The Daily COVID-19 Literature Surveillance Summary

June 30, 2020

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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

Climate:

- Italian Cardiologists discuss how low-quality evidence during the COVID-19 pandemic is an unavoidable step in the process of understanding an emerging infectious disease, but lacks utility for guiding patient management and may lead to widespread use of potentially ineffective treatments and increased public distrust.
- Authors affiliated with the Boston Health Care for the Homeless Program (BHCHP) clinic utilize the case report of a 66-year-old COVID-19 positive patient who developed diabetic ketoacidosis to highlight their newly implemented pandemic response system designed to improve care for this vulnerable population.

Epidemiology:

- Molecular biologists from Spain explore gender differences in COVID-19, hypothesizing that the location of the angiotensin-converting enzyme 2 (ACE2) gene on the X chromosome may explain the greater fatality rate in males compared with females.
- Researchers describe how the well-established Total Risk Assessment (TRA) evaluation and Infected Patient's Ratio (IPR) tools can be combined to create a model that predicts inflection points, plateaus, ICU and ventilator thresholds, and Total Fatality Ratios (TFR) for the COVID-19 pandemic. Their results suggest this tool can predict the impact of lockdown and social distancing measures and guide policy decision moving forward.

Understanding the Pathology:

- Authors from Columbia University Medical Center report the pathological findings of post-mortem adrenal glands in COVID-19 patients (n=5). Their findings include: arteriole fibrinoid necrosis in the parenchyma, capsule, and peri-adrenal adipose tissue; apoptotic endothelial cells with cellular debris; and red fibrinoid material staining with Masson's trichome stain. The underlying mechanism of adrenal vasculopathy is unclear, and warrants further investigation.
- Dutch authors concur with the above hypothesis that ACE2 gene location on X-chromosomes may explain greater disease severity in males with COVID-19, and postulate that co-expression of ACE2 and ADAM17 (also on X chromosome) may also produce increased ACE2 in circulation.

Transmission & Prevention:

- A review of 39 studies (n= 33,867) of influenza, SARS-CoV-1, and MERS outbreaks compared efficacy of N95, surgical, and cloth masks for preventing viral spread. They found that in healthcare settings, N95 masks were most effective at prevented SARS-CoV-1 transmission. However, in community settings, masking had little effect on influenza transmission (possibly due to noncompliance and greater usage during pandemics vs yearly flu).
- An international group of researchers propose a COVID-19 testing algorithm to prevent resurgence of the virus as nations begin to reopen, that balances the need to restart economies with the reality of limited testing resources. They prioritize those with the highest risk of exposure (i.e. essential workers) until testing capacity is appropriately scaled up.

Management:

- Anesthesiologists from India write to agree with a previous article by Gattinoni et al. stating that the lung disease of COVID-19 be split into two time-related phases, type L (low elastance and low ventilation:perfusion ratio) and type H (high elastance, high right-to-left shunt, high lung weight and high recruitability). The authors hypothesize type L may be caused by diffuse pulmonary microvascular thrombosis and should be treated with high flow nasal cannula and ECMO to prevent further lung injury and subsequent development of type H disease.
- A review of potential drug-drug interactions (DDIs) in patients taking medications for Alzheimer's Disease (AD) with concurrent COVID-19 infection recommends providers briefly review CYP450 metabolism of several key treatments used in both conditions. They note that memantine may be the safest Alzheimer's medication in this context due to its limited hepatic metabolism and low risk for DDIs.

Adjusting the Practice During COVID-19:

- Authors from Singapore describe their construction and implementation of an Emergency Medical Department (EMD) extension facility that successfully accommodated 5,004 suspected COVID-19 patients with no infection prevention and control breaches. They urge other hospitals to consider implementing similar facilities to increase surge capacity and reduce the demand on the main EMD isolation facilities.
- A systematic review that assessed the validity of tele-neuropsychology (TNP) in assessing older adults (aged 65+), concluding that specific cognitive screeners, language tests, attention/working memory tasks, and memory tests

demonstrated high validity, suggesting that TNP may be the preferred modality for this high-risk population during the COVID-19 pandemic.

- The importance of exercise during quarantine in type 2 diabetic patients: Authors describe how 150 minutes of aerobic and resistance exercise weekly can improve metabolic health, immune responses, and anti-inflammatory to pro-inflammatory cytokine ratio, suggesting that physical activity may be helpful in cultivating a better response to COVID-19 infection and could result in a less severe course.

R&D Diagnosis and Treatments:

- A bioinformatic analysis by authors from China compared the gold standard RT-PCR to a novel nanopore targeted sequencing (NTS) to accurately identify SARS-CoV-2, findings that NTS can identify SARS-CoV-2 and other respiratory viruses within 6-10 hours, and that the 22/61 suspected COVID-19 cases missed by RT-PCR were identified by NTS. Authors propose that NTS may complement RT-PCR for diagnosing COVID-19 patients despite the longer turnaround time and increased operational skill.
- Italian researchers review how dipeptidyl peptidase-4 (DPP4; also known as CD26 lymphocyte surface protein) can stimulate the production of IL-6 and TNF-α and has been implicated in pulmonary diseases. DPP4 inhibitors (gliptins), currently used in treatment of type-2 diabetes mellitus, have been shown to reduce lung inflammation and injury, suggesting a potential therapeutic use in patients with COVID-19.
- A commentary by the London Metropolitan University and University of Hartfordshire proposes using small extracellular vesicles (sEVs) from engineered mesenchymal stromal/stem cells (MSCs) as an alternative therapy to soluble recombinant ACE2 in SARS-CoV-2 infection. They cite the potential ability to inhibit viral binding to the ACE2R, increase phagocytic activity, and anti-inflammatory effects as theoretical mechanisms of protection.
- Researchers in New York review the current literature on passive immunization, finding that plasma infusions with SARS-CoV-2 antibodies may be an effective short-term treatment. They predict increased use of treatment with monoclonal antibodies within the next year, but also recommend close monitoring of these patients for antibody-mediated adverse events.

Mental Health and Resilience:

- Online surveying of 500 people from 45 US states between March 27 and April 5, 2020 revealed that job loss and social isolation had a statistically significant indirect impact on suicide risk through feelings of "perceived burdensomeness" and "thwarted belongingness". The authors advocate that increased awareness of these emotions during the pandemic by providers is needed to mitigate a potential secondary suicide crisis.

TABLE OF CONTENTS

CLIMATE

AFFECTING THE HEALTHCARE WORKFORCE

THOUGHTS ON THE SCIENTIFIC EVIDENCES IN THE COVID-19 ERA

Mugnai G, Paolini C, Bilato C.. Disaster Med Public Health Prep. 2020 Jun 24:1-3. doi: 10.1017/dmp.2020.213. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Cardiologists from Italy comment on the lower quality scientific evidence that has emerged during the COVID-19 pandemic, which may have value for hypothesis generation but is less helpful for managing patients with COVID-19. They caution against using public opinion and preliminary observations to guide clinical practice, as this can lead to widespread use of potentially ineffective and unsafe treatments.

DISPARITIES

CASE 21-2020: A 66-YEAR-OLD HOMELESS MAN WITH COVID-19

Gaeta JM, De Las Nueces D, Munson DG, Barocas JA, Walsh KE.. N Engl J Med. 2020 Jun 24. doi: 10.1056/NEJMcpc2002421. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

Authors detail a case report of a homeless 66-year-old man presenting to the Boston Health Care for the Homeless Program (BHCHP) clinic with dry cough and rhinorrhea who tested positive for COVID-19 infection and developed diabetic ketoacidosis during his clinical course. The authors utilize this case to introduce the BHCHP's creation of a COVID-19 response system for Boston's homeless population (Figure 1). The authors emphasize the high-risk of COVID-19 infection and morbidity in the homeless population, urging for increased collaborative efforts with similar domains as BHCHP's COVID-19 response system.

FIGURES

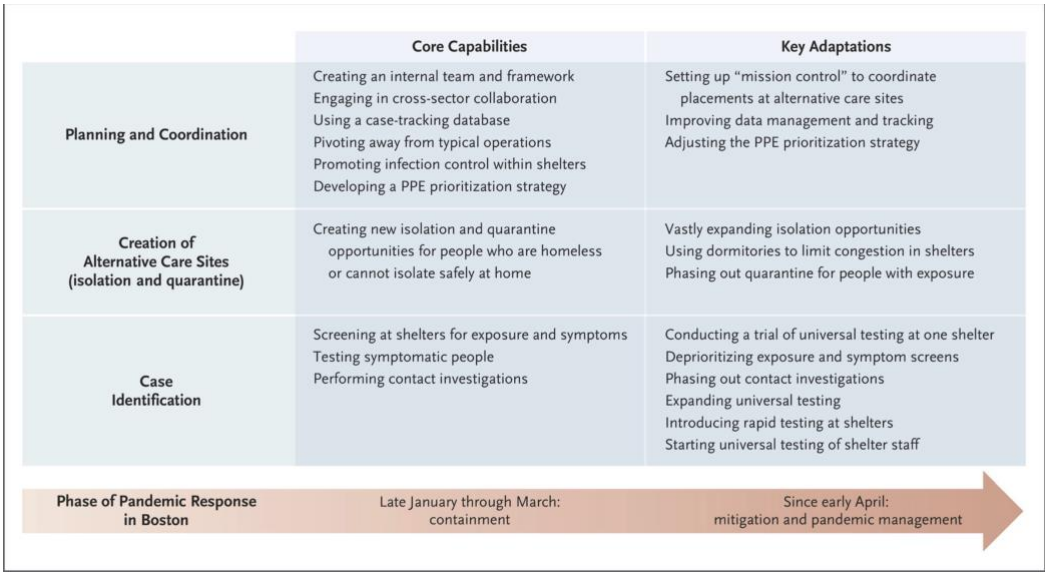


Figure 1. Design of the Covid-19 Response System for the Homeless Population.

EPIDEMIOLOGY

ACE2 IS ON THE X CHROMOSOME: COULD THIS EXPLAIN COVID-19 GENDER DIFFERENCES?

Culebras E, Hernández F.. Eur Heart J. 2020 Jun 24:ehaa521. doi: 10.1093/eurheartj/ehaa521. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Molecular biologists from Spain explore COVID-19 gender differences in this European Heart Journal commentary. They propose the location of the angiotensin-converting enzyme 2 (ACE2) gene on the X chromosome (location: Xp22.2) might explain the greater fatality rate in males compared with females, as having two gene copies (XX) is often protective against the deleterious effects of X-linked diseases. The authors acknowledge the need for further studies regarding ACE2 localization on the X chromosome.

MODELING

ASSESSMENT OF COUNTRIES' PREPAREDNESS AND LOCKDOWN EFFECTIVENESS IN CONFRONTING COVID-19

Amer F, Hammoud S, Farran B, Boncz I, Endrei D.. Disaster Med Public Health Prep. 2020 Jun 24:1-15. doi: 10.1017/dmp.2020.217. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

A modeling study conducted by researchers in Hungary established that the Total Risk Assessment (TRA) evaluation tool and the Infected Patient's Ratio (IPR) tool could be combined to create a model that predicts inflection points, infection plateau phases, ICU and ventilator thresholds, and Total Fatality Ratios (TFR) for the COVID-19 pandemic in Italy, Germany, Spain, France, and the United States. Their results show that in these countries, an inflection point is predicted within the first two weeks of April and that infections should plateau within another 30-80 days (Tables 1A and 2A). They suggest the TRA and IPR tools can be used together to predict the impact of varying lockdown methods and social distancing measures on the spread of COVID-19 moving forward.

ABSTRACT

OBJECTIVES: To assess the risks in confronting the COVID-19 pandemic and the ongoing lockdown effectiveness in each of Italy, Germany, Spain, France, and the USA using China's lockdown model simulation, and cases forecast until the plateau phase.
METHODS: Quantitative and qualitative historical data analysis. Total Risk Assessment (TRA) evaluation tool was used to assess the pre-pandemic stage risks, pandemic threshold fast responsiveness, and the ongoing performance till plateau. The Infected Patient's Ratio (IPR) tool was developed to measure the number of patients resulting from one infector during the incubation period. Both IPR and TRA were used together to forecast inflection points, plateau phases, ICUs' and ventilators' breakpoints, and the Total Fatality Ratio.
RESULTS: In Italy, Spain, France, Germany, and the USA, an inflection point is predicted within the first 15 days of April, to arrive at a plateau after another 30 to 80 days. Variations in IPR drop are expected due to variations in lockdown timing by each country, the extent of adherence to it, and the number of performed tests in each.
CONCLUSIONS: Both qualitative (TRA) and quantitative (IPR) tools can be used together for assessing and minimizing the pandemic risks and for more precise forecasting.

FIGURES

(Table 1A): Observed and simulated IPR values, stratified by incubation intervals (Int. = 10 days)									
Int.	**Italy**	**Int.**	**Spain**	**China**	**Germany**	**France**	**USA**	**Stage**	**IPR x̄ / stage**
Int. 1 Int. 2	**0** **15.38**	Int. 1 Int. 2 Int. 3	**0** **93** **27**	**0** **3.4** **38**	**0** **76** **6**	**0** **46** **8**	**0** **3** **16**	Pre-intervention	16
Int. 3	**6.3** $^{>\,*}$	Int. 4	**5.78** $^{\#\,'}$	**4** $^{<\,'}$	**8** $^{\#\,*}$	**6** $^{\#\,'}$	**18** $^{>\,'}$	**LD**	**6**
Int. 4	**2.41** $^{>\,*}$	Int. 5	**1.89** $^{\#\,''}$	**1.13** $^{<\,'}$	**2** $^{\#\,*}$	**3.6** $^{\#\,'}$	**3.6** $^{\#\,'}$		
Int. 5	**0.87**	Int. 6	*0.62*	**0.08**	*0.6* $^{\#\,*}$	*0.7* $^{\#\,''}$	*1* $^{\#\,''}$		Depends on: 1.The interval sequence 2.LD timing 3.LD adherence 4.Testing numbers increase
Int. 6	*0.4*	Int. 7	*0.31*	**0.04**	*0.17*	*0.27*	*0.5*		
Int. 7	*0.25*	Int. 8	*0.18*	**0.01**	*0.08*	*0.18*	*0.27*		
Int. 8	*0.16*	Int. 9	*0.12*	**0.03**	*0.04*	*0.12*	*0.17*		
Int. 10	0.08	Int. 10	*0.09*	**0.02**	*0.02*	*0.8*	*0.11*	Post-intervention	
Int. 11	0.05	*Int. 11*	*0.06*	*0*	*0.01*	*0.05*	*0.08*		
Int. 12	0.02	*Int. 12*	*0.05*	*0*	*0*	*0.02*	*0.06*		
Int. 13	0.01	*Int. 13*	*0.03*	*0*	*0*	*0.01*	*0.05*		
Int. 14	0	*Int. 14*	*0.2*	*0*	*0*	*0*	*0.04*		
Int. 15	0	*Int. 15*	*0.1*	*0*	*0*	*0*	*0.03*		
		Int. 16	*0*	*0*	*0*	*0*	*0.01*		
Int., interval; LD, lockdown; $^{>}$, loose lockdown adherence; $^{\#}$, intermediate lockdown adherence; $^{<}$, strict lockdown adherence; *, rapid testing increase; $^{''}$, intermediate testing increase; ', slow testing increase. Bold are Observed IPR, *Italic* are simulated IPR.									

Table 1A: Observed and simulated IPR values, stratified by incubation intervals (Int. = 10 days)

(Table 2A): Evaluation and approximate forecast until May using TRA and IPR tools							
Tool	Perspective/ Country	China	Italy	Germany	Spain	France	USA
TRA	TRA1 (pre-pandemic)	76	68	36	56	60	28
	TRA2 (pandemic threshold)	70	87	43	77	80	53
	TRA3 (post-threshold)	Finished	94	49	89	100	69
	(TRA1 to TRA3)	(-)	(+ / -)	(+ / -)	(+ / -)	(+ / +)	(+ / +)
IPR	Est.Total cases	86K	267K	171K	333K	253K	2M
	Est.total Deaths 1	3.5K	27K	2.2K	20K	16K	51K
	Est.total Deaths 2	7K	81K	7K	90K	87K	358K
	Est.TFR 1	4.1%	10.5%	1.3%	6.0 %	6.2%	2.5%
	Est.TFR 2	8.1%	31.4%	3.9%	26.9%	34.3%	17.4%
	Est.ICU total deficits*	0**	17K*	0**	7.6K*	2K*	0**
	Est.breakpoint period	Non	Mar. 6- May.14	Non	Mar.16- Jun.3	Mar.26- Apr.24	Mar.26 –May.24
IPR	Est.inflection P. (IPR<1)	15-Feb	02-Apr	11-Apr	11-Apr	11-Apr	11-Apr
	Est.days since LD	20 days	26 days	27 days	29 days	27 days	21 days
IPR	Est.plateau P. (IPR=0.08-0.04)	05-Mar	15-May	10-May	13-Jun	04-Jun	03-Jul
	Est.days since LD	39 days	79 days	51 days	92 days	81 days	104 days
Est., Estimated; F., Finished; LD, Lockdown; P, Point; TRA, Total Risk Assessment; TRA1, TRA in Pre-Pandemic Stage; TRA2, TRA in Pandemic-Threshold Stage; TRA3, TRA in Post-Threshold Stage; *, Cases of ICU beds capacity increased (a portion of this number will not die); **, only in certain states or cities if cases distribution is not uniformed in the country (e.g. New York, calculations need to be reconsidered for each state, city independently).							

Table 2A: Evaluation and approximate forecast until May using TRA and IPR tools

UNDERSTANDING THE PATHOLOGY

ADRENAL VASCULAR CHANGES IN COVID-19 AUTOPSIES

Iuga AC, Marboe CC, Yilmaz MM, Lefkowitch JH, Gauran C, Lagana SM.. Arch Pathol Lab Med. 2020 Jun 24. doi: 10.5858/arpa.2020-0248-LE. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

Authors from Columbia University Medical Center in New York report the pathological findings of post-mortem adrenal glands from patients with confirmed COVID-19 (n=5). Their findings include: arteriole fibrinoid necrosis in the parenchyma, capsule, and peri-adrenal adipose tissue; apoptotic endothelial cells with cellular debris; and red fibrinoid material staining with Masson's trichome stain (Figure 1). The authors note that the underlying mechanism of the adrenal vasculopathy is unclear, suggesting the need for further investigation of adrenal function in patients with COVID-19.

FIGURES

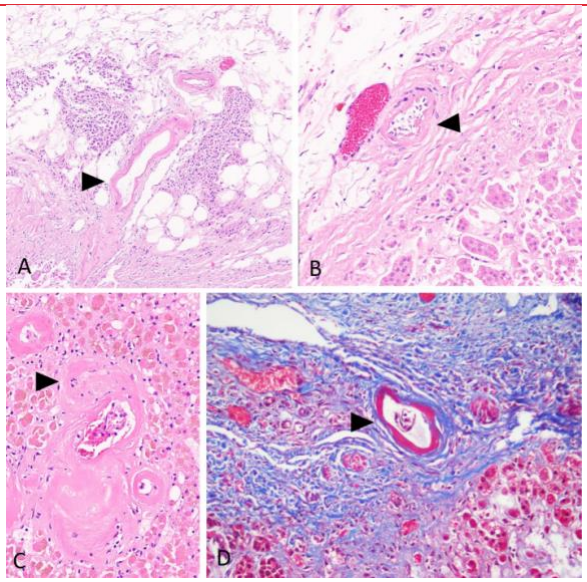


Figure 1. A. Fibrinoid hyaline vascupathy in periadrenal vessels indicated by black arrow head (hematoxylin and eosin stain, H&E, 10x magnification). B. Apoptosis in periadrenal and adrenal vessels (black arrow head points to apoptotic endothelial cells) (H&E stain, 20x magnification). C. Necrotic vessel with karyorrhectic debris at black arrow head (H&E stain, 20x magnification). D. Masson's trichrome stain highlights fibrinoid hyaline material in red, indicated by the black arrow head (Trichrome stain, 20x magnification).

MEN MORE VULNERABLE TO COVID-19: EXPLAINED BY ACE2 ON THE X CHROMOSOME?

Sama IE, Voors AA.. Eur Heart J. 2020 Jun 24:ehaa526. doi: 10.1093/eurheartj/ehaa526. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

In this correspondence authors from the University of Groningen in the Netherlands respond to the article, “ACE2 is on the x-chromosome: could this explain COVID-19 gender differences?” and agree with the article's hypothesis that the ACE2 gene’s location on the X chromosome could contribute to the greater COVID-19 disease severity in males. The authors of this letter also refer to their own previous hypothesis that co-expression of ACE2 and ADAM17 (also located on the X chromosome in the testes), membrane-bound proteins responsible for shedding ACE2 into circulation, could cause higher amounts of ACE2 in circulation and therefore greater disease severity in males.

MASKS FOR PREVENTION OF RESPIRATORY VIRUS INFECTIONS, INCLUDING SARS-COV-2, IN HEALTH CARE AND COMMUNITY SETTINGS: A LIVING RAPID REVIEW

Chou R, Dana T, Jungbauer R, Weeks C, McDonagh MS.. Ann Intern Med. 2020 Jun 24. doi: 10.7326/M20-3213. Online ahead of print.
Level of Evidence: 1 - Review / Literature Review

BLUF

Researchers from Oregon reviewed 39 studies (21 observational and 18 RCT, total n= 33,867; Table 2) on yearly influenza, SARS-CoV-1, and MERS outbreaks to investigate the efficacy of N95, surgical, and cloth masks for preventing viral spread. They found that in healthcare settings, N95 masks prevented the spread of SARS-CoV-1 better than other forms of masking; and while any mask use could decrease viral transmission, this may not apply to SARS-CoV-2 due to differences in transmission. In community settings, masking has little effect on influenza transmission (possibly due to noncompliance and increased usage during pandemics compared to yearly flu spikes; Figure 2). Authors conclude that more data needs to be collected on SARS-CoV-2 transmission to further analyze mask effectiveness during the current pandemic.

ABSTRACT

BACKGROUND: Recommendations on masks for preventing coronavirus disease 2019 (COVID-19) vary. PURPOSE: To examine the effectiveness of N95, surgical, and cloth masks in community and health care settings for preventing respiratory virus infections, and effects of reuse or extended use of N95 masks.
DATA SOURCES: Multiple electronic databases, including the World Health Organization COVID-19 database and medRxiv preprint server (2003 through 14 April 2020; surveillance through 2 June 2020), and reference lists.
STUDY SELECTION: Randomized trials of masks and risk for respiratory virus infection, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and observational studies of mask use and coronavirus infection risk were included. New evidence will be incorporated by using living review methods.
DATA EXTRACTION: One reviewer abstracted data and assessed methodological limitations; a second reviewer provided verification.
DATA SYNTHESIS: 39 studies (18 randomized controlled trials and 21 observational studies; 33 867 participants) were included. No study evaluated reuse or extended use of N95 masks. Evidence on SARS-CoV-2 was limited to 2 observational studies with serious limitations. Community mask use was possibly associated with decreased risk for SARS-CoV-1 infection in observational studies. In high- or moderate-risk health care settings, observational studies found that risk for infection with SARS-CoV-1 and Middle East respiratory syndrome coronavirus probably decreased with mask use versus nonuse and possibly decreased with N95 versus surgical mask use. Randomized trials in community settings found possibly no difference between N95 versus surgical masks and probably no difference between surgical versus no mask in risk for influenza or influenza-like illness, but compliance was low. In health care settings, N95 and surgical masks were probably associated with similar risks for influenza-like illness and laboratory-confirmed viral infection; clinical respiratory illness had inconsistency. Bothersome symptoms were common.
LIMITATIONS: There were few SARS-CoV-2 studies, observational studies have methodological limitations, and the review was done by using streamlined methods.
CONCLUSION: Evidence on mask effectiveness for respiratory infection prevention is stronger in health care than community settings. N95 respirators might reduce SARS-CoV-1 risk versus surgical masks in health care settings, but applicability to SARS-CoV-2 is uncertain.
PRIMARY FUNDING SOURCE: Agency for Healthcare Research and Quality.

Supplement Table 2. Inclusion criteria

	Include	Exclude
Population	Healthcare workers or community members at risk of contracting COVID-19 or other viral respiratory illnesses due to workplace or community-based exposure	Bacterial or other non-viral infection; non-respiratory infection
Intervention/exposure	N95 respirators or equivalent, surgical/medical masks, and cloth masks.	Powered air-purifying respirators (PAPR), reusable N95 elastomeric respirators, other types of personal protective equipment
Comparator	One type of mask versus another type of mask; mask use versus nonuse; mask single use versus re-use	Other personal protective equipment
Outcomes	Infection with SARS-CoV-2, SARS-CoV-1, or MERS-CoV Influenza-like illness, lab-confirmed viral infection, lab-confirmed influenza, and clinical respiratory illness Harms of mask usage	
Setting/context	Community or healthcare settings; mask use by healthcare workers (HCWs) or non-HCWs; all geographic areas; findings considered within social distancing and PPE/handwashing context	Masks for prevention of other epidemic viruses (e.g., Ebola) and bacterial infections (e.g., tuberculosis)
Study design	Randomized controlled trials, cohort studies, case-control studies	Systematic reviews (used to identify primary studies)

Figure 1. Inclusion/Exclusion Criteria

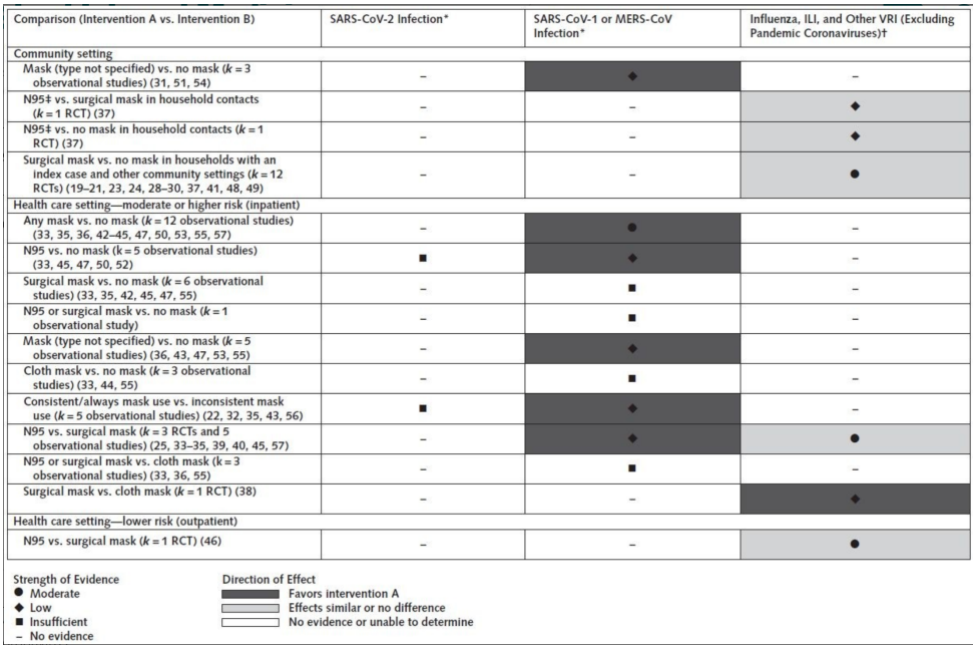


Figure 2. Masks for prevention of respiratory virus infection: evidence map.
ILI = influenza-like illness; RCT = randomized controlled trial; VRI = viral respiratory illness; MERS-CoV = Middle East respiratory syndrome coronavirus; SARS-CoV = severe acute respiratory syndrome coronavirus.
* Only observational evidence was included for these infections.
† Only RCT evidence was included for these infections.
‡ N95 respirator or equivalent (for example, P2 mask).

PREVENTION IN THE COMMUNITY

A PROPOSED COVID-19 TESTING ALGORITHM

Hart A, Bortolin M, Awoniyi O, Alhajjaj F, Ciottone G.. Disaster Med Public Health Prep. 2020 Jun 24:1-9. doi: 10.1017/dmp.2020.218. Online ahead of print.

Level of Evidence: Other - Guidelines and Recommendations

BLUF

This article written by an international group of researchers proposes a COVID-19 testing algorithm that could be used to prevent resurgence of the virus as nations begin to reopen their economies and eliminate or reduce social distancing mandates (see summary). This testing algorithm balances the need to restart economies with the reality of limited testing resources so that those with the highest risk of exposure (i.e. essential workers) are prioritized until testing capacity is appropriately scaled up.

SUMMARY

The main steps of the algorithm are as follows:

1. The algorithm will start by only being applied to essential workers (EW) while all other individuals should continue social distancing. This would limit societal exposure and save testing capacity for those on the front lines.

2. All EW who return to work should be tested via serology every 2 weeks. Those with evidence of previous infection would be considered immune and testing can be discontinued. Seronegative individuals would be re-tested every 2 weeks.

3. If an EW has a COVID-19 exposure or symptoms, they should get nasopharyngeal testing for active COVID-19 infection. Those with negative testing will re-enter into the normal serologic testing pathway.

4. A positive COVID-19 test via nasopharnyngeal swab will result in isolation for 14-21 days followed by serological testing after the infection has passed. If they are immune, they may exit the algorithm. If serological immunity is not seen upon testing, the individual will re-enter the serological testing phase and be tested every 2 weeks.

5. Once greater testing is available, the same algorithm could be used for the general public.

ABSTRACT

The Coronavirus pandemic has led to physical distancing measures in numerous countries in an attempt to control the spread. However, these measures are not without cost to the health and economies of the nations in which they are enacted. Nations are now looking for methods to remove physical distancing measures and return to full functioning. To prevent a massive second wave of infections, this must be done with a data-driven methodology. The purpose of this article is to propose an algorithm for coronavirus testing which would allow for physical distancing to be scaled back in a step-wise manner which limits ensuing infections and protects the capacity of the healthcare system.

MANAGEMENT

ACUTE CARE

CRITICAL CARE

SEVERE HYPOXEMIA IN EARLY COVID-19 PNEUMONIA

Bhatia P, Mohammed S.. Am J Respir Crit Care Med. 2020 Jun 24. doi: 10.1164/rccm.202004-1313LE. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Researchers in the Department of Anaesthesiology at the All India Institute of Medical Sciences located in New Delhi, India write to agree with a previous article by Gattinoni et al. which suggests the lung disease of COVID-19 be split into two time-related phases, type L (low elastance, low ventilation to perfusion ratio, low lung weight and low recruitability) and type H (high elastance, high right-to-left shunt, high lung weight and high recruitability). The authors suggest type L may be caused by diffuse pulmonary microvascular thrombosis and they agree that type L patients should be treated with high flow nasal cannula and ECMO to prevent further lung injury that may cause transition to type H disease.

GERIATRICS

THE ANOTHER SIDE OF COVID-19 IN ALZHEIMER'S DISEASE PATIENTS: DRUG-DRUG INTERACTIONS

Balli N, Kara E, Demirkan K.. Int J Clin Pract. 2020 Jun 27:e13596. doi: 10.1111/ijcp.13596. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A review of potential drug-drug interactions (DDIs) in patients taking medications for Alzheimer's Disease (AD) with concurrent COVID-19 infection was authored by pharmacists at Hacettepe University, Turkey. They caution providers to consider potential for DDIs in this vulnerable population and briefly review CYP450 metabolism of several key Alzheimer's and COVID-19 treatments. They note that memantine may be the safest Alzheimer's medication in this context due to its limited hepatic metabolism and low risk for DDIs.

ABSTRACT

Coronavirus Disease 2019 (COVID-19) outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a major public health problem. The elderly people are the most affected population by the COVID-19 outbreak in terms of mortality and morbidity. Delirium caused by hypoxia, a prominent clinical feature of COVID-19, may increase the need for treatment of Alzheimer's disease (AD) patients (1). Therefore, drug-drug interactions should be considered in AD patients while receiving COVID-19 treatment.

EMERGENCY MEDICINE

A SAFE AND EFFICIENT, NATURALLY VENTILATED STRUCTURE FOR COVID-19 SURGE CAPACITY IN SINGAPORE

Bagdasarian N, Mathews I, Alexander NJY, Choon ELH, Sin C, Mahadevan M, Fisher DA.. Infect Control Hosp Epidemiol. 2020 Jun 24:1-8. doi: 10.1017/ice.2020.309. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Authors from the National University Hospital in Singapore report success with a naturally ventilated structure (Figure 1) to serve as a temporary and inexpensive unit for suspected COVID-19 patients in an Emergency Medicine Department (EMD). The authors detail the construction of the EMD extension, including its open-air sides, a canvas cover, multiple ceiling fans and 25 patient cubicles, and report its successful capacity of 5,004 patients between February 14 and May 12, 2020 with no Infection Prevention and Control breaches. The authors urge other hospitals to consider using this EMD extension for suspected COVID-19 patients to mitigate the surge in capacity during the pandemic and reduce the demand on the main EMD isolation facilities.

FIGURES

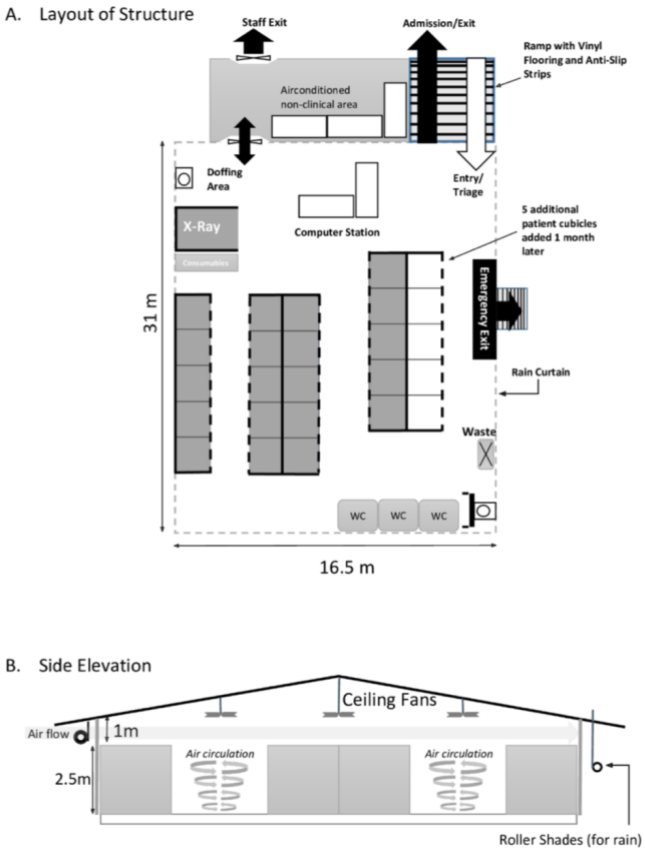


Figure 1. Layout and Side Elevation of Emergency Medicine Department Extension Facility*
*Not drawn to scale

NEUROLOGY

VALIDITY OF TELENEUROPSYCHOLOGY FOR OLDER ADULTS IN RESPONSE TO COVID-19: A SYSTEMATIC AND CRITICAL REVIEW

Marra DE, Hamlet KM, Bauer RM, Bowers D.. Clin Neuropsychol. 2020 Jun 10:1-42. doi: 10.1080/13854046.2020.1769192. Online ahead of print.
Level of Evidence: 1 - Systematic review of cross sectional studies with consistently applied reference standard and blinding

BLUF

This systematic review builds upon the results of Brearly et al., 2017, by analyzing 19 studies consisting of 10 counterbalanced cross-over studies published after January 1, 2016 and 9 studies from Brearly's analysis (Figure 1), to assess teleneuropsychology (TNP) validity among older adults (aged 65+). The authors conclude that specific cognitive screeners, language tests, attention/working memory tasks, and memory tests showed strong support for TNP validity (support for specific tests summarized below), suggesting that TNP may be the preferred modality during the COVID-19 social distancing period.

SUMMARY

The results for each cognitive domain are summarized below:

Cognitive screeners:
•Limited support for validity of The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
•Studies support the validity of the Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA, Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog) for TNP assessments.
Intelligence
•Limited support for the validity of the Matrix Reasoning and Vocabulary subtests from the Wechsler Adulty Intelligence Scale – 3rd edition (WAIS-III) in TNP assessments.

Attention/working memory tasks
•Limited validity evidence for Brief Test of Attention (BTA) in TNP assessments
•Moderate evidence of validity for Digit Span Forward and Digit Span Backwards in TNP assessment.
•Good validity evidence for Digital Span Total for TNP assessments

Processing Speed
•Some support for the validity of Oral Trails A in TNP assessments.

Language tests
•Insufficient evidence for the validity of Token Test, Picture Description, and Aural Comprehension of Words and Phrases in TNP assessment
•Some evidence of validity of Ponton-Satz Spanish Naming Test in TNP assessment among Spanish speaking Hispanics.
•Moderate validity for using category fluency for a TNP assessment
•Good support for the validity of Boston Naming Test (BNT) in TNP assessments
•Strong support for the validity of letter fluency in TNP assessment

Memory
•Strong support for the validity of Hopkins Verbal Learning Test – Revised (HVLT-R) in TNP assessments.

Executive functioning:
•Only moderate evidence for the reliability of Clock Drawing Test in TNP assessments.

ABSTRACT

Objective: Due to the recent COVID-19 pandemic, the field of neuropsychology must rapidly evolve to incorporate assessments delivered via telehealth, or teleneuropsychology (TNP). Given the increasing demand to deliver services electronically due to public health concerns, it is important to review available TNP validity studies. This systematic review builds upon the work of Brearly and colleagues' (2017) meta-analysis and provides an updated review of the literature, with special emphasis on test-level validity data.Method: Using similar methodology as Brearly and colleagues (2017) three internet databases (PubMed,

EBSCOhost, PsycINFO) were searched for relevant articles published since 2016. Studies with older adults (aged 65+) who underwent face-to-face and TNP assessments in a counterbalanced cross-over design were included. After review, 10 articles were retained. Combined with nine articles from Brearly's analysis, a total of 19 studies were included in the systematic review.Results: Retained studies included samples from 5 different countries, various ethnic/cultural backgrounds, and diverse diagnostic populations. Test-level analysis suggests there are cognitive screeners (MMSE, MoCA), language tests (BNT, Letter Fluency), attention/working memory tasks (Digit Span Total), and memory tests (HVLT-R) with strong support for TNP validity. Other measures are promising but lack sufficient support at this time. Few TNP studies have done in-home assessments and most studies rely on a PC or laptop.Conclusions: Overall, there appears to be good support for TNP assessments in older adults. Challenges to TNP in the current climate are discussed. Finally, a provisional outline of viable TNP procedures used in our clinic is provided.

FIGURES

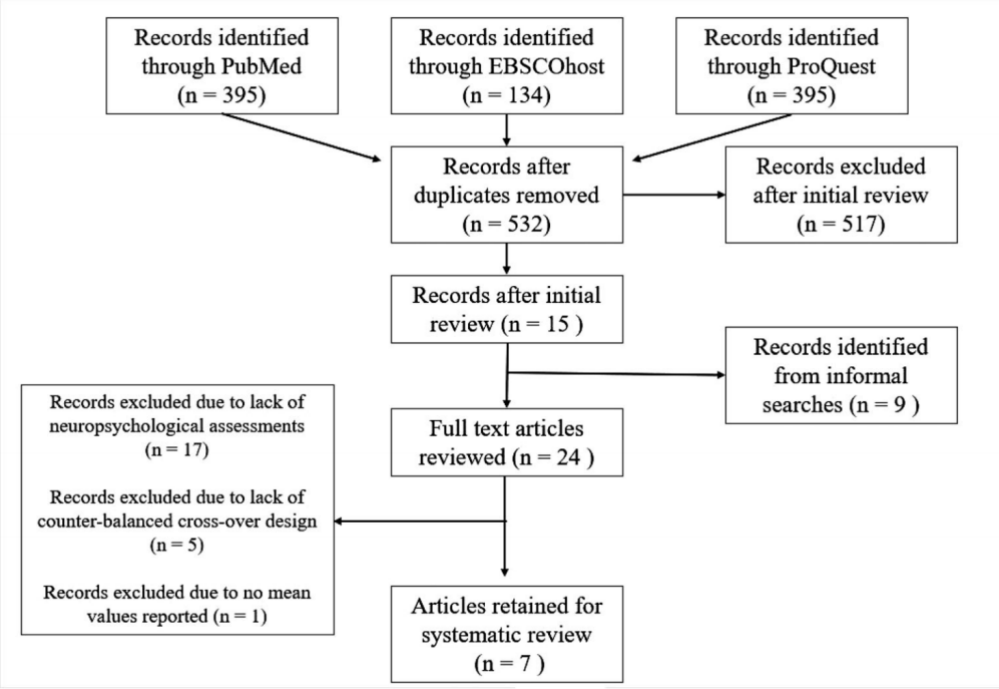


Figure 1. Flowchart of study selection. Note: Search was limited from 1/1/2016 to 3/22/2020 with the modifier of "older adult." Three of the articles excluded based on exclusion criteria were deemed important by the authors and retained for systematic review.

MEDICAL SUBSPECIALTIES

ENDOCRINOLOGY

SEDENTARINESS AND PHYSICAL ACTIVITY IN TYPE 2 DIABETES MELLITUS DURING THE COVID-19 PANDEMIC

Balducci S, Coccia EM.. Diabetes Metab Res Rev. 2020 Jun 27:e3378. doi: 10.1002/dmrr.3378. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

This commentary discusses how type 2 diabetic patients should strive to continue to achieve 150 minutes of aerobic and resistance exercise weekly during quarantine (Figure 1). The authors note that physical activity in these patients has been shown to improve metabolic health, immune responses, and anti-inflammatory to pro-inflammatory cytokine ratio suggesting that physical activity may be helpful in cultivating a better response to COVID-19 infection and could result in a less severe course.

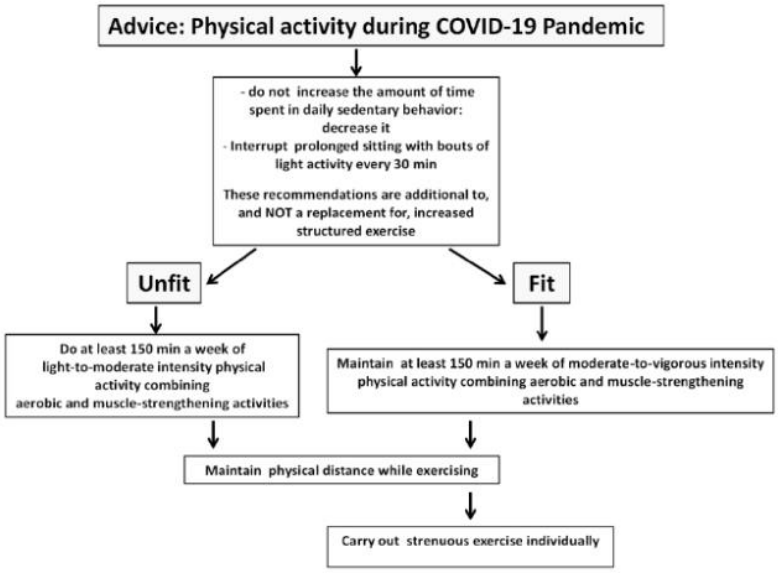


Figure 1. Lifestyle (Sedentary Time and Physical Activity) suggestions for T2DM patients during COVID-19 Pandemic

Figure 1. Lifestyle (Sedentary Time and Physical Activity) suggestions for T2DM patients during COVID-19 Pandemic

NANOPORE TARGETED SEQUENCING FOR THE ACCURATE AND COMPREHENSIVE DETECTION OF SARS-COV-2 AND OTHER RESPIRATORY VIRUSES

Wang M, Fu A, Hu B, Tong Y, Liu R, Liu Z, Gu J, Xiang B, Liu J, Jiang W, Shen G, Zhao W, Men D, Deng Z, Yu L, Wei W, Li Y, Liu T.. Small. 2020 Jun 24:e2002169. doi: 10.1002/smll.202002169. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A bioinformatic analysis by authors from China compared the gold standard RT-PCR to a novel nanopore targeted sequencing (NTS) to accurately identify SARS-CoV-2; this NTS method targets 12 nucleic acid fragments (i.e., virus encoding regions and ORF1ab). Findings show that NTS can identify SARS-CoV-2 and other respiratory viruses within 6-10 hours, and that the 22/61 suspected COVID-19 cases missed by RT-PCR were identified by NTS (Figure 6). The authors suggest that NTS may complement RT-PCR for diagnosing COVID-19 patients despite the longer turnaround time and increased operational skill (Figure 3).

ABSTRACT

The ongoing global novel coronavirus pneumonia COVID-19 outbreak has engendered numerous cases of infection and death. COVID-19 diagnosis relies upon nucleic acid detection; however, currently recommended methods exhibit high false-negative rates and are unable to identify other respiratory virus infections, thereby resulting in patient misdiagnosis and impeding epidemic containment. Combining the advantages of targeted amplification and long-read, real-time nanopore sequencing, herein, nanopore targeted sequencing (NTS) is developed to detect SARS-CoV-2 and other respiratory viruses simultaneously within 6-10 h, with a limit of detection of ten standard plasmid copies per reaction. Compared with its specificity for five common respiratory viruses, the specificity of NTS for SARS-CoV-2 reaches 100%. Parallel testing with approved real-time reverse transcription-polymerase chain reaction kits for SARS-CoV-2 and NTS using 61 nucleic acid samples from suspected COVID-19 cases show that NTS identifies more infected patients (22/61) as positive, while also effectively monitoring for mutated nucleic acid sequences, categorizing types of SARS-CoV-2, and detecting other respiratory viruses in the test sample. NTS is thus suitable for COVID-19 diagnosis; moreover, this platform can be further extended for diagnosing other viruses and pathogens.

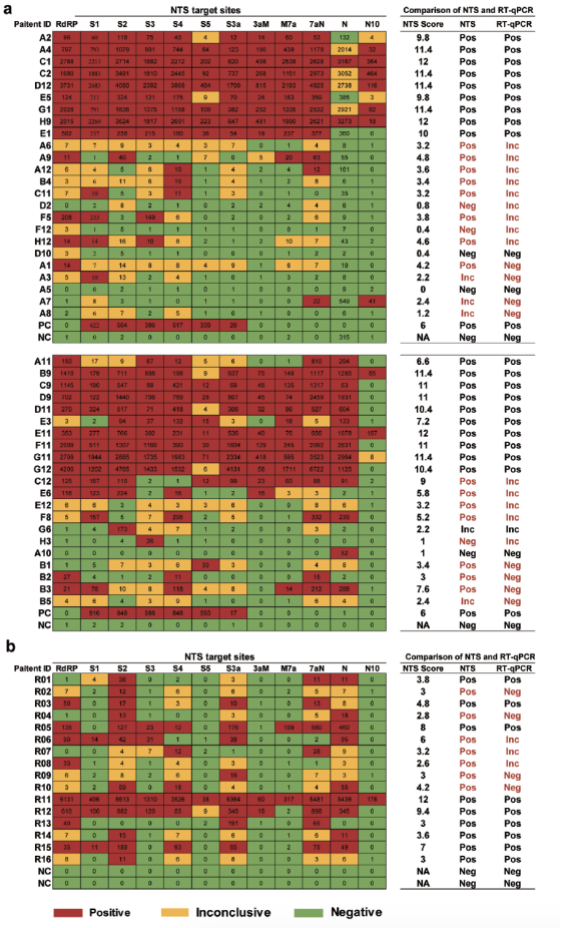


Figure 6. Comparison of 61 nucleic acid samples from clinical samples obtained using NTS (4 h) and RT-qPCR. a) Comparison of 45 nucleic acid samples from samples of patients with suspected COVID-19 obtained using NTS and RT-qPCR (kit 2). b) Comparison of 16 nucleic acid samples from patients with confirmed disease obtained using NTS and RT-qPCR (kit 1). The numbers in the table on the left represent the number of mapped reads according to our rules. PC: positive control. The plasmid harboring an S gene was used as a positive control in NTS testing; a positive sample in the kit served as a positive control in RT-qPCR testing. NC: negative control. TE buffer was used as a negative control in NTS testing; H2O in the kit served as a negative control in RTqPCR testing. All positive sample and negative sample in NTS were introduced from nucleic acid extraction. Pos: positive. Inc: inconclusive. Neg: Negative.

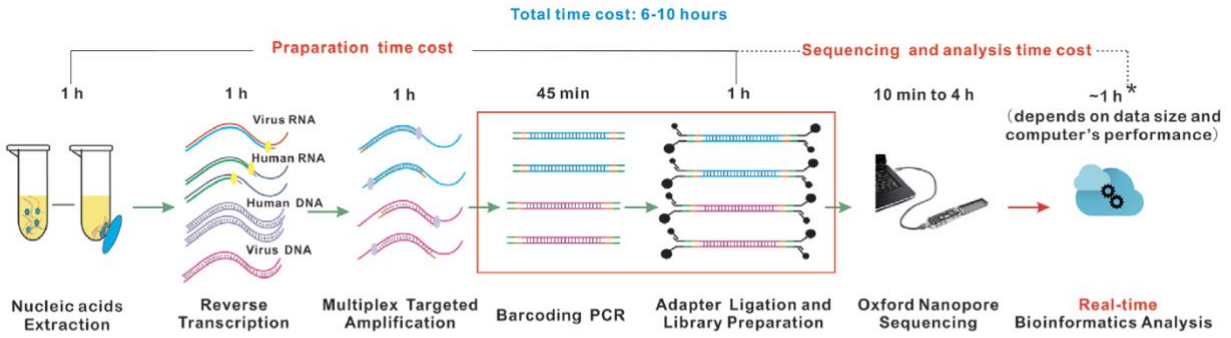


Figure 3. Turnaround time of NTS. The total nucleic acids, including single-stranded DNA/RNA and double-stranded DNA, were extracted, and the total RNA in the total nucleic acids was reverse transcript to cDNA. Specific regions of the DNA virus and cDNA of the RNA virus were amplified by multiplex PCR (one tube for SARS-CoV-2 and another tube for respiratory viruses). Next, the same barcode was added to both ends of the PCR product from the same sample using a barcoding PCR step. The barcoded products of each sample were pooled and used for sequencing library preparation. The barcoding PCR step in the red frame can be removed by directly ligating the barcode to products of multiplex PCR during library preparation using a commercial kit, the turnaround time and risk of cross-contamination could be further reduced. Time for bioinformatics analysis depends on data size and the computer's performance.

POTENTIAL ROLE OF INCRETINS IN DIABETES AND COVID-19 INFECTION: A HYPOTHESIS WORTH EXPLORING

Pantanetti P, Cangelosi G, Ambrosio G.. Intern Emerg Med. 2020 Jun 26. doi: 10.1007/s11739-020-02389-x. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

A review article by researchers in Italy explains how dipeptidyl peptidase-4 (DPP4; also known as CD26 lymphocyte surface protein) can stimulate the production of IL-6 and TNF-α and has been implicated in pulmonary diseases (Figure 1). DPP4 inhibitors (gliptins), currently used in treatment of type-2 diabetes mellitus, have been shown to reduce lung inflammation and injury, suggesting a potential therapeutic use in patients with COVID-19.

ABSTRACT

Patients with diabetes mellitus have been reported to be at a high risk of complications from SARS-CoV2 virus infection (COVID-19). In type 2 diabetes, there is a change in immune system cells, which shift from an anti-inflammatory to a predominantly pro-inflammatory pattern. This altered immune profile may induce important clinical consequences, including increased susceptibility to lung infections; and enhanced local inflammatory response. Furthermore, dipeptidyl peptidase 4 (DPP4) enzyme is highly expressed in the lung, and that it may have additional actions besides its effects on glucose metabolism, which might exert profound pro-inflammatory effects. We briefly review the impact on the inflammatory system of DPP4 for its possible detrimental effect on COVID-19 syndrome, and of DPP4 inhibitors (gliptins), currently used as glucose lowering agents, which may have the potential to exert positive pleiotropic effect on inflammatory diseases, in addition to their effects on glucose metabolism. Thanks to these ancillary effects, gliptins could potentially be "repurposed" as salutary drugs against COVID-19 syndrome, even in non-diabetic subjects. Clinical studies should be designed to investigate this possibility.

FIGURES

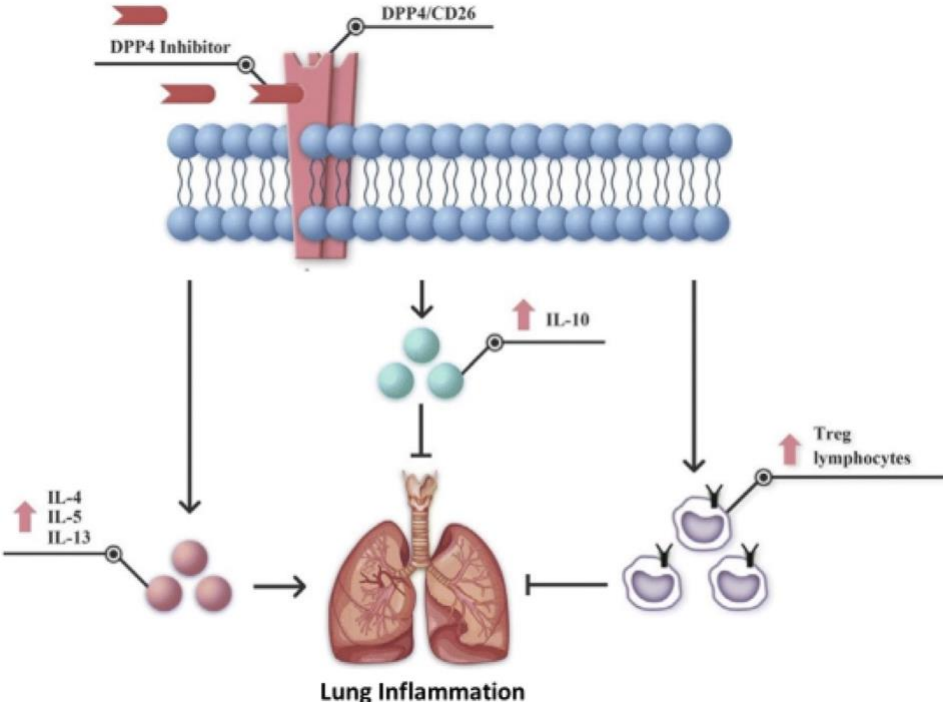


Figure 1: Mechanistic effects of DPP4 inhibition in lung injury (modified from Shao et al. 2020)

DECOY ACE2-EXPRESSING EXTRACELLULAR VESICLES THAT COMPETITIVELY BIND SARS-COV-2 AS A POSSIBLE COVID-19 THERAPY

Inal JM.. Clin Sci (Lond). 2020 Jun 26;134(12):1301-1304. doi: 10.1042/CS20200623.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A commentary by the London Metropolitan University and University of Hartfordshire proposes using small extracellular vesicles (sEVs) from engineered mesenchymal stromal/stem cells (MSCs) as an alternative therapy to soluble recombinant ACE2 in SARS-CoV-2 infection. The authors note the potential ability of ACE2+ MSCs-sEV to competitively inhibit SARS-CoV-2 from binding type II alveolar cells' ACE2 receptors (Figure 1) in addition to possibly inducing phagocytic activity and promoting anti-inflammatory effects, specifically in patients with COVID-19-induced acute respiratory distress syndrome (ARDS). Based on these observations, the authors call for investigation of ACE2+ MSCs-sEVs in animal models to uncover its potential as a therapy in SARS-CoV-2 infection.

ABSTRACT

The novel strain of coronavirus that appeared in 2019, SARS-CoV-2, is the causative agent of severe respiratory disease, COVID-19, and the ongoing pandemic. As for SARS-CoV that caused the SARS 2003 epidemic, the receptor on host cells that promotes uptake, through attachment of the spike (S) protein of the virus, is angiotensin-converting enzyme 2 (ACE2). In a recent article published by Batlle et al. (Clin. Sci. (Lond.) (2020) 134, 543-545) it was suggested that soluble recombinant ACE2 could be used as a novel biological therapeutic to intercept the virus, limiting the progression of infection and reducing lung injury. Another way, discussed here, to capture SARS-CoV-2, as an adjunct or alternative, would be to use ACE2+-small extracellular vesicles (sEVs). A competitive inhibition therapy could therefore be developed, using sEVs from engineered mesenchymal stromal/stem cells (MSCs), overexpressing ACE2.

FIGURES

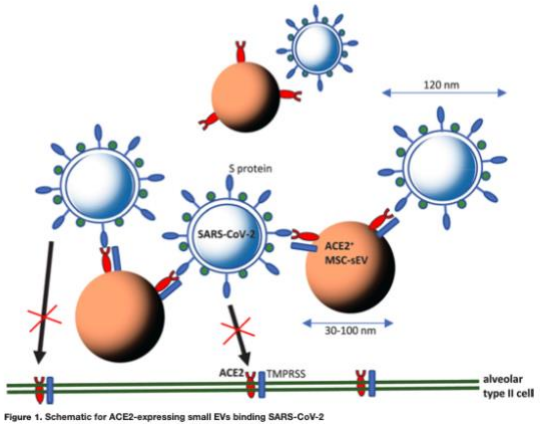


Figure 1. Schematic for ACE2-expressing small EVs binding SARS-CoV-2

Binding of SARS-CoV-2 S protein through ACE2 expressed on MSC-derived sEVs to competitively inhibit binding to ACE2 on alveolar type II cells and thereby limit infection. This could be tested using a human ACE2 transgenic mouse model and as a preliminary proof of concept study using sEVs from the tumour cell line, A549, a known model of alveolar type II cells [26] and thus a ready source of ACE2+ sEVs.

ANTIBODIES TO SARS-COV-2 AND THEIR POTENTIAL FOR THERAPEUTIC PASSIVE IMMUNIZATION

Klasse PJ, Moore JP.. Elife. 2020 Jun 23;9:e57877. doi: 10.7554/eLife.57877.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Researchers in New York reviewed the current literature on passive immunization and SARS-CoV-2 antibodies, finding that plasma infusions with SARS-CoV-2 antibodies may be an effective short-term treatment. The researchers believe monoclonal

antibodies may become more common in COVID-19 treatment within the next year but also warn that patients receiving antibody treatment should be monitored for antibody-mediated adverse events.

SUMMARY

Monoclonal antibody infusions seem to be an effective treatment via neutralizing receptors and clearing infections. However, the authors raise some concerns, acknowledging that most trials are studied on macaques and not humans. Given the limited evidence for human safety, they recommend that patients given new COVID-19 vaccines/treatment (monoclonal, polyclonal antibodies, combination, or recombinant receptor mimics) should be monitored for antibody-mediated adverse events due to differences in Fc receptors.

ABSTRACT

We review aspects of the antibody response to SARS-CoV-2, the causative agent of the COVID-19 pandemic. The topics we cover are relevant to immunotherapy with plasma from recovered patients, monoclonal antibodies against the viral S-protein, and soluble forms of the receptor for the virus, angiotensin converting enzyme 2. The development of vaccines against SARS-CoV-2, an essential public health tool, will also be informed by an understanding of the antibody response in infected patients. Although virus-neutralizing antibodies are likely to protect, antibodies could potentially trigger immunopathogenic events in SARS-CoV-2-infected patients or enhance infection. An awareness of these possibilities may benefit clinicians and the developers of antibody-based therapies and vaccines.

REMDESIVIR RECEIVES EMERGENCY USE AUTHORIZATION FOR SEVERELY ILL PATIENTS WITH COVID-19

Aschenbrenner DS.. Am J Nurs. 2020 Jul;120(7):26. doi: 10.1097/01.NAJ.0000688196.83625.b1.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

A nurse at Notre Dame of Maryland University reports that as of May 1st, 2020 the Food and Drug Administration (FDA) has approved the emergency use of intravenous remdesivir, reconstituted with normal saline, for patients with severe COVID-19 infection. The author also notes that remdesivir continues to be studied in clinical trials in order to asses its safety and efficacy. Clinicians should note the major adverse effects of remdesivir are increased liver enzymes and infusion reaction.

TARGETING SARS-COV-2 NON-STRUCTURAL PROTEIN 16: A VIRTUAL DRUG REPURPOSING STUDY

Tazikeh-Lemeski E, Moradi S, Raoufi R, Shahlaei M, Janlou MAM, Zolghadri S.. J Biomol Struct Dyn. 2020 Jun 23:1-14. doi: 10.1080/07391102.2020.1779133. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

An in silico study in Iran performed docking and molecular dynamic simulations on 1516 FDA-approved drugs that had high similarity to the S-adenosyl-L-methionine (SAM) analog sinefungin, which has been shown to inhibit Non-Structural Protein 16 (nsp-16, a viral RNA methyltransferase that has been targeted for COVID-19 therapeutics). Docking simulations, binding energy analysis, and molecular dynamic simulation (Tables 2-4) distinguished Raltegravir and Maraviroc as optimal candidates for COVID-19 therapies, suggesting further investigation and clinical trials on these two drugs are needed.

ABSTRACT

Non-Structural Protein 16 (nsp-16), a viral RNA methyltransferase (MTase), is one of the highly viable targets for drug discovery of coronaviruses including SARS-CoV-2. In this study, drug discovery of SARS-CoV-2 nsp-16 has been performed by a virtual drug repurposing approach. First, drug shape-based screening (among FDA approved drugs) with a known template of MTase inhibitor, sinefungin was done and best compounds with high similarity scores were selected. In addition to the selected compounds, 4 nucleoside analogs of anti-viral (Raltgravir, Maraviroc and Favipiravir) and anti-inflammatory (Prednisolone) drugs were selected for further investigations. Then, binding energies and interaction modes were found by molecular docking approaches and compouds with lower energy were selected for further investigation. After that, Molecular dynamics (MD) simulation was carried to test the potential selected compounds in a realistic environment. The results showed that Raltegravir and Maraviroc among other compounds can bind strongly to the active site of the protein compared to sinefungin, and can be potential candidates to inhibit NSP-16. Also, the MD simulation results suggested that the Maraviroc

and Raltegravir are more effective drug candidates than Sinefungin for inhibiting the enzyme. It is concluded that Raltegravir and Maraviroc which may be used in the treatment of COVID-19 after Invitro and invivo studies and clinical trial for final confirmation of drug effectiveness. Communicated by Ramaswamy H. Sarma.

FIGURES

Table 2. Theoretical binding free energies ($\Delta G_{binding}$ (kcal mol^{-1})) as obtained by tree different molecular docking experiments; Autodock vina, Autodock 4.2 and SwissDock.

		Local docking		
Ligand	Drug category	Autodock vina	Autodock 4.2	Blind docking Swissdock
Cladribine	Anticancer	−6.4	−6.59	−9.14
Vidarabine	Antiviral	−6.2	−5.04	−8.88
Fludarabine	Anticancer	−6.5	−5.77	−7.65
Clofarabine	Anticancer	−6.3	−6.05	−9.14
Maraviroc	Antiviral	**−8.3**	**−9.73**	**−9.15**
Raltegravir	Antiviral	**−10.4**	**−8.3**	**−8.21**
Fivapiravir	Antiviral	−5.3	−5.27	−6.79
Didanosine	Antiviral	−6.2	−5.95	−7.41
Prednisolone	Immunosuppressive and Anti-Inflammatory Agents	**−7.7**	**−6.66**	**−7.38**
Sinefungin	Anti-infective/Nucleoside Analog	**−7.2**	**−7.24**	**−8.14**

Table 3. Binding energies, inhibition constants and H-bond interaction of compounds against NSP-16.

Ligand	$\Delta G_{binding}$ (kcal mol^{-1})	Inhibition Constant (K_i)	H-Bond Interaction
Cladribine	−6.59	10.49 μM	Asp 6897 Cys 6913, Tyr 6930
Vidarabine	−5.04	194.14 μM	Gly 6911 Asp 6897 Cys 6913, Tyr 6930
Fludarabine	−5.77	58.92 μM	Asp6897 Tyr 6930, Asn6899, Leu6898 Cts 6913
Clofarabin	−6.05	36.77 μM	Tyr 6930, Cys 6913, Gly 6911, Leu 6898
Maraviroc	−9.73	73.54 nM	phe 6947
Prednisolone	−6.66	13.07 μM	Asp6897, Gly6911, Met6929
Didanosine	−5.95	43.7 μM	Cys6913, Tyr 6930, Asp 6928
Raltegravir	−8.3	818.66 nM	Phe 6947, Asp 6897
Favipiravir	−5.27	136.87 μM	Gly 6911, Gly 6869, Cys 6913
Sinefungin	−7.24	4.93 μM	Asp6897, Asp 6912, Asp 6928, Tyr 6930, Asn6899, Leu6898

Table 4. Total energy of Protein-drug interaction. All values were calculated as kJ/mol.

Hits	E_{vdw}	E_{ele}	E_{total}
Maraviroc	−138.24	−1125.73	−1263.97
Raltegravir	−131.31	−503.69	−634.10
Prednisolone	−65.57	−80.47	−146.04
Sinefungin	−88.64	−469.66	−558.31

THWARTED BELONGINGNESS AND PERCEIVED BURDENSOMENESS EXPLAIN THE ASSOCIATIONS OF COVID-19 SOCIAL AND ECONOMIC CONSEQUENCES TO SUICIDE RISK

Gratz KL, Tull MT, Richmond JR, Edmonds KA, Scamaldo K, Rose JP.. Suicide Life Threat Behav. 2020 Jun 26. doi: 10.1111/sltb.12654. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

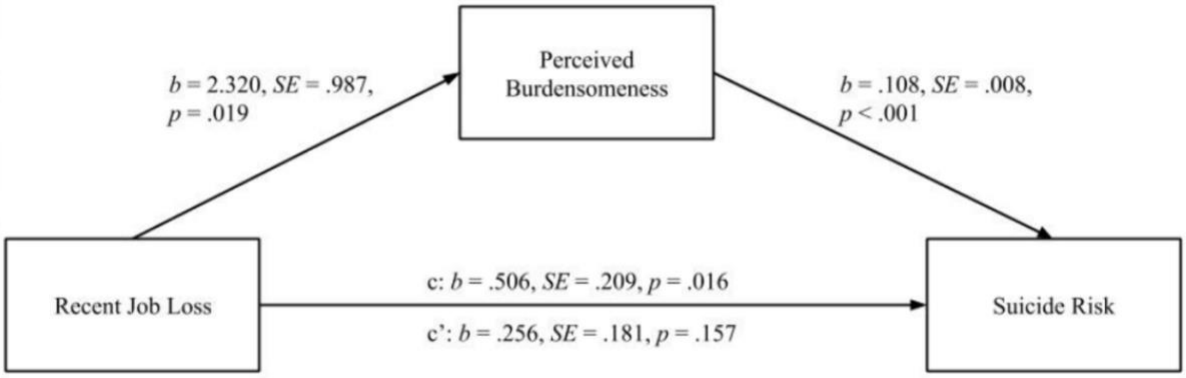
BLUF

Using an online survey, the authors evaluated 500 people from 45 states between March 27 and April 5, 2020 to determine if feelings of "thwarted belongingness" and "perceived burdensomeness", which they hypothesize to be a result of social distance measures and mass job losses, respectively, have contributed to increased suicide risk during the current climate. Analysis of the results revealed that job loss had a statistically significant ($p<001$) indirect impact on suicide risk through feelings of "perceived burdensomeness" and attributed to 29% of the variance of suicide risk (Figure 1). Similarly, social isolation had a significant ($p<001$) indirect impact on suicide risk, accounting for 11% of suicide risk variance (Figure 2). Thus, the authors emphasize that providers be are aware of feelings of "thwarted belongingness" and "perceived burdensomeness" as the underpinning of this increased risk and that social climate contributes to increased suicide risk.

ABSTRACT

OBJECTIVE: The social and economic consequences of COVID-19 and related public health interventions aimed at slowing the spread of the virus have been proposed to increase suicide risk. However, no research has examined these relations. This study examined the relations of two COVID-19 consequences (i.e., stay-at-home orders and job loss) to suicide risk through thwarted belongingness, perceived burdensomeness, and loneliness.
METHOD: Online data from a nationwide community sample of 500 adults (mean age = 40) from 45 states were collected between March 27 and April 5, 2020. Participants completed measures assessing thwarted belongingness, perceived burdensomeness, loneliness, and suicide risk, as well as whether they (a) were currently under a stay-at-home order and (b) had experienced a recent job loss due to the pandemic.
RESULTS: Results revealed a significant indirect relation of stay-at-home order status to suicide risk through thwarted belongingness. Further, whereas recent job loss was significantly correlated with suicide risk, neither the direct relation of job loss to suicide risk (when accounting for their shared relations to perceived burdensomeness) nor the indirect relation through perceived burdensomeness was significant.
CONCLUSIONS: Results highlight the potential benefits of interventions targeting thwarted belongingness and perceived burdensomeness to offset suicide risk during this pandemic.

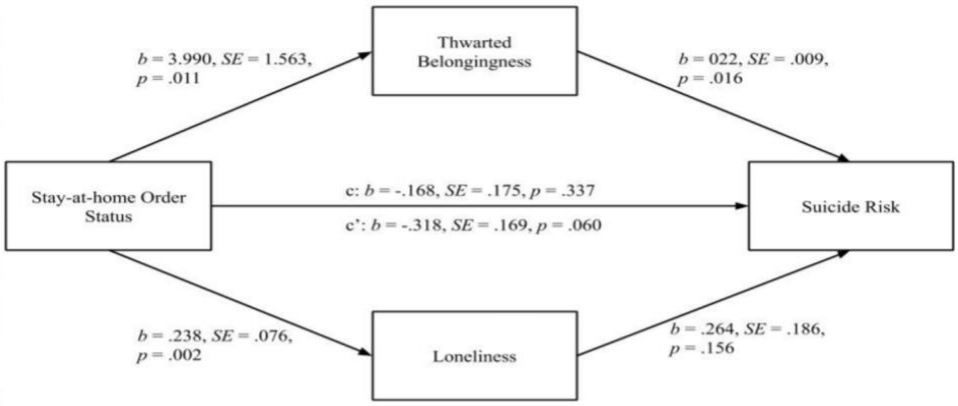
Figure 1. Indirect relation of recent job loss to suicide risk through perceived burdensomeness.



Indirect Effect			
Variable	*Effect*	*SE*	*95% Confidence Interval*
Perceived Burdensomeness	.250	.155	-.026, .581

Note. Covariates included in the model were age, sex, racial/ethnic background, income, and whether participants lived alone.

Figure 2. Indirect relations of stay-at-home order status to suicide risk through thwarted belongingness and loneliness.



Indirect Effects			
Variable	*Effect*	*SE*	*95% Confidence Interval*
Thwarted Belongingness	.087	.055	.001, .212
Loneliness	.063	.057	-.035, .193

Note. Covariates included in the model were age, sex, racial/ethnic background, income, and whether participants lived alone.

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