N, Baudry E, Bellin MF, Beurnier A, Choucha W, Corruble E, Dortet L, Hardy-Leger I, Radiguer F, Sportouch S, Verny C, Wyplosz B, Zaidan M, Becquemont L, Montani D, Monnet X.. JAMA. 2021 Mar 17. doi: 10.1001/jama.2021.3331. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

### BLUF

The Université Paris-Saclay Writing Committee for the COMEBAC Study Group conducted a prospective uncontrolled cohort study at Hôpital de Bicêtre involving follow-up assessments of patients 4 months after hospitalization for COVID-19 infection between March 1 and May 29, 2020 (Figure 1). Analysis found the presence of at least one new symptom compared to pre-COVID infection; most commonly fatigue, cognitive symptoms, and dyspnea (Figure 2). CT scan abnormalities in the lungs were present in 108/171 (63.2%) patients (Table 3) and 172/177 patients had positive serology for anti-SARS-CoV-2, however persistent cardiac dysfunction and kidney failure were less common. These findings are limited given no control group or pre-COVID-19 infection assessments of these patients. However, further research is indicated to better understand the longer-term outcomes of COVID-19 infection.

### ABSTRACT

Importance: Little is known about long-term sequelae of COVID-19. Objective: To describe the consequences at 4 months in patients hospitalized for COVID-19. Design, Setting, and Participants: In a prospective uncontrolled cohort study, survivors of COVID-19 who had been hospitalized in a university hospital in France between March 1 and May 29, 2020, underwent a telephone assessment 4 months after discharge, between July 15 and September 18, 2020. Patients with relevant symptoms and all patients hospitalized in an intensive care unit (ICU) were invited for further assessment at an ambulatory care visit. Exposures: Survival of hospitalization for COVID-19. Main Outcomes and Measures: Respiratory, cognitive, and functional symptoms were assessed by telephone with the Q3PC cognitive screening questionnaire and a checklist of symptoms. At the ambulatory care visit, patients underwent pulmonary function tests, lung computed tomographic scan, psychometric and cognitive tests (including the 36-Item Short-Form Health Survey and 20-item Multidimensional Fatigue Inventory), and, for patients who had been hospitalized in the ICU or reported ongoing symptoms, echocardiography. Results: Among 834 eligible patients, 478 were evaluated by telephone (mean age, 61 years [SD, 16 years]; 201 men, 277 women). During the telephone interview, 244 patients (51%) declared at least 1 symptom that did not exist before COVID-19: fatigue in 31%, cognitive symptoms in 21%, and new-onset dyspnea in 16%. There was further evaluation in 177 patients (37%), including 97 of 142 former ICU patients. The median 20-item Multidimensional Fatigue Inventory score (n = 130) was 4.5 (interquartile range,

3.0-5.0) for reduced motivation and 3.7 (interquartile range, 3.0-4.5) for mental fatigue (possible range, 1 [best] to 5 [worst]). The median 36-Item Short-Form Health Survey score (n = 145) was 25 (interquartile range, 25.0-75.0) for the subscale "role limited owing to physical problems" (possible range, 0 [best] to 100 [worst]). Computed tomographic lung-scan abnormalities were found in 108 of 171 patients (63%), mainly subtle ground-glass opacities. Fibrotic lesions were observed in 33 of 171 patients (19%), involving less than 25% of parenchyma in all but 1 patient. Fibrotic lesions were observed in 19 of 49 survivors (39%) with acute respiratory distress syndrome. Among 94 former ICU patients, anxiety, depression, and posttraumatic symptoms were observed in 23%, 18%, and 7%, respectively. The left ventricular ejection fraction was less than 50% in 8 of 83 ICU patients (10%). New-onset chronic kidney disease was observed in 2 ICU patients. Serology was positive in 172 of 177 outpatients (97%). Conclusions and Relevance: Four months after hospitalization for COVID-19, a cohort of patients frequently reported symptoms not previously present, and lung-scan abnormalities were common among those who were tested. These findings are limited by the absence of a control group and of pre-COVID assessments in this cohort. Further research is needed to understand longer-term outcomes and whether these findings reflect associations with the disease.

## FIGURES

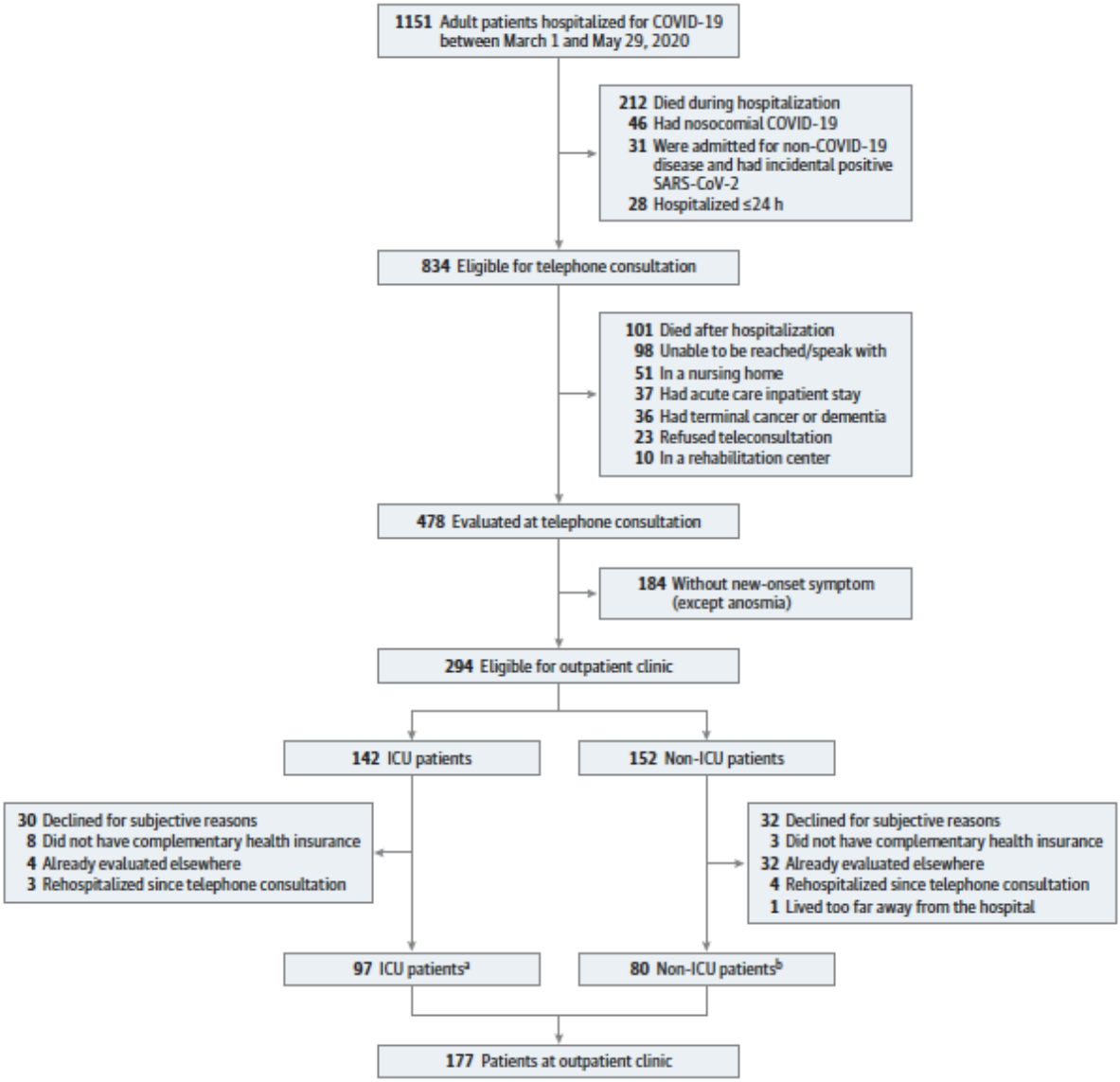


Figure 1: Flow of Patient Screening and Enrollment a Including 51 of 97 patients (53%) with invasive mechanical ventilation, 51 (53%) receiving vasopressors, and 8 (8%) with extracorporeal membrane oxygenation. b Including 44 of 80 patients (55%) with persistent neurologic symptoms, 27 (34%) with persistent respiratory symptoms, 5 (6%) with abnormal computed tomographic scan results, and 2 (3%) with persistent kidney failure.

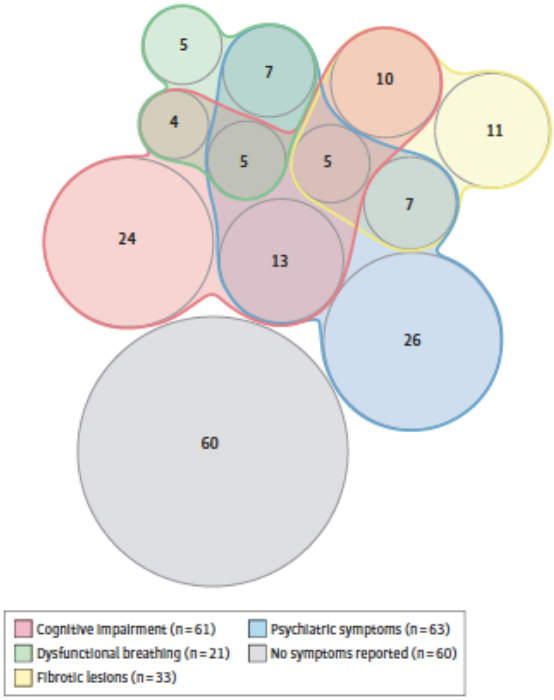


Figure 2. Visualization of Symptoms and Findings That Did Not Exist Before COVID-19 Infection in 177 Patients at the Outpatient Clinic, 4 Months After COVID-19 Hospitalization

Numbers represent patients with the symptoms/findings or association of symptoms; 60 patients did not report these symptoms or have these findings. Patients could have more than 1; hence, the sum of the groups exceeds 177.

| | No./total (%) | | |
|---|---|---|---|
| | All patients (n = 177) | Nonintubated (n = 126) | Intubated (n = 51) |
| Time from hospital discharge to outpatient clinic, median (IQR), d [No.] | 125 (107-144) [157] | 134 (116-150) [107] | 105 (90.2-119) [50] |
| Respiratory assessment | | | |
| mMRC scale score for dyspnea, median (IQR) [No.][a] | 2 (2-3) [115] | 2 (2-3) [80] | 2 (1.5-3) [35] |
| Persistent cough | 23/172 (13.4) | 19/123 (15.4) | 4/49 (8.2) |
| 6-Minute walk test, median (IQR), m [No.] | 462 (380-507) [161] | 464 (382-502) [112] | 462 (380-523) [49] |
| Abnormal lung CT scan result | 108/171 (63.2) | 71/122 (58.2) | 37/49 (75.5) |
| Persistent ground-glass opacities | 72/170 (42.4) | 45/121 (37.2) | 27/49 (55.1) |
| Lung fibrotic lesions | 33/170 (19.4) | 15/121 (12.4) | 18/49 (36.7) |
| $FEV_1$ (expressed as % of theory), median (IQR) [No.] | 92 (80-102) [157] | 92 (79-103) [108] | 90 (80-102) [49] |
| $FEV_1$/FVC, median (IQR) [No.] | 83 (79-87) [157] | 81 (78-86) [108] | 84 (82-87) [49] |
| TLC (expressed as % of theory) [No.] | 83 (15) [49] | 86 (15) [104] | 76 (14) [45] |
| DLCO <70% | 33/152 (21.7) | 16/105 (15.2) | 17/47 (36.2) |
| Echocardiography assessment | | | |
| RV dilatation on echocardiography | 20/79 (25.3) | 11/35 (31.4) | 9/44 (20.5) |
| LVEF 40%-50% on echocardiography[b] | 10/83 (12.0) | 2/38 (5.3) | 8/45 (17.8) |
| Neurologic and psychological assessment[a,c] | | | |
| Cognitive complaint (impaired McNair score, reported cognitive symptoms, or both) | 79/159 (49.7) | 55/109 (50.5) | 24/50 (48.0) |
| Cognitive impairment (impairment of either MoCA or d2-R score) | 61/159 (38.4) | 40/109 (36.7) | 21/50 (42.0) |
| Symptoms of anxiety (HADS-Anxiety) | 53/169 (31.4) | 40/119 (33.6) | 13/50 (26.0) |
| Symptoms of depression (BDI test) | 35/170 (20.6) | 26/120 (21.7) | 9/50 (18.0) |
| Insomnia (ISI score) | 90/168 (53.6) | 68/118 (57.6) | 22/50 (44.0) |
| Symptoms of PTSD (PCL-5 score) | 24/169 (14.2) | 19/119 (16.0) | 5/50 (10.0) |

Table 3. Results of the In-Person Outpatient Clinic Visit in Nonintubated and Intubated Patients

Abbreviations: BDI, Beck Depression Inventory; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; HADS-Anxiety, anxiety subscale of the Hospital Anxiety and Depression Scale; IQR, interquartile range; ISI, Insomnia Severity Index; LVEF, left ventricular ejection fraction; mMRC, modified Medical Research Council; MoCA, Montreal Cognitive Assessment; PTSD, posttraumatic stress disorder; RV, right ventricular; TLC, total lung capacity. a Signs were declared as new onset during or after hospitalization for COVID-19 and persistent at the assessment at the outpatient facility. bNo patient had an LVEF less than 40%. c The range, direction, and characteristics of the McNair, MoCA, and d2-R scores; of the anxiety subscale score of the HADS; of the BDI test results; and of the ISI and PCL-5 scores are shown in eTable 1 in the Supplement.

# UNDERSTANDING THE PATHOLOGY

## DEVELOPMENT OF NEUTRALIZING ANTIBODY RESPONSES AGAINST SARS-COV-2 IN COVID-19 PATIENTS

Teresa Valenzuela M, Urquidi C, Rodriguez N, Castillo L, Fernández J, Ramírez E.. J Med Virol. 2021 Mar 13. doi: 10.1002/jmv.26939. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

### BLUF

A prospective cohort study conducted by researchers from the Universidad de los Andes, Hospital Barros Luco Trudeau, and Instituto de Salud Public de Chile included 117 patients who were hospitalized with COVID-19 at Hospital Barros Luco Trudeau (HBL) between May and August 6, 2020, found the prevalence of IgG antibodies (ABs) and neutralizing (Nt) ABs to be 77.9% and 77.3% on first blood samples and 98.5% and 100% on second blood samples an average of 18.6 days after the first samples (p = 0.0002; Table 2), respectively. Favorable clinical outcome represented by hospital or ICU discharge was seen in 47 of the 68 patients who had second blood samples drawn. These findings highlight the presence of neutralizing ABs as early as 2 days after symptom onset, signifying rapid immune response and further informing decisions about the application of convalescent plasma therapies, as well as understanding the pathogenesis regarding development of the SARS-CoV-2 vaccine.

### SUMMARY

-The seropositivity of both antibodies increased significantly with longer disease period (Figure 2).

- The dynamics of Nt antibodies from the first to second blood samples is represented in Figure 4.

### ABSTRACT

The novel coronavirus SARS-CoV-2 and COVID-19 disease are new global problems. The understanding of the host immune response in COVID-19 and its implications in the development of therapeutic agents are new challenges. Here, we evaluated the development of IgG and Nt antibodies in symptomatic hospitalized COVID-19 patients. We followed up 117 COVID-19 confirmed patients from a reference health center for COVID-19 during the epidemic in Santiago de Chile. One and two sequential blood samples from 117 and 68 cases were respectively obtained to evaluate the immune response. Immunofluorescence and neutralization assays in Vero E6 cells with a Chilean SARS-CoV-2 strain were performed. Out of the 68 patients, 44% were women and 56% men, and most frequent comorbidities were hypertension (47.7%) and diabetes (27.4%). The most frequent symptoms or signs related to COVID-19 were dyspnea, cough, fever, myalgia, and headache. In the all study population, 76.1% and 60.7% of patients were positive for IgG and Nt antibodies in the first blood sample. All patients except one were positive for IgG and Nt antibodies in the second sample. IgG and Nt antibodies positivity increased significantly according to the disease evolution periods. Higher Nt antibody titers were observed in the first sample in patients under 60 years of age. Obese and diabetic patients had no increase in Nt antibodies, unlike normal weight and diabetes-free patients. Both hypertensive and normotensive patients showed a significant increase in Nt antibodies. These results show an early and robust immune response against SARS-CoV-2 infection during severe COVID-19. 

### FIGURES

| | First blood sample | Second blood sample |
|---|---|---|
| Days from onset of symptoms and blood sample, mean (min-max) | 11.1 (1-27) | 29.7 (13-57) |
| *Hospitalization Status* | | |
| Non-ICU hospitalization | 37 (54.4) | 29 (42.7) |
| Intensive care unit | 31 (45.6) | 11 (16.2) |
| Hospital discharge | -- | 28 (41.2) |
| IgG[1] | 53 (77.9) | 67 (98.5) |
| Nt[2] | 41 (77.3) | 67 (100) |

Table 2. IgG and Neutralizing antibodies positivity, and COVID-19 clinical course in patients with the first and second blood sample (n=68).

Absolute frequencies and percentages in parenthesis 1 Paired Chi square test second vs first blood sample: p=0.0002 2 Paired Chi square test second vs first blood sample: p<0.001

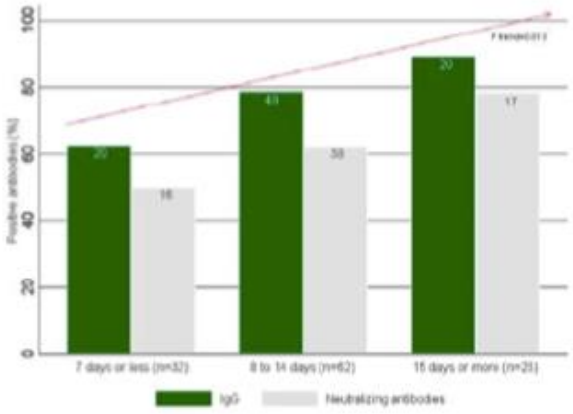


Figure 2. COVID-19 patients with IgG and neutralizing antibodies by disease evolution periods from the onset of signs or symptoms and first blood sample date (n=117). P trend: Chi-square statistic for the trend

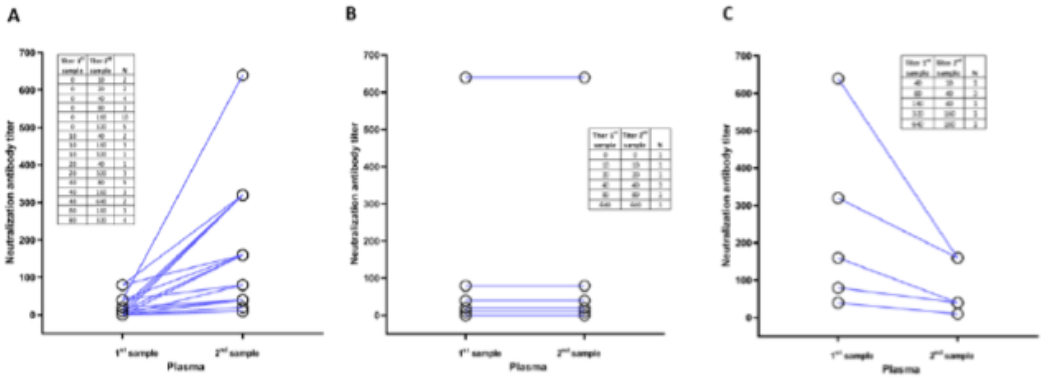


Figure 4. Comparison of Neutralization antibody titers for individual patients. Neutralization titers were determined by the reduction of cytopathic effect (CPE) in Vero E6 cells. Each line links two samples from each patient. (A) Patients with increase of Nt titers between first and second samples, (B) Patients with same Nt titers between first and second samples, (C) Patients with decrease of Nt titers between first and second samples.

# HEMATOLOGY AND ONCOLOGY

## COVID-19 VACCINE GUIDANCE FOR PATIENTS WITH CANCER PARTICIPATING IN ONCOLOGY CLINICAL TRIALS

Desai A, Gainor JF, Hegde A, Schram AM, Curigiliano G, Pal S, Liu SV, Halmos B, Groisberg R, Grande E, Dragovich T, Matrana M, Agarwal N, Chawla S, Kato S, Morgan G, Kasi PM, Solomon B, Loong HH, Park H, Choueiri TK, Subbiah IM, Pemmaraju N, Subbiah V; COVID19 and Cancer Clinical Trials Working Group.. Nat Rev Clin Oncol. 2021 Mar 15. doi: 10.1038/s41571-021-00487-z. Online ahead of print.
Level of Evidence: 5 - Guidelines and Recommendations

### BLUF

This article written by several physicians in the United States, China, Italy, and Australia advocates that patients currently enrolled in oncology clinical trials should be able to receive authorized COVID-19 vaccines, providing guidance on the best way to manage patients with proper documentation, timing of administration, and taking into account other special considerations (Table 1). Though little research is available on the outcomes of the COVID-19 vaccine in patients with cancer, specifically patients receiving treatment with anticancer drugs, this study suggests the COVID-19 vaccine be a standard of care as the benefits likely outweigh the vaccine-related risks.

### ABSTRACT

Emerging efficacy data have led to the emergency use authorization or approval of COVID-19 vaccines in several countries worldwide. Most trials of COVID-19 vaccines excluded patients with active malignancies, and thus data on the safety, tolerability and efficacy of the vaccines in patients with cancer are currently limited. Given the risk posed by the COVID-19 pandemic, decisions regarding the use of vaccines against COVID-19 in patients participating in trials of investigational anticancer therapies need to be addressed promptly. Patients should not have to choose between enrolling on oncology clinical trials and receiving a COVID-19 vaccine. Clinical trial sponsors, investigators and treating physicians need operational guidance on COVID-19 vaccination for patients with cancer who are currently enrolled or might seek to enrol in clinical trials. Considering the high morbidity and mortality from COVID-19 in patients with cancer, the benefits of vaccination are likely to far outweigh the risks of vaccine-related adverse events. Herein, we provide operational COVID-19 vaccine guidance for patients participating in oncology clinical trials. In our perspective, continued quality oncological care requires that patients with cancer, including those involved in trials, be prioritized for COVID-19 vaccination, which should not affect trial eligibility.

### FIGURES

Table 1 | **COVID-19 vaccine guidance for patients participating in oncology clinical trials**

| Trial, treatment and/or disease setting | Vaccination strategy and timing |
|---|---|
| ***Type of study*** | |
| Screening and/or prevention, quality of life, supportive care and/or palliative care, or natural history studies | On vaccine availability: for breast cancer screening trials, if possible, and when it does not unjustifiably interrupt management, screening exams should be conducted before the first dose of a COVID-19 vaccine or 4–6 weeks after the second dose of a COVID-19 vaccine |
| Phase I trials | For most novel investigational agents, the timing of vaccination should be mechanism-based |
| | Dose-escalation phase: with most anticancer agents, including TKIs, avoid vaccination on cycle 1 day 1. In general, defer initiation of the first cycle of investigational therapy until after all vaccine adverse effects have improved to grade ≤1 and for at least until 72 h after vaccination |
| | For immunotherapy agents with no known potential for cytokine-release syndrome, avoid vaccination on the day of infusions of intravenous immunotherapy, at least in the DLT period |
| | For immunotherapy agents associated with a potential risk of cytokine-release syndrome, defer vaccination until after the DLT window or delay administration of the investigational agent for 2 weeks after vaccine administration |
| | For first-in-human agents with an unknown adverse effect profile, delay administration until all adverse effects of the vaccine should have resolved to grade ≤1 |
| | Dose-expansion phase: on vaccine availability, with timing based on mechanism of action |
| Phase II and phase III trials (including placebo-controlled randomized trials) | On vaccine availability, with timing based on mechanism of action |
| ***Type of treatment*** | |
| Surgery clinical trials | Administer at discharge after recovery from post-operative complications or 1 week before surgery, whichever is most feasible |
| Radiation oncology clinical trials | On vaccine availability (the exception is total body radiation, after which vaccination might need to be delayed to provide time for immune reconstitution) |
| ***Solid tumours*** | |
| Cytotoxic chemotherapies | On vaccine availability (1–2 weeks before or 1–2 weeks after drug dose, when possible, to increase the potential for the immune system to mount a response) |
| Targeted therapy (e.g. TKIs) | On vaccine availability |
| Hormone therapy (e.g. anti-androgens or anti-oestrogen therapy) | On vaccine availability |
| Immunotherapy (e.g. immune-checkpoint inhibitors) | On vaccine availability |
| Epigenetic therapy | On vaccine availability |
| ***Haematological malignancies*** | |
| Intensive cytotoxic chemotherapies expected to result in profound and prolonged immunosuppression (e.g. anthracycline-based and/or cytarabine-based induction regimens) | Delay until absolute neutrophil count recovery |
| Epigenetic therapy | On vaccine availability |
| Targeted therapy (e.g. TKIs) | On vaccine availability |
| Immunotherapy (e.g. anti-CD20 antibodies) | On vaccine availability |
| Haematopoietic stem cell transplantation (allogenic or autologous) | >3 months after treatment |
| Adoptive cell therapies (for example, CAR T cells) | >3 months after treatment |

## TELEHEALTH STRATEGY TO MITIGATE THE NEGATIVE PSYCHOLOGICAL IMPACT OF THE COVID-19 PANDEMIC ON TYPE 2 DIABETES: A RANDOMIZED CONTROLLED TRIAL

Alessi J, de Oliveira GB, Franco DW, Becker AS, Knijnik CP, Kobe GL, Amaral BB, de Brito A, Schaan BD, Telo GH.. Acta Diabetol. 2021 Mar 15. doi: 10.1007/s00592-021-01690-1. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

### BLUF

A randomized control trial conducted by an interdisciplinary team of researchers in Brazil aimed to study whether mental health teleinterventions improve mental health outcomes in 91 Type 2 Diabetes patients during the COVID-19 pandemic (Table 1). The experimental group received phone calls with educational information about managing their mental health and diabetes while the control group only received access to a website with the same information. Results indicated a significant decrease in mental health disorders (p=0.04) and diabetes-related emotional distress (p=0.03) in the experimental group (Table 2, Figure 2). These findings suggest that remote follow-ups with healthcare professionals can significantly improve mental health disorders and diabetes-related emotional distress.

### SUMMARY

-Mental health outcomes were assessed through the Brazilian validated version of the Self Report Questionnaire-20 (SRQ20), Eating Attitudes Test (EAT-26), the Brazilian validated version of the Problem Areas in Diabetes Scale (B-PAID), and the Brazilian version of the Mini Sleep Questionnaire (MSQ) before and after 16 weeks in both groups.

-The stresses induced by the pandemic have had more pronounced effects in patients with diabetes.

### ABSTRACT

AIMS: To assess the impact of teleintervention on mental health parameters in type 2 diabetes patients during the coronavirus disease 2019 (COVID-19) pandemic. METHODS: This is a controlled randomized trial for a multidisciplinary telehealth intervention in Southern Brazil, with social distancing measures. Adults aged 18 years or older with previous diagnosis of type 2 diabetes were included in the study. The intervention performed was a set of strategies to help patients stay healthy during the COVID-19 pandemic and included the maintaining of telephone contacts and providing educational materials on issues related to mental health, healthy habits, and diabetes care. The primary outcome was a positive screening for mental health disorders (Self-Reporting Questionnaire) after 16 weeks of intervention. A positive screening for mental health disorders was considered when the survey scored greater than or equal to 7. Secondary outcomes included a positive screening for diabetes-related emotional distress (Problem Areas in Diabetes), eating (Eating Attitudes Test), and sleep disorders (Mini Sleep Questionnaire). Comparisons with chi2 tests for dichotomous outcomes, along with the Mann-Whitney U test, was used for between group analyses. RESULTS: A total of 91 individuals agreed to participate (46 intervention group and 45 control group). There were no differences in demographic and clinical data at baseline. After 16 weeks of follow-up, a positive screening for mental health disorders was found in 37.0% of participants in the intervention group vs. 57.8% in the control group (P = 0.04). Diabetes-related emotional distress was found in 21.7% of participants in the intervention group vs. 42.2% in the control group (P = 0.03). No differences were found between groups with regard to eating and sleep disorders. CONCLUSION: This study demonstrated that maintaining remote connections with health professionals during social distancing and quarantine have the potential to reduce the prevalence of positive screening for mental health disorders and diabetes-related emotional distress in adults with type 2 diabetes.

### FIGURES

| | Total (*N* = 91) | Active control group (*n* = 45) | Teleintervention group (*n* = 46) | P value |
|---|---|---|---|---|
| Age (years) | 61.3 ± 9.1 | 61.0 ± 9.0 | 61.6 ± 9.2 | 0.76 |
| Sex (% female) | 64.8% | 66.7% | 63.0% | 0.71 |
| Race/ethnicity (% white) | 78.0% | 73.3% | 82.6% | 0.29 |
| Marital status (% married) | 50.6% | 46.3% | 54.5% | 0.45 |
| Lower-middle income* (%) | 80.0% | 85.4% | 75.0% | 0.23 |
| Regular employment (%) | 30.6% | 31.7% | 29.5% | 0.82 |
| ***Diabetes aspects*** | | | | |
| Diabetes duration (years) | 18.1 ± 9.5 | 18.7 ± 9.0 | 17.5 ± 9.6 | 0.56 |
| HbA1c (%) (mmol/mol) | 8.8 ± 1.7<br>73.0 ± 18.6 | 9.0 ± 1.6<br>75.0 ± 17.5 | 8.5 ± 1.7<br>69.0 ± 18.6 | 0.11 |
| Diabetes complications | | | | |
| Retinopathy | 40.7% | 44.4% | 30.4% | 0.47 |
| Neuropathy | 29.7% | 28.9% | 37.0% | 0.87 |
| Nephropathy | 42.9% | 40.0% | 45.7% | 0.59 |
| Insulin use (%) | 83.5% | 82.2% | 84.8% | 0.74 |
| Metformin use (%) | 75.8% | 80.0% | 71.7% | 0.36 |
| ***Previous diseases*** | | | | |
| Systemic arterial hypertension (%) | 82.4% | 80.0% | 84.8% | 0.55 |
| Cardiovascular disease (%) | 39.6% | 34.8% | 44.4% | 0.35 |
| ACE or ARB inhibitors use (%) | 82.4% | 80.0% | 84.8% | 0.55 |
| Statins use (%) | 82.4% | 84.4% | 80.4% | 0.62 |
| ASA use (%) | 52.7% | 55.6% | 50.0% | 0.60 |
| ***History of mental disorders*** | | | | |
| Depression (%) | 20.9% | 20.0% | 21.7% | 0.84 |
| Anxiety (%) | 6.6% | 2.2% | 10.9% | 0.10 |
| Bipolar disorder (%) | 2.2% | 2.2% | 2.2% | 0.99 |
| Other psychiatric conditions (%) | 2.2% | 2.2% | 2.2% | 0.99 |
| SRI use (%) | 24.2% | 22.2% | 26.1% | 0.67 |
| Tricyclic antidepressant use (%) | 8.8% | 8.9% | 8.7% | 0.97 |
| Lithium use (%) | 2.2% | 2.2% | 2.2% | 0.99 |
| Antipsychotic use (%) | 6.6% | 4.4% | 8.7% | 0.41 |
| Benzodiazepine use (%) | 3.3% | 2.2% | 4.3% | 0.57 |
| ***Pandemic-related aspects*** | | | | |
| Social distancing (self-reported) | | | | |
| Partial<br>Total<br>None | 57.6%<br>32.9%<br>9.4% | 51.2%<br>36.6%<br>12.2% | 63.6%<br>29.5%<br>6.8% | 0.46 |
| Social contact | | | | |
| Only family<br>Family and friends<br>None | 69.4%<br>12.9%<br>17.6% | 73.2%<br>14.6%<br>12.2% | 65.9%<br>11.4%<br>22.7% | 0.43 |
| Reduction in family income (%) | 54.1% | 61.0% | 47.7% | 0.22 |
| Lost the job (%) | 5.9% | 2.4% | 9.1% | 0.19 |
| Presented respiratory symptoms (%) | 24.7% | 29.3% | 20.5% | 0.35 |
| Confirmed COVID-19 infection | 5.9% | 7.3% | 4.5% | 0.59 |
| Hospitalization | 7.1% | 4.9% | 9.1% | 0.45 |

Table 1 Baseline characteristics of study participants

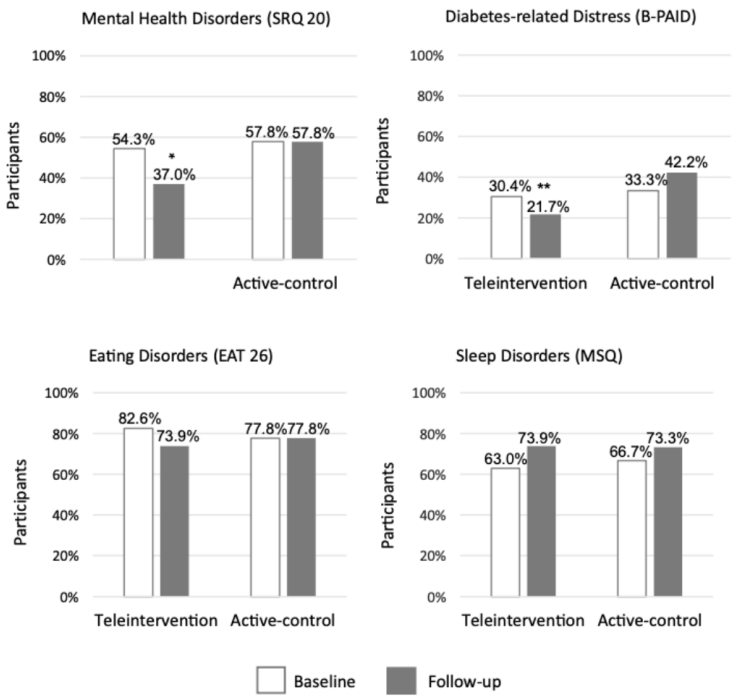


**Fig. 2** Participants with positive screening for the proposed assessments, based on cutoff values and comparison between intervention and control groups. Legend: number of participants who present positive screening based on pre-established cutoff values. For the evaluation of mental health disorders, a score greater than or equal to 7 on SRQ 20 is considered positive. Diabetes-related emotional distress is considered when the B-PAID score is greater than or equal to 40. The presence of positive screening for an eating disorder is considered when the EAT 26 score is greater than or equal to 20. A positive screening for sleep disorder is considered when a score greater than or equal to 31 is present in the MSQ. $*P=0.04$. $**P=0.03$

| | Active control group (*n* = 45) | Teleintervention group (*n* = 46) | P *value* |
|---|---|---|---|
| ***Mental health disorders (SRQ 20)*** | | | |
| Baseline | 6.0 (2.5 to 11.0) | 6.0 (3.0 to 9.3) | 0.76 |
| Follow-up | 8.0 (3.0 to 12.0) | 5.0 (2.0 to 9.0) | 0.09 |
| Change in scores | 0.0 (−0.3 to 1.4) | 0.0 (−0.3 to 0.7) | |
| Difference within-group (P *value*) | 0.32 | 0.53 | |
| ***Diabetes-related distress (B-PAID)*** | | | |
| Baseline | 18.0 (6.5 to 39.0) | 21.0 (11.8 to 8.0) | 0.43 |
| Follow-up | 27.0 (6.0 to 47.5) | 12.5 (6.0 to 29.5) | 0.08 |
| Change in scores | 0.1 (−0.6 to 0.1) | −0.3 (−0.7 to −0.3) | |
| Difference within-group (P *value*) | 0.29 | 0.04 | |
| ***Treatment adherence (SCI-R)*** | | | |
| Baseline | 51.0 (44.0 to 57.0) | 51.5 (46.8 to 6.0) | 0.80 |
| Follow-up | 53.0 (44.0 to 60.0) | 53.0 (46.8 to 7.3) | 0.73 |
| Change in scores | 0.0 (−0.2 to 0.2) | 0.0 (−0.1 to 0.2) | |
| Difference within-group (P *value*) | 0.54 | 0.25 | |
| ***Eating disorders (EAT 26)*** | | | |
| Baseline | 29.0 (20.5 to 32.5) | 26.5 (21.0 to 1.3) | 0.67 |
| Follow-up | 27.0 (20.0 to 33.0) | 24.5 (18.8 to 0.3) | 0.50 |
| Change in scores | −0.1 (0.3 to −0.1) | 0.0 (−0.3 to 0.3) | |
| Difference within-group (P *value*) | 0.44 | 0.58 | |
| ***Sleep disorders (MSQ)*** | | | |
| Baseline | 39.0 (27.5 to 48.0) | 35.0 (25.8 to 6.8) | 0.47 |
| Follow-up | 38.0 (28.0 to 52.0) | 36.0 (28.0 to 5.0) | 0.35 |
| Change in scores | 0.0 (−0.2 to 0.5) | 0.0 (−0.1 to 0.4) | |
| Difference within-group (P *value*) | 0.55 | 0.47 | |

Table 2 Comparison of questionnaires’ total scores for baseline and for follow-up after 16 weeks

# ACKNOWLEDGEMENTS


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