The Daily COVID-19 Literature Surveillance Summary

February 05, 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

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EXECUTIVE SUMMARY

Understanding the Pathology

- This review from Aarhus University Hospital, Denmark examines the cytotoxic effect of SARS-CoV-2 on capillary function and the subsequent hypoxemia which initiates a cycle of hypoxia-driven endothelial damage that may explain long-term complaints of patients recovering from COVID-19. The authors investigate angiotensin-converting enzyme 2 receptors, pericyte integrity, endothelial surface lining by glycocalyx, neutrophil migration, and microthrombosis in relation to systemic hypoxia secondary to COVID-19. The authors conclude with a discussion on long-term hypoxia, serotonin synthesis and mood disorders and emphasize a need for biomarkers of capillary function in order to quantify the effect of SARS-CoV-2 on capillary function.

R&D: Diagnosis & Treatments

- A prospective cohort study from emergency physicians in Argentina found that self-collected saliva samples may be an accurate alternative to the nasopharyngeal swab (NPS) in detecting SARS-CoV-2 infection. Results demonstrated that 63 out of 174 symptomatic patients in the emergency room tested positive via the gold standard NPS, with saliva samples detecting SARS-CoV-2 in 61/63 (98%) of these patients. The authors conclude that self-collected saliva sampling for the diagnosis of SARS-CoV-2 could be an accurate, less invasive way to test certain populations while conserving PPE and exposing fewer healthcare workers to SARS-CoV-2.

TABLE OF CONTENTS

ASSESSING THE POTENTIAL IMPACT OF TRANSMISSION DURING PROLONGED VIRAL SHEDDING ON THE EFFECT OF LOCKDOWN RELAXATION ON COVID-19

Tepekule B, Hauser A, Kachalov VN, Andresen S, Scheier T, Schreiber PW, Günthard HF, Kouyos RD.. PLoS Comput Biol. 2021 Jan 29;17(1):e1008609. doi: 10.1371/journal.pcbi.1008609. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

Researchers from the University of Zurich, Switzerland present a new model to predict epidemiological trends in SARS-CoV-2 transmission. This susceptible-exposed-infected-removed (SEIR) compartmental model (Figure 1) separated the population into "primarily infected" and "chronically infected" groups prior to relaxation of lockdown measure in Switzerland. Results demonstrated that inclusion of a "chronically infected" population (those with a prolonged period of infectiousness) is a plausible caveat that epidemiologists may consider including when modeling COVID-19 transmission and creating policy because it was able to accurately predict infectivity prior to the relaxation period (Figure 2).

ABSTRACT

A key parameter in epidemiological modeling which characterizes the spread of an infectious disease is the generation time, or more generally the distribution of infectiousness as a function of time since infection. There is increasing evidence supporting a prolonged viral shedding window for COVID-19, but the transmissibility in this phase is unclear. Based on this, we develop a generalized Susceptible-Exposed-Infected-Resistant (SEIR) model including an additional compartment of chronically infected individuals who can stay infectious for a longer duration than the reported generation time, but with infectivity reduced to varying degrees. Using the incidence and fatality data from different countries, we first show that such an assumption also yields a plausible model in explaining the data observed prior to the easing of the lockdown measures (relaxation). We then test the predictive power of this model for different durations and levels of prolonged infectiousness using the incidence data after the introduction of relaxation in Switzerland, and compare it with a model without the chronically infected population to represent the models conventionally used. We show that in case of a gradual easing on the lockdown measures, the predictions of the model including the chronically infected population vary considerably from those obtained under a model in which prolonged infectiousness is not taken into account. Although the existence of a chronically infected population still remains largely hypothetical, we believe that our results provide tentative evidence to consider a chronically infected population as an alternative modeling approach to better interpret the transmission dynamics of COVID-19.

FIGURES

a)

Notation	Description
S	Susceptible.
E	Exposed.
I_p	Primarily infected.
I_c	Chronically infected.
H	Hospitalized patients.
ICU	ICU patients.
X	Deceased.
R	Recovered.
C	Accumulated number of infecteds.

b)

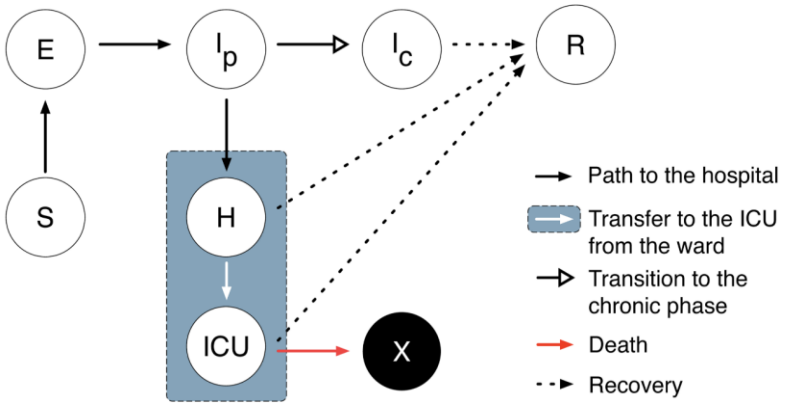

Figure 1. a) Notation of the compartments and their corresponding descriptions. b) Schematic of the dynamical model given by Eq set 1.

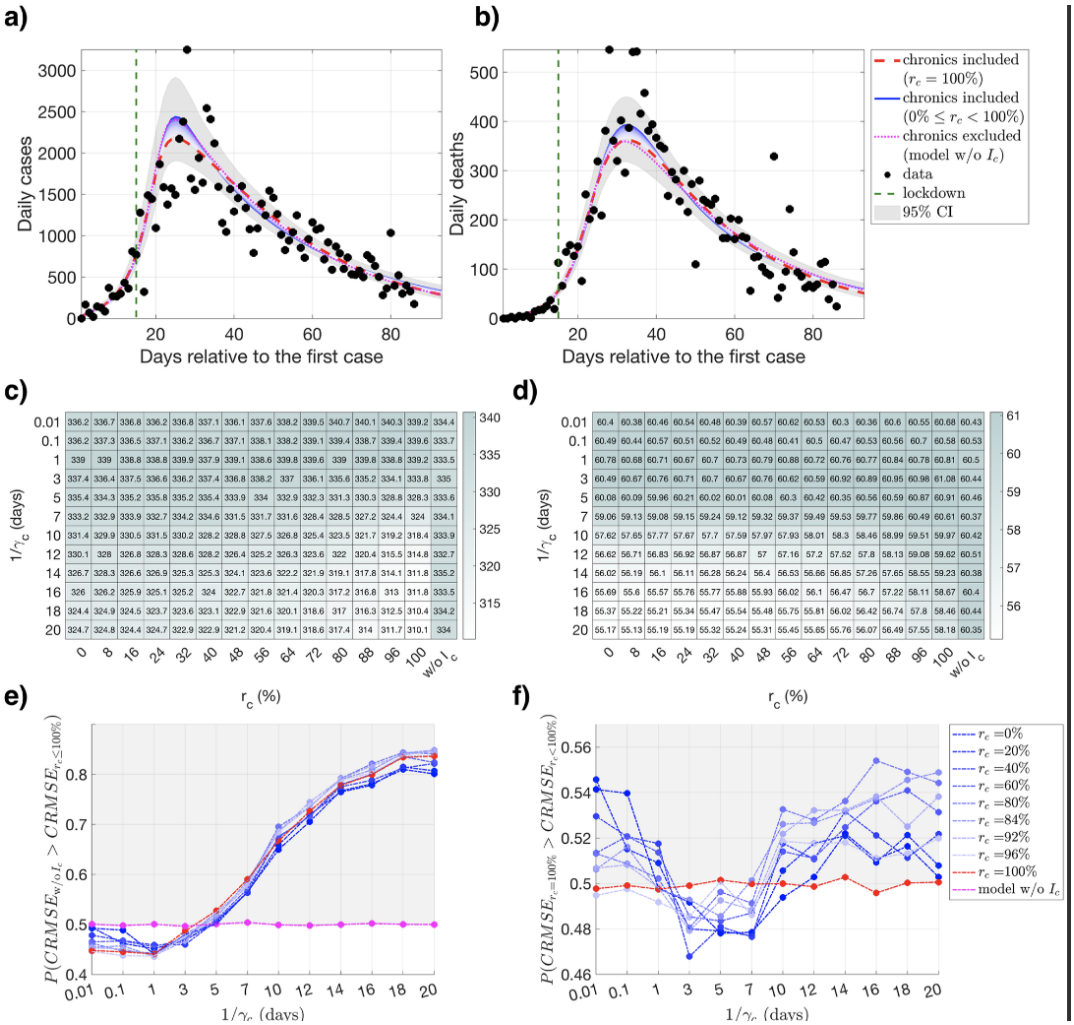

Figure 2. Fitting and RMSE results for Lombardy, calculated using different levels and durations of infectiousness for the chronically infected population. Model outcomes (presented for 1/γc = 14 days) for the number of a) daily confimed cases and b) daily deaths using the data until the introduction of relaxation for model fitting, respectively. Darker shades of blue represent the fitting results with increased infectiousness of the chronically infected population, i.e., lower rc values within the range 0 ≤ rc < 100%. Fitting results for rc = 100% are drawn in red, and the fitting results for the model without the Ic compartment (model w/o Ic) are drawn in pink. Data points that are used for fitting are drawn in black. Gray areas around the model outcomes represent the union of the 95% confidence intervals calculated for all models. RMSE values c) for the number of daily confirmed cases and d) the number of daily deaths for a given rc and γc value used for fitting, where model w/o Ic represents the results for the model without the Ic compartment. e) Probability of the model without the Ic compartment (model w/o Ic) having a greater combined RMSE (CRMSE) value than the model with the Ic compartment for all levels of reduced infectiousness (rc ≤ 100%) for different rc and γc values. f) Probability of the model where individuals are being diagnosed without being infectious (rc = 100%) having a greater combined RMSE (CRMSE) value than the model with individuals with a a prolonged infectiousness (rc < 100%) for different rc and γc values. Points in the gray areas represent the models that are providing a better fit more frequently than e) the model without the Ic compartment (model w/o Ic) and f) the model with rc = 100%.

SARS COV-2 RELATED MICROVASCULAR DAMAGE AND SYMPTOMS DURING AND AFTER COVID-19: CONSEQUENCES OF CAPILLARY TRANSIT-TIME CHANGES, TISSUE HYPOXIA AND INFLAMMATION

Østergaard L.. Physiol Rep. 2021 Feb;9(3):e14726. doi: 10.14814/phy2.14726.
Level of Evidence: 5 - Review / Literature Review

BLUF

This review from Aarhus University Hospital, Denmark examines the cytotoxic effect of SARS-CoV-2 on capillary function and the subsequent hypoxemia which initiates a cycle of hypoxia-driven endothelial damage (Figure 1) that may explain long-term complaints of patients recovering from COVID-19. The authors investigate angiotensin-converting enzyme 2 receptors, pericyte integrity, endothelial surface lining by glycocalyx, neutrophil migration, and microthrombosis in relation to systemic hypoxia secondary to COVID-19. The authors conclude with a discussion on long-term hypoxia, serotonin synthesis and mood disorders (Figure 3) and emphasize a need for biomarkers of capillary function in order to quantify the effect of SARS-CoV-2 on capillary function.

ABSTRACT

Corona virus disease 2019 (COVID-19) causes symptoms from multiple organs after infection by severe acute respiratory syndrome corona virus 2 (SARS CoV-2). They range from early, low blood oxygen levels (hypoxemia) without breathlessness ("silent hypoxia"), delirium, rashes, and loss of smell (anosmia), to persisting chest pain, muscle weakness and -pain, fatigue, confusion, memory problems and difficulty to concentrate ("brain fog"), mood changes, and unexpected onset of hypertension or diabetes. SARS CoV-2 affects the microcirculation, causing endothelial cell swelling and damage (endotheliitis), microscopic blood clots (microthrombosis), capillary congestion, and damage to pericytes that are integral to capillary integrity and barrier function, tissue repair (angiogenesis), and scar formation. Similar to other instances of critical illness, COVID-19 is also associated with elevated cytokine levels in the systemic circulation. This review examines how capillary damage and inflammation may contribute to these acute and persisting COVID-19 symptoms by interfering with blood and tissue oxygenation and with brain function. Undetectable by current diagnostic methods, capillary flow disturbances limit oxygen diffusion exchange in lungs and tissue and may therefore cause hypoxemia and tissue hypoxia. The review analyzes the combined effects of COVID-19-related capillary damage, pre-existing microvascular changes, and upstream vascular tone on tissue oxygenation in key organs. It identifies a vicious cycle, as infection- and hypoxia-related inflammation cause capillary function to deteriorate, which in turn accelerates hypoxia-related inflammation and tissue damage. Finally, the review addresses the effects of low oxygen and high cytokine levels in brain tissue on neurotransmitter synthesis and mood. Methods to assess capillary functions in human organs and therapeutic means to protect capillary functions and stimulate capillary bed repair may prove important for the individualized management of COVID-19 patients and targeted rehabilitation strategies.

FIGURES

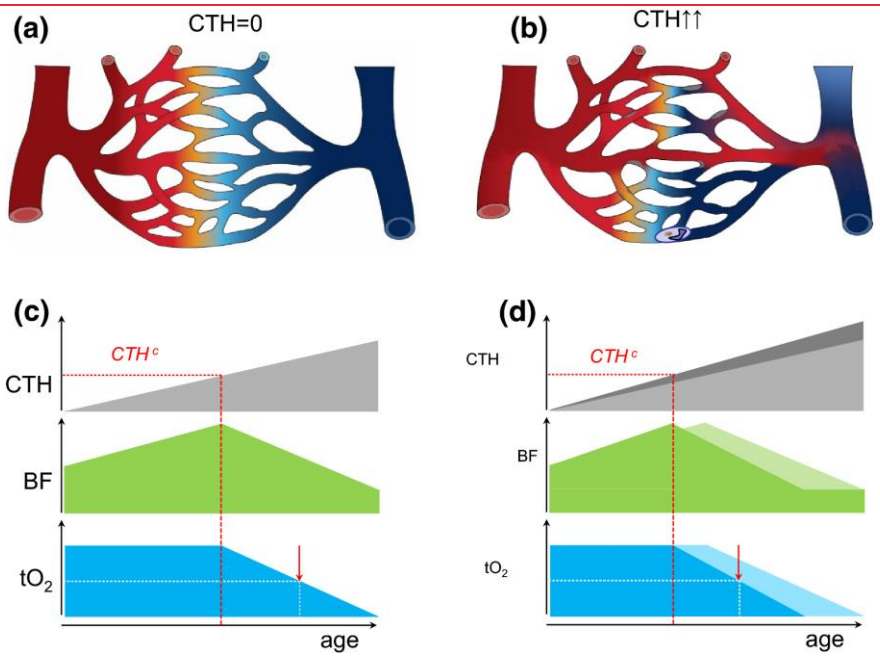

Figure 1. Capillary dysfunction and tissue oxygenation (a) Schematic capillary bed. Fully oxygenated blood is indicated by red and its transition to blue illustrates gradual deoxygenation as oxygen diffuses into tissue. In this illustration, the distribution of blood across parallel capillary paths is homogenous (no capillary transit‐time heterogeneity, i.e., CTH=0), providing optimal oxygen extraction. Modified from (Østergaard, 2020). (b) Capillary flow disturbances can be caused by either a narrowing or a widening of individual capillary segments, or by altered blood properties, such as reduced erythrocyte deformability or neutrophil adhesion after glycocalyx shedding. Note how the inability to homogenize capillary transit times across the capillary bed (CTH > 0) leads to poorer oxygen extraction although blood flow is identical to panel a. Modified from (Østergaard, 2020). (c) This panel illustrates how, for modest increases in CTH, tissue oxygen tension (tO2) can be maintained by a compensatory increase in blood flow, contrary to our current vascular disease paradigm (Østergaard, 2020). The dashed red line indicates CTHc, above which metabolic demands can only be met by limiting blood flow (Angleys et al., 2015; Jespersen & Østergaard, 2012). The lower blood supply causes tO2 to decrease, whereas the longer blood transit times and higher blood‐tissue oxygen concentration gradients provide more efficient oxygen extraction from blood, understood as a higher oxygen extraction fraction (OEF). The futility of increasing blood flow beyond the capillary bed's capacity to extract blood's oxygen may be reflected in reperfusion injury after ischemic episodes, during which capillaries irreversibly constrict (O'Farrell et al., 2017; Yemisci et al., 2009). As CTH increases beyond CTHc, BF, and tO2 gradually decreases. The red arrow indicates a 50% reduction in tissue oxygen tension to highlight the threat to critical, ATP‐sensitive cell processes and organ functions. (d) The curves illustrate how cardiovascular risk factors that accelerate capillary injury (Østergaard et al., 2016) modify the curves displayed in panel c (indicated in lighter, gray, green and blue, respectively). Note how CTHc and the onset of critically low tissue oxygen levels are expected to be reached earlier in the affected tissues. The clinical correlates of this earlier attenuation of blood flow may be earlier onset of endothelial dysfunction and hypertension, higher morbidity due to accelerated microvascular injury in critical organs, and lower life expectancy

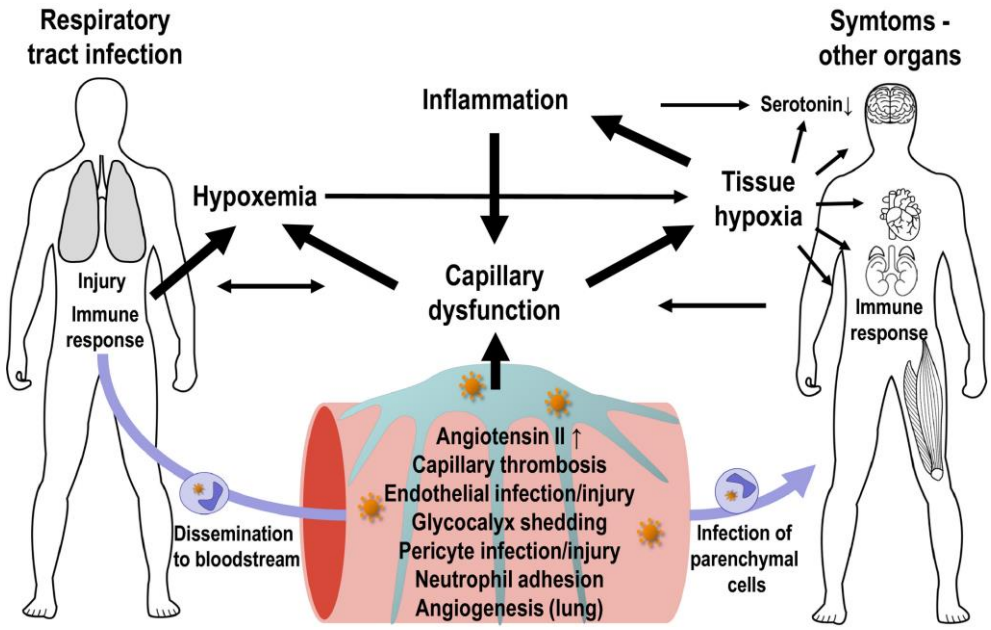

Figure 3. Interactions between capillary function, inflammation, hypoxia, and neurotransmission. The expression of ACE2 and other SARS‐CoV‐2 entry factors on parenchymal cells and observations of infected cells in biopsy material hold important clues to understand COVID‐19‐related organ damage

ENDOCRINOLOGY

POTENTIAL INTERACTION BETWEEN SARS-COV-2 AND THYROID: A REVIEW

Chen W, Tian Y, Li Z, Zhu J, Wei T, Lei J.. Endocrinology. 2021 Jan 11:bqab004. doi: 10.1210/endocr/bqab004. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A literature review conducted at West China Hospital of Sichuan University in early 2020 by the Thyroid and Parathyroid Surgery Center found that, while no current evidence points to thyroid injury due to infection, a novel report of subacute thyroiditis requires more research to understand the pathological mechanisms.

SUMMARY

Other notable points include:

- The detection of viral RNA in blood, stool, and urine samples suggests that ACE2 expressed in other organs may serve as sites of interaction for SARS-COV-2.

- One area lacking inquiry, in particular, is how thyroid hormones or thyroid diseases affect the pathogenesis of COVID-19 infections.

- Importantly, COVID-19 was neither detectable in thyroid tissues of postmortem COVID-19 patients, nor presenting with significant damage to thyroid follicles in morphology.

- While data on the impact of COVID-19 on thyroid structure is insufficient, one study may suggest that SARS-CoV-2 infections led to more extensive damage.

- While in some studies changes occurred in levels of thyroid hormones, other studies showed no significant change, and abnormalities in hormone levels returned to normal post-recovery from pneumonia.

- One proposed mechanism by which COVID-19 infection may disturb thyroid function is the proximity of the trachea to the gland; this, however, must be weighed against the fact that no SARS-CoV-2 was detectable by PCR analysis.

- So far, the literature demonstrates that low-dose glucocorticoids serves as effective treatment for subacute thyroiditis (SAT) caused by COVID-19 infection.

- Patients with existing dysfunctions in thyroid health do not present with increased risk of contracting viral illnesses, including COVID-19 infection.

- While T3 may, by some mechanisms, treat COVID-19 infections, the low T3 syndrome is not advisably treatable by T3 due to concerns for overall health.

- Heparin use to treat thyroid dysfunction in patients with COVID-19 must be weighed against significant changes in thyroid hormone levels.

ABSTRACT

The novel coronavirus disease COVID-19 produced by SARS-CoV-2 is sweeping the world in a very short time. Although much has been learned about the clinical course, prognostic inflammatory markers, and disease complications of COVID-19, the potential interaction between SARS-CoV-2 and the thyroid is poorly understood. In contrast to SARS-CoV-1, limited available evidence indicates there is no pathological evidence of thyroid injury caused by SARS-CoV-2. However, subacute thyroiditis (SAT) caused by SARS-CoV-2 has been reported for the first time. Thyroid dysfunction is common in patients with COVID-19 infection. By contrast, certain thyroid diseases may have a negative impact on the prevention and control of COVID-19. In addition, some anti-COVID-19 agents may cause thyroid injury or affect its metabolism. COVID-19 and thyroid disease may mutually aggravate the disease burden. Patients with SARS-CoV-2 infection should not ignore the effect in thyroid function, especially when there are obvious related symptoms. In addition, patients with thyroid diseases should follow specific management principles during the epidemic period.

SELF-COLLECTED SALIVA FOR SARS-COV-2 DETECTION: A PROSPECTIVE STUDY IN THE EMERGENCY ROOM

Echavarria M, Reyes NS, Rodriguez PE, Ypas M, Ricarte C, Rodriguez MP, Perez MG, Seoane A, Martinez A, Videla C, Stryjewski ME, Carballal G.. J Med Virol. 2021 Feb 2. doi: 10.1002/jmv.26839. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

A prospective cohort study from emergency physicians in Argentina found that self-collected saliva samples may be an accurate alternative to the nasopharyngeal swab (NPS) in detecting SARS-CoV-2 infection. Results demonstrated that 63 out of 174 symptomatic patients in the emergency room tested positive via the gold standard NPS (Table 1), with saliva samples detecting SARS-CoV-2 in 61/63 (98%) of these patients (Figure 1). The authors conclude that self-collected saliva sampling for the diagnosis of SARS-CoV-2 could be an accurate, less invasive way to test certain populations while conserving PPE and exposing fewer healthcare workers to SARS-CoV-2.

SUMMARY

-The 2 patients who tested positive only on NPS provided very small volume saliva samples (< 500 µl).
-One patient with pneumonia tested positive only on saliva and not on NPS
-An optimized home brew RT-PCR was more sensitive than the commercial RT-PCR

ABSTRACT

Current diagnostic standards involve SARS-CoV-2 detection in nasopharyngeal swabs (NPS), but saliva is an attractive and non-invasive option for diagnosis. The objectives were to determine the performance of saliva in comparison to NPS for detecting SARS-CoV-2 and to compare the optimized home brew RT-PCR with a commercial RT-PCR. Paired NPS and saliva specimens were prospectively collected and tested by RT-PCR from patients presenting at an emergency room with signs and symptoms compatible with COVID-19. A total of 348 samples from 174 patients were tested by RT-PCR assays. Among 174 patients with symptoms, 63 (36%) were SARS-CoV-2 positive in NPS using the optimized home-brew PCR. Of these 63 patients, 61 (98%) were also positive in saliva. An additional positive SARS-CoV-2 saliva was detected in a patient with pneumonia. Kappa Cohen's coefficient agreement between NPS and saliva was 0.96 (95%CI 0.90-0.99). Median Ct values in NPS versus saliva were 18.88 (IQR 15.60-23.58; Range: 11.97-38.10) versus 26.10 (IQR 22.75-30.06; Range: 13.78-39.22), respectively ($p < 0.0001$). The optimized home-brew RT-PCR demonstrated higher analytical and clinical sensitivity compared to the commercial RT-PCR assay. A high sensitivity (98%) and agreement (kappa 0.96) in saliva samples compared to NPS was demonstrated when using an optimized home-brew PCR even when the viral load in saliva was lower than in NPS. This non-invasive sample is easy to collect, requires less consumable and avoids discomfort to patients. Importantly, self-collection of saliva can diminish exposure to healthcare personnel.

Table 1. Baseline characteristics in patients presenting to the emergency room with COVID- 19 symptoms

Characteristics	Total (n= 174)	SARS-CoV2 positive PCR			SARS-CoV2 negative PCR
		Total (n= 64)[a]	Discharged (n= 55)	Admitted (n=9)	Discharged (n= 110)
Gender, n (%)					
Female	69 (59.8)	39 (60.9)	33 (60.0)	6 (66.7)	65 (59.1)
Male	70 (40.2)	25 (39.1)	22 (40.0)	3 (33.3)	45 (40.9)
Age (in years)					
Median (IQR)	38 (31-50)	38 (31-50,5)	35 (30-46,3)	55 (41-67)	38,5 (31-48,5)
Mean (Range)	41,1 (17-88)	41,8 (21-88)	39,3 (21-78)	56,2 (35-88)	40,7 (17-81)
Clinical Syndrome, n (%)					
URTI	165 (94.8)	55 (85.9)	55 (100)	0	110 (100)
Pneumonia	9 (5.2)	9 (14.1)	0	9 (100)	0

IQR: Interquartile Range; URTI: Upper Respiratory Tract Infection.

[a] 61 patients were positive in NPS and saliva; 1 patient was positive only in saliva; 2 patients were positive only in NPS.

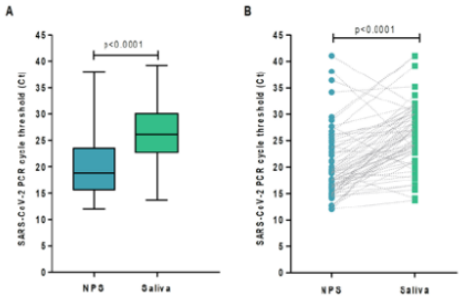

Figure 1. SARS-CoV-2 Ct in saliva and nasopharyngeal swabs (NPS). **A.** Ct median from positive nasopharyngeal swabs (n=63) and saliva samples (n =62) were compared (p< 0.0001). **B.** Patients matched positive and discrepant samples (n= 64) represented by the connecting lines were compared by a Wilcoxon rank sum test (p< 0.0001).

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