The Daily COVID-19 Literature Surveillance Summary

December 15, 2020

DISCLAIMER

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

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

NOW LIVE!

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

COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

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

EXECUTIVE SUMMARY

Climate

- What are the COVID-19 vaccine trial ethics once we have efficacious vaccines? An expert opinion penned by bioethicists from the National Institutes of Health and Fogarty International Center in Bethesda, MD explore the ethics of continuing blinded, placebo-controlled trials for COVID-19 vaccines in the wake of a safe and efficacious vaccine being approved for widespread use. Authors argue it is ethical to continue trials if participants consent and the risk-benefit profile of the trial remains acceptable, because continuing trials could lead to the discovery of longer lasting vaccines, better immunity, or greater efficacy in subpopulations. However, the authors emphasize trial participants in blinded, placebo-controlled trials should be informed of the availability of the vaccine and allowed to leave the trial if they desire.

Understanding the Pathology

- The L37F mutation may be critical to asymptomatic COVID-19 infection and transmission. Computer scientists from the University of Illinois analyzed 75,775 SARS-CoV-2 complete genome isolates to explore virological characteristics in asymptomatic COVID-19. They found patients with asymptomatic COVID-19 were significantly more likely to have the SARS-CoV-2 single nucleotide mutation 11083G>T-(L37F) on Non-Structural Protein 6 (NSP 6)($r=0.61$, $p=5.42\times10^{-56}$) and countries with the highest L37F mutation ratio had lower death ratio. Artificial intelligence (AI), topological data analysis (TDA), and network analysis revealed L37F destabilized NSP6's structure in a way that impeded viral assembly and replication. Authors suggest L37F mutation as a possible explanation for asymptomatic COVID-19 and encourage further research on therapies targeting NSP6.

Transmission & Prevention

- Transmissibility of COVID-19 depends on the viral load around onset in adult and symptomatic patients. Infectious disease specialists and microbiologists from the Toyama University Graduate School of Medicine and Pharmaceutical Sciences in Japan conducted a case-control study comparing patients with 14 COVID-19 who did ("index patients") and 14 who did not transmit SARS-CoV-2 to another patient. They found index patients showed higher viral loads at onset compared to non-index patients (6.6 [5.2 to 8.2] log copies/μL vs. 3.1 [1.5 to 4.8]) and that, in general, symptomatic patients had a higher initial viral load (2.8 log copies/μL) than asymptomatic patients (0.9 log copies/μL, $p<0.01$). Authors suggest elevated nasopharyngeal viral load contributes to secondary transmission of SARS-CoV-2, and that understanding the viral threshold for infectivity can better quarantine and isolation policies.

- Peripheral oxygen saturation does not decrease in older persons wearing nonmedical face masks in community settings. Internists from McMaster University in Canada conducted a crossover study of 25 retirement home residents older than 65 to monitor self-measured peripheral oxygen saturation (SpO2) with use of a three-layer disposable nonmedical face mask. They found pooled mean SpO2 was 96.1%, 96.5%, 96.3% in the hour prior to use, during one hour of use, and one hour after wearing the masks, respectively. Authors suggest despite some public concerns about mask safety, the use of nonmedical face masks is not associated with a decrease in SpO2 in older populations.

TABLE OF CONTENTS

CLIMATE

COVID-19 VACCINE TRIAL ETHICS ONCE WE HAVE EFFICACIOUS VACCINES

Wendler D, Ochoa J, Millum J, Grady C, Taylor HA.. Science. 2020 Dec 11;370(6522):1277-1279. doi: 10.1126/science.abf5084. Epub 2020 Dec 3.
Level of Evidence: 5 - Expert Opinion

BLUF

An expert opinion penned by bioethicists from the National Institutes of Health and Fogarty International Center in Bethesda, MD explore the ethics of continuing blinded, placebo-controlled trials for COVID-19 vaccines in the wake of a safe and efficacious vaccine being approved for widespread use. Authors argue it is ethical to continue trials if participants consent and the risk-benefit profile of the trial remains acceptable, because continuing trials could lead to the discovery of longer lasting vaccines, better immunity, or greater efficacy in subpopulations. However, the authors emphasize trial participants in blinded, placebo-controlled trials should be informed of the availability of the vaccine and allowed to leave the trial if they desire.

ABSTRACT

Some placebo-controlled trials can continue ethically after a candidate vaccine is found to be safe and efficacious.

ADULTS

ASSOCIATION OF SEX, AGE, AND COMORBIDITIES WITH MORTALITY IN COVID-19 PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B.. Intervirology. 2020 Dec 9:1-12. doi: 10.1159/000512592. Online ahead of print.

Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

Pharmacists from University of Rajshahi in Bangladesh conducted a systematic review (Figure 1) of 20 articles examining the association of sex, age, and comorbidities on mortality published from February 2, 2020, to May 21, 2020 (Table 1). They found male sex (RR 1.86: 95% CI 1.67–2.07; p<0.00001; i2=0.53)(Figure 2) and age >50 (RR 15.44: 95% CI 13.02–18.31; p<0.00001; i2=0.19)(Figure 3) increased risk of mortality. Cancer, cardiovascular disease, cerebrovascular disease, diabetes, hypertension, kidney disease, and respiratory disease were also associated with significantly increased mortality risk (Figure 4). Authors suggest that COVID-19 patients who are male, over age 50, or with the above comorbidities are at increased mortality risk and should receive interventions and protection to mitigate this risk.

ABSTRACT

INTRODUCTION: Although severe acute respiratory syndrome coronavirus-2 infection is causing mortality in considerable proportion of coronavirus disease-2019 (COVID-19) patients, however, evidence for the association of sex, age, and comorbidities on the risk of mortality is not well-aggregated yet. It was aimed to assess the association of sex, age, and comorbidities with mortality in COVID-2019 patients. METHODS: Literatures were searched using different keywords in various databases. Relative risks (RRs) were calculated by RevMan software where statistical significance was set as p < 0.05. RESULTS: COVID-19 male patients were associated with significantly increased risk of mortality compared to females (RR 1.86: 95% confidence interval [CI] 1.67-2.07; p < 0.00001). Patients with age >=50 years were associated with 15.4-folds significantly increased risk of mortality compared to patients with age <50 years (RR 15.44: 95% CI 13.02-18.31; p < 0.00001). Comorbidities were also associated with significantly increased risk of mortality; kidney disease (RR 4.90: 95% CI 3.04-7.88; p < 0.00001), cereborovascular disease (RR 4.78; 95% CI 3.39-6.76; p < 0.00001), cardiovascular disease (RR 3.05: 95% CI 2.20-4.25; p < 0.00001), respiratory disease (RR 2.74: 95% CI 2.04-3.67; p < 0.00001), diabetes (RR 1.97: 95% CI 1.48-2.64; p < 0.00001), hypertension (RR 1.95: 95% CI 1.58-2.40; p < 0.00001), and cancer (RR 1.89; 95% CI 1.25-2.84; p = 0.002) but not liver disease (RR 1.64: 95% CI 0.82-3.28; p= 0.16). CONCLUSION: Implementation of adequate protection and interventions for COVID-19 patients in general and in particular male patients with age >=50 years having comorbidities may significantly reduce risk of mortality associated with COVID-19.

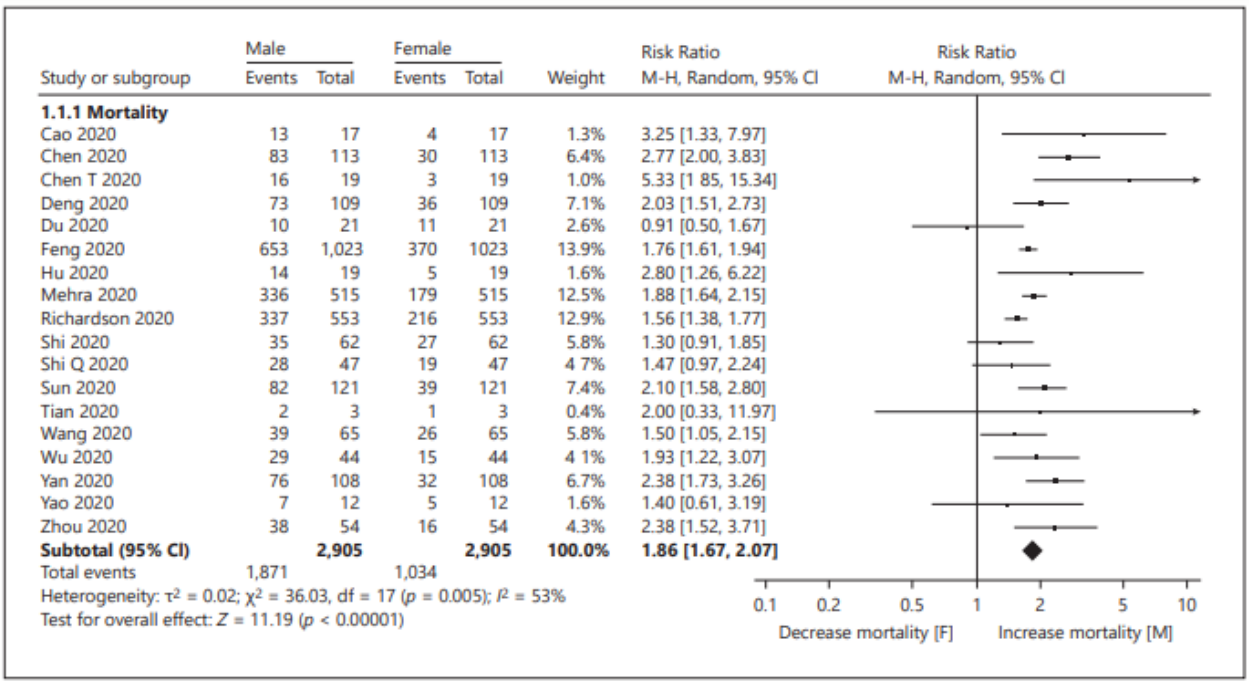
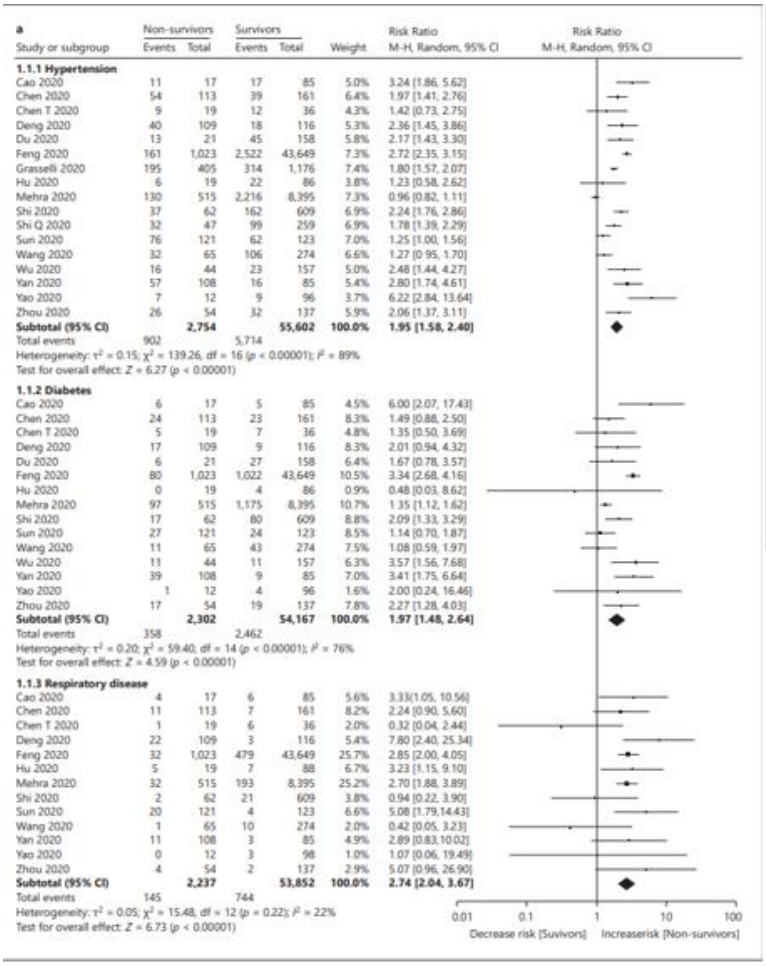


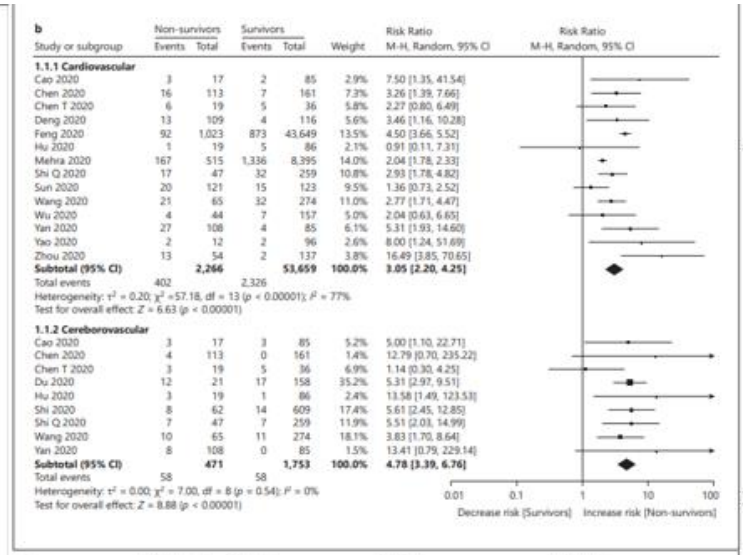
Fig. 2. Forest plot of the pooled effects of COVID-19 male patients against female patients on the risk of mortality. M, male; F, female; CI, confidence interval; COVID-19, coronavirus disease-2019.

Table 1. Baseline characteristics of included studies

Author	Country	Study design	Sample size	Male, *n* (%)	Median age (interquartile range)/ mean ± SD, years	Follow-up/ observation period/ data collection period, days
Cao et a. [18]	China	Retrospective study	102	53 (52.0)	54 (37–67)	30
Chen et al. [19]	China	Retrospective study	274	171 (62.4)	62 (44–70)	30
Chen et al. [20]	China	Retrospective study	203	108 (53.2)	54 (20–91)	41
Deng et al. [21]	China	Retrospective study	225	124 (55.1)	54.5 (48–66)	52
Du et al. [22]	China	Prospective study	179	97 (54.2)	57.6±13.7	13
Feng et al. [24]	China	Observational study	44,672	22,981 (51.4)	na	43
Grasselli et al. [36]	Italy	Retrospective study	1,591	1,304 (82.0)	63.0	34
Hu et al. [23]	China	Retrospective study	105	54 (51.4)	60.8±16.3	29
Mehra et al. [32]	Multinational	Observational study	8,910	5,339 (59.9)	52.3±15.9	40
Palaiodimos et al. [33]	USA	Retrospective study	200	98 (49.0)	64 (50–73.5)	35
Richardson et al. [37]	USA	Retrospective study	5,700	3,437 (60.3)	63.0	35
Shi et al. [25]	China	Retrospective study	671	322 (48.0)	63.0	54
Shi et al. [34]	China	Retrospective study	306	150 (49.0)	64 (56–72)	68
Sun et al. [26]	China	Retrospective study	244	133 (54.5)	69.5	36
Tian et al. [35]	China	Retrospective study	262	127 (48.5)	47.5	21
Wang et al. [27]	China	Retrospective study	339	166 (49.0)	69.0	37
Wu et al. [28]	China	Retrospective study	201	128 (63.7)	51 (43–60)	51
Yan et al. [29]	China	Retrospective study	193	114 (59.1)	64.0	45
Yao et al. [30]	China	Retrospective study	108	43 (39.8)	52.0	12
Zhou et al. [31]	China	Retrospective study	191	119 (62.3)	56 (46–67)	34

na, not available.





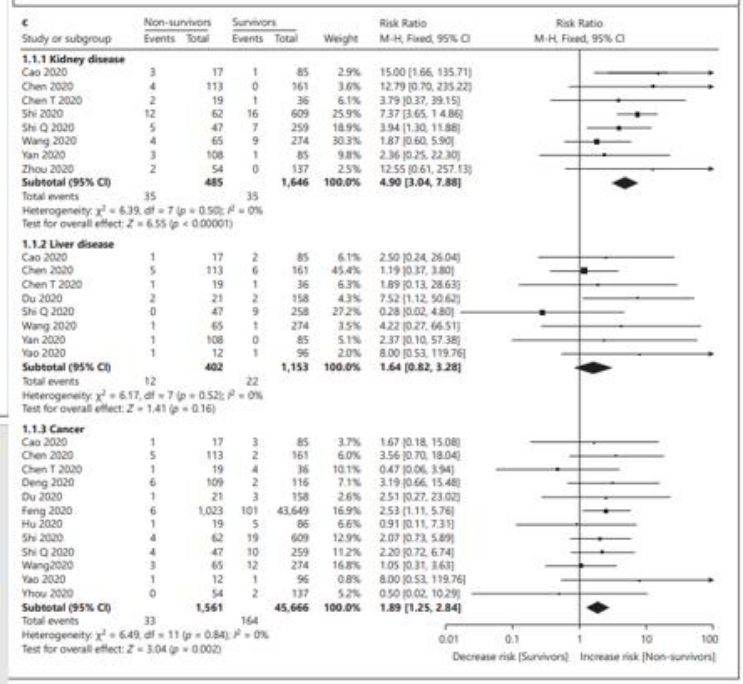
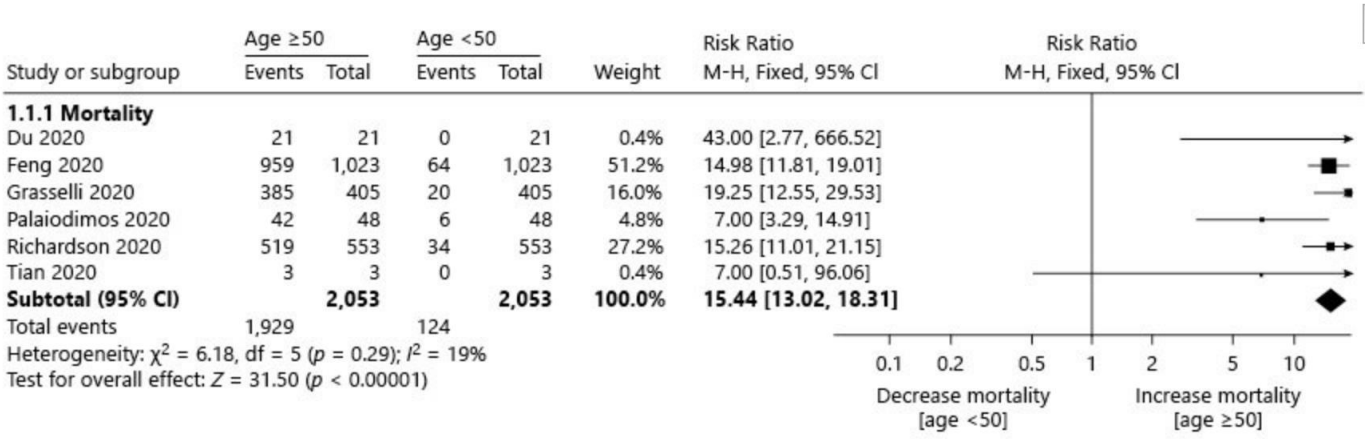


Fig. 4. **a** Forest plot of the pooled effects of comorbidities on the risk of mortality associated with hypertension, diabetes or respiratory disease. **b** Forest plot of the pooled effects of comorbidities on the risk of mortality associated with cardiovascular or cereborovascular disease. **c** Forest plot of the pooled effects of comorbidities on the risk of mortality associated with kidney disease, liver disease, or cancer. Incre, increase; CI, confidence interval.



PEDIATRICS

MUCOCUTANEOUS MANIFESTATIONS OF MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN DURING THE COVID-19 PANDEMIC

Young TK, Shaw KS, Shah JK, Noor A, Alperin RA, Ratner AJ, Orlow SJ, Betensky RA, Shust GF, Kahn PJ, Oza VS.. JAMA Dermatol. 2020 Dec 9. doi: 10.1001/jamadermatol.2020.4779. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A medical student and dermatologist from New York University Grossman School of Medicine analyzed the mucocutaneous finding of 35 pediatric patients who met criteria for multisystem inflammatory syndrome (MIS-C) (see summary) between April 1 and July 14, 2020 (Table). They found 29 patients (83%) had mucocutaneous changes, occurring at an average of 2.7 days after fever onset. Findings consisted of conjunctival injection (21/35 [60%]), palmoplantar erythema (18/35 [51%]), lip hyperemia (17/35 [49%]), periorbital erythema and edema (7/35 [20%]), strawberry tongue (8/35 [23%]), malar erythema (6/35 [17%]), scarlatiniform eruptions (5/35 [14%]), morbilliform eruptions (3/35 [9%]), urticarial eruptions (3/35 [9%]), and reticulated eruptions (3/35 [9%])(Figures 1, 2). The authors concluded that mucocutaneous findings may serve as important clues in the recognition of MIS-C.

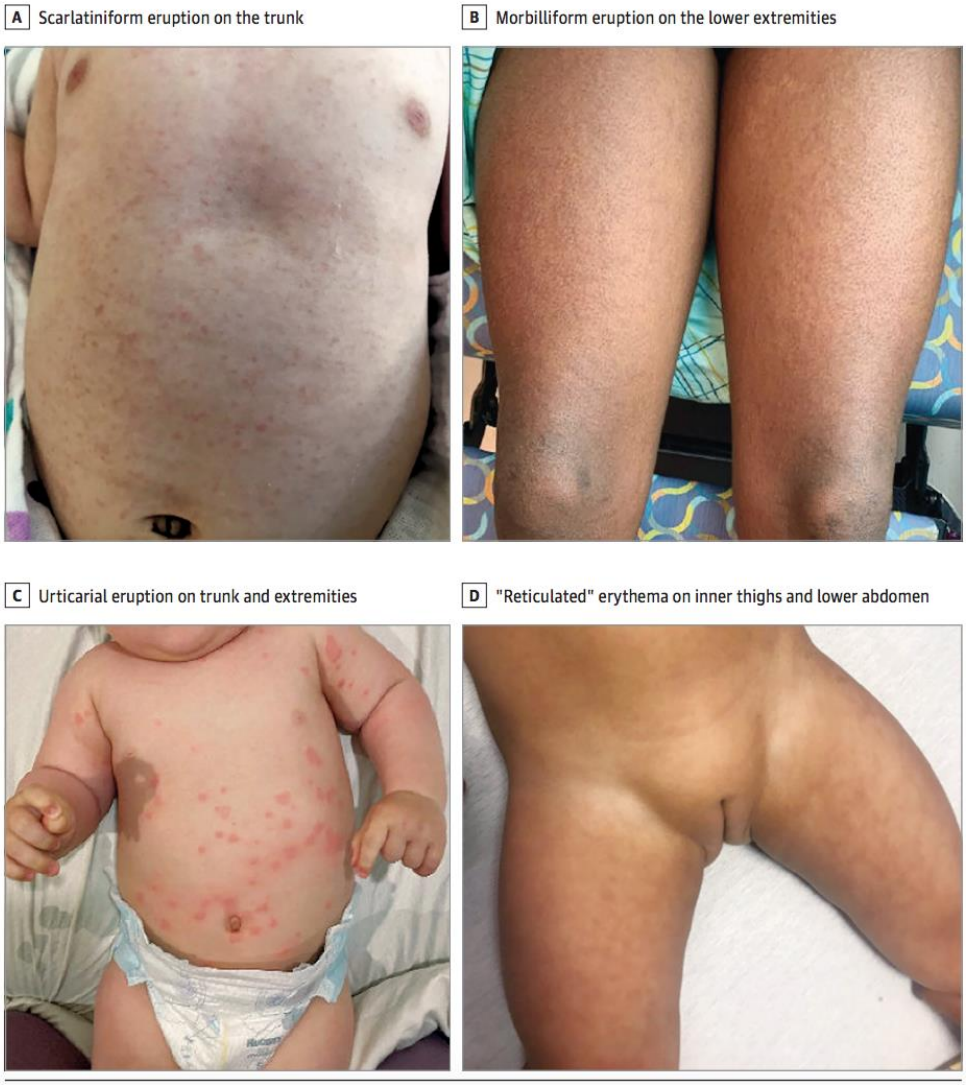
SUMMARY

Centers for Disease Control and Prevention case definition of MIS-C:
1. Aged 21 years or younger presenting with fever, laboratory evidence of inflammation, and severe illness requiring admission;
2. Involvement of at least 2 organ systems; and
3. No alternative plausible diagnosis

ABSTRACT

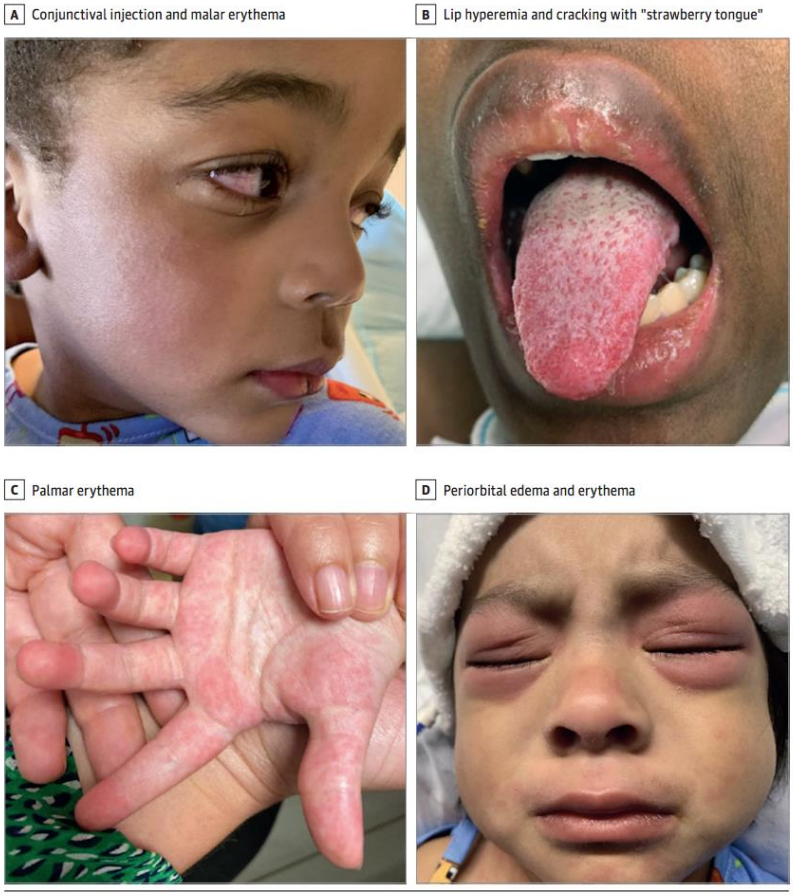
Importance: To date, no study has characterized the mucocutaneous features seen in hospitalized children with multisystem inflammatory syndrome in children (MIS-C) or the temporal association of these findings with the onset of systemic symptoms. Objective: To describe the mucocutaneous findings seen in children with MIS-C during the height of the coronavirus disease 2019 (COVID-19) pandemic in New York City in 2020. Design, Setting, and Participants: A retrospective case series was conducted of 35 children admitted to 2 hospitals in New York City between April 1 and July 14, 2020, who met Centers for Disease Control and Prevention and/or epidemiologic criteria for MIS-C. Main Outcomes and Measures: Laboratory and clinical characteristics, with emphasis on mucocutaneous findings, of children who met criteria for MIS-C. The characterization of mucocutaneous features was verified by 2 board-certified pediatric dermatologists. Results: Twenty-five children (11 girls [44%]; median age, 3 years [range, 0.7-17 years]) were identified who met definitional criteria for MIS-C; an additional 10 children (5 girls [50%]; median age, 1.7 years [range, 0.2-15 years]) were included as probable MIS-C cases (patients met all criteria with the exception of laboratory test evidence of severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection or known exposure). The results of polymerase chain reaction tests for SARS-CoV-2 were positive for 10 patients (29%), and the results of SARS-CoV-2 immunoglobulin G tests were positive for 19 patients (54%). Of the 35 patients, 29 (83%) exhibited mucocutaneous changes, with conjunctival injection (n = 21), palmoplantar erythema (n = 18), lip hyperemia (n = 17), periorbital erythema and edema (n = 7), strawberry tongue (n = 8), and malar erythema (n = 6) being the most common findings. Recognition of mucocutaneous findings occurred a mean of 2.7 days (range, 1-7 days) after the onset of fever. The duration of mucocutaneous findings varied from hours to days (median duration, 5 days [range, 0-11 days]). Neither the presence nor absence of mucocutaneous findings was significantly associated with overall disease severity. Conclusions and Relevance: In this case series of hospitalized children with suspected MIS-C during the COVID-19 pandemic, a wide spectrum of mucocutaneous findings was identified. Despite their protean and transient nature, these mucocutaneous features serve as important clues in the recognition of MIS-C.

Figure 2. Notable Cutaneous Findings Observed on the Trunk and Extremities of Hospitalized Children With Multisystem Inflammatory Syndrome



A, Scarlatiniform eruption on the trunk. B, Morbilliform eruption on the lower extremities. C, Urticarial eruption on trunk and extremities. D, Lacy "reticulated" erythema on the bilateral inner thighs and lower abdomen.

Figure 1. Notable Acrofacial Findings Observed in Hospitalized Children With Multisystem Inflammatory Syndrome



A, Nonexudative, limbic-sparing conjunctival injection and malar erythema. B, Lip hyperemia and cracking with prominent papillae noted on the dorsal surface of the tongue, consistent with a "strawberry tongue." C, Palmar erythema. D, Periorbital edema and erythema.

Table. Demographic and Clinical Characteristics of Patients With Multisystem Inflammatory Syndrome in Children

Characteristic	Patients, No. (%) (N = 35)[a]
Age, median (range), y	2 (0.2-17)
Female	16 (46)
Race/ethnicity[b]	
Hispanic	12 (34)
Black	10 (29)
White	6 (17)
Asian	4 (11)
Pacific Islander or Native Hawaiian	1 (3)
Unknown or not reported	2 (6)
COVID-19 diagnosis or exposure	
Positive laboratory test result (PCR and/or IgG)	21 (60)
SARS-CoV-2	
Nasopharyngeal PCR and IgG positive	8 (23)
Nasopharyngeal PCR positive only[c]	2 (6)
IgG positive only	11 (31)
Known exposure to a contact with COVID-19	17 (49)
Negative laboratory test results	
Known COVID-19 contact	4 (11)
Unknown COVID-19 contact	10 (29)
Mucosal findings	
Conjunctivitis	21 (60)
Any oral mucosal change	20 (57)
Strawberry tongue	8 (23)
Lip	
Hyperemia	17 (49)
Cracking	13 (37)
Cutaneous findings (rash)	28 (80)
Patients in whom fever developed before rash	19/28 (68)
Days of fever before rash onset, mean (SD)	2.7 (1.6)
Patients in whom rash developed before fever	5/28 (18)
Days of rash before fever, mean (SD)	1.4 (0.6)
Duration of cutaneous symptoms, median (range), d	5 (0-11)
Palmoplantar	
Erythema	18 (51)
Edema	14 (40)
Periorbital erythema and edema	7 (20)
Morbilliform eruption	3 (9)
Erythema	
Malar	6 (17)
Lacy or reticular	3 (9)
Macular	4 (11)
Eruption	
Scarlatiniform	5 (14)
Urticarial	3 (9)
Other[d]	4 (11)
Patients who met criteria for Kawasaki disease[e]	
Kawasaki disease	
Typical	14 (40)
Incomplete	7 (20)
Kawasaki shock syndrome	4 (11)
Treatments[f]	
Intravenous immunoglobulin	27 (77)
Systemic corticosteroids[g]	24 (69)
Aspirin	22 (63)
Remdesivir	3 (9)
Anakinra	3 (9)
Hospitalization	
Admitted to ICU	10 (29)
ICU length of stay, median (range), d	6 (3-28)
Hospital length of stay, median (range), d	5 (2-55)

UNDERSTANDING THE PATHOLOGY

DECODING ASYMPTOMATIC COVID-19 INFECTION AND TRANSMISSION

Wang R, Chen J, Hozumi Y, Yin C, Wei GW.. J Phys Chem Lett. 2020 Dec 3;11(23):10007-10015. doi: 10.1021/acs.jpclett.0c02765. Epub 2020 Nov 12.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Computer scientists from the University of Illinois analyzed 75,775 SARS-CoV-2 complete genome isolates collected through October 19, 2020 (Table 1) to explore virological characteristics in asymptomatic COVID-19. They found patients with asymptomatic COVID-19 were significantly more likely to have the SARS-CoV-2 single nucleotide mutation 11083G>T-(L37F) on Non-Structural Protein 6 (NSP 6)(r=0.61, p=5.42×10^-56)(Figure 4) and countries with the highest L37F mutation ratio had lower death ratio (Table 3). Artificial intelligence (AI), topological data analysis (TDA), and network analysis revealed L37F destabilized NSP6's structure in a way that impeded viral assembly and replication. Authors suggest L37F mutation as a possible explanation for asymptomatic COVID-19 (Figure 4) and encourage further research on therapies targeting NSP6.

ABSTRACT

One of the major challenges in controlling the coronavirus disease 2019 (COVID-19) outbreak is its asymptomatic transmission. The pathogenicity and virulence of asymptomatic COVID-19 remain mysterious. On the basis of the genotyping of 75775 SARS-CoV-2 genome isolates, we reveal that asymptomatic infection is linked to SARS-CoV-2 11083G>T mutation (i.e., L37F at nonstructure protein 6 (NSP6)). By analyzing the distribution of 11083G>T in various countries, we unveil that 11083G>T may correlate with the hypotoxicity of SARS-CoV-2. Moreover, we show a global decaying tendency of the 11083G>T mutation ratio indicating that 11083G>T hinders the SARS-CoV-2 transmission capacity. Artificial intelligence, sequence alignment, and network analysis are applied to show that NSP6 mutation L37F may have compromised the virus's ability to undermine the innate cellular defense against viral infection via autophagy regulation. This assessment is in good agreement with our genotyping of the SARS-CoV-2 evolution and transmission across various countries and regions over the past few months.

FIGURES

sample size	with 11803G>T	with patient status	asymptomatic	symptomatic
75 775	6052	9912	76	461

Table 1: " Characteristics of the Customized Data Set".

country/region	N_{L37F}	N_S	mutation ratio	total cases	total deaths	death ratio (%)
Singapore	555	825	0.673	57 965	28	0.05
Japan	89	528	0.169	96 534	1711	1.77
Turkey	29	126	0.230	359 784	9727	2.70
Jordan	7	22	0.318	50 750	540	1.06
India	237	1890	0.125	7 864 811	118 534	1.51
Norway	28	207	0.135	17 232	279	1.62
Australia	335	7324	0.046	27 499	905	3.29
South Korea	140	275	0.509	25 836	457	1.77
United Kingdom	2734	27 365	0.100	854 014	44 745	5.23
Canada	145	1285	0.113	211 732	9888	4.67
Vietnam	5	80	0.062	1160	35	3.02
Belgium	45	869	0.052	320 931	10 796	3.36
Malaysia	69	93	0.742	25 742	221	0.86
China	18	326	0.055	91 675	4746	5.18
France	39	984	0.040	1055942	34362	3.25
United States	728	20 101	0.036	84 031 217	222 507	0.26
Brazil	10	358	0.028	5 353 656	156 471	2.92
Spain	48	866	0.055	1 046 132	34 752	3.32
Russia	5	479	0.010	1 513 877	26 050	1.72

[a] N_{L37F} and N_S represent the total number of sequences with 11083G>T-(L37F) and the total number of sequences in each country listed in our data set, respectively.

Table 3: "11083G>T-(L37F) Mutation Ratio and Death Ratio in Each Country as of October 19, 2020".

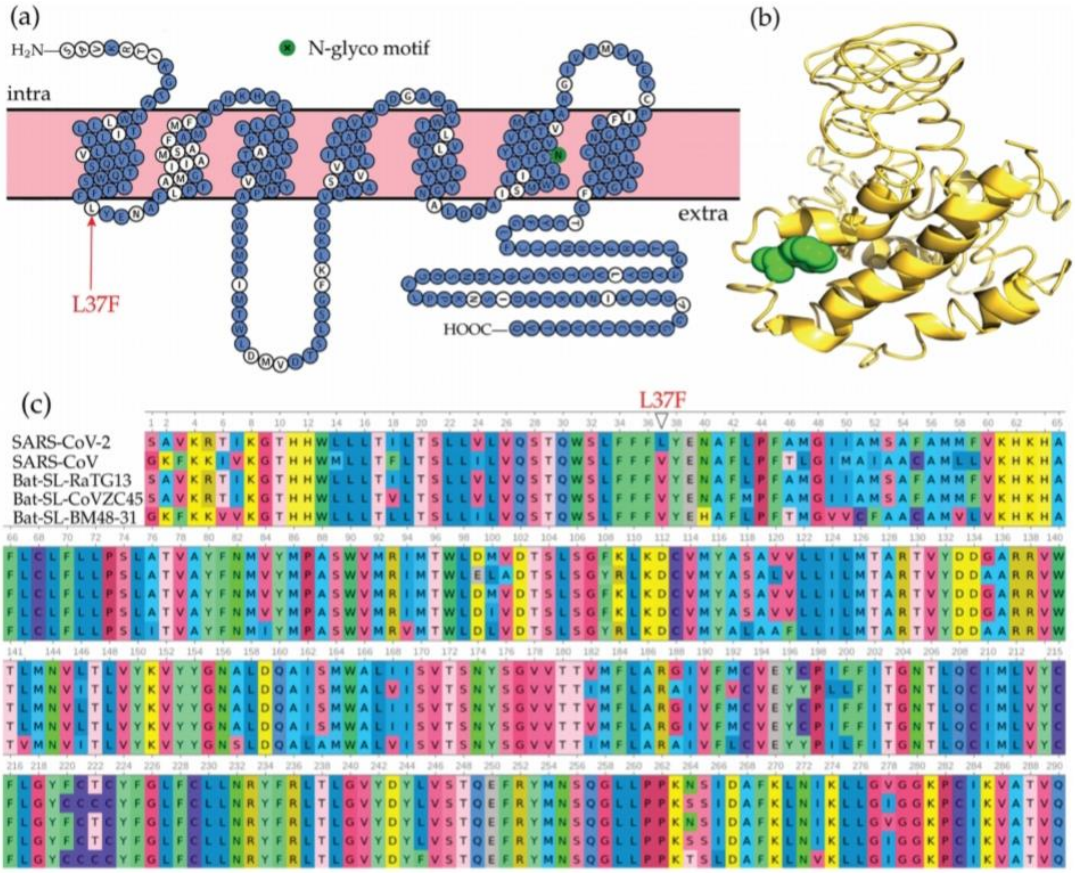


Figure 4: "(a) Visualization of SARS-CoV-2 NSP6 proteoform. The 11083G>T mutation in the genome sequence leads to the residue 37 leucine (L) mutant to phenylalanine (F). We use a red arrow to point out the mutation detected at residue 37. According to the sequence alignment results in (c), we color the conservative SARS-CoV-2 NSP6 residues blue. (b) Three-dimensional structure of the SARS-CoV-2 NSP6 protein. Green represents the mutation residue at position 37 of NSP6. (c) Sequence alignments for the NSP6 proteins of SARS-CoV-2, SARS-CoV, bat coronavirus RaTG13, bat coronavirus CoVZC45, and bat coronavirus BM48-31. The numbering is generated according to SARS-CoV-2."

IN ANIMAL MODELS

SIMULATION OF THE CLINICAL AND PATHOLOGICAL MANIFESTATIONS OF CORONAVIRUS DISEASE 2019 (COVID-19) IN A GOLDEN SYRIAN HAMSTER MODEL: IMPLICATIONS FOR DISEASE PATHOGENESIS AND TRANSMISSIBILITY

Chan JF, Zhang AJ, Yuan S, Poon VK, Chan CC, Lee AC, Chan WM, Fan Z, Tsoi HW, Wen L, Liang R, Cao J, Chen Y, Tang K, Luo C, Cai JP, Kok KH, Chu H, Chan KH, Sridhar S, Chen Z, Chen H, To KK, Yuen KY.. Clin Infect Dis. 2020 Dec 3;71(9):2428-2446. doi: 10.1093/cid/ciaa325.

Level of Evidence: 5 - Modeling

BLUF

This experimental animal model study conducted by researchers at the Microbiology Department of The University of Hong Kong found that performing SARS-CoV-2 challenges (n=21) on a sample of Syrian hamsters showed hamster-to-hamster transmission (Figure 2B) while also satisfying Koch's postulates of clinical and pathological reproduction similar to humans infected by the virus and detection of viral neutralizing antibody. This suggests that the hamster model could serve as a significant study tool for the SARS-CoV-2 virus where a small animal model did not previously exist.

ABSTRACT

BACKGROUND: A physiological small animal model that resembles COVID-19 with low mortality is lacking. METHODS: Molecular docking on the binding between angiotensin-converting enzyme 2 (ACE2) of common laboratory mammals and the

receptor-binding domain of the surface spike protein of SARS-CoV-2 suggested that the golden Syrian hamster is an option. Virus challenge, contact transmission, and passive immunoprophylaxis were performed. Serial organ tissues and blood were harvested for histopathology, viral load and titre, chemokine/cytokine assay, and neutralising antibody titre. RESULTS: The Syrian hamster could be consistently infected by SARS-CoV-2. Maximal clinical signs of rapid breathing, weight loss, histopathological changes from the initial exudative phase of diffuse alveolar damage with extensive apoptosis to the later proliferative phase of tissue repair, airway and intestinal involvement with virus nucleocapsid protein expression, high lung viral load, and spleen and lymphoid atrophy associated with marked cytokine activation were observed within the first week of virus challenge. The lung virus titre was between 105-107 TCID50/g. Challenged index hamsters consistently infected naive contact hamsters housed within the same cage, resulting in similar pathology but not weight loss. All infected hamsters recovered and developed mean serum neutralising antibody titre >=1:427 fourteen days post-challenge. Immunoprophylaxis with early convalescent serum achieved significant decrease in lung viral load but not in lung pathology. No consistent non-synonymous adaptive mutation of the spike was found in viruses isolated from infected hamsters. CONCLUSIONS: Besides satisfying the Koch's postulates, this readily available hamster model is an important tool for studying transmission, pathogenesis, treatment, and vaccination against SARS-CoV-2.

FIGURES

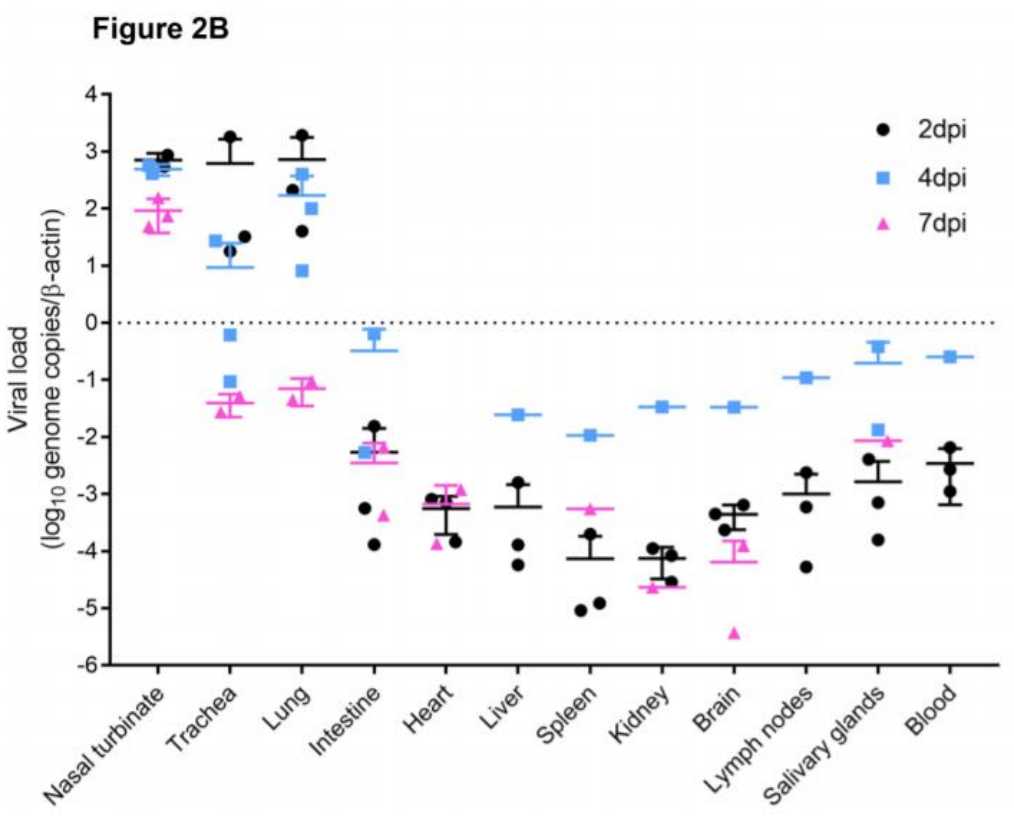


Figure 2B. Viral load by qRT-PCR assay in the respiratory tract tissues, extrapulmonary organ tissues, and blood of SARS-CoV-2-challenged hamsters at 2dpi, 4dpi, and 7dpi (n=3 per day).

TRANSMISSIBILITY OF COVID-19 DEPENDS ON THE VIRAL LOAD AROUND ONSET IN ADULT AND SYMPTOMATIC PATIENTS

Kawasuji H, Takegoshi Y, Kaneda M, Ueno A, Miyajima Y, Kawago K, Fukui Y, Yoshida Y, Kimura M, Yamada H, Sakamaki I, Tani H, Morinaga Y, Yamamoto Y.. PLoS One. 2020 Dec 9;15(12):e0243597. doi: 10.1371/journal.pone.0243597. eCollection 2020.

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

BLUF

Infectious disease specialists and microbiologists from the Toyama University Graduate School of Medicine and Pharmaceutical Sciences in Japan conducted a case-control study comparing patients with COVID-19 who did ("index patients", n=14) and did not transmit SARS-CoV-2 to another patient (n=14) between April 13 and May 7, 2020 (Table 1). They found index patients showed higher viral loads at onset compared to non-index patients (6.6 [5.2 to 8.2] log copies/μL vs. 3.1 [1.5 to 4.8])(Figure 1) and that, in general, symptomatic patients had a higher initial viral load (2.8 log copies/μL) than asymptomatic patients (0.9 log copies/μL, p<0.01). Authors suggest elevated nasopharyngeal viral load contributes to secondary transmission of SARS-CoV-2, and that understanding the viral threshold for infectivity can better quarantine and isolation policies.

ABSTRACT

OBJECTIVE: To investigate the relationship between viral load and secondary transmission in novel coronavirus disease 2019 (COVID-19). METHODS: Epidemiological and clinical data were obtained from immunocompetent laboratory-confirmed patients with COVID-19 who were admitted to and/or from whom viral loads were measured at Toyama University Hospital. Using a case-control approach, index patients who transmitted the disease to at least one other patient were analysed as "cases" (index patients) compared with patients who were not the cause of secondary transmission (non-index patients, analysed as "controls"). The viral load time courses were assessed between the index and non-index symptomatic patients using non-linear regression employing a standard one-phase decay model. RESULTS: In total, 28 patients were included in the analysis. Median viral load at the initial sample collection was significantly higher in symptomatic than in asymptomatic patients and in adults than in children. Among symptomatic patients (n = 18), non-linear regression models showed that the estimated viral load at onset was higher in the index than in the non-index patients (median [95% confidence interval]: 6.6 [5.2-8.2] vs. 3.1 [1.5-4.8] log copies/muL, respectively). In adult (symptomatic and asymptomatic) patients (n = 21), median viral load at the initial sample collection was significantly higher in the index than in the non-index patients (p = 0.015, 3.3 vs. 1.8 log copies/muL, respectively). CONCLUSIONS: High nasopharyngeal viral loads around onset may contribute to secondary transmission of COVID-19. Viral load may help provide a better understanding of why transmission is observed in some instances, but not in others, especially among household contacts.

FIGURES

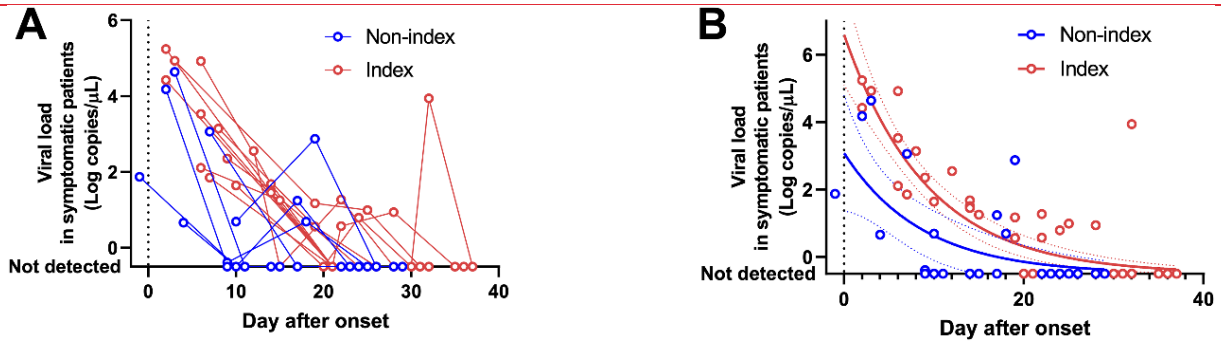


Fig 1. Trends in viral loads in the symptomatic patients.

(A) Viral load time courses of index (red) and non-index patients (blue). (B) Nonlinear regression models of index (red) and non-index patients (blue). The models were calculated by using all the data of the index or non-index patients. When no virus was detected, the data were hypothetically plotted as −0.5 log copies/μL. Solid curves are best-fit models and dotted lines indicate the 95% confidence interval of each model.

Characteristics	Study population
Age, median, y	45.5
0–17, n (%)	7 (25.0)
18–64, n (%)	14 (50.0)
≥65, n (%)	7 (25.0)
Sex	
Male, n (%)	15 (53.6)
Situation, n (%)	
Index	14 (50.0)
0–17, n (%)	4 (14.3)
18–64, n (%)	6 (21.4)
≥65, n (%)	4 (14.3)
Secondary	10 (35.7)
Sporadic	4 (14.3)
Presence of symptoms, n (%)	
Asymptomatic	10 (35.7)
Symptomatic	18 (64.3)
Mild	12 (42.9)
Moderate	5 (17.9)
Severe	1 (3.6)

https://doi.org/10.1371/journal.pone.0243597.t001

Table 1. Basic characteristics of the patients.

PREVENTION IN THE COMMUNITY

PERIPHERAL OXYGEN SATURATION IN OLDER PERSONS WEARING NONMEDICAL FACE MASKS IN COMMUNITY SETTINGS

Chan NC, Li K, Hirsh J.. JAMA. 2020 Dec 8;324(22):2323-2324. doi: 10.1001/jama.2020.21905.
Level of Evidence: 3 - Local non-random sample

BLUF

Internists from McMaster University in Canada conducted a crossover study of 25 retirement home residents older than 65 (Table 1) to monitor self-measured peripheral oxygen saturation (SpO2) with use of a three-layer disposable nonmedical face mask. They found pooled mean SpO2 was 96.1%, 96.5%, 96.3% in the hour prior to use, during one hour of use, and one hour after wearing the masks, respectively (Table 2). Authors suggest despite some public concerns about mask safety, the use of nonmedical face masks is not associated with a decrease in SpO2 in older populations.

Characteristics	No. (%) of participants (N = 25)
Age, mean (SD), y	76.5 (6.1)
Sex	
Men	13 (52)
Women	12 (48)
Medical conditions	
Hypertension	6 (24.0)
Respiratory	3 (12)
Bronchitis	1 (4)
Interstitial lung disease	1 (4)
Asthma	1 (4)
Cardiac surgery	2 (8)
Diabetes	2 (8)
Smoking	1 (4)
Medications	
Statins	12 (48)
ACEIs or ARBs	10 (40)
Diuretics	8 (24)
Calcium channel blockers	4 (16)
Anticoagulants	4 (16)
β-Blockers	4 (16)
Acetylsalicylic acid	2 (8)
Oral hypoglycemic agents	2 (8)
Prednisone	1 (4)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 1: "Baseline Characteristics of Participants".

	Spo_2, mean (SD), %
No. of participants	25
Before mask wearing, Spo_2 reading	
1	96.1 (1.3)
2	95.8 (2.1)
3	96.3 (1.6)
Pooled mean Spo_2, % (95% CI)[a]	96.1 (95.5-96.7)
While mask wearing, Spo_2 reading	
1	96.4 (1.2)
2	96.5 (1.3)
3	96.7 (1.1)
Pooled mean Spo_2, % (95% CI)[a]	96.5 (96.1-97.0)
After mask wearing, Spo_2 reading	
1	96.4 (1.3)
2	96.4 (1.4)
3	96.2 (1.4)
Pooled mean Spo_2, % (95% CI)[a]	96.3 (95.8-96.8)

Abbreviation: Spo_2, oxygen saturation measured using a portable oximeter.

[a] 95% CIs are 2-sided.

Table 2: "2. Oxygen Saturation Before, While, and After Wearing Nonmedical Face Masks".

USE AND COST-EFFECTIVENESS OF A TELEHEALTH SERVICE AT A CENTRALIZED COVID-19 QUARANTINE CENTER IN TAIWAN: COHORT STUDY

Yen YF, Tsai YF, Su VY, Chan SY, Yu WR, Ho H, Hou CM, Chen CC, Woung LC, Huang SJ.. J Med Internet Res. 2020 Dec 11;22(12):e22703. doi: 10.2196/22703.
Level of Evidence: 3 - Local non-random sample

BLUF

A multidisciplinary team of Taiwanese physicians conducted a prospective cohort study to analyze the role and cost-effectiveness of telehealth for COVID-19 monitoring among 217 international travelers quarantined at the Taiwan Yangmingshan quarantine center from March 30 to April 15, 2020 who initially tested negative by RT-PCR upon arrival in Taiwan. A multidisciplinary telehealth team monitored 28 ill persons twice daily (Table 1) and recommended hospitalization for three patients with fever; all three later tested negative again for SARS-CoV-2 via RT-PCR (Figure 2). Overall cost of the the 14-day quarantine was US$894/person (Table 2). Authors suggest these findings illustrate the vital role of telehealth in combating the global spread of COVID-19 by reducing the direct exposure of healthcare workers in quarantine centers in a cost-effective manner.

ABSTRACT

BACKGROUND: Telehealth has been recommended for monitoring the progression of non-severe infections in patients with the coronavirus disease of 2019 (COVID-19). However, telehealth has not been widely implemented in monitoring severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in quarantined individuals. Moreover, studies on the cost-effectiveness of the COVID-19 quarantine are scarce. OBJECTIVE: This cohort study aimed to use telehealth to monitor COVID-19 infections in 217 quarantined Taiwanese travelers and analyze the cost-effectiveness of the quarantine. METHODS: Travelers were quarantined for 14 days at the Taiwan Yangmingshan quarantine center and monitored until they were discharged. Travelers' clinical symptoms were evaluated twice daily. A multi-disciplinary medical team used the telehealth system to provide timely assistance for ill travelers. The cost of the mandatory quarantine was calculated according to data from the Ministry of Health and Welfare, Taiwan. RESULTS: In 217 quarantined travelers, the SARS-CoV-2 testing was negative upon admission to the quarantine center. During the quarantine, 28 (12.9%) travelers became ill and were evaluated via telehealth. Three travelers with fever were hospitalized after the telehealth assessment, and subsequent tests for COVID-19 were negative for all three patients. The total costs during the quarantine were 193,938 USD, which equated to 894 USD per individual. CONCLUSIONS: Telehealth is an effective instrument in monitoring COVID-19 infection in quarantined travelers and could help provide timely disease management in those who are ill. It is imperative to screen and quarantine international travelers for SARS-COV-2 infection to reduce the nationwide spread of COVID-19. CLINICALTRIAL:

FIGURES

Characteristic	Total (N=217)	Evaluated with telehealth (n=28)	Not evaluated with tele-health (n=189)	*P* value
Age (years), mean (SD)	30.0 (19.40)	33.0 (18.1)	29.6 (17.3)	0.33
Age (years), n (%)				0.68
<20	78 (35.9)	8 (28.6)	70 (37.0)	
20-39	54 (24.9)	8 (28.6)	46 (24.3)	
≥40	85 (39.2)	12 (42.8)	73 (38.7)	
Sex, n (%)				0.61
Female	130 (59.9)	10 (35.7)	77 (40.7)	
Male	87 (40.1)	18 (64.3)	112 (59.3)	
Number of family members, n (%)				<.001
1	79 (36.4)	19 (67.9)	60 (31.7)	
≥2	138 (63.6)	9 (32.1)	129 (68.3)	
Fever during the 14-day quarantine, n (%)				<.001
No	214 (98.6)	25 (89.3)	189 (100)	
Yes	3 (1.4)	3 (10.7)	0 (0)	
Hospitalization, n (%)				<.001
No	214 (98.6)	25 (89.3)	189 (100)	
Yes	3 (1.4)	3 (10.7)	0 (0)	

Table 1: "Characteristics of Taiwanese travelers who were and were not evaluated with telehealth at a centralized quarantine center".

Variable	Personnel, n	Cost (US $), amount (%)
Personnel costs		
Multidisciplinary medical team	15	72,334 (37.30)
Police officers	18	66,427 (34.25)
Janitors	3	10,880 (5.61)
Logistic group	10	8033 (4.14)
Administration staff	1	894 (0.46)
Nonpersonnel costs		
Telehealth equipment	N/A[a]	2838 (1.46)
Personal protective equipment	N/A	16,016 (8.26)
Disinfecting equipment	N/A	115 (0.06)
Infectious waste disposal	N/A	1400 (0.72)
Staff uniform disinfection	N/A	6667 (3.44)
Meals and daily supplies for quarantined travelers	N/A	8334 (4.30)
Total	47	193,938 (100)

[a]N/A: not applicable.

Table 2: "Cost analysis of the 14-day mandatory quarantine of 217 Taiwanese travelers".

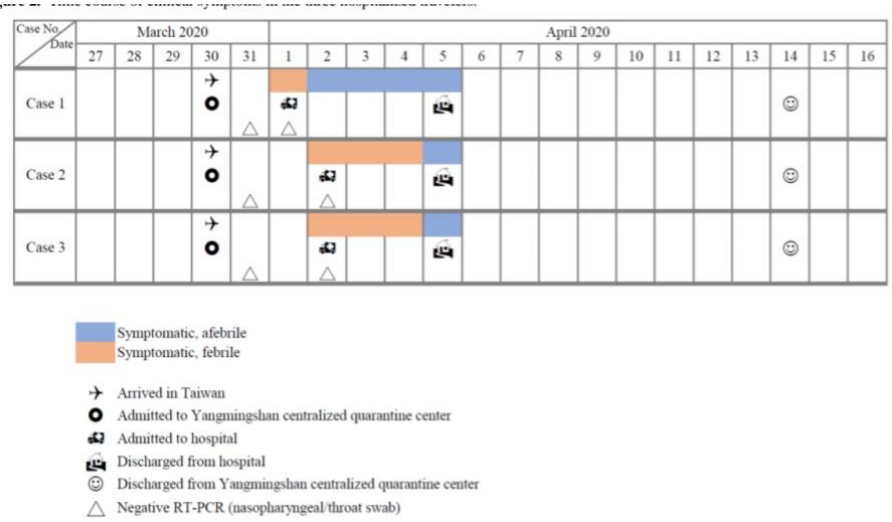


Figure 2: "Time course of clinical symptoms in the three hospitalized travelers".

REMOTE FINGERSTICK BLOOD COLLECTION FOR SARS-COV-2 ANTIBODY TESTING

Garcia-Beltran WF, Miller TE, Kirkpatrick G, Nixon A, Astudillo MG, Yang D, Mahanta LM, Murali M, Dighe AS, Lennerz J, Thierauf J, Naranbhai V, Iafrate AJ.. Arch Pathol Lab Med. 2020 Dec 2. doi: 10.5858/arpa.2020-0713-SA. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

Pathologists from Massachusetts General Hospital in Boston investigated a new method for SARS-CoV-2 antibody testing by combining volumetric absorptive microsampling (Mitra) of dried fingerpick blood with electrochemiluminescence immunoassay (Roche Elecsys) of SARS-CoV-2 IgG/IgM/IgA anti-nucleocapsid antibodies. Using samples from 48 COVID-19 patients and 48 pre-pandemic donors, they found the Mitra-Roche combination detects antibodies in diluted serum samples (1:20) and contrived dried blood extract with high precision (R^2=0.97, Figure 1). Given this method satisfactorily detects SARS-CoV-2 antibodies and can be carried out remotely or at home, authors suggests using the Mitra dried blood collection device with the Roche Elecsys antibody assay provides an alternative to routine serum sample collection by venous blood sampling that may be useful for individual testing and larger seroprevalence studies (Figure 2).

ABSTRACT

The rapid worldwide spread of severe acute respiratory system coronavirus 2 (SARSCoV-2) infection has propelled the rapid development of serological tests that can detect anti-SARS-CoV-2 antibodies. These have been used for studying the prevalence and spread of infection in different populations, helping establish a recent diagnosis of coronavirus disease 2019 (COVID-19), and will likely be used to confirm humoral immunity after infection or vaccination. However, nearly all lab-based high-throughput SARS-CoV-2 serological assays require a serum sample from venous blood draw, limiting their applications and scalability. Here, we present a method that enables large scale SARS-CoV-2 serological studies by combining self or office collection of fingerprick blood with a volumetric absorptive microsampling device (Mitra, Neoteryx, LLC) with a high-throughput electrochemiluminescence-based SARS-CoV-2 total antibody assay (Roche Elecsys, Roche Diagnostics, Inc.) that is emergency use authorization (EUA) approved for use on serum samples and widely used by clinical laboratories around the world. We found that the Roche Elecsys assay has a high dynamic range that allows for accurate detection of SARS-CoV-2 antibodies in serum samples diluted 1:20 as well as contrived dried blood extracts. Extracts of dried blood from Mitra devices acquired in a community seroprevalence study showed near identical sensitivity and specificity in detection of SARS-CoV-2 antibodies as compared to neat sera using predefined thresholds for each specimen type. Overall, this study affirms the use of Mitra dried blood collection device with the Roche Elecsys SARS-CoV-2 total antibody assay for remote or at-home testing as well as large-scale community seroprevalence studies.

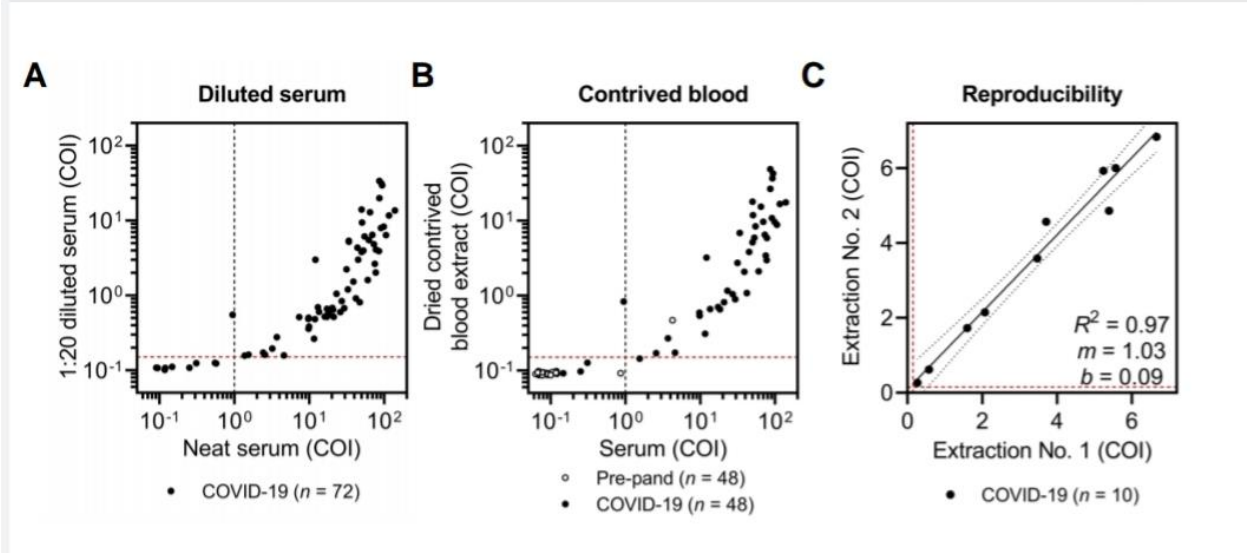


Figure 1: "Roche Elecsys SARS-CoV-2 total antibody assay can accurately detect antibodies in diluted serum samples and dried blood extracted from Mitra devices. (A) Serum samples from COVID-19 patients (n = 72) were run as neat serum as well as serum diluted 1:20 in extraction buffer on the Roche Elecsys SARS-CoV-2 total antibody assay on the Roche Cobas 8000 instrument, with cut-off index (COI) values reported. (B) Contrived blood from COVID-19 patients (n = 48) and pre-pandemic individuals (n = 48) was collected and stored on Mitra devices and subsequently extracted and run on the Roche Elecsys assay along with paired neat serum. (C) Duplicate Mitra devices were used to collect contrived blood from COVID-19 patients (n = 10), and extractions were performed in two separate facilities and run on the same Roche Elecsys assay and Roche Cobas 8000 instrument; Pearson correlation resulted in the following: coefficient of determination (R 2) = 0.97, slope (m) = 1.03, and intercept (b) = 0.09. For all, the dotted black line indicates the manufacturer-established COI threshold of 1.0 (for serum) and the dotted red line indicates the new COI threshold of 0.15 (for diluted or extracted samples)".

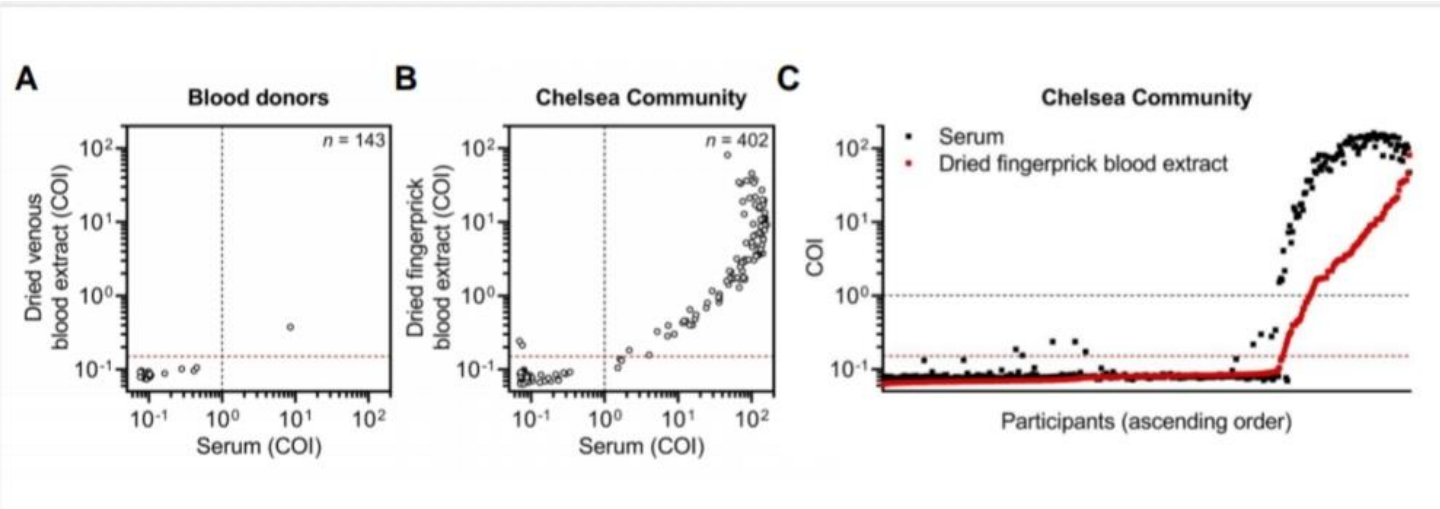


Figure 2: "Mitra-Roche assay serves as a high-throughput platform for seroprevalence studies. (A) Serum and dried venous blood extracted from Mitra devices were collected from pre-screened blood donors (n = 143) and run on the Roche Elecsys assay. (B) Serum from antecubital vein phlebotomy and dried fingerprick blood extracted from Mitra devices were collected from participants in a Chelsea community seroprevalence study (n = 407) an run on the Roche Elecsys assay. (C) COI values from the serum (black squares) and dried fingerprick blood extracted from Mitra devices (red squares) for each participant are overlaid and presented in ascending order (according to COI from dried fingerprick blood extract). For all, the dotted black line indicates the manufacturer-established COI threshold of 1.0 for serum and the dotted red line indicates the new COI threshold of 0.15 for extracted samples".

ACKNOWLEDGEMENTS

CONTRIBUTORS

Brad Mott
Jonathan Baker
Julia Ghering
Kersti Bellardi
Krithika Kumarasan

EDITORS

Justin Doroshenko
Maresa Woodfield

SENIOR EDITORS

Allison Hansen
Kyle Ellingsen

SENIOR EXECUTIVE EDITOR

Thamanna Nishath

CHIEF EDITOR

Brennan Enright

ADVISOR

Will Smith