# The Daily COVID-19 Literature Surveillance Summary

## November 03, 2020

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**COVID-19 Daily Literature Surveillance**

COVID19LST

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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

**Climate**

- Hospital Volumes during the COVID-19 Pandemic in 2 US Medical Centers, Stanford University Medical Center and New York-Presbyterian/Weill Cornell Medical Center, were explored with the incidence of 5 medical emergencies: acute MI, ischemic stroke, nontraumatic subarachnoid hemorrhage, ectopic pregnancy, and appendicitis. Authors found decreased incidence of acute myocardial infarction, non-traumatic subarachnoid hemorrhage, and ischemic stroke cases in both centers, a decrease in appendicitis cases in New York, and no changes in ectopic pregnancy cases at either center. They implicate that deferring seeking care for acute conditions due to the fear of contracting COVID-19 could be leading to the higher rates of at-home death of patients during the pandemic.

**Transmission & Prevention**

- Operation Warp Speed's Strategy and Approach are outlined by an affiliated physician scientist. It is a partnership of the Department of Health and Human Services, Department of Defense, and the private sector. Their goal is to advance "development, manufacturing, and distribution of vaccines, therapeutics, and diagnostics" to establish control over the COVID-19 pandemic. The initiative set objectives of delivering ~300 million doses of the SARS-COV-2 vaccine by mid-2021 with strict criteria by which companies have to comply in order to be accepted. Currently there are "eight vaccines in [their] portfolio which include "Moderna and Pfizer/BioNTech (both mRNA), AstraZeneca and Janssen (both replication-defective live-vector), and Novavax and Sanofi/GSK (both recombinant-subunit-adjuvanted protein).

**Management**

- Among 89 COVID -19 ICU Patients at Newark Beth Israel Medical Center one study found 8.9% (n=8) developed nosocomial candidemia over an average ICU stay of 25 days. Compared to the control, they found that COVID-19 ICU patients with higher BMI, prolonged mechanical ventilation, and superimposed bacterial infections were associated with concomitant candidemia, but in-hospital mortality was not significantly changed. Authors suggest that providers be aware of systemic fungal infections as a potential complication in COVID-19 ICU patients.

**R&D: Diagnosis & Treatments**

- The efficacy and safety of SARS-CoV-2 Neutralizing Antibody LY-CoV555, an antispike neutralizing monoclonal antibody, were analyzed in a randomized, double-blind, controlled trial. The investigators examined the antibody's effect on viral load, symptom scores, and clinical outcome of 452 patients across 41 centers in the United States receiving one of three doses (700 mg, 2800 mg, or 7000 mg) or a placebo. Although the authors acknowledge the need for further studies, the trial so far indicates possible reduction in symptom severity and a reduction in viral load with higher doses of LY-CoV555, suggesting that LY-CoV555 could become a useful treatment for patients with a recent diagnosis of COVID-19.

**Mental Health & Resilience Needs**

- Risk and Protective Factors for Prospective Changes in Adolescent Mental Health during the COVID-19 Pandemic were examined in a survey of 248 adolescents in the urban areas of New South Wales, Australia. Findings show that adolescents have increased anxiety and depressive symptoms, and decreased life satisfaction due to the governmental restrictions posed to control viral spread. The authors suggest a call for action to increase close monitoring of these adolescents and find ways to support and maintain social engagements for them.

# TABLE OF CONTENTS

# CLIMATE

## HOSPITAL VOLUMES OF 5 MEDICAL EMERGENCIES IN THE COVID-19 PANDEMIC IN 2 US MEDICAL CENTERS

Bhambhvani HP, Rodrigues AJ, Yu JS, Carr JB 2nd, Hayden Gephart M.. JAMA Intern Med. 2020 Oct 26. doi: 10.1001/jamainternmed.2020.3982. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

### BLUF

Neurosurgeons from Stanford, CA and New York, NY assessed the association of the COVID-19 pandemic with the incidence of 5 medical emergencies (acute MI, ischemic stroke, nontraumatic subarachnoid hemorrhage, ectopic pregnancy, and appendicitis) seen at Stanford University Medical Center and New York-Presbyterian/Weill Cornell Medical Center. They found decreased incidence of acute myocardial infarction, non-traumatic subarachnoid hemorrhage, and ischemic stroke cases in both centers, a decrease in appendicitis cases in New York, and no changes in ectopic pregnancy cases at either center. The authors implicate that deferring seeking care for acute conditions due to the fear of contracting COVID-19 could be leading to the higher rates of at-home death of patients during the pandemic.

### FIGURES

| | | Mean daily count | | Time series analysis | |
|---|---|---|---|---|---|
| Institution | Condition | Pre-COVID-19 | Post-COVID-19 | Relative risk (95% CI) | *P* value |
| Stanford | Acute MI | 10.95 | 9.25 | 0.74 (0.68-0.80) | <.001 |
| Stanford | Ischemic stroke | 22.19 | 19.93 | 0.84 (0.79-0.89) | <.001 |
| Stanford | ntSAH | 2.10 | 1.50 | 0.79 (0.64-0.98) | .03 |
| Stanford | Appendicitis | 2.53 | 2.26 | 0.85 (0.71-1.01) | .07 |
| Stanford | Ectopic pregnancy | 0.58 | 0.52 | 0.76 (0.53-1.09) | .14 |
| NYP | Acute MI | 3.64 | 2.29 | 0.61 (0.52-0.72) | <.001 |
| NYP | Ischemic stroke | 9.09 | 4.93 | 0.51 (0.45-0.56) | <.001 |
| NYP | ntSAH | 0.92 | 0.61 | 0.67 (0.47-0.93) | .03 |
| NYP | Appendicitis | 2.04 | 1.06 | 0.58 (0.46-0.74) | <.001 |
| NYP | Ectopic pregnancy | 0.68 | 0.52 | 0.84 (0.59-1.20) | .33 |

Figure 1. Trends in Hospital Volume of 5 Emergency Medical Conditions Before and After the Start of the COVID-19 Pandemic

# DISPARITIES

## SUBSTANCE USE DISORDER LINKED TO HIGHER COVID-19 RISK

Rubin R.. JAMA. 2020 Oct 27;324(16):1598. doi: 10.1001/jama.2020.19686.
Level of Evidence: Other - Expert Opinion

### BLUF

A senior writer from JAMA suggests that people with substance use disorder (SUD) are at greater risk for COVID-19, citing a recent case-control study (Wang et al., 2020) that included the director of the National Institute on Drug Abuse (NIDA) as a coauthor. Wang et al.'s study analyzed 12,030 COVID-19 patient charts and found a statically significant increase risk in those with SUD, opioid use being the greatest, verses those without SUD. The author suggests that the greater cardiovascular and pulmonary comorbidities and possible decreased access to healthcare among people with SUD may contribute to this population's increased risk for COVID-19.

# UNDERSTANDING THE PATHOLOGY

## SARS-COV-2 INFECTION DYSREGULATES THE METABOLOMIC AND LIPIDOMIC PROFILES OF SERUM

Bruzzone C, Bizkarguenaga M, Gil-Redondo R, Diercks T, Arana E, García de Vicuña A, Seco M, Bosch A, Palazón A, San Juan I, Laín A, Gil-Martínez J, Bernardo-Seisdedos G, Fernández-Ramos D, Lopitz-Otsoa F, Embade N, Lu S, Mato JM, Millet O..
iScience. 2020 Oct 23;23(10):101645. doi: 10.1016/j.isci.2020.101645. Epub 2020 Oct 5.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

### BLUF

A cohort study conducted by interdisciplinary researchers from Spain used NMR spectroscopy to analyze serum metabolic and lipidomic profiles of COVID-19 patients (n=263 "training" cohort and n=135 " validation" cohort) compared to pre-COVID patient controls (n=280; profiles from 2018-2019). They found COVID-19 patients had alterations in lipoprotein constitution and size consistent with increased atherosclerotic risk, in addition to elevations in ketone bodies and markers of oxidative stress (Figures 2,3,4). Authors suggest pathogenesis of SARS-CoV-2 may induce liver damage due to oxidative stress and dyslipidemia.

### SUMMARY

Additional study details as follows:
- NMR analysis was used to quantify metabolic and lipoprotein serum profiling including Apo-A1, Apo-A2, Apo-B, total and free cholesterol, phospholipids and triglycerides (Figures 3,4).
- Unsupervised Principal Component Analysis (PCA) quantified 40 metabolites and showed a significant difference between COVID-19 and pre-COVID cohorts, suggesting SARS-CoV-2 infection may cause changes in the blood lipoprotein composition.
- Supervised orthogonal partial least square discriminant analysis (OPLS-DA) of sera metabolic and lipoprotein subclasses showed a statistically significant difference between groups ($p<0.01$) with good predictability (AUROC validation=0.977; Figure 2).

### ABSTRACT

COVID-19 is a systemic infection that exerts significant impact on the metabolism. Yet, there is little information on how SARS-CoV-2 affects metabolism. Using NMR spectroscopy, we measured the metabolomic and lipidomic serum profile from 263 (training cohort) + 135 (validation cohort) symptomatic patients hospitalized after positive PCR testing for SARS-CoV-2 infection. We also established the profiles of 280 persons collected before the coronavirus pandemic started. PCA analyses discriminated both cohorts, highlighting the impact that the infection has in overall metabolism. The lipidomic analysis unraveled a pathogenic redistribution of the lipoprotein particle size and composition to increase the atherosclerotic risk. In turn, metabolomic analysis reveals abnormally high levels of ketone bodies (acetoacetic acid, 3-hydroxybutyric acid and acetone) and 2-hydroxybutyric acid, a readout of hepatic glutathione synthesis and marker of oxidative stress. Our results are consistent with a model in which SARS-CoV-2 infection induces liver damage associated with dyslipidemia and oxidative stress.

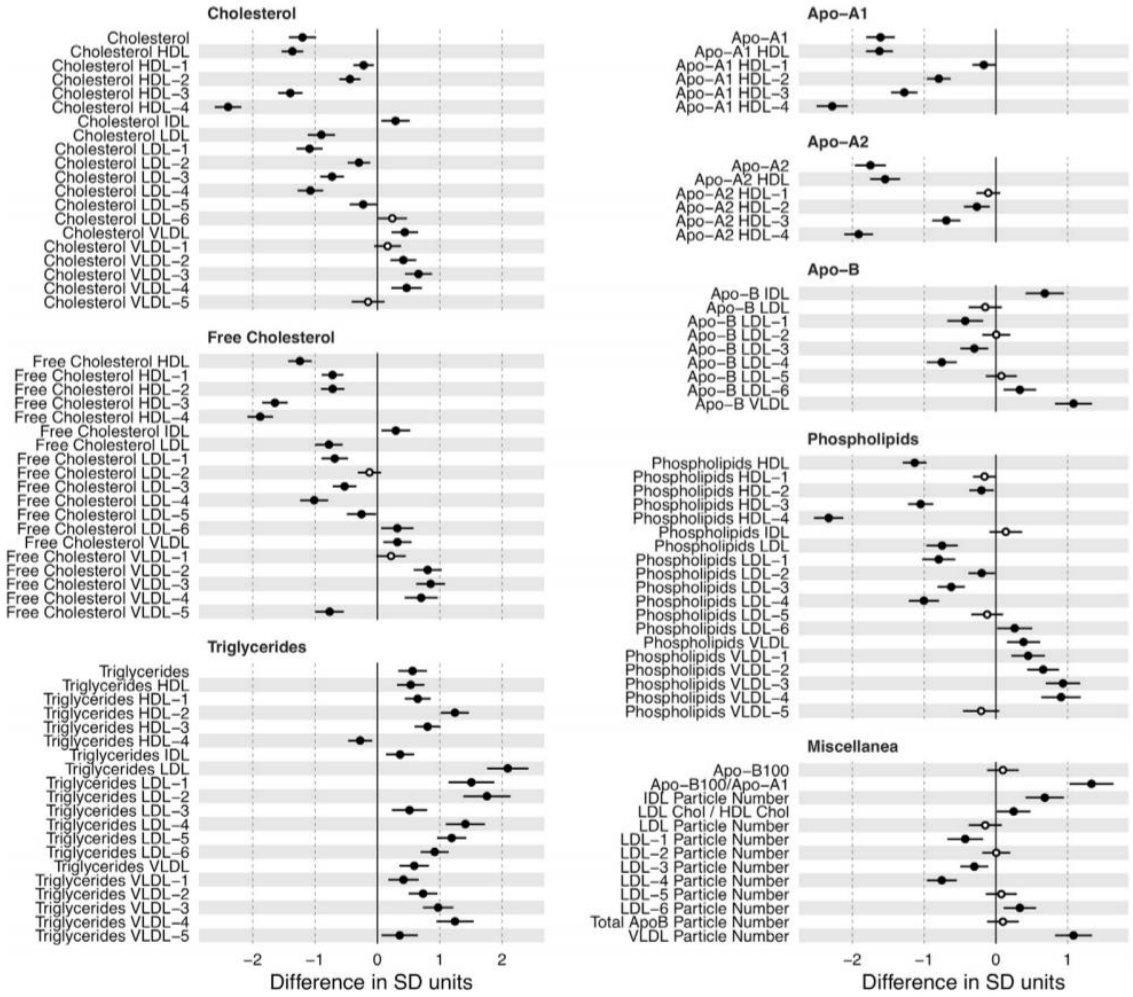


Figure 3: Average Effect of COVID-19 for Each Lipoprotein Subclass Horizontal axis is the number of standard deviations that a variable is on average increased (or decreased) when an individual is positive for COVID-19. Circles are positioned in the specific mean increase (decrease) value, whereas horizontal black bars are the 95% confidence interval. Statistically significant differences (p value < 0.05) are represented with filled circles.

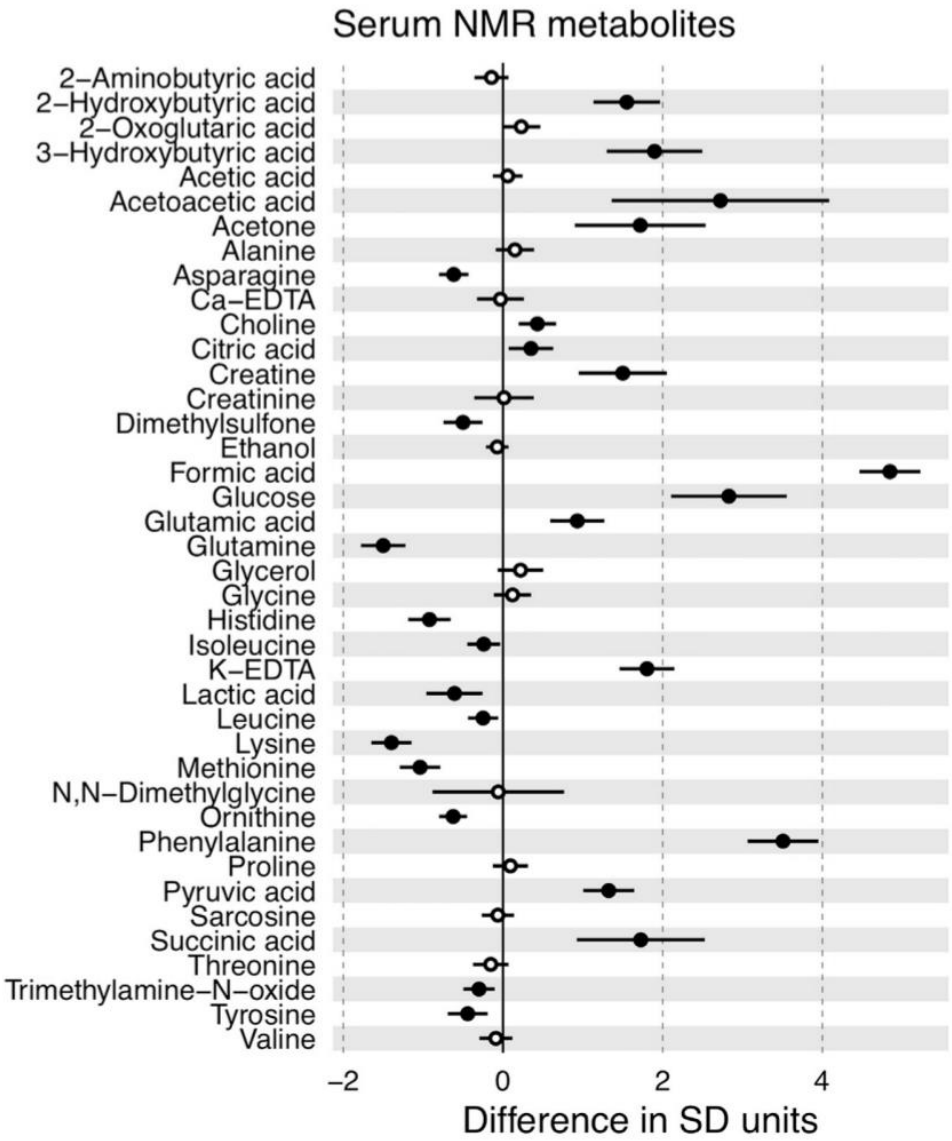


Figure 4: Average Effect of COVID-19 for Each Metabolite Horizontal axis is the number of standard deviations that a variable is on average increased (or decreased) when an individual is positive for COVID-19. Circles are positioned in the specific mean increase (decrease) value, whereas horizontal black bars are the 95% confidence interval. Statistically significant differences (p value < 0.05) are represented with filled circles.

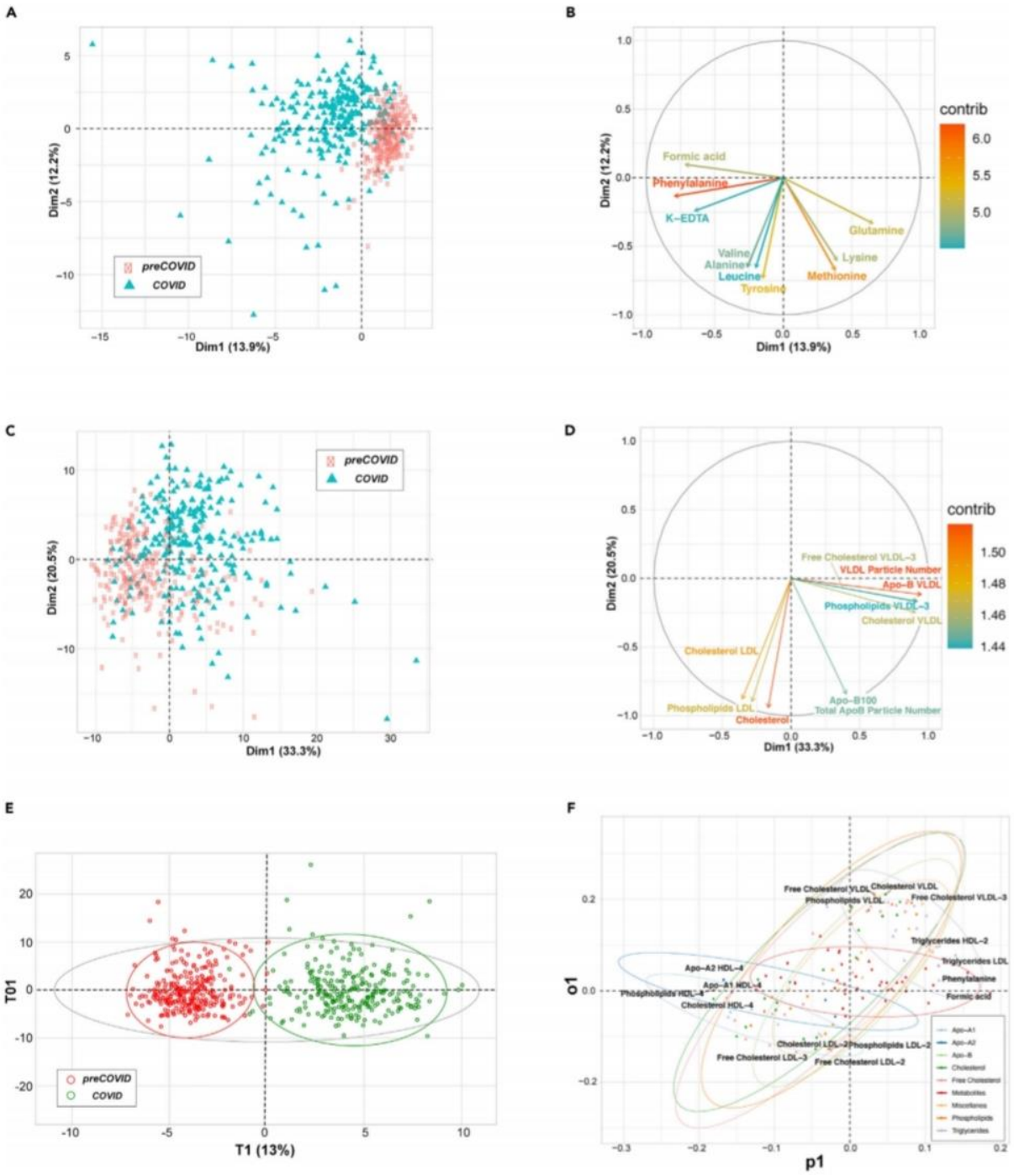


Figure 2: Summary of Multivariate Unsupervised (PCA) and Supervised (OPLS-DA) Analyses (A and C) Score plots representing first two principal components from PCA of serum metabolites (A) and lipoprotein subclasses (C), colored by cohort. Each axis indicates the percentage of total variability explained by the component. (B and D) Loading plots from serum metabolites PCA (B) and lipoprotein subclasses PCA (D). They show the top 10 variables with the highest contribution to the first two PCA components. Their direction indicates how their weight is distributed in both components, and the color is the percentage of contribution. (E) Score plot from OPLS-DA between COVID (green) and preCOVID (red) cohorts, using the full list of metabolites and lipoprotein subclasses. The plot shows the main component versus the first orthogonal component. (F) Loading plot from the previous OPLS-DA. Each type of variable (metabolites or the lipoprotein subclasses) is represented with different colors. For each type, ellipses surround the area that includes 95% of their members. For each direction, the four variables that most contribute to the component are labeled.

## COVID-19, VARYING GENETIC RESISTANCE TO VIRAL DISEASE, AND IMMUNE TOLERANCE CHECKPOINTS

Goodnow CC.. Immunol Cell Biol. 2020 Oct 28. doi: 10.1111/imcb.12419. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

### BLUF

A literature review, written by an immunology researcher from the Garvan Institute of Medical Research (Australia), discusses strategies that can be utilized to overcome zoonotic viruses and specifically SARS-CoV-2. The author writes that knowledge of genetic differences that lead to viable pathology and responses to zoonotic viruses such as SARS-CoV-2 — including differential presence of viral receptors on host cells, differences in innate and adaptive immune response, and different viral load tolerance thresholds in B and T lymphocyte populations — will be crucial to combatting this and other zoonotic viruses. Since alternating levels of pathology increase transmission and decrease predictability of response to treatment, knowledge of these differences between individuals will allow laboratory scientists to develop methods to decrease transmission and give clinicians a better understanding of how to manage immune responses to infection.

### ABSTRACT

COVID-19 is a zoonosis like most of the great plagues sculpting human history, from smallpox to pandemic influenza and human immunodeficiency virus. When viruses jump into a new species the outcome of infection ranges from asymptomatic to lethal, historically ascribed to "genetic resistance to viral disease". People have exploited these differences for good and bad, for developing vaccines from cowpox and horsepox virus, controlling rabbit plagues with myxoma virus, and introducing smallpox during colonisation of America and Australia. Differences in resistance to viral disease are at the core of the SARS-CoV-2 crisis, yet our understanding of the mechanisms in any interspecies leap falls short of the mark. Here I review how the two key parameters of viral disease are countered by fundamentally different genetic mechanisms for resistance: 1. virus transmission, countered primarily by activation of innate and adaptive immune responses; and 2. pathology, countered primarily by tolerance checkpoints to limit innate and adaptive immune responses. I discuss tolerance thresholds and the role of CD8 T cells to limit pathological immune responses, the problems posed by tolerant superspreaders, and the signature coronavirus evasion strategy of eliciting only short-lived neutralising antibody responses. Pinpointing and targeting the mechanisms responsible for varying pathology and short-lived antibody was beyond reach in previous zoonoses, but this time we are armed with genomic technologies and more knowledge of immune checkpoint genes. These known unknowns must now be tackled to solve the current COVID-19 crisis and the inevitable zoonoses to follow.

## CARDIAC INVOLVEMENT AFTER RECOVERING FROM COVID-19

Filippetti L, Pace N, Marie PY.. JAMA Cardiol. 2020 Oct 28. doi: 10.1001/jamacardio.2020.5279. Online ahead of print.
Level of Evidence: Other - Expert Opinion

### BLUF

Cardiologists and Nuclear Medicine physicians from Nancy, France respond to Puntmann et al. (2020) and argue against their findings of a moderate increase in myocardial T1 and T2 among a cohort of COVID-19 patients suggesting potential long-term persistence of myocardial inflammation. This editorial suggests that an increase in myocardial T1 and T2 is "not specific to inflammation and may relate to a noninflammatory edema." The authors call for future longitudinal studies to investigate the mechanism underpinning cardiac tissue damage related to COVID-19.

# DISCHARGE MAY NOT BE THE END OF TREATMENT: PAY ATTENTION TO PULMONARY FIBROSIS CAUSED BY SEVERE COVID-19

Zhang C, Wu Z, Li JW, Tan K, Yang W, Zhao H, Wang GQ.. J Med Virol. 2020 Oct 27. doi: 10.1002/jmv.26634. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

## BLUF

A literature review, conducted by a group affiliated with Peking University First Hospital (China), proposes a mechanism of pulmonary fibrosis linked to COVID-19 (Figure 1) and suggests treatments for ongoing pulmonary fibrosis after severe COVID-19. The authors speculate that repeated cycles of damage and repair during COVID-19 may stimulate the TGF-β (Figure 2), WNT, and YAP/TAZ pro-inflammatory signal pathways excessively, leading to fibrosis. Currently, the only FDA-approved treatments for pulmonary fibrosis are Pirfenidone and Nintedanib, two anti-inflammatory and anti-fibrosis drugs, although further anti-pulmonary fibrosis drug trials are ongoing.

## ABSTRACT

Since December 2019, COVID-19 has rapidly swept the world. So far, more than 30 million people have been infected and nearly one million have died. Although the world is still in the stage of COVID-19 pandemic, the treatment of new cases and critically ill patients is the focus of the current work. However, COVID-19 patients lead to pulmonary fibrosis, such a serious threat to the prognosis of complications were also worthy of our attention. First of all, we proposed the possible mechanism of pulmonary fibrosis caused by SARS-CoV-2, based on the published data of COVID-19 ((1)Direct evidence: pulmonary fibrosis was found in autopsy and pulmonary puncture pathology.(2)Indirect evidence: increased levels of fibrosis-related cytokines[TGF- beta, TNF- alpha, IL-6, etc.] in peripheral blood of severe patients.). What's more, we summarized the role of three fibrosis-related signaling pathways (TGF- beta signal pathway, WNT signal pathway and YAP/TAZ signal pathway) in pulmonary fibrosis. Finally, we suggested the therapeutic value of two drugs (Pirfenidone and Nintedanib) for idiopathic pulmonary fibrosis in COVID-19-induced pulmonary fibrosis. This article is protected by copyright. All rights reserved.

## FIGURES

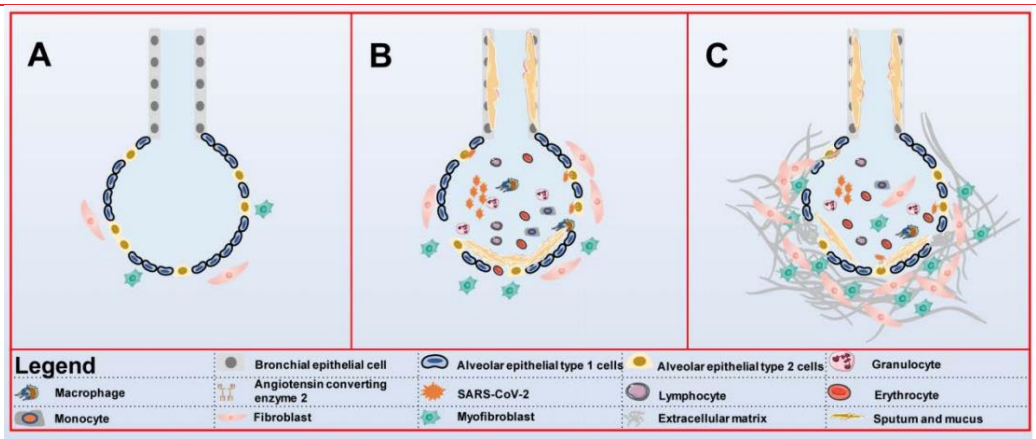


Figure 1 Pathological pattern of pulmonary fibrosis caused by COVID-19. (A) In normal alveolar tissue, there were little fibroblasts and myofibroblasts in the pulmonary interstitial. (B) In the acute stage of COVID-19 infection, the SARS-CoV-2 bound to type II alveolar epithelial cells, resulting in the infiltration of a large number of inflammatory cells (such as granulocytes, macrophages, lymphocytes, etc.) in the lung tissue, and the integrity of the alveoli was destroyed. The terminal bronchioles and alveolar cavity were filled with mucus and pulmonary interstitial edema. At the same time, alveolar regeneration and repair was initiated, fibroblasts and myofibroblasts began to differentiate, and the fibrosis process began. (C) In the convalescent period of COVID-19 infection, with the progress of the disease, the pulmonary inflammation gradually alleviated, but the repair and regeneration of the injured alveoli continued. Fibrous connective tissue continues to proliferate, and with the accumulation of more and more extracellular matrix, SARS-CoV-2-induced secondary pulmonary fibrosis was progressively aggravated.

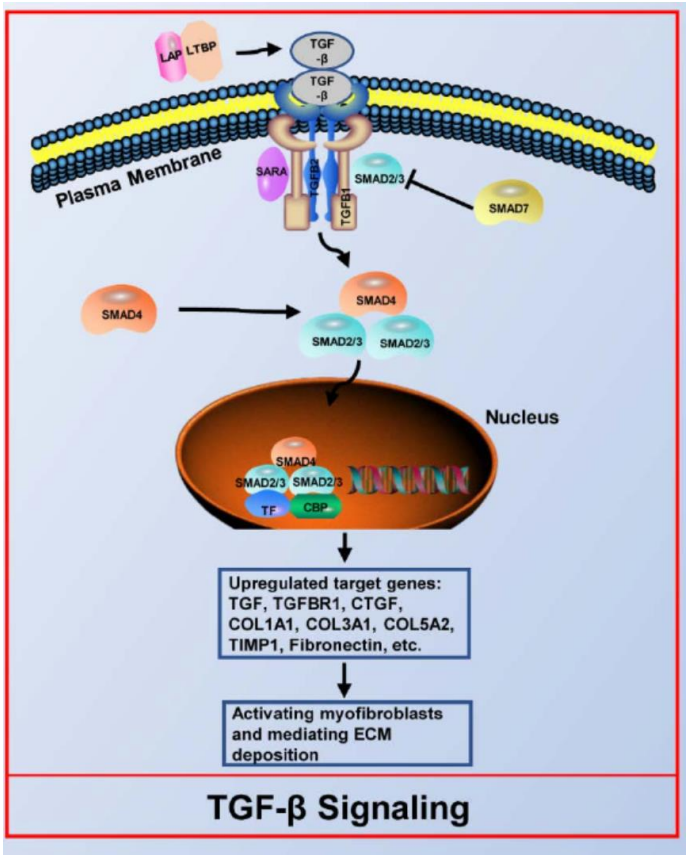


Figure 2 TGF-B signaling in pulmonary fibrosis. Under the stimulation of inflammation or other harmful factors, firstly, TGF-B dissociates from the LAP/LTBP complex and binds to the TGFB2 on the cell membrane. After TGFB2 is phosphorylated, it forms a heterotrimeric complex with TGFB1 and SARA. Secondly, SMAD4 combines with phosphorylated SMAD2/3 to form an active heterotrimer complex. Finally, the activated SMAD2/3/4 complex enters the nucleus and forms a transcription module with TF and CBP to promote the transcription of target genes.

Abbreviation: TGF-B: transforming growth factor - beta; LAP: latency-associated peptides; LTBP: latent TGF-B-binding proteins; TGFB1: type I receptors of TGF-B; TGFB2: type II receptors of TGF-B; TF: transcription factors; CBP: CREB binding protein

# IN VITRO

## NEUTRALIZING AND BINDING ACTIVITIES AGAINST SARS-COV-1/2, MERS-COV, AND HUMAN CORONAVIRUSES 229E AND OC43 BY NORMAL HUMAN INTRAVENOUS IMMUNOGLOBULIN DERIVED FROM HEALTHY DONORS IN JAPAN

Kubota-Koketsu R, Terada Y, Yunoki M, Sasaki T, Nakayama EE, Kamitani W, Shioda T.. Transfusion. 2020 Oct 26. doi: 10.1111/trf.16161. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

### BLUF

Japanese microbiologists assessed the binding activity of normal-intravenous immunoglobulin (N-IVIG) manufactured prior to the COVID-19 pandemic (2000-2018) against human coronaviruses by indirect immunofluorescence assay. They observed no neutralizing or binding activities against either SARS-CoV-1/2 or MERS-CoV, weak neutralization against HCoV229E, and substantial neutralizing and binding activity against HCoV OC43 (Table 1). Authors suggest pre-COVID N-IVIG may not be an effective treatment for SARS-CoV-2 induced inflammation and cellular immune response, and they advocate for further research to determine usefulness of N-IVIG in COVID-19 patient management.

## ABSTRACT

BACKGROUND: There are several types of coronaviruses that infect humans and cause disease. The latest is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is an emerging global threat with no current effective treatment. Normal intravenous immunoglobulin (N-IVIG) has been administered to coronavirus disease 2019 (COVID-19) patients to control severe inflammation and the cellular immune response. However, the neutralizing activity of N-IVIG against SARS-CoV-2 has not yet been fully evaluated. The aim of this study was to determine whether N-IVIG manufactured before the start of the COVID-19 pandemic contained IgG antibodies against the circulating human coronaviruses (HCoVs) that cross-react with the highly pathogenic coronaviruses SARS-CoV-1, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2. No cases of SARS-CoV-1 or MERS-CoV have been reported in Japan. STUDY DESIGN AND METHODS: The neutralizing and binding activities of N-IVIG against SARS-CoV-1, MERS-CoV, SARS-CoV-2, HCoV 229E, and HCoV OC43 were evaluated. Nine N-IVIG lots manufactured between 2000 and 2018, derived from donors in Japan, were tested. Binding activity was evaluated by indirect immunofluorescence assay. RESULTS: None of the N-IVIG lots tested displayed neutralizing or binding activity against SARS-CoV-1, MERS-CoV, or SARS-CoV-2. However, they displayed substantial neutralizing and binding activity against HCoV OC43 and weak neutralizing and substantial binding activity against HCoV 229E. CONCLUSION: N-IVIG derived from healthy donors in Japan before the start of the COVID-19 pandemic had no direct effect against SARS-CoV-2. Further studies are warranted to determine the effects of N-IVIG manufactured after the start of the COVID-19 pandemic against SARS-CoV-2.

## FIGURES

| Sample | | SARS-CoV-1 | | | MERS-CoV | | | SARS-CoV-2 | | HCoV 229E | | | HCoV OC43 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Exp 1 | Exp 2 | | Exp 1 | Exp 2 | | Exp 2 | | Exp 1 | Exp 2 | | Exp 2 | |
| Lot | Manufacturing year | VN | VN | IFA | VN | VN | IFA | VN | IFA | VN | VN | IFA | VN | IFA |
| A | 2000 | <10 | <8 | <40 | <10 | <8 | <40 | <8 | <40 | <10 W | 8 | 1600 | 1280 | 12 800 |
| B | 2003 | <10 | <8 | <40 | <10 | <8 | <40 | <8 | <40 | <10 W | 8 | 1600 | 640 | 12 800 |
| C | 2006 | <10 | <8 | <40 | <10 | <8 | <40 | <8 | <40 | <10 W | 8 | 1600 | 640 | 12 800 |
| D | 2009 | <10 | <8 | <40 | <10 | <8 | <40 | <8 | <40 | <10 W | 8 | 1600 | 640 | 12 800 |
| E | 2012 | <10 | <8 | <40 | <10 | <8 | <40 | <8 | <40 | <10 W | 8 | 1600 | 1280 | 12 800 |
| F | 2015 | <10 | <8 | <40 | <10 | <8 | <40 | <8 | <40 | <10 W | 8 | 1600 | 1280 | 12 800 |
| G | 2015 | <10 | NT | NT | <10 | NT | NT | NT | NT | <10 W | NT | NT | NT | NT |
| H | 2015 | <10 | NT | NT | <10 | NT | NT | NT | NT | <10 W | NT | NT | NT | NT |
| I | 2018 | NT | <8 | <40 | NT | <8 | <40 | <8 | <40 | NT | 8 | 1600 | 1280 | 12 800 |

Abbreviations: <, no neutralizing or binding activity was observed at the minimum dilution point; Exp, experiment; NT, not tested; VN, virus neutralization assay; W, weak reactivity, namely, a mild cytopathic effect was observed at the indicated minimum dilution point.

Table 1. Neutralizing and binding activities of IVIG lots against coronavirus types.

## DEVELOPING SAFE AND EFFECTIVE COVID VACCINES - OPERATION WARP SPEED'S STRATEGY AND APPROACH

Slaoui M, Hepburn M.. N Engl J Med. 2020 Oct 29;383(18):1701-1703. doi: 10.1056/NEJMp2027405. Epub 2020 Aug 26.
Level of Evidence: 5 - Expert Opinion

### BLUF

A physician scientist associated with Operation Warp Speed (OWS - a partnership of the Department of Health and Human Services, Department of Defense, and the private sector) describes the organization's inception, purpose, and advancements made thus far (Summary). Their goal is to advance "development, manufacturing, and distribution of vaccines, therapeutics, and diagnostics" to establish control over the COVID-19 pandemic.

### SUMMARY

Important highlights:
1. The initiative set objectives of delivering ~300 million doses of the SARS-COV-2 vaccine by mid-2021.
2. They have strict criteria by which companies have to comply in order to be accepted by the OWS including:
   a. Robust preclinical data
   b. Potential to enter large phase 3 field efficacy trials by the summer of 2020
   c. Be able to deliver outcomes by late 2020-early 2021
   d. Demonstrate scalability in high yield, and use a vaccine-platform considered to be safe by OWS.
3. Currently there are "eight vaccines in OWS's portfolio which include "Moderna and Pfizer/BioNTech (both mRNA), AstraZeneca and Janssen (both replication-defective live-vector), and Novavax and Sanofi/GSK (both recombinant-subunit-adjuvanted protein)

# CRITICAL CARE

## FUNGEMIA IN COVID -19 ICU PATIENTS, A SINGLE MEDICAL CENTER EXPERIENCE

Bishburg E, Okoh A, Nagarakanti SR, Lindner M, Migliore C, Patel P.. J Med Virol. 2020 Oct 27. doi: 10.1002/jmv.26633. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

### BLUF

Infectious Disease specialists at Newark Beth Israel Medical Center conducted a case control study from March 10th-April 10th 2020, and found that among 89 COVID-19 adults admitted to the ICU, 8.9% (n=8) developed nosocomial candidemia over an average ICU stay of 25 days (Table 1, 2). Compared to control, they found that COVID-19 ICU patients with higher BMI, prolonged mechanical ventilation and superimposed bacterial infections were associated with concomitant candidemia, but in-hospital mortality was not significantly changed. Authors suggest that providers be aware of systemic fungal infections as a potential complication in COVID-19 ICU patients.

### ABSTRACT

A known proportion of patients who are admitted for the novel coronavirus disease 2019 (COVID-19) requires Intensive Care Unit (ICU) level of care. Prolonged ICU stay is a risk factor for the development of nosocomial candidemia. The current study aimed to investigate the incidence and risk factors associated with the development of nosocomial candidemia among patients admitted to the ICU for COVID-19. Patients who developed nosocomial candidemia were identified, and their clinical course was reported. A 1:3 case control matching was used to identify non-candidemia patients who served as controls. 89 patients were admitted to the ICU for COVID-19 during the study period. The incidence of nosocomial candidemia was 8.9% (n=8). Case-control matching identified 24 patients with similar disease severity at the time of ICU admission. Median time to first isolation of yeast was 26 days. Candidemia patients reported longer median ICU stay than controls. (40 vs. 10 days, p=0.004). In hospital death rates were comparable in both groups (38% vs. 54%, p=0.548). Prolonged mechanical ventilation support was associated with the development of nosocomial candidemia. 

**Table 1: Clinical characteristics, microbiological features, and treatment modalities of COVID-19 patients with candidemia**

| Variable | Distribution (n=8) |
|---|---|
| Age (yrs.) | 63 (44, 73) |
| Sex (M/F) | 4/4 |
| Candida Species | |
| *Tropicalis* | 2 (25) |
| *Albicans* | 2 (25) |
| *Glabrata* | 2 (25) |
| *Parapsilosis* | 2 (25) |
| Time to first Isolate from admission (days) | 26 (21, 35) |
| Treatment | |
| Caspofungin + Diflucan | 4 (50) |
| Diflucan alone | 3 (38) |
| Caspofungin alone | 1 (12) |
| Other Treatment | |
| Antibiotics* | 8 (100) |
| Steroids | 8 (100) |
| Tocilizumab | 4 (50) |

Antibiotics: Azithromycin, Ampicillin, Doxycycline, Cefepime, Vancomycin, Flagyl

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| | | | |
|---|---|---|---|
| CPK | 448 (115, 790) | 250 (93, 1047) | 0.564 |
| Fibrinogen | 616 (390, 700) | 483 (445, 576) | 0.523 |
| Treatment | | | |
| Other Treatment | | | |
| Antibiotics* | 8 (100) | 14 (58) | 0.004 |
| Steroids | 8 (100) | 7 (29) | 0.001 |
| Tocilizumab | 4 (50) | 10 (42) | 0.353 |
| Pre-ICU Stay (days) | 3 (1, 5) | 2 (0, 5) | 0.738 |
| Total ICU Stay | 40 (22, 50) | 10 (4, 19) | 0.004 |
| Mechanical Ventilation (days) | 38 (20, 47) | 7 (2, 16) | 0.006 |
| Superimposed Infection | 6 (75) | 6 (27) | 0.018 |
| In-hospital mortality | 3 (38) | 13 (54) | 0.548 |

BMI: Body mass index; SOFA: Sequential organ failure assessment; WBC: White Blood Cell; LDH: Lactate Dehydrogenase; CPK: Creatinine Phosphokinase; LOS: Length of stay; ICU: Intensive Care Unit; Antibiotics: Azithromycin, Ampicillin, Doxycycline, Cefepime, Vancomycin, Flagyl

Table 2 continued.

# DERMATOLOGY

## "MASK TINEA": TINEA FACIEI POSSIBLY POTENTIATED BY PROLONGED MASK USAGE DURING THE COVID-19 PANDEMIC

Agarwal A, Hassanandani T, Das A, Panda M, Chakravorty S.. Clin Exp Dermatol. 2020 Oct 24. doi: 10.1111/ced.14491. Online ahead of print.
Level of Evidence: 4 - Case-series

### BLUF

Investigators within dermatology and microbiology describe 7 cases in India of tinea faciei infection with facial lesions associated with mask covered areas (Table 1, Figure 1). The lesions presented after mask use with average duration of mask-wearing of 6-7 hours daily and re-using unwashed masks for about 6-7 days. Further, 5 patients had tinea lesions elsewhere on the body prior to the facial lesions, and 4 patients reported tinea infections within the family with 3 of these patients using masks worn by other family members. Based on these observations, the authors suggest that dermatologists should be aware of "mask tinea" within their patients and should also educate their patients on proper mask hygiene and use.

### ABSTRACT

The COVID-19 pandemic emerged when India was already facing an epidemic-like situation of superficial dermatophytosis (tinea). The prevalence of tinea in India is currently 27.6%, with tinea faciei accounting for 1.8% cases.1 The use of face masks although necessary, has the potential to aggravate a worrisome situation in India.

### FIGURES

| | Age/Sex | Fungal culture | Location of tinea on face | Mean duration of mask use per day | Tinea lesions elsewhere in the body | Mean duration between washing masks | Family history of tinea | Sharing of mask among family members | Concurrent disease and medication |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 50/Male | T.rubrum | Above left nasolabial fold | 8-10 hours | Tinea corporis ,cruris and T.unguium( toe) | 7 days | Yes | No | Type 2 DM on Insulin(Uncontr olled) |
| 2 | 35/female | T.rubrum | Neck region | 6 hours | No | 7 days | Yes | Yes | Type 2 diabetes mellitus on Metformin(con trolled) |
| 3 | 30/Male | T.Mentagro phytes | Right cheek | 8 hours | Tinea cruris | 3-4 days | No | No | - |
| 4 | 40/Female | T.Mentagro phytes | Left cheek | 6-8 hours | No | 5 days | Yes | Yes | Type 2 Diabetes mellitus on metformin(Con trolled) |
| 5 | 25/Male | T.Mentagro phytes | Left cheek | 8-10 hours | Tinea cruris, corporis and T.unguium( finger) | 5-7days | Yes | Yes | - |
| 6 | 43/Male | T.rubrum | Right cheek | 6-8hours | Tinea cruris | 10days | No | No | - |
| 7 | 18/Female | T.Mentagrp hytes | Right cheek | 6 hours | Tinea cruris | 7 days | No | No | - |

Table 1. Characteristics of patients presenting with mask tinea

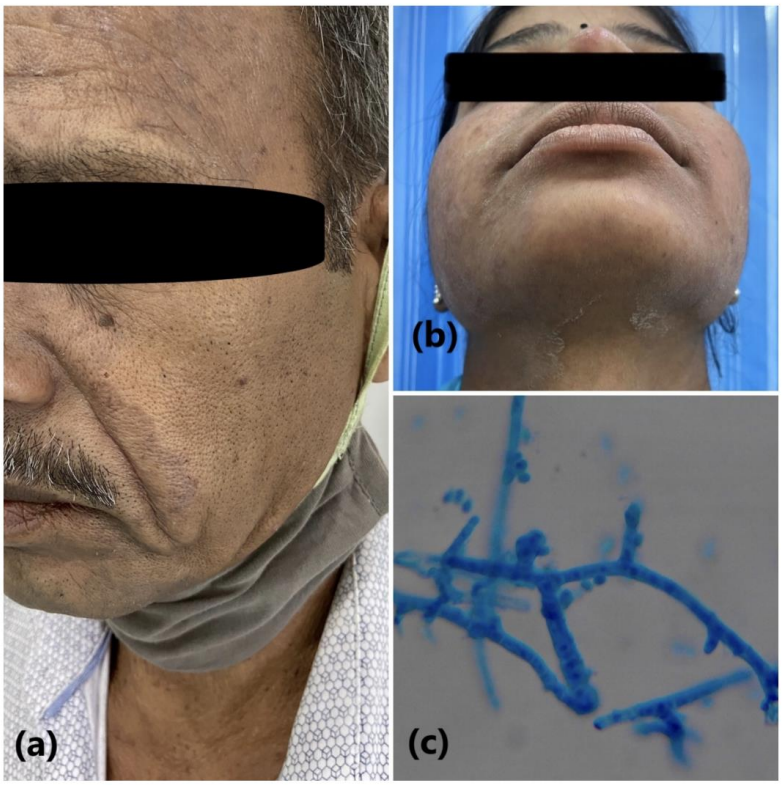


Figure 1(a) Tinea faciei in form of serpiginous plaque localised above left nasolabial fold (Patient 1) 1(b) Tinea faciei in form of scaly plaque with a defined margin seen in neck region (Patient 2) 1(c) Lactophenol cotton blue mount showing tear drop microconidia consistent with Trichophyton rubrum (Patient 1)

# PEDIATRICS

## PEDIATRIC STROKE ASSOCIATED WITH A SEDENTARY LIFESTYLE DURING THE SARS-COV-2 (COVID-19) PANDEMIC: A CASE REPORT ON A 17-YEAR-OLD

Lam K, Lee JH, Cheng P, Ajani Z, Salem MM, Sangha N.. Neurol Sci. 2020 Oct 28. doi: 10.1007/s10072-020-04857-w. Online ahead of print.
Level of Evidence: Other - Case Report

### BLUF

Investigators within neurology and pediatric cardiology at Los Angeles Medical Center describe a 17-year-old boy who presented with ischemic stroke in the anterior medial left thalamus (Figure 1), with affiliated symptoms improving over 2 days and subsequent discharge on daily aspirin. The patient had no significant past medical history, but his parents reported that he sat for about 10 hours daily playing video games. Based on this case, the authors suggest that increased sedentary activities during the COVID-19 pandemic possibly can increase stroke risk among the pediatric population.

### ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic-associated quarantine has led to a more sedentary lifestyle in teenagers. This may increase the risk for venous thromboembolism and a subsequent source of an ischemic stroke through a patent foramen ovale (PFO). Here, we report a pediatric stroke case likely due to these factors.

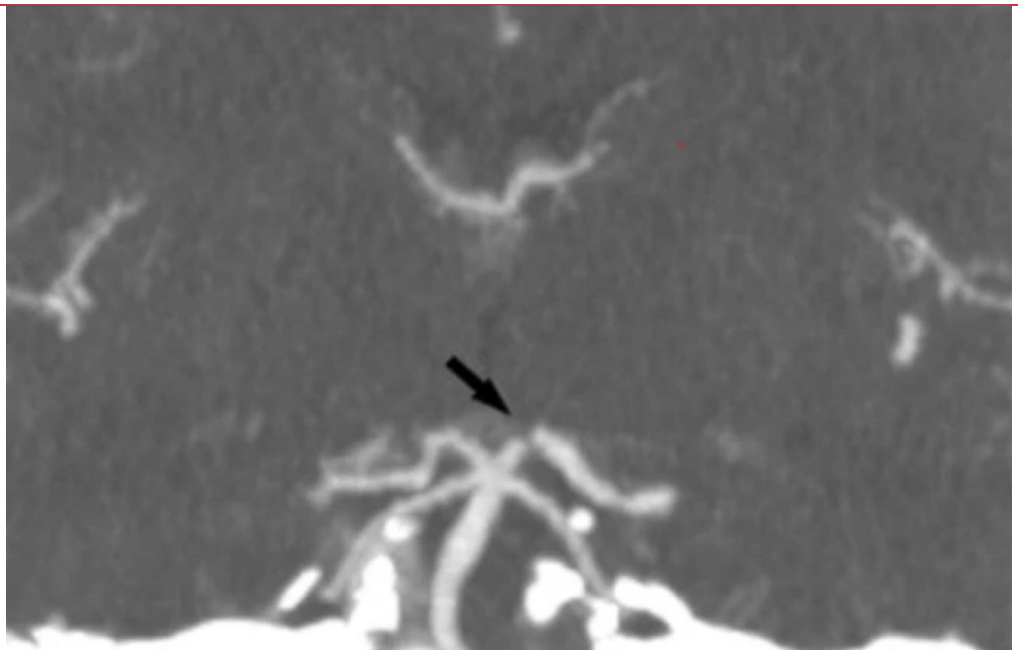

Figure 1. Filling defect in the left P1 segment

## SARS-COV-2 NEUTRALIZING ANTIBODY LY-COV555 IN OUTPATIENTS WITH COVID-19

Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Adams AC, Van Naarden J, Custer KL, Shen L, Durante M, Oakley G, Schade AE, Sabo J, Patel DR, Klekotka P, Skovronsky DM; BLAZE-1 Investigators.. N Engl J Med. 2020 Oct 28. doi: 10.1056/NEJMoa2029849. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

### BLUF

A randomized, double-blind, controlled trial analyzed the efficacy and safety of LY-CoV555, an antispike neutralizing monoclonal antibody, during its stage 2 phase from June 17 through August 21, 2020. The investigators examined the antibody's effect on viral load, symptom scores, and clinical outcome of 452 patients across 41 centers in the United States receiving one of three doses (700 mg, 2800 mg, or 7000 mg) or a placebo (Figure 1). Although the authors acknowledge the need for further studies, the trial so far indicates possible reduction in symptom severity and a reduction in viral load with higher doses of LY-CoV555 (Figure 2) suggesting that LY-CoV555 could become a useful treatment for patients with a recent diagnosis of COVID-19.

### ABSTRACT

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (Covid-19), which is most frequently mild yet can be severe and life-threatening. Virus-neutralizing monoclonal antibodies are predicted to reduce viral load, ameliorate symptoms, and prevent hospitalization. METHODS: In this ongoing phase 2 trial involving outpatients with recently diagnosed mild or moderate Covid-19, we randomly assigned 452 patients to receive a single intravenous infusion of neutralizing antibody LY-CoV555 in one of three doses (700 mg, 2800 mg, or 7000 mg) or placebo and evaluated the quantitative virologic end points and clinical outcomes. The primary outcome was the change from baseline in the viral load at day 11. The results of a preplanned interim analysis as of September 5, 2020, are reported here. RESULTS: At the time of the interim analysis, the observed mean decrease from baseline in the log viral load for the entire population was -3.81, for an elimination of more than 99.97% of viral RNA. For patients who received the 2800-mg dose of LY-CoV555, the difference from placebo in the decrease from baseline was -0.53 (95% confidence interval [CI], -0.98 to -0.08; P = 0.02), for a viral load that was lower by a factor of 3.4. Smaller differences from placebo in the change from baseline were observed among the patients who received the 700-mg dose (-0.20; 95% CI, -0.66 to 0.25; P = 0.38) or the 7000-mg dose (0.09; 95% CI, -0.37 to 0.55; P = 0.70). On days 2 to 6, the patients who received LY-CoV555 had a slightly lower severity of symptoms than those who received placebo. The percentage of patients who had a Covid-19-related hospitalization or visit to an emergency department was 1.6% in the LY-CoV555 group and 6.3% in the placebo group. CONCLUSIONS: In this interim analysis of a phase 2 trial, one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11. (Funded by Eli Lilly; BLAZE-1 ClinicalTrials.gov number, NCT04427501.).

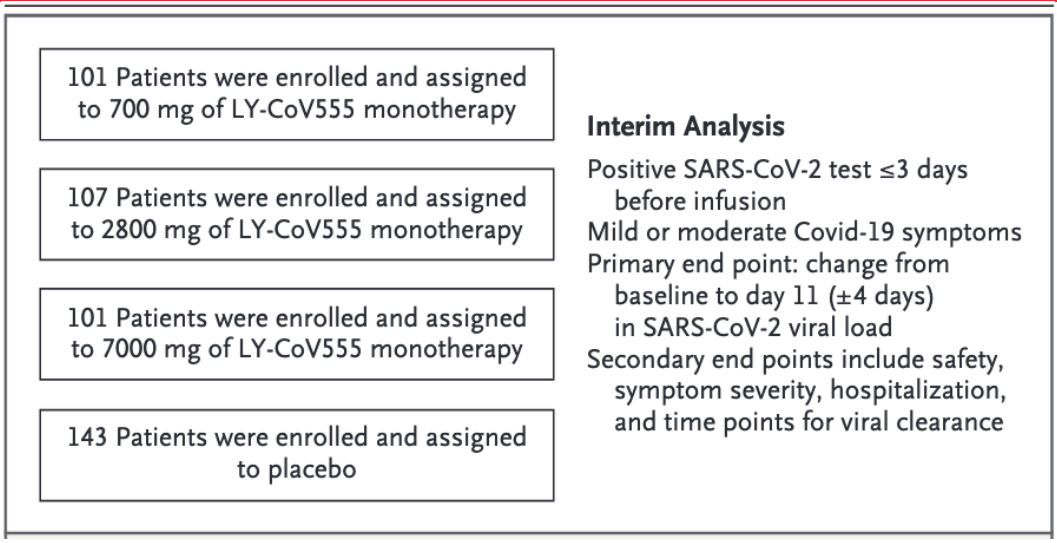


Figure 1. Enrollment and Trial Design.

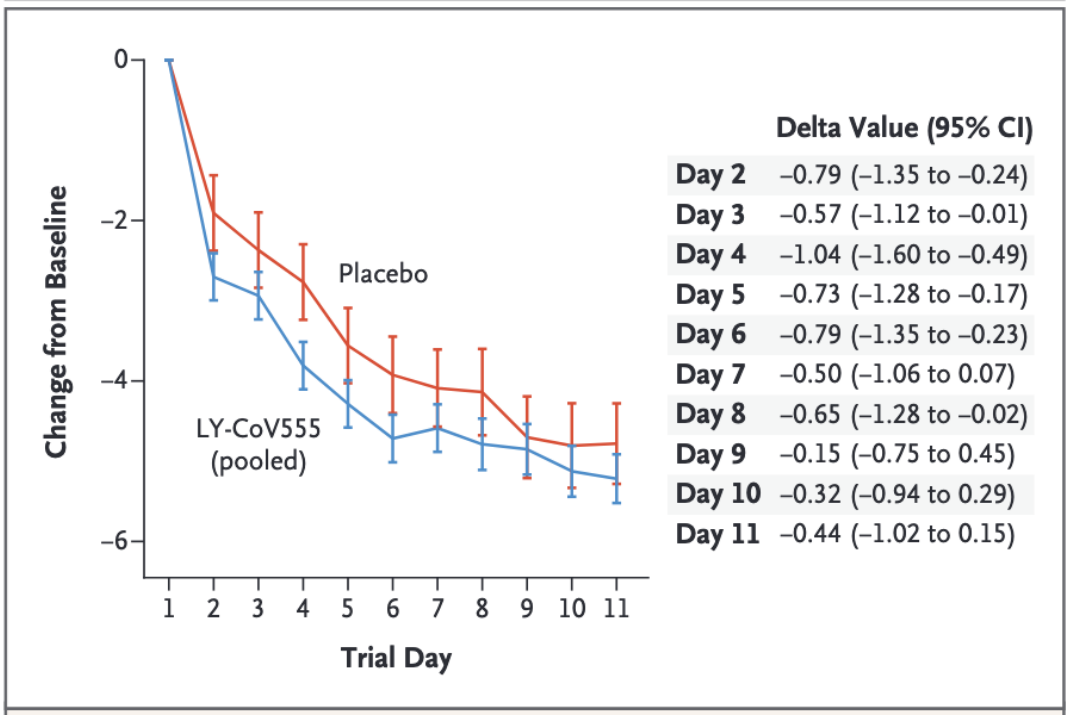


Figure 2. Symptom Scores from Day 2 to Day 11.Shown is the difference in the change from baseline (delta value) in symptom scores between the LY-CoV555 group and the placebo group from day 2 to day 11. The symptom scores ranged from 0 to 24 and included eight domains, each of which was graded on a scale of 0 (no symptoms) to 3 (severe symptoms). The I bars represent 95% confidence intervals. Details about the symptom-scoring methods are provided in the Supplementary Appendix.

# MENTAL HEALTH & RESILIENCE NEEDS

## RISK AND PROTECTIVE FACTORS FOR PROSPECTIVE CHANGES IN ADOLESCENT MENTAL HEALTH DURING THE COVID-19 PANDEMIC

Magson NR, Freeman JYA, Rapee RM, Richardson CE, Oar EL, Fardouly J.. J Youth Adolesc. 2020 Oct 27. doi: 10.1007/s10964-020-01332-9. Online ahead of print.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

### BLUF

Psychologists surveyed 248 adolescents in the urban areas of New South Wales, Australia to examine the changes in their mental health due to the COVID-19 pandemic (Summary). Findings show that adolescents have increased anxiety and depressive symptoms, and decreased life satisfaction due to the governmental restrictions posed to control viral spread. The authors suggest a call for action to increase close monitoring of these adolescents and find ways to support and maintain social engagements for them.

### SUMMARY

The sample population of adolescents are from a part of the larger longitudinal Risk to Adolescent Wellbeing Project and have been completing surveys every year for the past four years. The factors examined in this mental health survey included generalized anxiety, depressive symptoms, life satisfaction, COVID-19 related stress, disruptions to schooling, media exposure, interpersonal conflict, social connectedness, and adherence to COVID-19 Australian government stay-at-home directive. From these surveys, the authors note that the mental health of adolescents had slightly deteriorated, possibly due to the restrictions posed on these adolescents to control the viral spread instead of the virus itself. Thus, the researchers suggest the need for closer monitoring of these adolescents and finding ways to support and maintain social engagements for them.

### ABSTRACT

The restrictions put in place to contain the COVID-19 virus have led to widespread social isolation, impacting mental health worldwide. These restrictions may be particularly difficult for adolescents, who rely heavily on their peer connections for emotional support. However, there has been no longitudinal research examining the psychological impact of the COVID-19 pandemic among adolescents. This study addresses this gap by investigating the impact of the COVID-19 pandemic on adolescents' mental health, and moderators of change, as well as assessing the factors perceived as causing the most distress. Two hundred and forty eight adolescents (Mage = 14.4; 51% girls; 81.8% Caucasian) were surveyed over two time points; in the 12 months leading up to the COVID-19 outbreak (T1), and again two months following the implementation of government restrictions and online learning (T2). Online surveys assessed depressive symptoms, anxiety, and life satisfaction at T1 and T2, and participants' schooling, peer and family relationships, social connection, media exposure, COVID-19 related stress, and adherence to government stay-at-home directives at T2 only. In line with predictions, adolescents experienced significant increases in depressive symptoms and anxiety, and a significant decrease in life satisfaction from T1 to T2, which was particularly pronounced among girls. Moderation analyses revealed that COVID-19 related worries, online learning difficulties, and increased conflict with parents predicted increases in mental health problems from T1 to T2, whereas adherence to stay-at-home orders and feeling socially connected during the COVID-19 lockdown protected against poor mental health. This study provides initial longitudinal evidence for the decline of adolescent's mental health during the COVID-19 pandemic. The results suggest that adolescents are more concerned about the government restrictions designed to contain the spread of the virus, than the virus itself, and that those concerns are associated with increased anxiety and depressive symptoms, and decreased life satisfaction.

## MEDICINE AND GRIEF DURING THE COVID-19 ERA: THE ART OF LOSING

Maitra A.. JAMA Intern Med. 2020 Oct 26. doi: 10.1001/jamainternmed.2020.5635. Online ahead of print.
Level of Evidence: Other - Opinion

### BLUF

An internal medicine physician associated with Harvard Medical School in Cambridge, Massachusetts reflects on her personal experience dealing with loss during the COVID-19 pandemic. She narrates her hardship of moving across the world, finding solace in medicine, and grieving her grandparents' deaths virtually from a distance. She concludes that the impact of grief and loss may manifest in unexpected ways and encourages others to positively reflect on them.

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