The Daily COVID-19 Literature Surveillance Summary

April 19, 2021

DISCLAIMER

This free and open source document represents a good faith effort to provide real time, distilled information for guiding best practices during the COVID-19 pandemic. This document is not intended to and cannot replace the original source documents and clinical decision making. These sources are explicitly cited for purposes of reference but do not imply endorsement, approval or validation.

This is not an official product or endorsement from the institutions affiliated with the authors, nor do the ideas and opinions described within this document represent the authors' or their affiliated institutions' values, opinions, ideas or beliefs. This is a good faith effort to share and disseminate accurate summaries of the current literature.

NOW LIVE!

Daily audio summaries of the literature in 10 minutes or less.
https://www.covid19lst.org/podcast/

COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

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

R&D: Diagnosis & Treatments

- There appears to be no effect of Ivermectin on time to resolution of symptoms among adults with mild COVID-19. A double-blind randomized control trial conducted at a single site in Cali, Columbia by researchers affiliated with multiple medical institutions in Columbia included 476 adult patients with mild COVID-19 disease and symptoms for ≤ 7 days between July 15 and November 30, 2020 to receive either ivermectin 300 g/kg/day (n= 200) for 5 days or placebo (n=200). The median time to resolution of symptoms was 10 days for ivermectin (IQR, 9-13) compared to 12 days in placebo group (IQR, 9-13) (Hazard ratio, 1.07 (95% CI, 0.87 to 1.32), p = 0.53), however there was no statistically significant difference between groups. Resolved symptoms were noted in 82% of ivermectin group and 79% of placebo group by Day 21. There was no significant improvement of time to resolution of symptoms with the use of ivermectin compared to placebo, thus this study does not support ivermectin use for mild COVID-19 infection, although larger studies may be necessary to determine use for other clinically relevant outcomes.

TABLE OF CONTENTS

CHANGES IN ALCOHOL USE AND DRINKING CONTEXT DUE TO THE COVID-19 PANDEMIC: A MULTIMETHOD STUDY OF COLLEGE STUDENT DRINKERS

Jackson KM, Merrill JE, Stevens AK, Hayes KL, White HR.. Alcohol Clin Exp Res. 2021 Mar 23. doi: 10.1111/acer.14574. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Two studies, including a qualitative interview study (n=18) and a quantitative survey study (n=312), conducted from March to June 2020 by behavioral researchers at Brown University and Rutgers University assessed changes in alcohol use behaviors of college students, pre and post COVID-19 campus closures and found different reasons (limitations, motives) for decreased/increased drinking patterns. Researchers recommended that assessment of students' alcohol drinking patterns is necessary for administrators and parents during the pandemic, because a decrease in social activity and disease-related stressful conditions potentially influence problematic drinking patterns and other complications.

SUMMARY

In the first study, researchers interviewed 18 heavy episodic drinker (HED) college students, reporting a decrease in quantity but an increase in frequency of drinking alcohol due to decreased access of in-person social activities (parties) and also living with parents, where heavy drinking is not acceptable.

The second study showed a general decline in alcohol use, especially a decrease in the frequency of drunkenness in heavy episodic drinkers (HED), (p-value<0.001, Table 3). The most common reason for changing behavior was reduced social opportunities and setting (89%, Table 5).

Between students that had increased in alcohol consumption frequency and quantity in heavy drinkers, after campus closure, their most common reason was seeking virtual social interactions (66%, Table 6)

ABSTRACT

BACKGROUND: In spring 2020, U.S. universities closed campuses to limit the transmission of COVID-19, resulting in an abrupt change in residence, reductions in social interaction, and in many cases, movement away from a heavy drinking culture. The present mixed-methods study explores COVID-19-related changes in college student drinking. We characterize concomitant changes in social and location drinking contexts and describe reasons attributed to changes in drinking. METHODS: We conducted two studies of the impact of the COVID-19 pandemic on drinking behavior, drinking context, and reasons for both increases and decreases in consumption among college students. Study 1 (qualitative) included 18 heavy-drinking college students (Mage = 20.2; 56% female) who completed semi-structured interviews. Study 2 (quantitative) included 312 current and former college students who reported use of alcohol and cannabis (Mage = 21.3; 62% female) and who completed an online survey. RESULTS: In both studies, COVID-19-related increases in drinking frequency were accompanied by decreases in quantity, heavy drinking, and drunkenness. Yet, in Study 2, although heavier drinkers reduced their drinking, among non-heavy drinkers several indices of consumption increased or remained stable . Both studies also provided evidence of reductions in social drinking with friends and roommates and at parties and increased drinking with family. Participants confirmed that their drinking decreased due to reduced social opportunities and/or settings, limited access to alcohol, and reasons related to health and self-discipline. Increases were attributed to greater opportunity (more time) and boredom and to a lesser extent, lower perceived risk of harm and to cope with distress. CONCLUSION: This study documents COVID-19-related changes in drinking among college student drinkers that were attributable to changes in context, particularly a shift away from heavy drinking with peers to lighter drinking with family. Given the continued threat of COVID-19, it is imperative for researchers, administrators, and parents to understand these trends as they may have lasting effects on college student drinking behaviors.

FIGURES

Table 3. Drinking Behavior at Preclosure and Postclosure in Study 2

	Full sample (n = 312)		No HED[a] (n = 144)		HED (n = 167)	
	Preclosure	Postclosure	Preclosure	Postclosure	Preclosure	Postclosure
Days drink/typical week	2.81	3.07*	2.00	2.53**	3.50	3.52 ns
# drinks/typical week	10.95	9.44**	4.03	5.42**	16.91	12.95**
Max drinks per day/typical week	4.46	3.13***	1.85	1.92 ns	6.70	4.17***
Average drinks per drinking day/typical week	3.40	2.81***	1.57	1.47 ns	4.97	2.97***
Frequency drunk[b]	3.48	2.73***	2.89	2.41***	3.93	2.98***
Beer (ref = no)	73%	78% ns	71%	79% ns	74%	77% ns
Liquor (ref = no)	87%	64%***	81%	67%**	91%	62%***
Wine (ref = no)	64%	68% ns	61%	62% ns	66%	72% ns

Significance of tests for pre–post change is indicated in asterisks: *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.
ns = not significant.
[a]The No HED group includes nondrinkers as well as non-HED drinkers. One participant had a missing value for the sex variable and was not assigned a HED status variable because it was computed based on sex.
[b]Frequency of getting drunk while drinking alcohol ranged from never (1) to every time (5).

Table 3. Drinking Behavior at Preclosure and Postclosure in Study 2

Table 5. Reasons for Decreases in Alcohol Consumption in Study 2

Reason	Decrease in Frequency (n = 125)	Decrease in Quantity (n = 148)
Context[a]	88.8%	83.8%
Reduced social opportunities[b]	88.8%	80.4%
Heavy drinking is not part of the culture where I am currently living	–[f]	23.6%
Access/opportunity[a]	36.0%	29.7%
I have limited access to alcohol	23.2%	19.6%
I don't have the time	11.2%	8.1%
Financial reasons	7.2%	8.1%
Upbringing[a]	21.6%	38.5%
Rules at home prohibit/limit drinking[c]	14.4%	16.2%
Don't want to drink in front of parents[d]	9.6%	33.8%
I have to hide my drinking	9.6%	8.1%
Don't want to drink in front of siblings[e]	8.8%	14.9%
Self-control[a]	41.6%	38.5%
I'm trying to be more disciplined about what I consume	26.4%	23.0%
I have decided to use this opportunity to drink less	22.4%	18.2%
It makes me feel out of control and there is already too much in my life that I cannot control now	5.6%	6.1%
I am drinking more frequently, so trying to drink less when I do drink	–[f]	6.1%
Risk of harm[a]	40.0%	34.5%
I'm trying to stay as healthy as possible	38.4%	33.8%
Alcohol interferes with my sleep	4.8%	4.0%

[a]Domain percentages equal percentage of all participants who endorsed any reason within that domain.
[b]Frequency: "Drinking is a social activity for me and there have been few social opportunities"; Quantity: "It feels odd to drink a lot at home/outside of a social situation
[c]Frequency: "I am not allowed to drink at home"; Quantity: "Rules at home prohibit/limit drinking"
[d]Frequency: "My parents/caregivers are not aware that I drink"; Quantity: "I don't want to be drunk in front of my parents"
[e]Frequency: "I do not want to drink in front of my siblings"; Quantity: "I do not want to be drunk in front of my siblings"
[f]No corresponding item for frequency, given the nature of the item.

Table 5. Reasons for Decreases in Alcohol Consumption in Study 2
Reason

Representative Quotes	ID, sex
Theme 1 Students' drinking frequency increased, while their drinking quantity decreased	
Instead of like drinking a lot, like multiple drinks on the weekend, I'll have like one drink per night. I'll like have a beer with dinner, instead of like 4 mixed drinks before I go to a party or like at a party – so it's definitely changed – It's been more spaced out and more low key – I definitely haven't been getting drunk.	1018, female
I'm doing more like one beer a night. … It's more casual now and less with the intention of getting drunk. More like, "I have a few beers in the fridge, so I'm going to have a beer". So it feels more distributed than the high concentration drinking nights of the semester. There is nothing really to be drinking for now I guess.	1005, male
I definitely drink a lot less now than I did before. At school, I drink as a social thing. At home, there's no reason for me to drink. Occasionally I would have a drink with my parents, but that's all the drinking I did.	1003, female
It's definitely changed my drinking habits. I still will like occasionally have something to drink but it definitely was less often. Probably on a night that I'm going out, it would be about 8 or 9 drinks, but that would be spread out over a couple of hours – some at the pregame and some at the party. Whereas now it's probably like 4 or 5.	1012, male
Theme 2: The type of alcohol students consumed changed, from hard liquor to wine and/or beer.	
I'm drinking a lot less hard alcohol and more wine and beer.	1004, female
…less hard alcohol for sure. Definitely more wine and beer. I think because normally I would drink more shots of liquor and hard alcohol at like outdoor gathering functions and because those aren't really available anymore, I just have more at home where I drink more casually, slowly, more with just like eating dinner.	1010, male
My drinking changed a little bit in terms of the type of alcohol I was using, especially since I focused more on drinking wine. I have been sort of re-evaluating my drinking and sort of seeing what kind of substitutes I can be using for the things I was doing before, and found that wine was something I really enjoyed and so I probably had a couple of glasses every day with dinner and stuff. Before, with parties and things and going out a lot more, it was beer and hard liquor were much more common, but now it's a lot less. Before, wine was more like for a personal moment or something that's only saved for special occasions and beer or liquor would be a lot more common, but I think that transition from those two types of alcohol to more so wine during dinner.	1011, male
Theme 3: A main contributor to changes in drinking behavior is a decrease in in-person social interaction and different contexts of drinking.	
I like to drink when I go out dancing and so that's definitely changed. I also think much more of my drinking at home is more like casual – I'm like making dinner and I have some wine or I'm doing homework and I have a cider. Or the other circumstance would be like being on Facetime with friends and having like a Zoom party, but I'm not. …it's much calmer and that changes. Also like the desire to be intoxicated is less. There still like is that element but because I'm alone, it's changed.	1017, female
Now with COVID-19, it's sort of been similar that I drink on the weekends, but it's a different kind of drinking because it's with a couple of friends rather than a large group or an actual party, so it's more relaxed. I have maybe 2 people over on the weekends now. …It's less as well definitely. Even if the time spans the same, I still have fewer drinks.	1007, male
As a first-year at college, I would say the large majority of my drinking is social drinking. With that limited social activity, that's not happening. That's been the limiting agent in my drinking behavior. If I do drink [now] it's with a meal. Then it's 1-2 beverages, which is not what it would be at school.	1009, male
I would say I drink a lot more at [school] just because I'm surrounded by people, like a social event where I would (a) drink more and (b) drink more heavily	1016, female
Theme 4: Another contributor to changes in drinking behavior is a change in living situation, particularly a move off campus and home with parents	
I'm not comfortable drinking around my mom at least not anything past a single glass of wine so that's definitely changed it.	1017, female
I would also drink less because there's no big incentive to drinking at home. It's also harder to get alcohol at home.	1002, female
I have relocated from my off-campus apartment to my parents' house. Only one person in my family drinks alcohol at all, so there's really not a lot of it in the house and I didn't bring any with me. … [at school] I have alcohol on hand, I have a large bottle of vodka on hand I can pour from whenever I feel like it. But here, unless I go out and buy beer for instance, there just won't be any. …Additionally, since only one person in the house drinks there is sort of a reverse social pressure. Moralizing aside, you don't want to be the only drunk person. And the one person in the house who drinks is very moderate, only one or two drinks with dinner. I would say my pattern has also shifted to more or less exclusively one or two beers with dinner.	1006, non-binary female
[My parents] are fine with drinking, but obviously like they wouldn't want me to be like super, super drunk, but they're OK with me having a couple drinks. I still see my girlfriend, and like on weekends we'll maybe have some wine or some mixed drinks or something but it's usually not very much since we have to be at one of our houses, even if our parents are asleep, they could wake up so we can't get like blasted.	1012, male

Table 6. Reasons for Increases in Alcohol Consumption in the Study 2 Sample

AFFECTING THE HEALTHCARE WORKFORCE

COVID-19 MORTALITY AND STRESS TO THE HOSPITAL SYSTEM FROM HIGH PATIENT LOAD

Soria A, Lapadula G, Bonfanti P.. JAMA Intern Med. 2021 Apr 12. doi: 10.1001/jamainternmed.2021.0599. Online ahead of print.

Level of Evidence: 5 - Expert Opinion

BLUF

A letter to the editor conducted by physician researchers affiliated with the Clinic of Infectious Disease at University of Milano-Bicocca in Italy discussed the strong association between higher prevalence of COVID-19 and increased in-hospital mortality. Lombardy, Italy had a severe COVID-19 wave after February 2020 with a sharp increase in critically ill patients requiring rapid expansion of capacity and hospital staffing, which was thus associated with poorer hospital performance and patient outcomes. Determining and evaluating variables for estimating and more accurately reflecting hospital stress in association with in-hospital mortality could provide a way to ameliorate hospital performance even in times of difficult conditions.

RAPID DETECTION OF SARS-COV-2 VARIANTS OF CONCERN, INCLUDING B.1.1.28/P.1, IN BRITISH COLUMBIA, CANADA

Matic N, Lowe CF, Ritchie G, Stefanovic A, Lawson T, Jang W, Young M, Dong W, Brumme ZL, Brumme CJ, Leung V, Romney MG.. Emerg Infect Dis. 2021 Mar 30;27(6). doi: 10.3201/eid2706.210532. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Canadian researchers screened 2,392 COVID-19 patients in St. Paul's Hospital, British Columbia through a rRT-PCR-based algorithm to detect SARS-CoV-2 variant strains. Screening found 77 people with SARS-CoV-2 variants, of whom 57 had B.1.1.7, 7 had B.1.351, and 13 had the B1.1.28/P.1 variant (Figure). They concluded that this rRT-PCR-based algorithm was a rapid method to detect SARS-CoV-2 variants of concern (VOC), allowing for proper surveillance of VOC spread in the community.

ABSTRACT

To screen all severe acute respiratory syndrome coronavirus 2-positive samples in British Columbia, Canada, and determine whether they represented variants of concern, we implemented a real-time reverse transcription PCR-based algorithm. We rapidly identified 77 samples with variants: 57 with B.1.1.7, 7 with B.1.351, and an epidemiologic cluster of 13 with B.1.1.28/P.1.

FIGURES

Figure

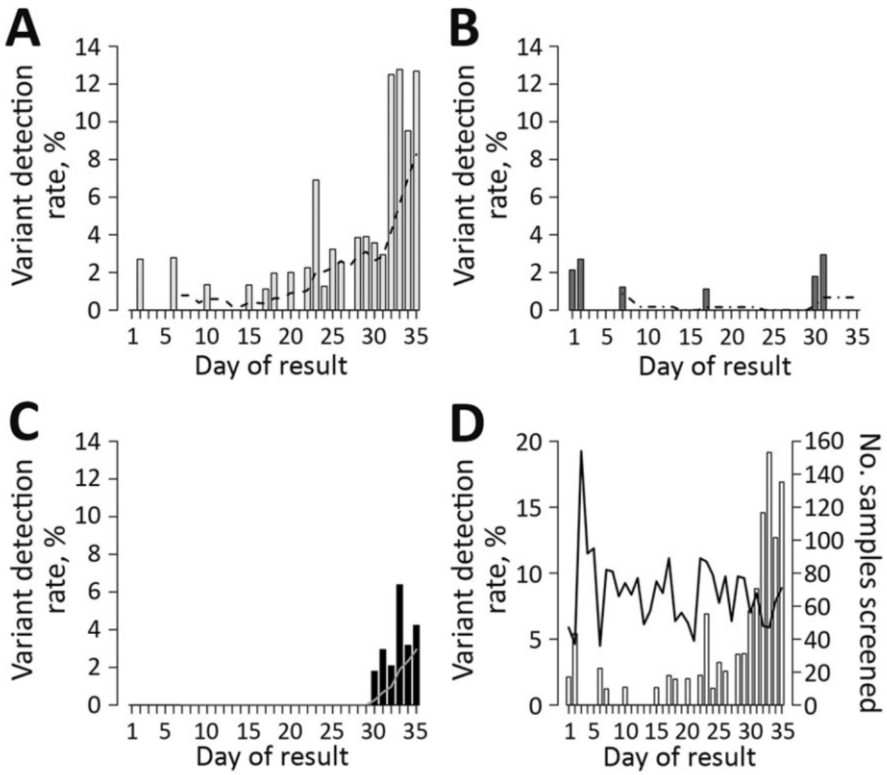


Figure. Rate of detection of severe acute respiratory syndrome coronavirus 2 variants of concern, by day of result, January 26–March 1, 2021, with 7-day moving average. A) B.1.1.7 (UK); dashed line indicates 7-day moving average. B) B.1.351 (South Africa); dashed line indicates 7-day moving average; C) B.1.1.28/P.1 (Brazil),;solid line indicates 7-day moving average; D) all variants of concern; solid line indicates number of samples screened.

Figure. Rate of detection of severe acute respiratory syndrome coronavirus 2 variants of concern, by day of result, January 26–March 1, 2021, with 7-day moving average. A) B.1.1.7 (UK); dashed line indicates 7-day moving average. B) B.1.351 (South Africa); dashed line indicates 7-day moving average; C) B.1.1.28/P.1 (Brazil),;solid line indicates 7-day moving average; D) all variants of concern; solid line indicates number of samples screened.

CRITICAL CARE

DOES A SURGICAL MASK IMPROVE OXYGENATION IN COVID-19 PATIENTS?

Matsui Y, Takazawa T, Takemae A, Saito S.. JA Clin Rep. 2021 Apr 14;7(1):34. doi: 10.1186/s40981-021-00439-7.
Level of Evidence: 5 - Case Report

BLUF

A letter to the editor conducted by researchers affiliated with the ICU at Gunma University hospital in Japan discuss how current recommendations indicate patients should receive oxygen through oxygen masks placed over a surgical mask after extubation and anesthesia to prevent spread of respiratory aerosols. They instead devised a method of oxygen delivery through nasal cannula underneath a surgical mask for maximal oxygenation that still prevents aerosolization (Figure 1). The partial pressure of oxygen (PaO2) decreased with the oxygen mask compared to nasal cannula, however pH, partial pressure of CO2, base excess, and respiratory rate were not changed (Table 1). It was also observed that there was a higher inhaled oxygen concentration when oxygen was administered with a nasal cannula. These findings suggest that wearing a surgical mask over the nasal cannula allows for maintenance of high PaO2 and improved oxygenation, while also preventing spread of COVID-19 infections thus further investigation with studies including more patients should be conducted.

FIGURES

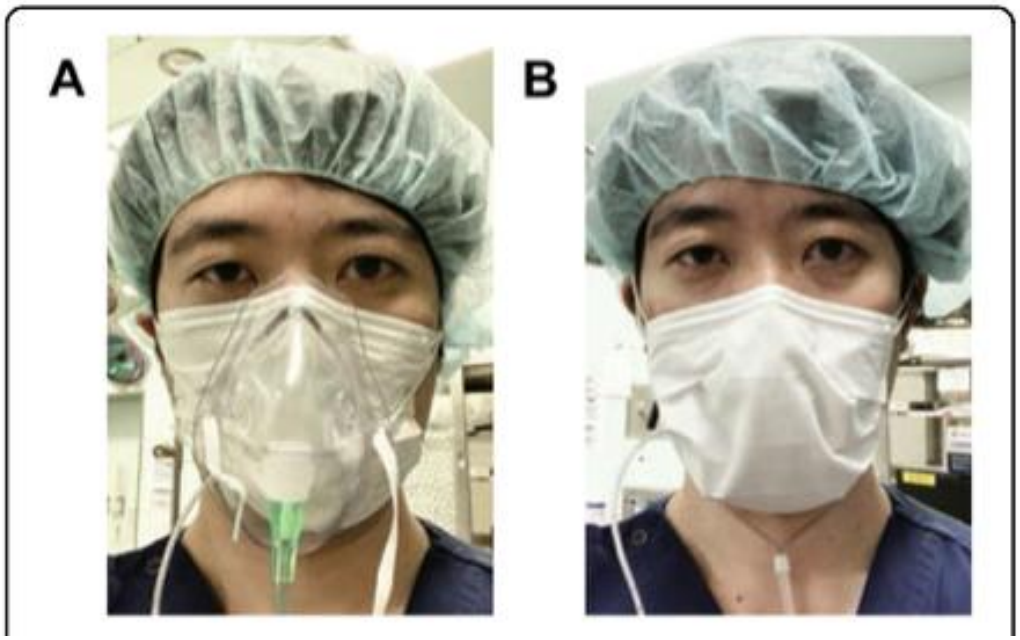


Fig. 1 The two different oxygen administration methods tested. Image showing wearing an oxygen mask above the surgical mask (a) and wearing a nasal cannula below the surgical mask (b)

Oxygen supply device	Nasal cannula	Oxygen mask	Nasal cannula
Oxygen flow rate (L/min)	4	4	4
pH	7.38	7.41	7.41
PaO_2 (mmHg)	154	108	150
$PaCO_2$ (mmHg)	36.1	32.9	32.6
Base excess (mmol/L)	−3.5	−3.4	−3.8
Respiratory rate (breaths/min)	29	30	28

Table 1: Results of blood gas analysis in the COVID-19 patient

We collected arterial blood samples and performed blood gas analysis when the patient wore a nasal cannula under the surgical mask and when the patient wore an oxygen mask over the surgical mask. Blood samples were taken between 15 and 60 min after the change in oxygen administration method, i.e., after the patient received oxygen for at least 15 min by the method being tested. This was to clarify that the results of blood gas analysis were due to the different methods of oxygen administration. Arterial blood was analyzed by a blood gas analyzer (ABL800 FLEX, Radiometer Medical ApS, Denmark). PaO2, partial pressure of oxygen in arterial blood; PaCO2, partial pressure of carbon dioxide in arterial blood

EFFECT OF IVERMECTIN ON TIME TO RESOLUTION OF SYMPTOMS AMONG ADULTS WITH MILD COVID-19: A RANDOMIZED CLINICAL TRIAL

López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, Díazgranados JA, Oñate JM, Chavarriaga H, Herrera S, Parra B, Libreros G, Jaramillo R, Avendaño AC, Toro DF, Torres M, Lesmes MC, Rios CA, Caicedo I.. JAMA. 2021 Apr 13;325(14):1426-1435. doi: 10.1001/jama.2021.3071.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

A double-blind randomized control trial conducted at a single site in Cali, Columbia by researchers affiliated with multiple medical institutions in Columbia included 476 adult patients with mild COVID-19 disease and symptoms for ≤ 7 days between July 15 and November 30, 2020 (Figure 1) to receive either ivermectin 300 g/kg/day (n= 200) for 5 days or placebo (n=200). The median time to resolution of symptoms was 10 days for ivermectin (IQR, 9-13) compared to 12 days in placebo group (IQR, 9-13) (Hazard ratio, 1.07 (95% CI, 0.87 to 1.32), p = 0.53) (Table 2), however there was no statistically significant difference between groups. Resolved symptoms were noted in 82% of ivermectin group and 79% of placebo group by Day 21 (Figure 2). There was no significant improvement of time to resolution of symptoms with the use of ivermectin compared to placebo, thus this study does not support ivermectin use for mild COVID-19 infection, although larger studies may be necessary to determine use for other clinically relevant outcomes.

ABSTRACT

Importance: Ivermectin is widely prescribed as a potential treatment for COVID-19 despite uncertainty about its clinical benefit. Objective: To determine whether ivermectin is an efficacious treatment for mild COVID-19. Design, Setting, and Participants: Double-blind, randomized trial conducted at a single site in Cali, Colombia. Potential study participants were identified by simple random sampling from the state's health department electronic database of patients with symptomatic, laboratory-confirmed COVID-19 during the study period. A total of 476 adult patients with mild disease and symptoms for 7 days or fewer (at home or hospitalized) were enrolled between July 15 and November 30, 2020, and followed up through December 21, 2020. Intervention: Patients were randomized to receive ivermectin, 300 mug/kg of body weight per day for 5 days (n = 200) or placebo (n = 200). Main Outcomes and Measures: Primary outcome was time to resolution of symptoms within a 21-day follow-up period. Solicited adverse events and serious adverse events were also collected. Results: Among 400 patients who were randomized in the primary analysis population (median age, 37 years [interquartile range {IQR}, 29-48]; 231 women [58%]), 398 (99.5%) completed the trial. The median time to resolution of symptoms was 10 days (IQR, 9-13) in the ivermectin group compared with 12 days (IQR, 9-13) in the placebo group (hazard ratio for resolution of symptoms, 1.07 [95% CI, 0.87 to 1.32]; P = .53 by log-rank test). By day 21, 82% in the ivermectin group and 79% in the placebo group had resolved symptoms. The most common solicited adverse event was headache, reported by 104 patients (52%) given ivermectin and 111 (56%) who received placebo. The most common serious adverse event was multiorgan failure, occurring in 4 patients (2 in each group). Conclusion and Relevance: Among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms. The findings do not support the use of ivermectin for treatment of mild COVID-19, although larger trials may be needed to understand the effects of ivermectin on other clinically relevant outcomes. Trial Registration: ClinicalTrials.gov Identifier: NCT04405843.

FIGURES

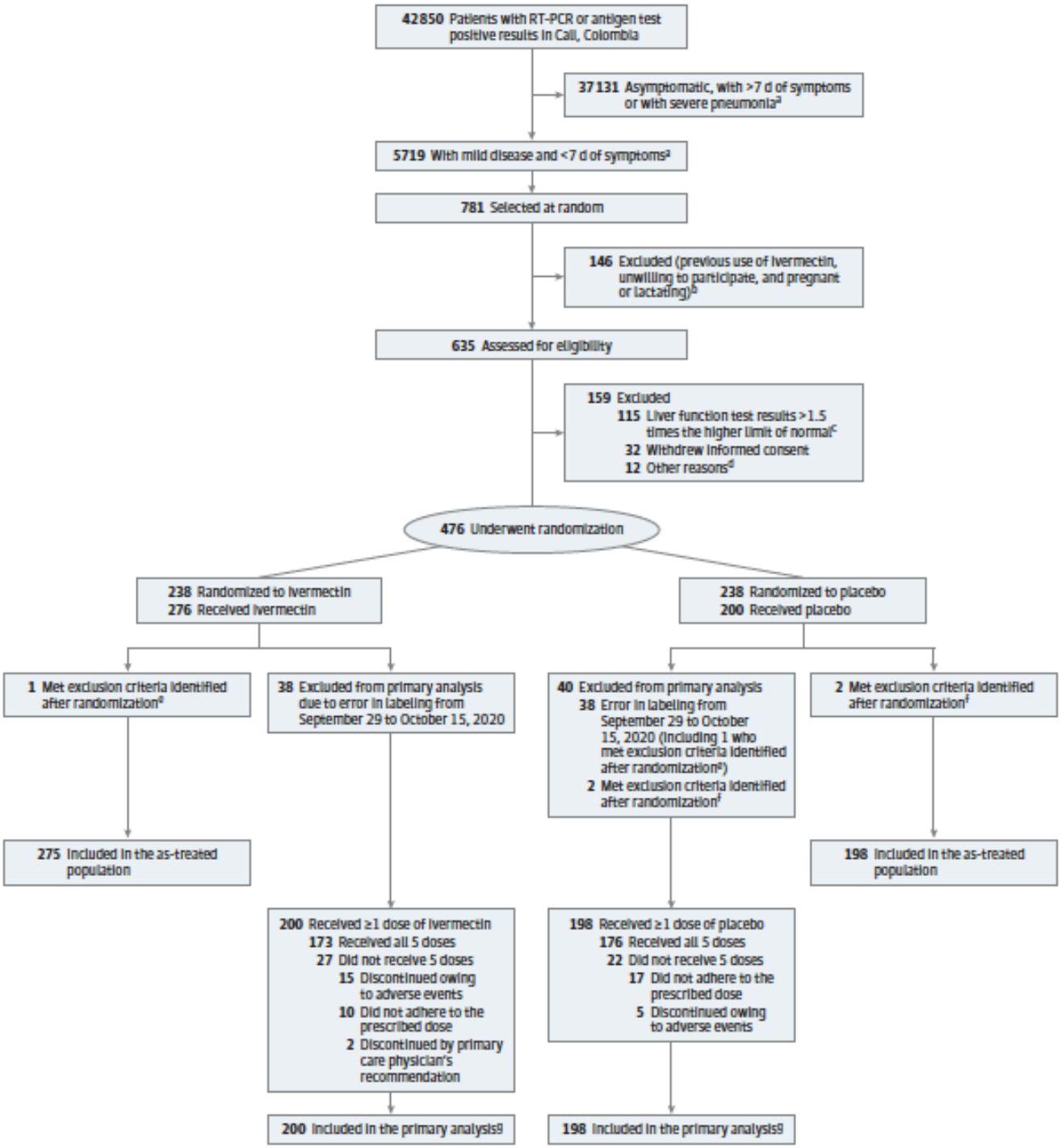


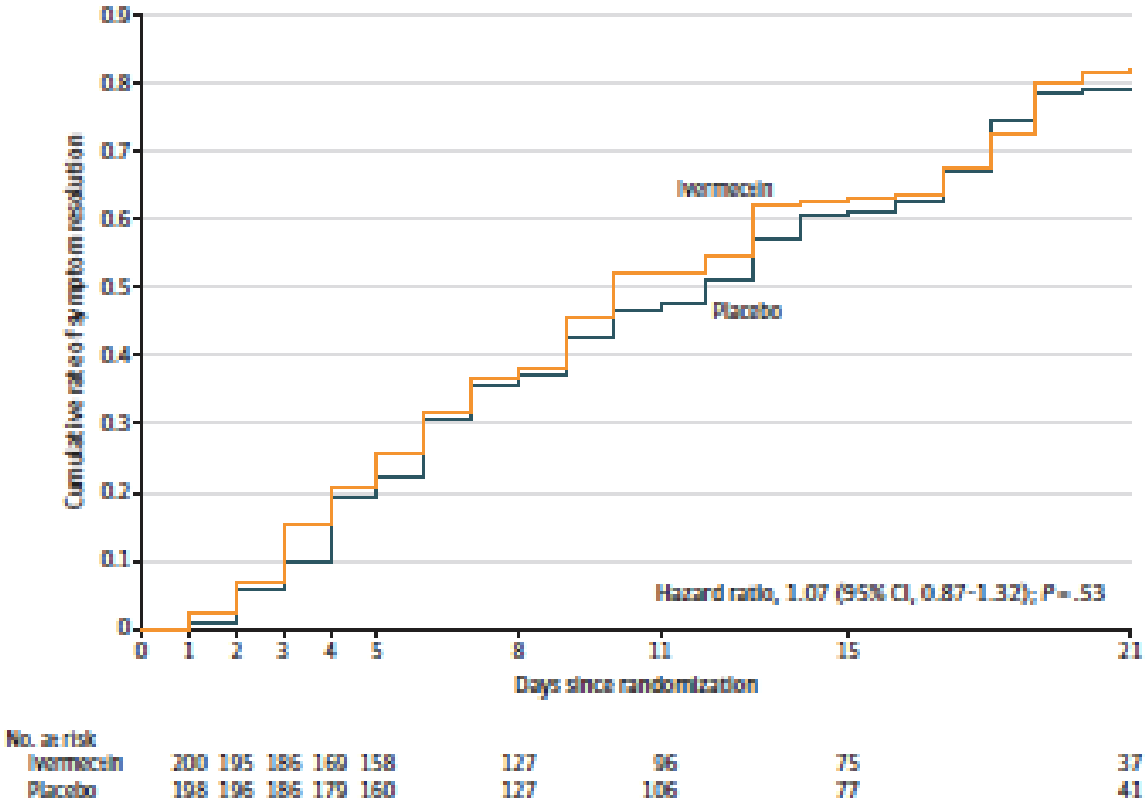
Figure 1. Enrollment, Randomization, and Treatment Assignment

RT-PCR indicates reverse transcriptase–polymerase chain reaction.
a Patients with mild disease were at home or hospitalized but not receiving high-flow nasal oxygen or mechanical ventilation (invasive or noninvasive). Patients with severe pneumonia were receiving high-flow nasal oxygen, mechanical ventilation (invasive or noninvasive), or extracorporeal membrane oxygenation.
b The numbers of patients with these exclusion criteria were not collected.
c Aspartate aminotransferase and alanine aminotransferase.
d Eight patients used ivermectin within 5 days prior to randomization, 1 had a positive pregnancy test, 1 was asymptomatic, 1 lived in an inaccessible area, and 1 had onset of symptoms 8 days prior to randomization.
e Patient was asymptomatic and was randomized to receive placebo but received ivermectin.
f Use of ivermectin before randomization.
g Includes deaths and recoveries.

Characteristic	No. (%)		Absolute difference (95% CI)	Effect estimate (95% CI)	*P* value
	Ivermectin (n = 200)	Placebo (n = 198)			
Primary outcome: resolution of symptoms[a]					
Time to resolution of symptoms, median No. of days (IQR)	10 (9-13)	12 (9-13)	−2 (−4 to 2)[b]	1.07 (0.87 to 1.32)[c]	.53
Symptoms resolved at 21 d	164 (82.0)	156 (79.0)	3.21 (−4.58 to 11.01)[d]	1.23 (0.75 to 2.01)[e]	
Secondary outcomes					
Deterioration by ≥2 points in an ordinal 8-point scale[f]	4 (2.0)	7 (3.5)	−1.53 (−4.75 to 1.69)[d]	0.56 (0.16 to 1.93)[e]	
Fever since randomization[g]	16 (8.0)	21 (10.6)	−2.61 (−8.31 to 3.09)[d]	0.73 (0.37 to 1.45)[e]	
Duration of febrile episode, median (IQR), d	1.5 (1-3)	2 (1-3)	−0.5 (−1.0 to 2.0)[b]		
Escalation of care since randomization[h]	4 (2.0)	10 (5.0)	−3.05 (−6.67 to 0.56)[d]	0.38 (0.12 to 1.24)[e]	
Duration, median (IQR) d[i]	13 (3.5-21)	6 (3.7-10.7)	7 (−5 to 16.5)[b]		
Deaths	0	1 (0.5)			
Post hoc outcomes					
Escalation of care occurring ≥12 h since randomization[h]	4 (2.0)	6 (3.0)	−1.0 (−4.11 to 2.05)[d]	0.65 (0.18 to 2.36)[e]	
Duration, median (IQR), d[i]	13 (3.5-21)	8 (4.2-13.2)	5 (−8.5 to 16)[b]		
Emergency department visits or telemedicine consultations, No. of patients	16 (8.0)	13 (6.6)	1.43 (−3.67 to 6.54)[d]	1.24 (0.56 to 2.74)[e]	

Table 2. Outcomes in the Primary Analysis Population

Abbreviation: IQR, interquartile range.
a Resolution of symptoms was defined as the first day free of symptoms.
b Absolute difference is the median difference with 95%CIs estimated by bootstrap sampling.
c Hazard ratio for resolution of symptoms was estimated by the Cox proportional-hazard model. The P value for this ratio was calculated with the log-rank test.
d Absolute difference is the difference in proportions.
e Effect estimate is odds ratio (2-sided 95%CI) from a logistic model.
f Ordinal scale: 0 = no clinical evidence of infection; 1 = not hospitalized and no limitation of activities; 2 = not hospitalized, with limitation of activities, home oxygen requirement, or both; 3 = hospitalized, not requiring supplemental oxygen; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, requiring nasal high-flow oxygen, noninvasive mechanical ventilation, or both; 6 = hospitalized, requiring extracorporeal membrane oxygenation, invasive mechanical ventilation, or both; and 7 = death.
g Fever defined as an axillary temperature38 °C. Patients took their own temperatures while at home.
h Escalation of care defined as new-onset hospitalization in the general ward or intensive care unit or new-onset supplementary oxygen requirement for more than 24 hours.
i Number of days that patients required hospitalization or supplementary oxygen. If both were required, the longer duration was recorded.



No. at risk

Ivermectin	200	195	186	169	158	127	96	75	37
Placebo	198	196	186	179	160	127	106	77	41

Figure 2. Time to Resolution of Symptoms in the Primary Analysis Population

The cumulative rate of symptom resolution is the percentage of patients who experienced their first day free of symptoms. All patients were followed up for 21 days.

ACKNOWLEDGEMENTS

CONTRIBUTORS

Ankita Dharmendran
Renate Meckl
Reza Aghaei

EDITORS

John Michael Sherman
Julia Ghering

SENIOR EDITORS

Allison Hansen

SENIOR EXECUTIVE EDITOR

Thamanna Nishath

CHIEF EDITOR

Jasmine Rah

ADVISOR

Will Smith