The Daily COVID-19 Literature Surveillance Summary

February 01, 2021

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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

Epidemiology

- What does the literature say about face mask usage against COVID-19? A large international, interdisciplinary group summarize the evidence supporting mask wearing to mitigate the spread of COVID-19. They reviewed direct epidemiological evidence, population-level impacts, transmission characteristics, laboratory-based source control experiments, personal protective equipment efficacy research, sociological considerations, and implementation policies. Authors conclude all evidence indicates mask wearing effectively reduces viral droplet transmission and should be encouraged by officials to help minimize the spread of COVID-19.

- Immunologic response against SARS-CoV-2 may be compromised in multiple sclerosis (MS) patients. A case control study of 48 suspected COVID-19 cases and 45 COVID-19 positive cases conducted at the Multiple Sclerosis Centre of Catalonia (Cemcat) in Barcelona, Spain found similar incidence and outcomes of COVID-19 in MS patients compared to the general population. However, far fewer MS patients on long-term anti-CD20 therapies created SARS-CoV-2 antibodies than patients not on these medications (17.6% and 45.6%, respectively), suggesting this specific patient population may be at a higher risk of COVID-19 reinfection. It is unknown if this immunosuppressed population would be unable to generate immunity from the COVID-19 vaccines as well.

Understanding the Pathology

- ABO blood group showed minimal differences in SARS-CoV-2 antibody response but blood group B had higher neutralizing antibody titers. A multicenter prospective cohort study conducted by Johns Hopkins University, Mississippi Valley Regional Blood Center in Springfield, IL, Washington University School of Medicine in St. Louis, MO, Mayo Clinic in Rochester, MN, and National Institute of Health in Baltimore, MD involved 202 individuals who were eligible to donate COVID-19 convalescent plasma at the beginning of the pandemic. They found there was no difference in anti-SARS-CoV-2 spike IgA or IgG between ABO groups, but significantly higher neutralizing antibody (nAb) titers were present in blood group B (44%) compared to blood groups A (25%), O (20%) and AB (0%). These findings suggest blood group B may have higher nAb titers after recovery from COVID-19 infection and thus greater protection against future infection with SARS-CoV-2, however further studies correlating ABO blood groups and disease severity are needed to further support these findings.

- Microthrombi is a major cause of cardiac injury in COVID-19. A pathologic analysis conducted by CVPath Institute, Inc and the University of Maryland of 40 autopsied hearts of patients who died while hospitalized for COVID-19 at Ospedale Papa Giovanni XXIII hospital in Bergamo, Italy found the microthrombi isolated in COVID-19 patients were richer in fibrin and terminal compliment immunostaining compared to aspirated thrombi from percutaneous coronary intervention in other COVID-19 infected and uninfected patients with STEMI. This is most likely due to SARS-CoV-2 activation of multiple compliment levels. Microthrombi were found to be significantly associated with focal myocyte necrosis in 82% (9/11) cases of the 14 overall cases with myocyte necrosis. These findings suggest the majority of cardiac injury found in subjects dying with COVID-19 is due to cardiac microthrombi, indicating a likely cause of cardiac injury among hospitalized COVID-19 patients, and highlights need for further studies on the targeted use of anti-platelet, anti-coagulant, and anti-complement therapies specifically tailored for microthrombi.

Transmission & Prevention

- Further robust research is necessary to deduce the link, if any between COVID-19 vaccination efficacy and obesity. Researchers from Harvard Medical School, Massachusetts General Hospital and ConscienHealth in Pittsburgh refute previous speculations that obesity could be associated with reduced efficacy of the COVID-19 vaccines. Data from Phase 3 vaccine trial results show Pfizer-BioNTech has 95.4% efficacy (CI: 86.0 - 99.1%) in people with obesity compared to 94.8% (CI: 87.4-98.3%) in people without obesity and Moderna efficacy of 91.2% (CI:32.0-98.9%) in people with severe obesity and 94.8% (CI: 89.3-96.8%) overall. Since obesity is one of the most significant risk factors for severe outcomes from COVID-19, these authors suggest that ongoing placebo-controlled vaccine trials designed with necessary power for detecting differences among classes of obesity are important for post-vaccine risk stratification and public health strategy.

- A nanomechanical study found SARS-CoV-2 to survive best on polystyrene compared to other tested inanimate surfaces. A nanomechanical study by researchers in Alberta, Canada and Changsha, Shenzhen, and Guangdong, China tested SARS-CoV-2 survival on four different surfaces and found that the spike protein on the outer surface of the SARS-CoV-2 virion, which is responsible for transmission via fomites, survived the best on polystyrene, then stainless steel, then gold, and then on glass, suggesting that fomite transmission of SARS-CoV-2 is prevalent and that more surfaces need to be tested to get a better understanding for both prevention and tracking transmission of the virus.

TABLE OF CONTENTS

EPIDEMIOLOGY

AN EVIDENCE REVIEW OF FACE MASKS AGAINST COVID-19

Howard J, Huang A, Li Z, Tufekci Z, Zdimal V, van der Westhuizen HM, von Delft A, Price A, Fridman L, Tang LH, Tang V, Watson GL, Bax CE, Shaikh R, Questier F, Hernandez D, Chu LF, Ramirez CM, Rimoin AW.. Proc Natl Acad Sci U S A. 2021 Jan 26;118(4):e2014564118. doi: 10.1073/pnas.2014564118.
Level of Evidence: 5 - Review / Literature Review

BLUF

A large international, interdisciplinary group summarize the evidence supporting mask wearing to mitigate the spread of COVID-19. They reviewed direct epidemiological evidence, population-level impacts (Figure 1), transmission characteristics, laboratory based source control experiments, personal protective equipment efficacy research, sociological considerations, and implementation policies (see summary below). Authors conclude all evidence indicates mask wearing effectively reduces viral droplet transmission and should be encouraged by officials to help minimize the spread of COVID-19.

SUMMARY

The authors review evidence in several categories, with the following conclusions:

1. Direct epidemiological evidence from randomized controlled trials, systematic reviews/meta-analyses:
- "direct evidence of the efficacy of mask use is supportive, but inconclusive. Since there are no RCTs, only one observational trial, and unclear evidence from other respiratory illnesses, we will need to look at a wider body of evidence"
- one observational study showed that face masks were 79% effective in preventing transmission
- a Cochrane review of 67 randomized controlled trials (not specifically of SARS-CoV-2) suggested mask-wearing could help interrupt spread of respiratory viruses, as did a review by the Usher Institute

2. Population-level impact (ecological studies, modeling)(Figure 1):
-"mask use may have been an important driver of differences in SARS-CoV-2 outcomes in different regions. These outcomes are in line with models that predict substantial population level impacts of widespread mask use"

3. Laboratory based source control experiments:
- No studies have measured the amount of infectious SARS-CoV-2 particles in relation to mask wearing in normal human actions
- " there is laboratory-based evidence that household masks have filtration capacity in the relevant particle size range, as well as efficacy in blocking aerosols and droplets from the wearer"

4. Personal protective equipment (PPE) efficacy research:
-"cloth face covers can provide good fit and filtration for PPE in some community contexts, but results will vary depending on material and design, the way they are used, and the setting in which they are used."

5. Sociological considerations:
- concerns that masks might increase other risky behavior has been proven incorrect
- there is stigma associated with mask-wearing which should be addressed, especially if only sick people wear them.
- Historically stigmatized groups, especially Black people in America, may feel reluctant to wear masks for fear of being seen as a criminal.
- The authors further suggest “Universal mask wearing could serve as a visible signal and reminder of the pandemic. Signaling participation in health behaviors by wearing a mask as well as visible enforcement can increase compliance with public mask wearing, but also other important preventative behaviors"

6. Implementation Considerations:
- there has been a global shortage of PPE, which has been managed with sterilization, equipment reuse, and asking the public to not use medical grade supplies
- face shields may provide eye protection as well as "better visibility of facial expressions and fewer obstacles for...people who rely on lip reading for communication"
- several studies indicate government-mandated mask wearing increases adherence

ABSTRACT

The science around the use of masks by the public to impede COVID-19 transmission is advancing rapidly. In this narrative review, we develop an analytical framework to examine mask usage, synthesizing the relevant literature to inform multiple areas: population impact, transmission characteristics, source control, wearer protection, sociological considerations, and implementation considerations. A primary route of transmission of COVID-19 is via respiratory particles, and it is known to be transmissible from presymptomatic, paucisymptomatic, and asymptomatic individuals. Reducing disease spread requires two things: limiting contacts of infected individuals via physical distancing and other measures and reducing the transmission probability per contact. The preponderance of evidence indicates that mask wearing reduces transmissibility per contact by reducing transmission of infected respiratory particles in both laboratory and clinical contexts. Public mask wearing is most effective at reducing spread of the virus when compliance is high. Given the current shortages of medical masks, we recommend the adoption of public cloth mask wearing, as an effective form of source control, in conjunction with existing hygiene, distancing, and contact tracing strategies. Because many respiratory particles become smaller due to evaporation, we recommend increasing focus on a previously overlooked aspect of mask usage: mask wearing by infectious people ("source control") with benefits at the population level, rather than only mask wearing by susceptible people, such as health care workers, with focus on individual outcomes. We recommend that public officials and governments strongly encourage the use of widespread face masks in public, including the use of appropriate regulation.

FIGURES

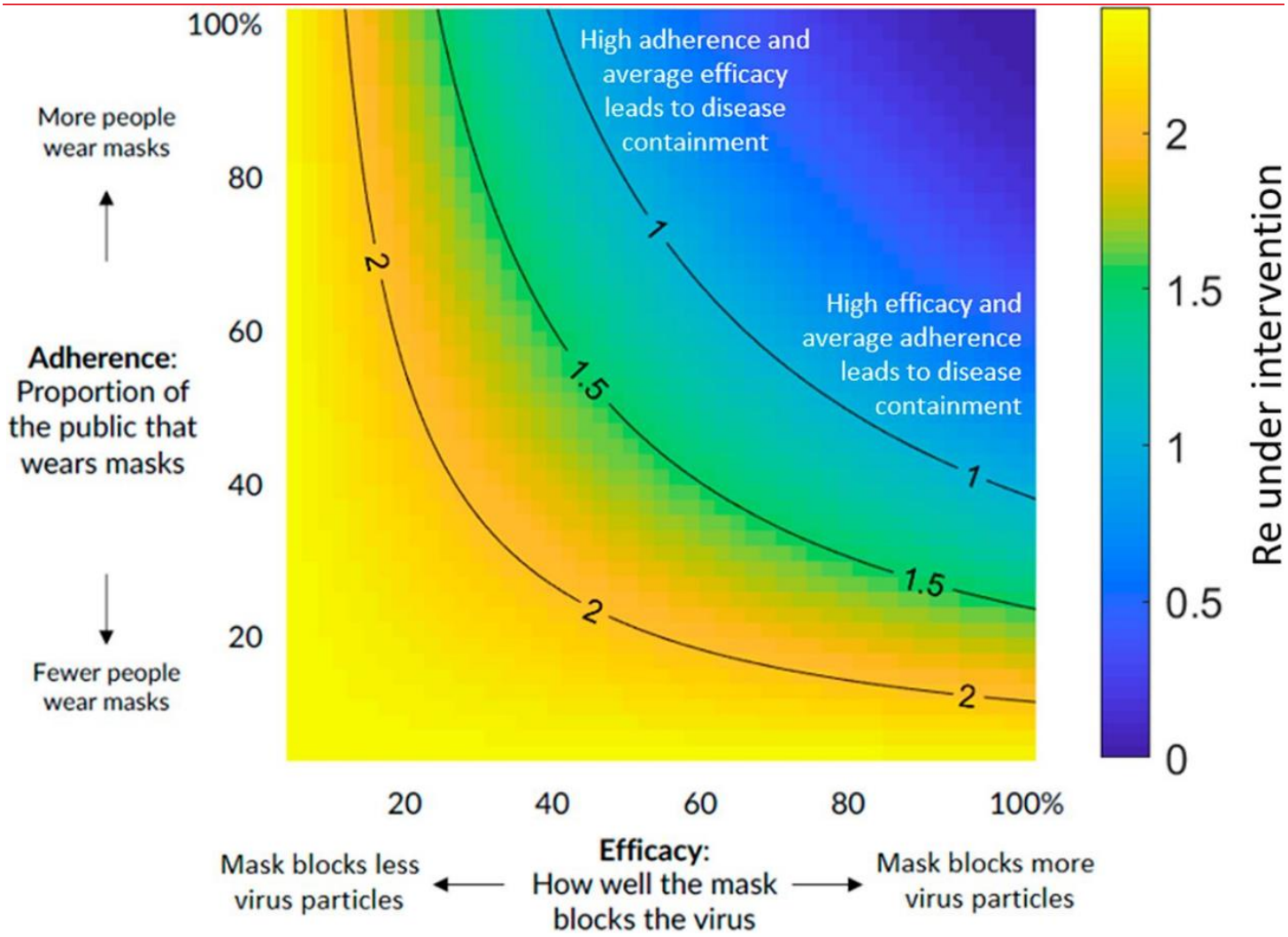

Fig. 1.

Impact of public mask wearing under the full range of mask adherence and efficacy scenarios. The color indicates the resulting reproduction number Re from an initial R0 of 2.4 (40). Blue area is what is needed to slow the spread of COVID-19. Each black line represents a specific disease transmission level with the effective reproduction number Re indicated.

ADULTS

COVID-19 IN MS PATIENTS: SUSCEPTIBILITY, SEVERITY RISK FACTORS AND SEROLOGICAL RESPONSE

Zabalza A, Cárdenas-Robledo S, Tagliani P, Arrambide G, Otero-Romero S, Carbonell-Mirabent P, Rodriguez-Barranco M, Rodríguez-Acevedo B, Restrepo Vera JL, Resina-Salles M, Midaglia L, Vidal-Jordana A, Río J, Galan I, Castillo J, Cobo-Calvo Á, Comabella M, Nos C, Sastre-Garriga J, Tintore M, Montalban X.. Eur J Neurol. 2020 Dec 19. doi: 10.1111/ene.14690. Online ahead of print.
Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

A case control study of 48 suspected COVID-19 cases and 45 COVID-19 positive cases conducted at the Multiple Sclerosis Centre of Catalonia (Cemcat) in Barcelona, Spain conducted from February - May, 2020 found similar incidence and outcomes of COVID-19 in MS patients compared to the general population. However, far fewer MS patients on long-term anti-CD20 therapies created SARS-CoV-2 antibodies than patients not on these medications (17.6% and 45.6%, respectively), suggesting this specific patient population may be at a higher risk of COVID-19 reinfection (Figures 2 and 3). It is unknown if this immunosuppressed population would be unable to generate immunity from the COVID-19 vaccines as well.

ABSTRACT

BACKGROUND: Information regarding multiple sclerosis (MS) patients with COVID-19 is scarce. The study objective is to describe the incidence and characteristics of MS patients with COVID-19, to identify susceptibility and severity risk factors, and to assess the proportion of positive SARS-CoV-2 serologies according to disease modifying treatments (DMTs). METHODS: Retrospective study of an MS cohort analysing data collected between February and May 2020. Cases were identified through an email survey and clinical visits. We examined the relationship of demographic and MS characteristics with COVID-19 and of the DMTs with SARS-CoV-2 serostatus. RESULTS: We collected data from 48 suspected cases out of 758 valid respondents and from 45 COVID-19 cases identified through clinical visits. Incidence was 6.3%. Nineteen(20.3%) patients were hospitalized and 2(2.2%) died. Multivariable models determined that age (odds ratio per 10 years:0.53[95% CI,0.34-0.85]), contact with a confirmed case (OR:197.02[56.36-688.79]), residence in Barcelona (OR:2.23[1.03-4.80]), MS duration (OR per 5y:1.41[1.09-1.83]), and time on anti-CD20-treatment (OR per 2y: 3.48[1.44-8.45]) were independent factors for presenting COVID-19 and age (OR per 10y:2.71[1.13-6.53]) for a severe COVID-19. Out of the 79 (84.9%) with serological test, 45.6% generated antibodies, but only 17.6% of those on anti-CD20 therapies. Lymphopenia or immunoglobulins levels did not relate with COVID-19. CONCLUSIONS: MS patients present similar incidence, risk factors, and outcomes for COVID-19 than the general population. Patients treated with an anti-CD20 therapy for a longer period of time might be in a higher risk of COVID-19 and less than 20% generate antibody response. Only age was related with severity.

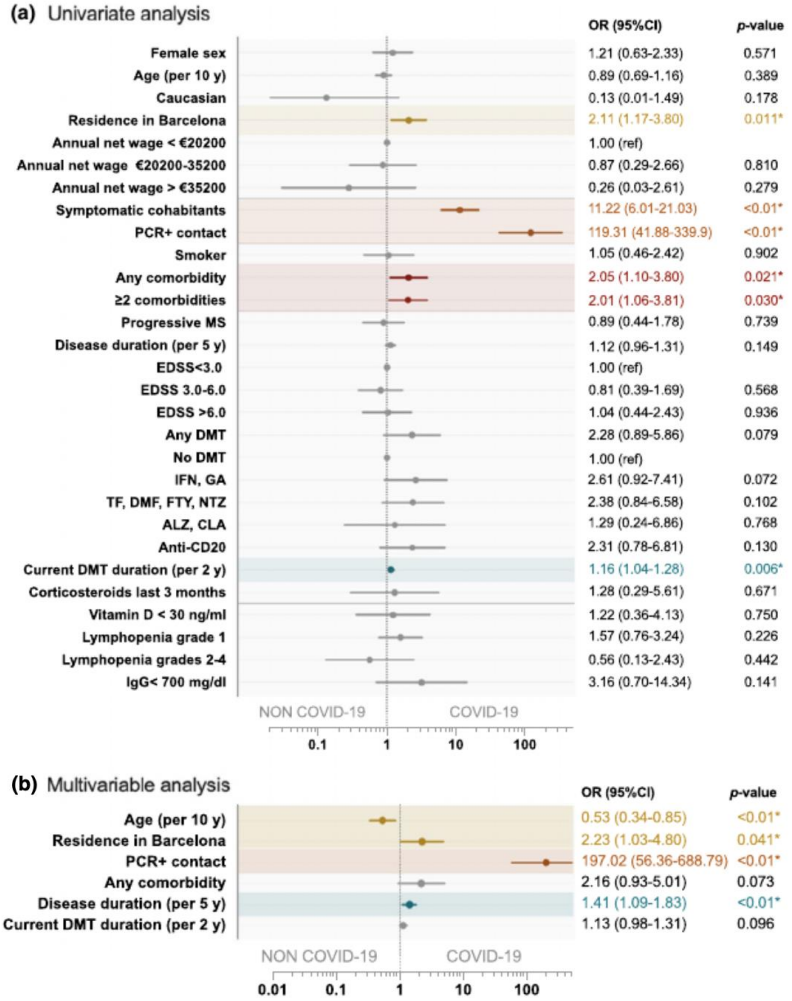

Figure 2: Risk factors for COVID-19 susceptibility. (a) Univariate analysis. (b) Multivariable analysis. Forest plot depicting unadjusted odds ratio (OR) for presenting COVID-19 in our cohort.

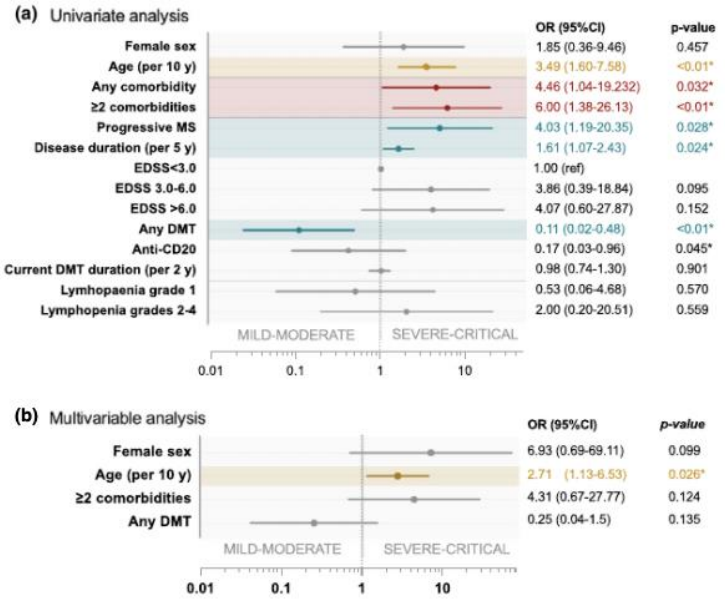

Figure 3: Risk factors for a severe-critical course of COVID-19. (a) Univariate analysis. (b) Multivariate analysis. Forest plot depicting unadjusted odds ratio (OR) for presenting severe COVID019 in our cohort.

ABO BLOOD GROUP AND SARS-COV-2 ANTIBODY RESPONSE IN A CONVALESCENT DONOR POPULATION

Bloch EM, Patel EU, Marshall C, Littlefield K, Goel R, Grossman BJ, Winters JL, Shrestha R, Burgess I, Laeyendecker O, Shoham S, Sullivan D, Gehrie EA, Redd AD, Quinn TC, Casadevall A, Pekosz A, Tobian AAR.. Vox Sang. 2021 Jan 25. doi: 10.1111/vox.13070. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A multicenter prospective cohort study conducted by Johns Hopkins University, Mississippi Valley Regional Blood Center in Springfield, IL, Washington University School of Medicine in St. Louis, MO, Mayo Clinic in Rochester, MN, and National Institute of Health in Baltimore, MD involved 202 individuals who were eligible to donate COVID-19 convalescent plasma at the beginning of the pandemic. They found there was no difference in anti-SARS-CoV-2 spike IgA or IgG between ABO groups (See Figure 1) but significantly higher neutralizing antibody (nAb) titers present in blood group B (44%) compared to blood groups A (25%), O (20%) and AB (0%) (See Table 2). These findings suggest blood group B may have higher nAb titers after recovery from COVID-19 infection and thus greater protection against future infection with SARS-CoV-2, however further studies correlating ABO blood groups and disease severity are needed to further support these findings.

ABSTRACT

BACKGROUND AND OBJECTIVES: ABO blood group may affect risk of SARS-CoV-2 infection and/or severity of COVID-19. We sought to determine whether IgG, IgA and neutralizing antibody (nAb) to SARS-CoV-2 vary by ABO blood group. MATERIALS AND METHODS: Among eligible convalescent plasma donors, ABO blood group was determined via agglutination of reagent A1 and B cells, IgA and IgG were quantified using the Euroimmun anti-SARS-CoV-2 ELISA, and nAb titres were quantified using a microneutralization assay. Differences in titre distribution were examined by ABO blood group using non-parametric Kruskal-Wallis tests. Adjusted prevalence ratios (aPR) of high nAb titre (>=1:160) were estimated by blood group using multivariable modified Poisson regression models that adjusted for age, sex, hospitalization status and time since SARS-CoV-2 diagnosis. RESULTS: Of the 202 potential donors, 65 (32%) were blood group A, 39 (19%) were group B, 13 (6%) were group AB, and 85 (42%) were group O. Distribution of nAb titres significantly differed by ABO blood group, whereas there were no significant differences in anti-spike IgA or anti-spike IgG titres by ABO blood group. There were significantly more individuals with high nAb titre (>=1:160) among those with blood group B, compared with group O (aPR = 1 9 [95%CI = 1 1-3 3], P = 0 029). Fewer individuals had a high nAb titre among those with blood group A, compared with group B (aPR = 0 6 [95%CI = 0 4-1 0], P = 0 053). CONCLUSION: Eligible CCP donors with blood group B may have relatively higher neutralizing antibody titres. Additional studies evaluating ABO blood groups and antibody titres that incorporate COVID-19 severity are needed.

FIGURES

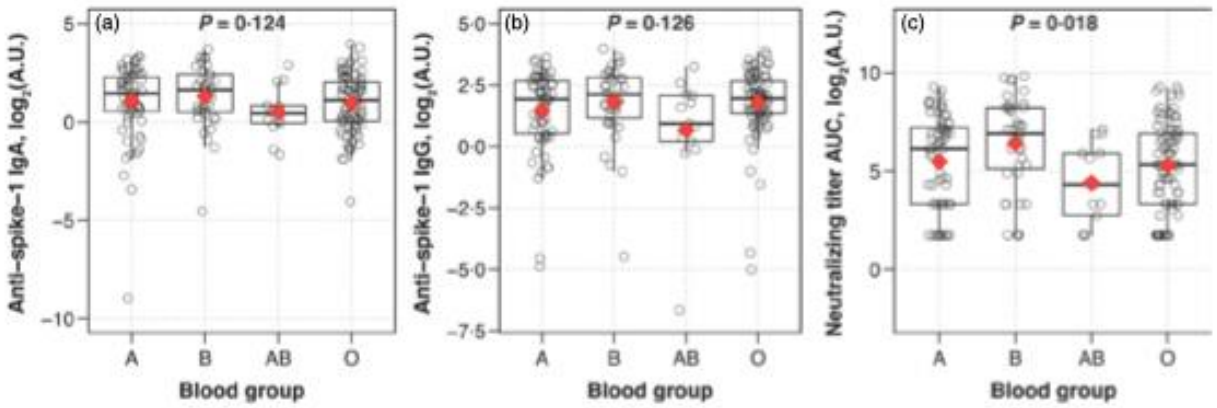

Fig. 1 Distribution of IgA, IgG and neutralizing antibody titres to SARS-CoV-2 by ABO blood group in eligible convalescent plasma donors. Box-and-whisker plots were used to depict the median (thick horizontal line), interquartile ranges and upper/lower extreme limits. The red diamond depicts thearithmetic mean. Circles depict the individual data points. P values were determined from non-parametric Kruskal–Wallis tests

	SARS-CoV-2 neutralizing titre AUC, log2(arbitrary units)			
	Univariable		Multivariable	
Blood group (vs. reference blood group)	β (95% CI)[a]	*P* value	β (95% CI)[b]	*P* value
A vs. O	0·2 (−0·6, 0·9)	0·637	0·0 (−0·7, 0·7)	0·994
B vs. O	1·1 (0·2, 2·0)	0·014	0·9 (0·1, 1·8)	0·026
AB vs. O	−0·9 (−2·2, 0·5)	0·201	−1·0 (−2·3, 0·3)	0·116
A vs. B	−0·9 (−1·9, −0·0)	0·048	−0·9 (−1·8, −0·1)	0·031
AB vs. B	−2·0 (−3·5, −0·5)	0·008	−2·0 (−3·4, −0·6)	0·005
A vs. AB	1·1 (−0·3, 2·5)	0·131	1·0 (−0·3, 2·4)	0·120
	SARS-CoV-2 neutralizing titre AUC ≥ 160 arbitrary units			
	Univariable		Multivariable	
Blood group (vs. reference blood group)	Crude PR (95% CI)[c]	*P* value	Adjusted PR (95% CI)[d]	*P* value
A vs. O	1·2 (0·7, 2·2)	0·500	1·1 (0·6, 2·0)	0·684
B vs. O	2·2 (1·2, 3·8)	0·006	1·9 (1·1, 3·3)	0·029
AB vs. O[e]	-	-	-	-
A vs. B	0·6 (0·3, 1·0)	0·044	0·6 (0·4, 1·0)	0·053
AB vs. B[e]	-	-	-	-
A vs. AB[e]	-	-	-	-

Table 2 Association of ABO blood group with neutralizing antibody titres to SARS-CoV-2 in eligible convalescent plasma donors.

Abbreviations: AUC, area under the curve; CI, confidence interval; PR, prevalence ratio.Bold values correspond to statistically significant findings.ab represents the absolute difference in log(SARS-CoV-2) nAb AUC value with the reference group as estimated by univariable linear regression.bb represents the absolute difference in log2SARS-CoV-2 nAb AUC value with the reference group after adjusting for blood group, age, sex, hospitalization status and time since first PCR + test for SARS-CoV-2 infection, as estimated by multivariable linear regression.cCrude prevalence ratios for SARS-CoV-2 nAb AUC ≥ 160 were estimated from univariable modifed Poisson regression models with robust variance.dAdjusted prevalence ratios for SARS-CoV-2 nAb AUC ≥ 160 were estimated from multivariable Poisson regression models with robust variance. The multivariable model included adjustment for age, sex, hospitalization status and time since first PCR + test for SARS-CoV-2 infection. Group AB had no observations with SARS-CoV-2 nAb AUC ≥ 160; thus, estimates were not calculated

INCREASED VON WILLEBRAND FACTOR ANTIGEN AND LOW ADAMTS13 ACTIVITY ARE RELATED TO POOR PROGNOSIS IN COVID-19 PATIENTS

Rodríguez Rodríguez M, Castro Quismondo N, Zafra Torres D, Gil Alos D, Ayala R, Martinez-Lopez J.. Int J Lab Hematol. 2021 Jan 27. doi: 10.1111/ijlh.13476. Online ahead of print.

Level of Evidence: 4 - Local non-random sample

BLUF

Hematologists from the 12th Columbus University Hospital in Madrid, Spain studied the role of metallopeptidase with Thrombospondin Type 1 Motif 13 (ADAMTS13) in endothelial dysfunction associated with SARS-CoV-2 infection in 100 patients hospitalized with COVID-19. Authors found patients with severe disease (n=50; see summary for definition) had significantly lower ADAMTS13 activity and higher concentration of von Willebrand Factor antibody compared to those with milder disease. ADAMTS13 levels below 61% was associated with in-hospital death (p=0.011)(Figure 1, Table 2). Authors suggest ADAMTS13 could be used as a prognostic marker in patients hospitalized with COVID-19.

SUMMARY

Authors classified patients as severe if they had:

1. "hypoxaemia in need for invasive mechanical ventilation,"
2. "D-dimer plasma concentration >3000 ng/mL"
3. At least 3 of: CRP > 15 mg/dL, ferritin > 1000 ng/mL, D-dimer > 1,500 ng/mL, lymphopenia < 800 x 109/L and/or IL-6 > 40

All other patients were considered to have non-severe disease.

Parameter	Whole sample (100)	Nonsevere COVID-19 (50)	Severe COVID-19 (50)	Significance *P* (nonsevere vs severe)
ADAMTS13, median (IQR)	61% (47.2-74.6)	69% (54.2-84.9)	53.2% (38.8-65.3)	<.0001
VWF-Ag, median (IQR)	289% (228-382)	261.4% (213-326)	355% (267-400)	<.0001

Parameter	Survivors (81)	Nonsurvivors (19)	Significance *P*
ADAMTS13, median (IQR)	62.8% (52.3-80.1)	42.4% (33.8-57.3)	<.0001
VWF-Ag, median (IQR)	270% (218-353)	395% (294-400)	.002

Parameter	Severe disease survivors (31)	Nonsurvivors (19)	Significance *P*
ADAMTS13, median (IQR)	59.1% (46.2-69.8)	42.4% (33.8-57.3)	.016
VWF-Ag, median (IQR)	315% (236-400)	395% (294-400)	.18

Table 2. ADAMTS13 activity and VWF Ag plasma concentration. ADAMTS13 activity and VWF Ag plasma concentration in survivors and nonsurvivors. ADAMTS13 activity and VWF Ag plasma concentration in nonsurvivors and severe disease survivors

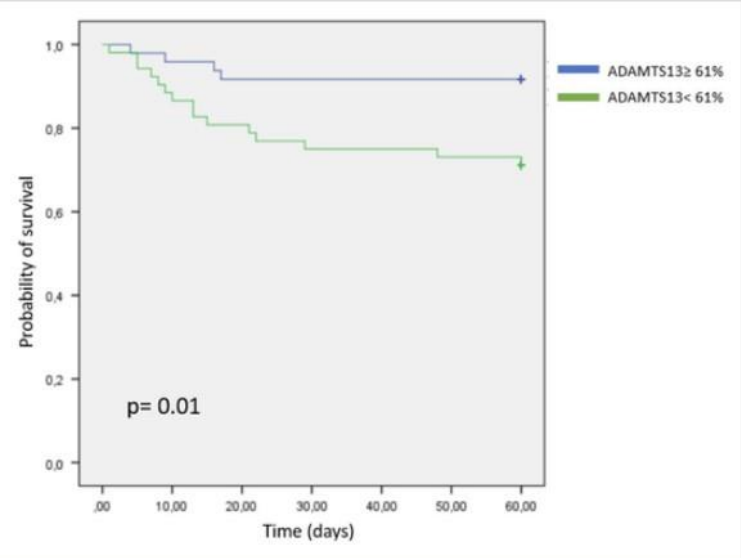

Figure 1. The Kaplan-Meier survival analysis according to A disintegrin-like and metalloprotease with thrombospondin type 1 motif no. 13 activity levels: 15 deaths were observed in the group with values <61%

MICROTHROMBI AS A MAJOR CAUSE OF CARDIAC INJURY IN COVID-19: A PATHOLOGIC STUDY

Pellegrini D, Kawakami R, Guagliumi G, Sakamoto A, Kawai K, Gianatti A, Nasr A, Kutys R, Guo L, Cornelissen A, Faggi L, Mori M, Sato Y, Pescetelli I, Brivio M, Romero M, Virmani R, Finn AV.. Circulation. 2021 Jan 22. doi: 10.1161/CIRCULATIONAHA.120.051828. Online ahead of print.
Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

A pathologic analysis conducted by CVPath Institute, Inc and the University of Maryland of 40 autopsied hearts of patients who died while hospitalized for COVID-19 at Ospedale Papa Giovanni XXIII hospital in Bergamo, Italy found the microthrombi isolated in COVID-19 patients were richer in fibrin and terminal compliment immunostaining compared to aspirated thrombi from percutaneous coronary intervention in other COVID-19 infected and uninfected patients with STEMI (See Figure 3), most likely due to SARS-CoV-2 activation of multiple compliment levels. Microthrombi were found to be significantly associated with focal myocyte necrosis in 82% (9/11) cases (See Table 2) of the 14 overall cases with myocyte necrosis (See Table 4). These findings suggest the majority of cardiac injury found in subjects dying with COVID-19 is due to cardiac microthrombi, indicating a likely cause of cardiac injury among hospitalized COVID-19 patients, and highlights need for further studies on the targeted use of anti-platelet, anti-coagulant, and anti-complement therapies specifically tailored for microthrombi.

ABSTRACT

Background: Cardiac injury is common in hospitalized patients with COVID-19 and portends poorer prognosis. However, the mechanism and the type of myocardial damage associated with SARS-CoV-2 remain uncertain. Methods: We conducted a systematic pathologic analysis of 40 hearts from hospitalized patients dying of Coronavirus Disease 2019 (COVID-19) in Bergamo, Italy to determine the pathologic mechanisms of cardiac injury. We divided the hearts according to presence or absence of acute myocyte necrosis and then determined the underlying mechanisms of cardiac injury. Results: Of the 40 hearts examined, 14 (35%) had evidence of myocyte necrosis, predominantly of the left ventricle. As compared to subjects without necrosis, subjects with necrosis tended to be female, have chronic kidney disease, and shorter symptom onset to admission. The incidence of severe coronary artery disease (i.e., >75% cross sectional narrowing) was not significantly different between those with and without necrosis. 3/14 (21 .4%) subjects with myocyte necrosis showed evidence of acute myocardial infarction defined as >=1 cm2 area of necrosis while 11/14 (78.6%) showed evidence of focal (> 20 necrotic myocytes with an area of >= 0.05 mm2 but <1 cm2) myocyte necrosis. Cardiac thrombi were present in 11/14 (78.6%) cases with necrosis, with 2/14 (14.2%) having epicardial coronary artery thrombi while 9/14 (64.3%) had microthrombi in myocardial capillaries, arterioles, and small muscular arteries. We compared cardiac microthrombi from COVID-19 positive autopsy cases to intramyocardial thromboemboli from COVID-19 cases as well as to aspirated thrombi obtained during primary percutaneous coronary intervention from uninfected and COVID-19 infected patients presenting with ST-segment elevation myocardial infarction (STEMI). Microthrombi had significantly greater fibrin and terminal complement C5b-9 immunostaining as compared to intramyocardial thromboemboli from COVID-19 negative subjects and to aspirated thrombi. There were no significant differences between the constituents of thrombi aspirated from COVID-19 positive and negative STEMI patients. Conclusions: The most common pathologic cause of myocyte necrosis was microthrombi. Microthrombi were different in composition as compared to intramyocardial thromboemboli from COVID-19 negative subjects and to coronary thrombi retrieved from COVID-19 positive and negative STEMI patients. Tailored anti-thrombotic strategies may be useful to counteract the cardiac effects of COVID-19 infection.

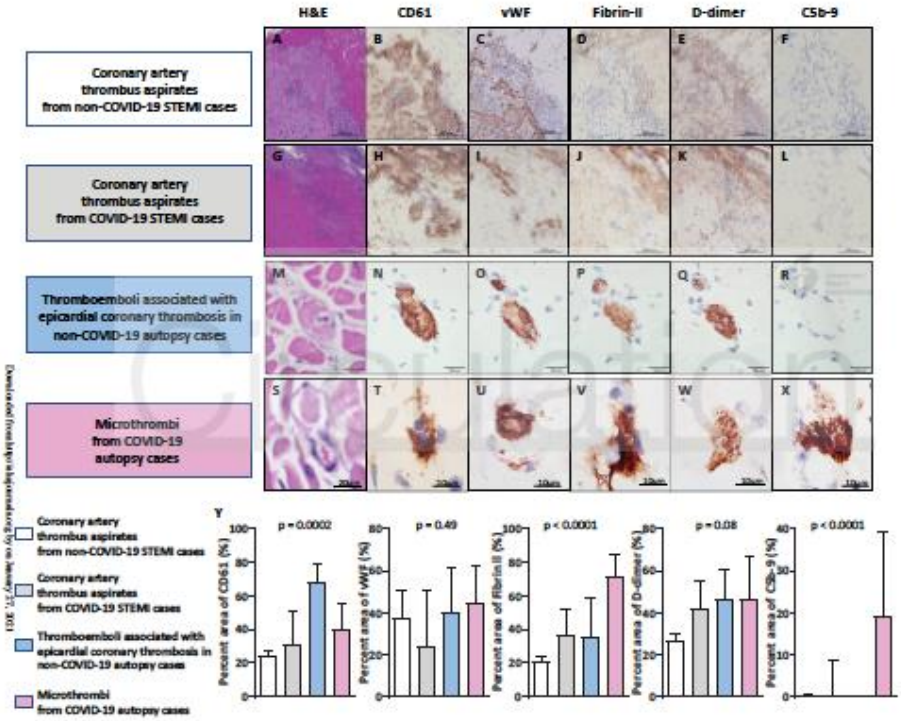

Figure 3. Analysis of Thrombi Aspirated from Culprit Lesions of COVID-19 Positive and Negative STEMI Cases, Myocardial Thromboemboli from COVID-19 Negative Autopsy Subjects, and Cardiac Microthrombi from COVID-19 Positive Autopsy Subjects. A-L.The histology images of thrombus aspirates were obtained from the same patient of non-COVID-19 (A-F) and COVID-19 (G-L) during primary PCI stained for indicated targets. Thrombus is composed primarily of platelets and fibrin but terminal complement is not present. M-R: The histology images of intramyocardial thromboemboli associated with epicardial coronary thrombosis from non-COVID-19 autopsy cases.S-X: Histology images of COVID-19 microthrombi. Microthrombi immunostaining for the same targets shows they are strongly positive for CD61, vWF, Fibrin-ll, D-dimer, and C5b-9. Y. Quantitative analyses of thrombus components among epicardial coronary arteries thrombus aspirates obtained from STEMI (both non-COVID-19 [n=5] and COVID-19 [n=5]) patients, intramyocardial thromboemboli associated with epicardial coronary thrombosis from non-COVID-19 autopsy cases (n=5) and microthrombus in COVID-19 autopsy cases (n=5). Overall p value for each analysis is shown (Wilcoxon Rank Sum Test); Data are expressed as median with interquartile range. Abbreviations: C: complement, CD: cluster of differentiation, COV: COVID-19, COV-: COVID-19 negative, COV+: COVID-19 positive, COVID-19: coronavirus disease 2019, H&E: hematoxylin and eosin stain, ns: not significant, STEMI: ST-elevation myocardial infarction, vWF: von Willebrand factor

	Total (n = 40)	Myocardial necrosis (n = 14)	No necrosis (n = 26)	P value
Myocardial necrosis				
Acute myocardial infarction (≥ 1 cm²)	3 (7.5%)	3 (21.4%)	0 (0%)	0.014
Focal myocyte necrosis (≥ 0.05 mm² but < 1 cm²)	11 (27.5%)	11 (78.6%)	0 (0%)	<0.001
Thrombus				
Epicardial coronary artery thrombus	3 (7.5%)	2 (14.2%)	1 (3.8%)*	0.23
Microthrombi	9 (22.5%)	9 (64.3%)	0 (0%)	<0.001
Coronary artery disease				
Coronary stent	6 (15%)	3 (21.4%)	3 (11.5%)	0.40
Single vessel disease (>75% C-S area)	9 (22.5%)	3 (21.4%)	6 (23.1%)	0.91
Multi-vessel disease (>75% C-S area in ≥ 2 epicardial vessels)	9 (22.5%)	3 (21.4%)	6 (23.1%)	0.91
Other cardiac findings				
Myocarditis	0 (0%)	0 (0%)	0 (0%)	-
Hypertrophy of myocardium	29 (72.5%)	10 (71.4%)	19 (73.1%)	0.91
Valvular heart disease	2 (5.0%)	2 (14.3%)†	0 (0%)	0.21
Cardiac amyloidosis	6 (14.3%)	2 (14.3%)	4 (15.4%)	0.93
Lung Findings				
Diffuse alveolar damage	36 (92.3%)	12 (92.3%)	24 (88.9%)	0.51
Pulmonary artery thrombus	18 (46.2%)	5 (38.5%)	13 (48.1%)	0.39
Microthrombi in alveolar septa	10 (25.6%)	5 (38.5%)	5 (18.5%)	0.25

Categorical variables were shown as numbers and percentages.
*Sudden Cardiac Death.
† Status post-aortic valve replacement (n=1), Moderate aortic stenosis (n=1).
Abbreviations; C-S: cross sectional.

Table 2. Pathological Findings of the Heart and Lung in Subjects With and Without Myocardial Necrosis.

Case	Type of myocardial injury	Location of acute myocardial necrosis	Epicardial coronary artery acute thrombus	Coronary intervention	Epicardial CA stenosis	Healed MI	Type of thrombus in myocardium
1	AMI (Reperfused, Transmural infarction)	Anterior, V Septum, Lateral, Ant RV	Yes (LAD)	Yes, LAD (stented acutely)	50% RCA, 10% LM, 70% LAD*, 70% LCX	no	PCI related intramyocardial thrombus
2	AMI (Reperfused, Subendocardial infarction)	Lateral, Inferior, Anterior - LV	Yes (LCX)	Yes, LCX (In-stent restenosis and acute DCB treatment), RCA (Previous stent, open), LAD (In-stent restenosis and acute DCB treatment)	RCA 50%, 40% LM, 40% LAD, 40% LCX*	Yes	DCB (PCI) related intramyocardial thrombus
3	AMI (Focal areas of myocyte necrosis, transmural myocyte necrosis due to shock)	Circumferential	ϕ	no	50% RCA, 50% LM, 50% LAD, 40% LCX	no	Microthrombus
4	Focal myocyte necrosis	Lateral, Inferior- LV	no	Yes, RCA(Previous stent, 30%)	80% RCA, 35% LM, 50% LAD, 50% LCX	Yes	Microthrombus
5	Focal myocyte necrosis	Inferior-LV, Inferior- RV	no	no	60% RCA, 75% LM, 75% LAD, 70% LCX	Yes	Microthrombus
6	Focal myocyte necrosis	Inferior, Anterior, Lateral-LV	no	no	65% RCA, 40% LM, 65% LAD, 50% LCX	no	Microthrombus
7	Focal myocyte necrosis	V Septum, Inferior-RV	no	no	40% RCA, 40% LM, 60% LAD, 70% LCX	no	Microthrombus
8	Focal myocyte necrosis	Inferior-LV	no	no	75% RCA, 30% LM, 65% LAD, 40% LCX	no	Microthrombus
9	Focal myocyte necrosis	V Septum	no	no	CTO RCA, 50% LM, 80% LAD, 70% LCX	no	Microthrombus
10	Focal myocyte necrosis	Lateral-LV, RA	no	no	40% RCA, 20% LM, 30% LAD, 50% LCX	no	Microthrombus
11	Focal myocyte necrosis	Anterior, V Septum Lateral, Inferior-LV	no	no	50% RCA, 20% LM, 50% LAD, 0% LCX	no	Microthrombus
12	Focal myocyte necrosis	V Septum, Inferior-RV	no	no	25% RCA, 25% LM, 25% LAD, 25% LCX	no	no
13	Focal myocyte necrosis	Inferior-RV	no	no	15% RCA, 30% LM, 30% LAD, 25% LCX	Yes	no
14	Focal myocyte necrosis	Inferior-LV	no	no	20% RCA, 5% LM, 30% LAD, 20% LCX	no	no

*Culprit vessel of acute myocardial infarction.
Abbreviations; AMI: acute myocardial infarction, CA: coronary artery, CAD: coronary artery disease, CTO: chronic total occlusion, DCB: drug-coated balloon, LAD: left anterior descending artery, LCX: left circumflex artery, LM: left main trunk, LV: left ventricle, MI: myocardial infarction, PCI: percutaneous coronary intervention, RA: right atrium, RCA: right coronary artery, RV: right ventricle, V: ventricular.

Table 4. Pathological Findings of the Heart in Subjects with Myocardial Necrosis.

COVID-19-ASSOCIATED NONOCCLUSIVE FIBRIN MICROTHROMBI IN THE HEART

Bois MC, Boire NA, Layman AJ, Aubry MC, Alexander MP, Roden AC, Hagen CE, Quinton RA, Larsen C, Erben Y, Majumdar R, Jenkins SM, Kipp BR, Lin PT, Maleszewski JJ.. Circulation. 2021 Jan 19;143(3):230-243. doi: 10.1161/CIRCULATIONAHA.120.050754. Epub 2020 Nov 16.
Level of Evidence: 4 - Case-series

BLUF

Pathologists and cardiologists from the Mayo Clinic in Minnesota examined post-mortem heart tissue from patients who had COVID-19 (n=15), Influenza A/B (n=6), and non-viral illness (n=6)(Table 1). They found patients with COVID-19 were more likely to have non-occlusive fibrin microthrombi (without evidence of ischemic damage)(p=0.006, Table 3) and had lower arteriolar angiotensin-converting enzyme 2 endothelial expression (p=0.004). Five patients with COVID-19 had evidence of myocarditis, and there was no evidence of SARS-CoV-2 in the tissues of COVID-19 patients (Table 3). Although conclusions are limited by sample size, the authors suggest there is limited evidence for direct viral injury and that the frequency of cardiac microthrombi indicate a role for anticoagulation in COVID-19 management.

ABSTRACT

Background: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and its resultant clinical presentation, COVID-19, is an emergent cause of mortality worldwide. Cardiac complications secondary to this infection are common; however, the underlying mechanisms of such remain unclear. A detailed cardiac evaluation of a series of COVID-19 individuals undergoing postmortem evaluation is provided, with four aims: 1) describe the pathologic spectrum of the myocardium; 2) compare to an alternate viral illness; 3) investigate angiotensin converting enzyme 2 (ACE2) expression; and 4) provide the first description of the cardiac findings in patients with cleared infection. Methods: Study cases were identified from institutional files and included COVID-19 (n=15; 12 active, 3 cleared), influenza A/B (n=6), and non-virally mediated deaths (n=6). Salient information was abstracted from the medical record. Light microscopic findings were recorded. An ACE2 immunohistochemical H-score was compared across cases. Viral detection encompassed SARS-CoV-2 immunohistochemistry, ultrastructural examination, and droplet digital polymerase chain reaction (ddPCR). Results: Male sex was more common in the COVID-19 group (p=0.05). Non-occlusive fibrin microthrombi (without ischemic injury) were identified in 16 cases (12 COVID-19, 2 influenza, and 2 controls), and were more common in the active COVID-19 cohort (p=0.006). Four active COVID-19 cases showed focal myocarditis, while one case of cleared COVID-19 showed extensive disease. Arteriolar ACE2 endothelial expression was lower in COVID-19 cases versus controls (p=0.004). ACE2 myocardial expression did not differ by disease category, sex, age or number of patient comorbidities (p=0.69, p=1.00, p=0.46, p=0.65, respectively). SARS-CoV-2 immunohistochemistry showed non-specific staining, while ultrastructural examination and ddPCR were negative for viral presence. Four (26.7%) COVID-19 patients had underlying cardiac amyloidosis. Cases with cleared infection had variable presentations. Conclusions: This detailed histopathologic, immunohistochemical, ultrastructural and molecular cardiac series

showed no definitive evidence of direct myocardial infection. COVID-19 cases frequently have cardiac fibrin microthrombi, without universal acute ischemic injury. Moreover, myocarditis is present in 33.3% of active and cleared COVID-19 patients, but is usually limited in extent. Histologic features of resolved infection are variable. Cardiac amyloidosis may be an additional risk factor for severe disease.

FIGURES

Demographics and clinical characteristics	COVID-19* (n=15)	Influenza (n=6)	Controls (n=6)	*P* value
Age, median (interquartile range)	78 (71–86)	52 (46– 80)	74 (65–81)	0.20†
Male sex, n (%)	12 (80.0)	2 (33.3)	2 (33.3	0.05‡
Comorbidities per patient,§ median (interquartile range)	2 (1–3)	2.5 (1–3)	0.5 (0–1)	0.18†
Medications influencing coagulation, n (%)‖				
Aspirin	5/9 (55.6)	2/3 (66.7)	2/4 (50.0)	1.0‡
Heparin/enoxaparin	2/9 (22.2)	0/3 (0.0)	0/4 (0.0)	1.0‡
Clopidogrel	0/9 (0.0)	0/3 (0.0)	1/4 (25.0)	0.44‡
Apixaban	1/9 (11.1)	0/3 (0.0)	1/4 (25.0)	1.0‡
Warfarin	1/9 (11.1)	0/3 (0.0)	0/4 (0.0)	1.0‡
Coagulation parameters				
Platelet count (×109/L)				
n	12	4	5	0.82†
Median (range)	215 (33–670)	144.5 (55–461)	222 (102–374)	
D-Dimer, ng/mL				
n	7	1	3	0.8†
Median (range)	1145 (1.9–2475)	14065	336 (0–775)	
Prothrombin time, s				
n	9	4	6	0.70†
Median (range)	15.9 (12.2–51.7)	18.7 (12.9–27.6)	15.5 (10.6–91.8)	
Activated partial thromboplastin time				
n	7	4	5	0.22†
Median (range)	32 (27–83)	38.5 (35–63)	35 (24–39)	
International normalized ratio				
n	10	5	6	0.59†
Median (range)	1.5 (1.1–4.6)	1.8 (1.2–2.5)	1.3 (1.0–8.2)	
Thrombin time, s				
n	1	1	1	Not applicable
Median	34.7	28.4	21.6	
Fibrinogen, mg/dL				
n	5	4	2	0.36†
Median (range)	574 (236–774)	465 (345–576)	249 (71–427)	
High-sensitivity troponin, ng/L				
n	8	4	6	0.28†
Median (range)	19.5 (0–461)	82 (28–223)	19 (0–90)	
History of angiotensin-converting enzyme inhibitor use, n (%)	6/9 (66.7)	2/3 (66.7)	0/4 (0)	0.10‡

*Including both patients with active and cleared severe acute respiratory syndrome coronavirus 2 viral infection.
†Kruskal-Wallis test.
‡Fisher exact test.
§Defined as underlying chronic conditions, including systemic hypertension, hyperlipidemia, type 2 diabetes, and chronic kidney disease.
‖Medications immediately preceding or during terminal illness and hospitalization; denominator denoted number of patients in each category with information present in the medical record.

Table 1. Cohort Demographics and Relevant Clinical Characteristics

Characteristics	COVID-19* (n=15)	Active COVID-19† (n=12)	Influenza (n=6)	Controls (n=6)	*P* value‡	Pairwise comparison for significant values
Gross characteristics						
Heart weight, g, median (range)	443.1 (286.3–545.0)	474.0 (286.3–545.0)	398.4 (269.0–592.0)	244.5 (197.0–560.3)	0.22§	
Expected heart weight,‖ %, median (range)	1.42 (0.97–1.94)	1.49 (0.97–1.94)	1.35 (1.04–2.13)	0.89 (0.78–2.11)	0.17§	
Histopathologic characteristics						
Microthrombosis, n (%)	12 (80.0)	11 (91.7)	2 (33.3)	2 (33.3)	0.006¶	COVID-19 vs influenza, *P*=0.02
						COVID-19 vs control, *P*=0.02
Involved arterioles, median % of total (range)	6.3 (0.0–28.6)	7.3 (0.0–28.6)	0.0 (0.0–6.1)	0.0 (0.0–4.7)	0.003§	COVID-19 vs influenza, *P*=0.01
						COVID-19 vs control, *P*=0.003
Myocarditis, n (%)	5 (33.3)	4 (33.3)	1 (16.7)	0 (0.0)	0.38¶	
Interstitial edema, n (%)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	0.11¶	
Acute ischemic injury, n (%)	2 (13.3)	2 (16.7)	2 (33.3)	0 (0.0)	0.32¶	

COVID-19 indicates coronavirus disease 2019.
*Including both patients with active and cleared severe acute respiratory syndrome coronavirus 2 viral infection.
†COVID-19 cases with cleared infection excluded (n=3).
‡Denotes overall *P* value including active COVID-19, influenza, and control cases.
§Kruskal-Wallis test.
‖Compared with age-, sex-, and weight-based controls.[13]
¶Fisher exact test.

Table 3. Summary of Cardiac Pathology

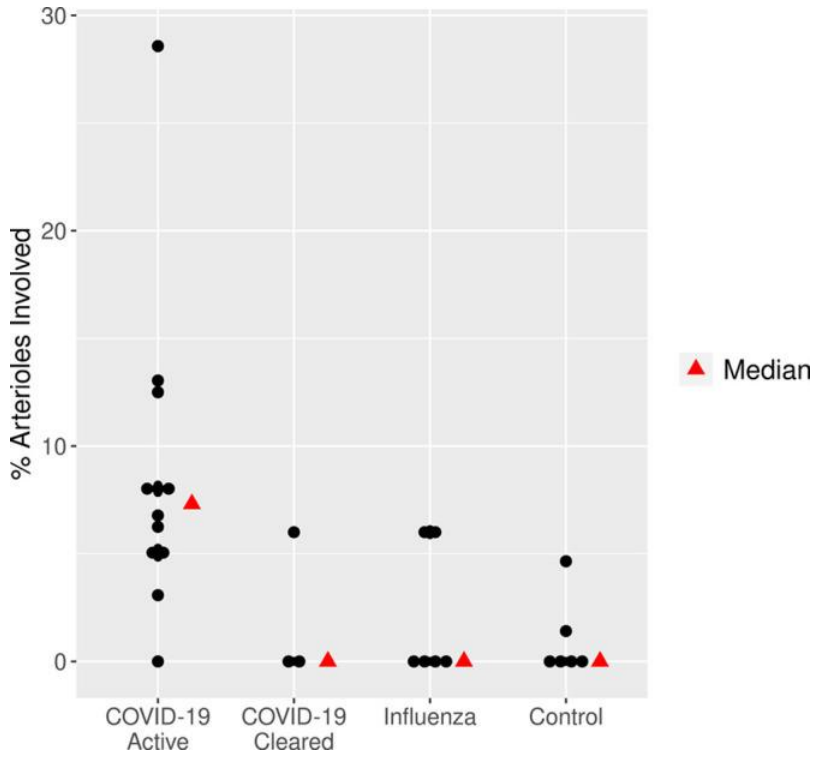

Figure 3. Frequency of fibrin microthrombi. Active coronavirus disease 2019 (COVID-19) cases showed more frequent fibrin microthrombi than other postmortem control groups, including both virally mediated (Influenza) and nonvirally mediated (Control) deaths.

TRANSMISSION & PREVENTION

COVID-19 VACCINATION AND OBESITY: OPTIMISM AND CHALLENGES

Townsend MJ, Kyle TK, Stanford FC.. Obesity (Silver Spring). 2021 Jan 28. doi: 10.1002/oby.23131. Online ahead of print.
Level of Evidence: 5 - Opinion

BLUF

Researchers from Harvard Medical School, Massachusetts General Hospital and ConscienHealth in Pittsburgh refute previous speculations that obesity could be associated with reduced efficacy of the COVID-19 vaccines. Data from Phase 3 vaccine trial results show Pfizer-BioNTech has 95.4% efficacy (CI: 86.0 - 99.1%) in people with obesity compared to 94.8% (CI: 87.4-98.3%) in people without obesity and Moderna efficacy of 91.2% (CI:32.0-98.9%) in people with severe obesity and 94.8% (CI: 89.3-96.8%) overall. Since obesity is one of the most significant risk factors for severe outcomes from COVID-19, these authors suggest that ongoing placebo-controlled vaccine trials designed with necessary power for detecting differences among classes of obesity are important for post-vaccine risk stratification and public health strategy.

ABSTRACT

Researchers have speculated that vaccines to prevent COVID-19 may be less effective for individuals with obesity, a major risk factor for mortality and morbidity from COVID-19. Initial results from the Pfizer-BioNTech and Moderna COVID-19 vaccine trials, though limited by inadequate power to compare subgroups and incomplete stratification of high-risk groups, appear to have similar efficacy among individuals with and without obesity. Careful follow up in placebo-controlled studies is required to generate data on long-term vaccine immunogenicity, particularly in high-risk groups. Subsequent analyses should stratify safety and efficacy results by each class of obesity. Speculation about variable effectiveness of COVID-19 vaccines in obesity likely increases vaccine hesitancy among individuals with obesity, who face not only a higher risk of severe outcomes from COVID-19 but also weight stigma which reduces healthcare engagement at baseline. Clinical and public health messaging must be data-driven, transparent, and sensitive to these biological and sociological vulnerabilities.

DEVELOPMENTS IN TRANSMISSION & PREVENTION

EARLY EVIDENCE OF EFFECTIVENESS OF DIGITAL CONTACT TRACING FOR SARS-COV-2 IN SWITZERLAND

Salathé M, Althaus C, Anderegg N, Antonioli D, Ballouz T, Bugnon E, Čapkun S, Jackson D, Kim SI, Larus J, Low N, Lueks W, Menges D, Moullet C, Payer M, Riou J, Stadler T, Troncoso C, Vayena E, von Wyl V.. Swiss Med Wkly. 2020 Dec 16;150:w20457. doi: 10.4414/smw.2020.20457. eCollection 2020 Dec 14.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

This proof-of-principle cohort study conducted in Switzerland from July 23 to September 10, 2020 found that the contact tracing app SwissCovid was able to estimate proximity between phones of different individuals with the downloaded app and use symptoms, test results, and location to effectively trace COVID-19 across the country (Figure 2). There were 12,546 confirmed SARS-CoV-2 cases during the study period, and 2,447 were given Covidcodes (a validation code to start the SwissCovid symptom tracker app). 1,645 participants used the app to track symptoms, suggesting this app and similar apps may be beneficial in future contact tracing.

ABSTRACT

In the wake of the pandemic of coronavirus disease 2019 (COVID-19), contact tracing has become a key element of strategies to control the spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Given the rapid and intense spread of SARS-CoV-2, digital contact tracing has emerged as a potential complementary tool to support containment and mitigation efforts. Early modelling studies highlighted the potential of digital contact tracing to break transmission chains, and Google and Apple subsequently developed the Exposure Notification (EN) framework, making it available to the vast majority of smartphones. A growing number of governments have launched or announced EN-based contact tracing apps, but their effectiveness remains unknown. Here, we report early findings of the digital contact tracing app deployment in Switzerland. We demonstrate proof-of-principle that digital contact tracing reaches exposed contacts, who then test positive for SARS-CoV-

2. This indicates that digital contact tracing is an effective complementary tool for controlling the spread of SARS-CoV-2. Continued technical improvement and international compatibility can further increase the efficacy, particularly also across country borders.

FIGURES

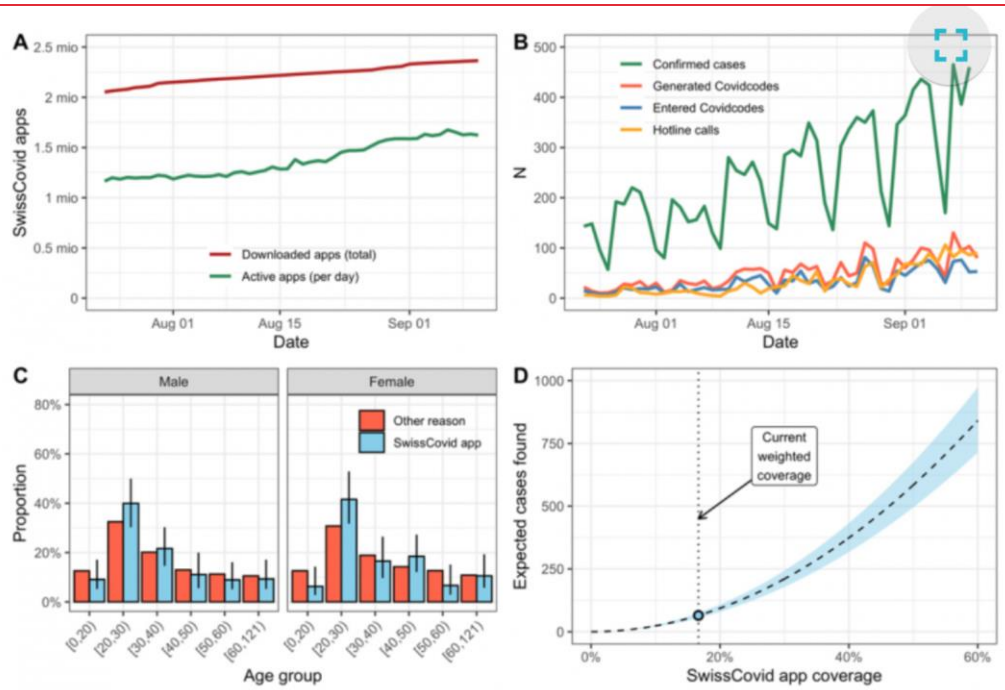

Figure 2. SwissCovid app measures. (A) Total number of downloaded apps and daily number of active apps. (B) Daily number of confirmed SARS-CoV-2 cases, generated Covidcodes, entered Covidcodes and hotline calls. (C) Age distribution of cases stratified by the reason for RT-PCR test (either SwissCovid app or other reason). (D) Expected number of RT-PCR-confirmed cases that were tested because of a notification by the app as a function of hypothetical app coverage during the study period. Error bars and the blue shaded area correspond to 95% confidence intervals.

A NANOMECHANICAL STUDY ON DECIPHERING THE STICKINESS OF SARS-COV-2 ON INANIMATE SURFACES

Xie L, Liu F, Liu J, Zeng H.. ACS Appl Mater Interfaces. 2020 Dec 30;12(52):58360-58368. doi: 10.1021/acsami.0c16800. Epub 2020 Dec 18.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A nanomechanical study by researchers in Alberta, Canada and Changsha, Shenzhen, and Guangdong, China tested SARS-CoV-2 survival on four different surfaces and found that the spike protein on the outer surface of the SARS-CoV-2 virion, which is responsible for transmission via fomites, survived the best on polystyrene, then stainless steel, then gold, then did not survive as well on glass (Figure 2), suggesting that fomite transmission of SARS-CoV-2 is prevalent and that more surfaces need to be tested to get a better understanding for both prevention and tracking transmission of the virus.

ABSTRACT

The SARS-CoV-2 virus that causes the COVID-19 epidemic can be transmitted via respiratory droplet-contaminated surfaces or fomites, which urgently requires a fundamental understanding of intermolecular interactions of the coronavirus with various surfaces. The corona-like component of the outer surface of the SARS-CoV-2 virion, named spike protein, is a key target for the adsorption and persistence of SARS-CoV-2 on various surfaces. However, a lack of knowledge in intermolecular interactions between spike protein and different substrate surfaces has resulted in ineffective preventive measures and inaccurate information. Herein, we quantified the surface interaction and adhesion energy of SARS-CoV-2 spike protein with a series of inanimate surfaces via atomic force microscopy under a simulated respiratory droplet environment. Among four target

surfaces, polystyrene was found to exhibit the strongest adhesion, followed by stainless steel (SS), gold, and glass. The environmental factors (e.g., pH and temperature) played a role in mediating the spike protein binding. According to systematic quantification on a series of inanimate surfaces, the adhesion energy of spike protein was found to be (i) 0-1 mJ/m2 for hydrophilic inorganics (e.g., silica and glass) due to the lack of hydrogen bonding, (ii) 2-9 mJ/m2 for metals (e.g., alumina, SS, and copper) due to the variation of their binding capacity, and (iii) 6-11 mJ/m2 for hydrophobic polymers (e.g., medical masks, safety glass, and nitrile gloves) due to stronger hydrophobic interactions. The quantitative analysis of the nanomechanics of spike proteins will enable a protein-surface model database for SARS-CoV-2 to help generate effective preventive strategies to tackle the epidemic.

FIGURES

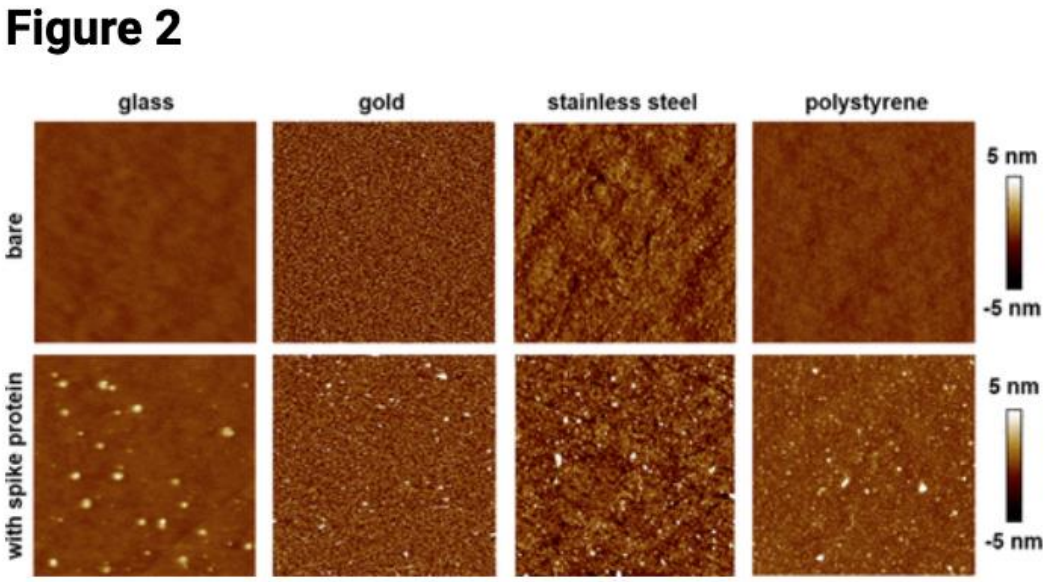

Figure 2. AFM topography images (5 × 5 μm2) of glass, gold, SS, and PS before and after the adsorption of spike protein.

PROGNOSIS OF SEVERE AND CRITICAL PATIENTS WHO HAVE RECOVERED FROM COVID-19: A THREE-MONTH FOLLOW-UP

Zhong CH, Zhou ZQ, Ye F, Guo WL, Gu WL, Guo ZY, Li SY.. Respiration. 2021 Jan 21:1-4. doi: 10.1159/000512686. Online ahead of print.

Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

BLUF

This prospective study aimed to investigate the prognosis of severe and critical COVID-19 patients after having been discharged from the hospital through an app-based chat system popular in China known as WeChat (figure 1, see summary for method details). The results of this study found that all patients self-reported overall stable health for the duration of the study. One patient was required to return to the hospital for acute chest pain, but was discharged after a negative acute coronary syndrome workup. Overall, this study showed that an app based communication system could be useful in monitoring patient conditions after being discharged from the hospital.

SUMMARY

The patients were determined to be severe or critical based on the "interim guide for novel coronavirus pneumonia published by the National Health Commission of the People's Republic of China". A mini-program was developed within the WeChat App that included a survey to monitor the patient's condition; in addition, the patients were sent tools to keep track of their vitals signs in order to record this information in the app.

FIGURES

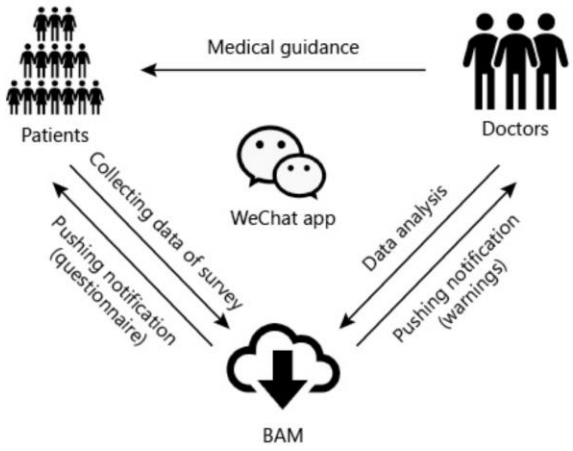

Figure 1. Pattern of Follow-up

SMALL MOLECULE STABILIZATION OF NON-NATIVE PROTEIN-PROTEIN INTERACTIONS OF SARS-COV-2 N PROTEIN AS A MECHANISM OF ACTION AGAINST COVID-19

Fernández JF, Lavecchia MJ.. J Biomol Struct Dyn. 2020 Dec 28:1-8. doi: 10.1080/07391102.2020.1860828. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Researchers in Argentina with support from NVIDIA Corporation and OpenEye used a previously studied mechanism of MERS-CoV, specifically stabilization of non-native protein-protein interactions (PPIs) within the nucleocapsid protein as a mechanism of viral replication inhibition, and applied this to their in silico study with SARS-CoV-2 and found that this PPI stabilization can also inhibit viral replication of the novel coronavirus (Figure 1). This suggests that pharmacotherapy mimicking this mechanism and promoting PPI stabilization could be used as a potential treatment for COVID-19, and that this mechanism could be useful in further drug design, particularly with candidates that have a common catechin skeleton.

SUMMARY

Authors state that in vitro testing is needed to confirm these findings.

ABSTRACT

The outbreak of COVID-19, the disease caused by SARS-CoV-2, continues to affect millions of people around the world. The absence of a globally distributed effective treatment makes the exploration of new mechanisms of action a key step to address this situation. Stabilization of non-native Protein-Protein Interactions (PPIs) of the nucleocapsid protein of MERS-CoV has been reported as a valid strategy to inhibit viral replication. In this study, the applicability of this unexplored mechanism of action against SARS-CoV-2 is analyzed. During our research, we were able to find three inducible interfaces of SARS-CoV-2 N protein NTD, compare them to the previously reported MERS-CoV stabilized dimers, and identify those residues that are responsible for their formation. A drug discovery protocol implemented consisting of docking, molecular dynamics and MM-GBSA enabled us to find several compounds that might be able to exploit this mechanism of action. In addition, a common catechin skeleton was found among many of these molecules, which might be useful for further drug design. We consider that our findings could motivate future research in the fields of drug discovery and design towards the exploitation of this previously unexplored mechanism of action against COVID-19. Communicated by Ramaswamy H. Sarma.

FIGURES

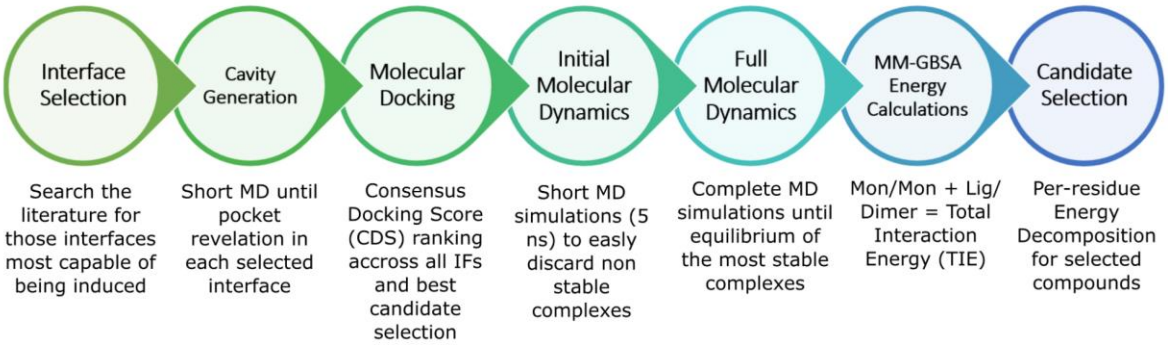

Figure 1: General scheme of the protocol developed for the present study.

ACTION OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS ON SARS-COV-2 MAIN PROTEASE

Klein T, Nar H, Schnapp G, Hucke O, Hardman TC.. ChemMedChem. 2020 Dec 21. doi: 10.1002/cmdc.202000921. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Researchers from GmbH&Co Niche Science & Technology Ltd. in Wien, Austria conducted an enzymatic assay measuring the effects of DPP-4 inhibitors and their analogs against Mpro, the main protease of SARS-CoV-2, and found that they are inactive against Mpro (Figure 1). This is in contrast to previous studies that have shown that DPP-4 inhibitors already approved for treatment of diabetes mellitus can inhibit Mpro, suggesting DPP-4 inhibitors are not indicated in the treatment of COVID-19.

ABSTRACT

In a recent publication in this journal Eleftheriou et al. proposed inhibitors of dipeptidyl peptidase-4 (DPP-4) to be functional inhibitors of the main protease (M pro) of SARS-CoV-2. Their predictions prompted the authors to suggest linagliptin, a DPP-4 inhibitor and approved anti-diabetes drug, as a repurposed drug candidate against the ongoing COVID-19 pandemic. We used an enzymatic assay measuring inhibition of M pro catalytic activity in the presence of four different commercially available gliptins (linagliptin, sitagliptin, alogliptin and saxagliptin) and several structural analogues of linagliptin to study binding of DPP-4 inhibitors to M pro and their functional activity. We show here that DPP-4 inhibitors like linagliptin, other gliptins and structural analogues are inactive against M pro .

FIGURES

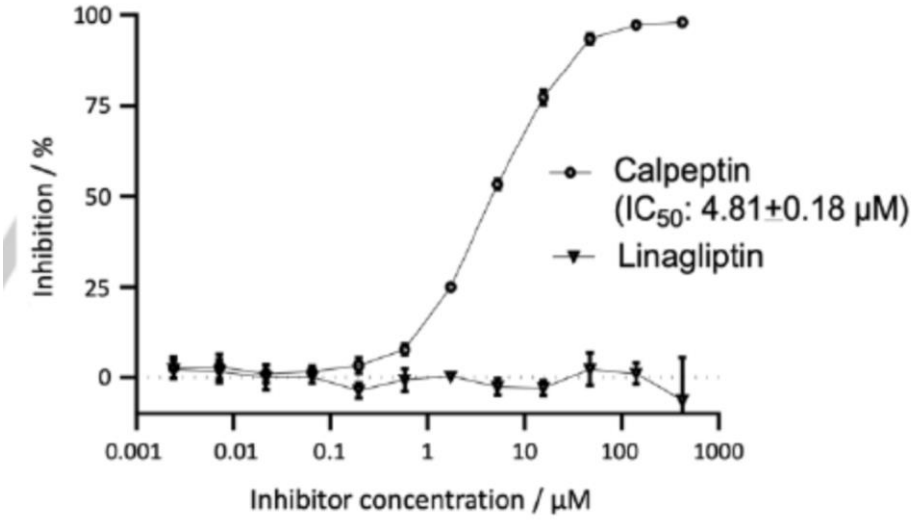

Figure 1: Inhibition curve of SARS-Cov-2 Mpro with calpeptin and linagliptin. Data shown are mean (SD) values from three independent experiments.

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