The Daily COVID-19 Literature Surveillance Summary

November 02, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

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

EXECUTIVE SUMMARY

Climate

- No-Fault Compensation for Vaccine Injury and Equitable Access to Covid-19 Vaccines are explored by Public Health experts associated with Yale University. They discuss the concept of Vaccine Nationalism, the creation of the COVAX facility, and the plight of low- and middle-income countries during the COVID-19 pandemic. To address the concerns regarding the benefits and risks of the COVID-19 vaccine as well as vaccine manufacturers protection and liability, the authors suggest utilizing a no-fault compensation for vaccine injury.

Epidemiology

- A compromised specific humoral immune response against the SARS-CoV-2 receptor-binding domain is related to viral persistence and periodic shedding in the gastrointestinal tract according to a cohort study conducted by various medical institutions in Shenzhen and Guangzhou, China. They found 21/289 Chinese patients with COVID-19 were readmitted due to persistent SARS-CoV-2 positivity. Among them, anal viral detection was positive in 15/21 (71.4%) patients and there was replication in the GI tract in 3/16 (18.7%) patients, with no respiratory tract replication. They hypothesize there is viral rebound due to decreased levels of IgA and IgG antibodies to the viral receptor-binding domain (RBD) and thus, a lack of protective humoral immune response suggesting this leads to persistence of SARS-CoV-2 in the GI tract along with active viral shedding.

Transmission & Prevention

- Climatic influence on the magnitude of COVID-19 outbreak was explored via a stochastic model-based global analysis. Researchers evaluated the effect of climates on COVID-19 transmission in 228 cities across 3 climatic zones. They found that the temperature and humidity may be major contributors to COVID-19 transmission. Average temperatures and relative humidity were the primary contributors in Europe, diurnal temperatures were most important for India, and temperature seasonality was most important for Brazil. These findings highlight the relationship between climates and COVID-19 spread and provide more insight into COVID-19 transmission.

R&D: Diagnosis & Treatments

- Two sample pooling strategies for SARS-CoV-2 RNA detection for efficient screening of COVID-19 were compared. Using 23 pools each containing 1 positive sample and either 5 or 9 negatives, authors demonstrated a similar diagnostic sensitivity to individual tests ($p<0.005$) but pooling viral transport medium resulted in a false negative while pooling swabs resulted in diagnosis without loss of sensitivity. Authors suggests pooling swabs may facilitate testing in higher quantities at lower costs, which could be used where resources are limited, however this strategy would require collecting double swab samples for individual re-testing should a pool test positive.

- Accuracy of serological testing for SARS-CoV-2 antibodies were presented based on first results from a large mixed-method evaluation study. The study looked at 3 ELISAs for accuracy: nucleoprotein (N), S1 domain of spike protein (S1), and Lateral Flow Immunoassay (LFI) for the full-length spike protein. From 1477 patient samples, 112 of which were COVID-19 positive by RT-PCR, authors found specificities exceeded 94% for all 3 assays, with varying sensitivities (88.4% for RBD, 89.3% for S1, and 72.9% for N protein). Within one month follow-up, 52/54 COVID-19 positive samples of tested sera at serum dilutions ≥1:16 were indicative of protective immunity. The authors argue that ELISAs that target the RBD and S1 protein are good candidates for detecting protective immunity from the COVID-19 virus, and thus require further investigation.

TABLE OF CONTENTS

CLIMATE

RANDOMIZED CONTROLLED TRIALS VS REAL-WORLD DATA IN THE COVID-19 ERA: A FALSE NARRATIVE

Lyman GH, Kuderer NM.. Cancer Invest. 2020 Oct 22:1-13. doi: 10.1080/07357907.2020.1841922. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Dr. Gary Lyman (editor-in-chief of Cancer Investigation) and Dr. Nicole M Kuderer (guest editor) discuss the role and importance of real world data (RWD) in comparison with randomized controlled trials (RCTs) regarding the COVID-19 pandemic. The authors write that while RCTs are the gold standard for evaluating therapies, RWD, particularly when studies are designed a priori, can reveal significant and important data rapidly, which is particularly important during the COVID-19 pandemic. For this reason, the authors believe that RCTs are not necessarily better than RWD and that these two sources must be used together in addressing questions regarding the efficacy of interventions in the real world.

ABSTRACT

While randomized controlled trials (RCTs) remain the gold standard for evaluating therapeutic efficacy, the role of studies based on real world data (RWD) has gained increasing relevance and importance. While both approaches have strengths and limitations, we believe that the narrative of RCTs vs RWD is a false narrative. Clearly, both approaches are needed to capture the totality of evidence and answer critical clinical questions in as comprehensive and timely manner as possible. They represent complementary approaches which often appear synergistic with one another. RCTs are generally slow and costly to develop and conduct and limited by the eligible and accrued population included while RWD is subject to confounding by both unknown factors as well as known factors not available in the data at hand. At the same time, not all RWD are created equal with the gold standard for RWD represented by prospective cohort studies designed a priori to capture specific data to answer important pressing questions. A great strength of RWD is the ability to capture information on large numbers of individuals at speed and scale. It is essential to acknowledge, however, that while larger numbers may enhance the precision of the effect estimates provided, in and of themselves, larger numbers do not increase the accuracy of estimates if patient selection and other biases have crept in. While we have become increasingly sophisticated in efforts to adjust for such potential bias, the risk of residual confounding remains including confounding my indication with patients with greater illness more likely to receive certain treatments based on clinical judgment rather than by randomization. Nevertheless, in crises situations, like a pandemic, it is important to gather as much information on risk factors and complications including mortality as rapidly as possible to inform clinical and public health decision making and provide a solid framework for clinical trials that follow. We need both carefully designed, conducted and interpreted RCTs and RWD to definitively answer critical questions rapidly in times of crises like COVID-19 and in a real-world setting.

DISPARITIES

NO-FAULT COMPENSATION FOR VACCINE INJURY - THE OTHER SIDE OF EQUITABLE ACCESS TO COVID-19 VACCINES

Halabi S, Heinrich A, Omer SB.. N Engl J Med. 2020 Oct 28. doi: 10.1056/NEJMp2030600. Online ahead of print.
Level of Evidence: 2 - Guidelines and Recommendations

BLUF

Public Health Experts associated with Yale University in New Haven, CT describe the concept of Vaccine Nationalism, the creation of the COVAX facility, and the plight of low and middle income countries during the COVID-19 pandemic (Summary). To address the concerns regarding the benefits and risks of the COVID-19 vaccine as well as vaccine manufacturers protection and liability, the authors suggest utilizing a no-fault compensation for vaccine injury.

SUMMARY

The concept of vaccine nationalism is the concept that “Wealthy governments that have invested in vaccine candidates have made bilateral agreements with developers that could result in vaccine doses being reserved for the highest-income countries.” This would lead to people in economically disadvantaged countries vulnerable to Covid-19. The COVAX Facility is

“an international partnership that aims to financially support leading vaccine candidates and ensure access to vaccines for lower-income countries.” “The dilemma for low- and middle-income countries, therefore, involves whether to refuse to offer manufacturers protection against liability and go without Covid-19 vaccines or to extend liability protections (if doing so is constitutionally possible) and risk having a large number of people injured to whom the government is unable to offer compensation.” Their proposition consists of the following:

1. Countries with existing no-fault vaccine-injury compensation systems could incorporate Covid-19 vaccines into these programs. This mechanism requires that the recipient country agree to indemnify the WHO, donors, manufacturers, and health care workers who vaccinate people; the WHO then provides compensation to people who have a serious adverse event.

2. To efficiently handle a high volume of claims from throughout the world, they believe that “the COVAX Facility should establish a procedure for compensating people who have a severe adverse event after immunization.”

3. A COVAX compensation system could be funded by earmarking committed resources from higher-income countries or by charging manufacturers a per-dose tax to support its purpose.

A COMPROMISED SPECIFIC HUMORAL IMMUNE RESPONSE AGAINST THE SARS-COV-2 RECEPTOR-BINDING DOMAIN IS RELATED TO VIRAL PERSISTENCE AND PERIODIC SHEDDING IN THE GASTROINTESTINAL TRACT

Hu F, Chen F, Ou Z, Fan Q, Tan X, Wang Y, Pan Y, Ke B, Li L, Guan Y, Mo X, Wang J, Wang J, Luo C, Wen X, Li M, Ren P, Ke C, Li J, Lei C, Tang X, Li F.. Cell Mol Immunol. 2020 Oct 9. doi: 10.1038/s41423-020-00550-2. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A cohort study conducted by various medical institutions in Shenzhen and Guangzhou, China found 21/289 Chinese patients with COVID-19 were readmitted due to persistent SARS-CoV-2 positivity. Among them, anal viral detection was positive in 15/21 (71.4%) and there was replication in the GI tract in 3/16 (18.7%) of patients, with no respiratory tract replication (Figure 1). They hypothesize there is viral rebound due to decreased levels of IgA and IgG antibodies to the viral receptor-binding domain (RBD) (Figures 3 & 4) and thus, a lack of protective humoral immune response suggesting this leads to persistence of SARS-CoV-2 in the GI tract along with active viral shedding.

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been redetected after discharge in some coronavirus disease 2019 (COVID-19) patients. The reason for the recurrent positivity of the test and the potential public health concern due to this occurrence are still unknown. Here, we analyzed the viral data and clinical manifestations of 289 domestic Chinese COVID-19 patients and found that 21 individuals (7.3%) were readmitted for hospitalization after detection of SARS-CoV-2 after discharge. First, we experimentally confirmed that the virus was involved in the initial infection and was not a secondary infection. In positive retests, the virus was usually found in anal samples (15 of 21, 71.4%). Through analysis of the intracellular viral subgenomic messenger RNA (sgmRNA), we verified that positive retest patients had active viral replication in their gastrointestinal tracts (3 of 16 patients, 18.7%) but not in their respiratory tracts. Then, we found that viral persistence was not associated with high viral titers, delayed viral clearance, old age, or more severe clinical symptoms during the first hospitalization. In contrast, viral rebound was associated with significantly lower levels of and slower generation of viral receptor-binding domain (RBD)-specific IgA and IgG antibodies. Our study demonstrated that the positive retest patients failed to create a robust protective humoral immune response, which might result in SARS-CoV-2 persistence in the gastrointestinal tract and possibly in active viral shedding. Further exploration of the mechanism underlying the rebound in SARS-CoV-2 in this population will be crucial for preventing virus spread and developing effective vaccines.

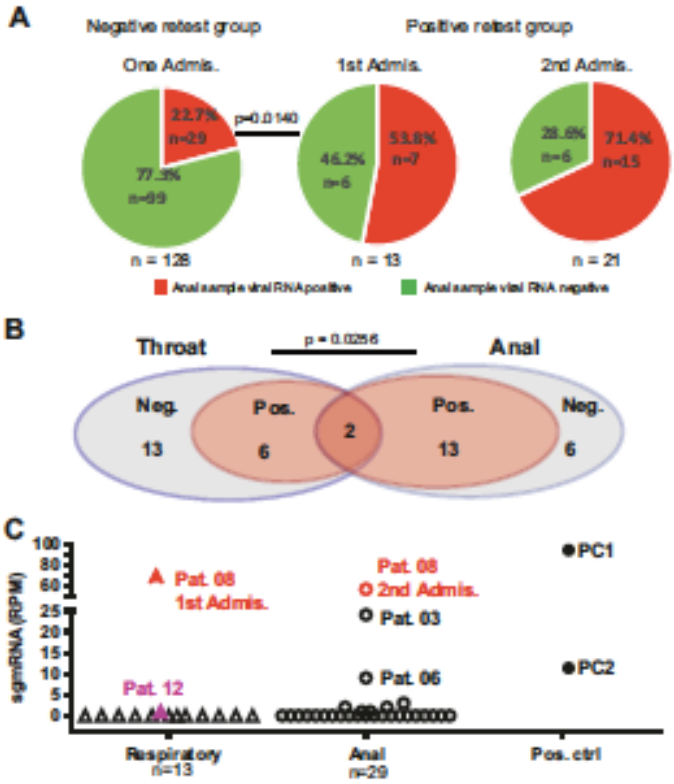

Fig. 1 Existence of active replicating SARS-CoV-2 in anal samples from positive retest patients. a Frequency of viral RNA detection in anal samples between the negative retest and positive retest groups. The percentage (%) and number (n) are labeled. The total case number (n) is shown under the pie chart. p Values (chi-square test) are indicated. b Viral detection in positive retest patients during the second admission. Throat and anal samples are shown. Neg. negative samples, Pos. positive samples. c sgmRNA reads in samples from positive retest patients. The read numbers were normalized to reads per million (RPM) to minimize sequencing size variation. Patient numbers are shown. The positive controls were two intracellular nucleic acid samples extracted from cells with actively replicating SARS-CoV-2 (dilution factor PC1: 1 × 10−4, PC2: 1 × 10−5). Red triangle, throat sample from Patient 08 during the first admission; red circle, anal sample from Patient 08 during the second admission; pink triangle, throat sample from Patient 12 during the second admission

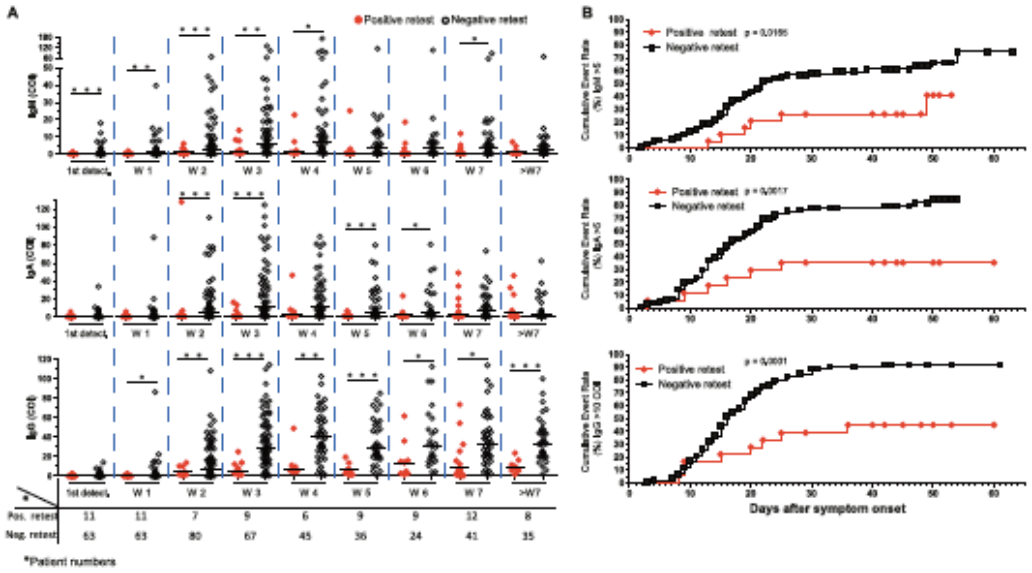

Fig. 3 Features of anti-RBD-specific IgM, IgA, and IgG. a Concentrations (cut-off index, COI) of anti RBD-specific IgM (upper), IgA (middle), and IgG (bottom) antibodies at different time points. Times (weeks after symptom onset, W) are as marked. First, serum detection for each patient within 1 week after symptom onset was grouped separately as "1st detect." Patient numbers at each timepoint are labeled separately for the positive retest group (red filled circle, positive retest.) and the negative retest group (black open circle, negative retest.). An unpaired t test with Welch's correction was used. p Value: *p < 0.05, **p < 0.01, ***p < 0.001. b The speed of anti-RBD-specific antibody generation. Cumulative patient numbers (%) with anti-RBD IgM > 5 COI (upper), IgA > 5 COI (middle), and IgG > 10 (bottom) are shown. Positive retest group, red filled circle; negative retest group, black filled square. p Values (calculated by the log-rank (Mantel–Cox) test) are shown

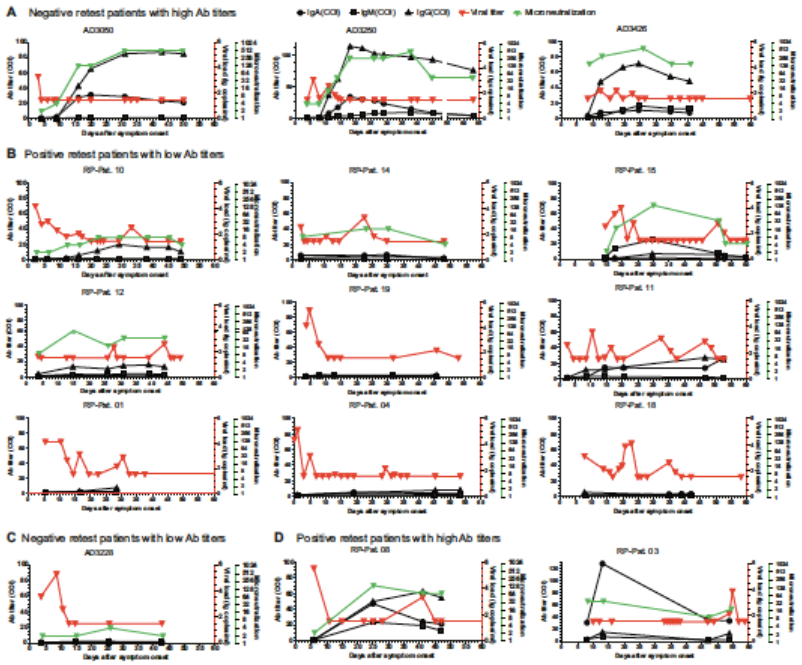

Fig. 4 Kinetics of viral RNA, anti-RBD antibodies, and neutralizing capacity. a Profiles of three representative negative retest COVID-19 patients with high levels of anti-RBD antibodies. Fifty-eight of 60 negative retest patients were in this group (see Supplementary Fig. 4). b Profiles of nine representative positive retest COVID-19 patients with low levels of anti-RBD antibodies. Seventeen of 19 positive retest patients were included in this group. c Profiles of one negative retest patient with low anti-RBD antibody titers and nonprotective neutralizing activity. Two of 60 negative retest patients were in this group. d Profiles of two positive retest patients with high levels of antibodies and neutralizing activity. Two of 19 positive retest patients were in this group. Black lines, IgM, IgA, and IgG; red line, viral load; green line, serum microneutralization. Patient ID numbers are shown on the top. Viral RNA below the detection limit was set at 1.44 log10. Folds of serum dilution were used as microneutralization titers

UNDERSTANDING THE PATHOLOGY

PROLONGED ADAPTIVE IMMUNE ACTIVATION IN COVID-19: IMPLICATIONS FOR MAINTENANCE OF LONG-TERM IMMUNITY?

Mudd PA, Remy KE.. J Clin Invest. 2020 Oct 26:143928. doi: 10.1172/JCI143928. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Emergency and Pediatrics/Internal Medicine physicians affiliated with St. Louis School of Medicine in St. Louis, MO review the findings (summarized below) of a recently published study by Files et al. (2020), which explored "the temporal evolution of the immune response in follow-up samples obtained from their non-hospitalized" COVID-19 patients. The authors call for future studies to further investigate the effectiveness of relevant immune modifying therapies (i.e., administration of interleukin-7 or Ox40) to prevent COVID-19 viral entry, replication, and secondary infection.

SUMMARY

The authors summarize the following key findings from Files et al. (2020) study:

- A significant increase in CD4+ and CD8+ T cell activation, including upregulation of CD69, Ox40, HLA-DR, CD154, and CD38 was observed among hospitalized patients compared to non-hospitalized patients.
- A number of above-mentioned markers of activation were increased among non-hospitalized patients 30 to 45 days after the onset of COVID-19 symptoms.
- Among non-hospitalized COVID-19 patients, "HLA-DR, Ox40, and Tim3 were increased over time on CD4+ T cells" and "HLA-DR, TIGIT, and PD-L1 were increased while enduring significant decreases in CD27 and CD28 on the surface of CD8+ T cells on repeat sampling."
- An evaluation of B cell surface markers showed an increased level of CD69, CD27, and PD-1 among hospitalized and non-hospitalized COVID-19 patients, "suggesting increased B cell activation."

Figure 1 depicts how the cellular immune system may remain activated even after SARS-CoV-2 clearance in COVID-19.

ABSTRACT

Ongoing observational clinical research has prioritized understanding the human immune response to the SARS-CoV-2 during the COVID-19 pandemic. Several recent studies suggest that immune dysregulation with early and prolonged adaptive immune system activation can result in cellular exhaustion. In this issue of the JCI, Files et al. compared cellular immune phenotypes during the first two months of COVID-19 in hospitalized and less severe, non-hospitalized patients. The authors utilized flow cytometry to analyze circulating peripheral blood mononuclear cells. Both patient-cohorts maintained B and T cell phenotypes consistent with activation and cellular exhaustion throughout the first two months of infection. Additionally, follow-up samples from the non-hospitalized patient cohort showed that activation markers and cellular exhaustion increased over time. These findings illustrate the persistent nature of the adaptive immune system changes that have been noted in COVID-19 and suggest longer-term effects that may shape the maintenance of immunity to SARS-CoV-2.

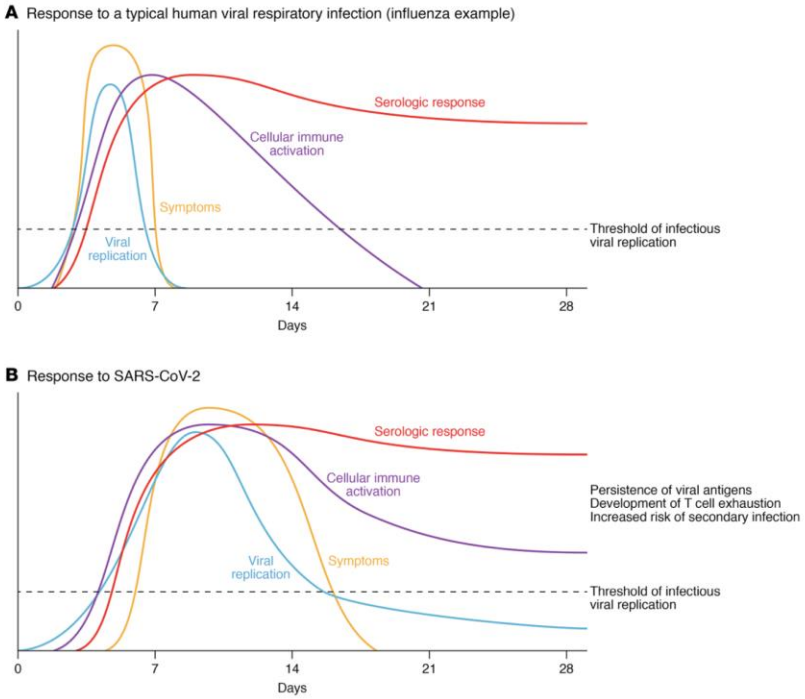

Figure 1. Response to human viral respiratory infections.

A. In a typical influenza infection symptoms and viral replication peak within a few days and resolve after the first week; serologic response peaks within the first two weeks and remains high. Notably, with influenza, the cellular immune activation peaks at week one and resolves by week three.

B. In contrast, with SARS-CoV-2 infection, the cellular immune system remains activated despite viral clearance. The persistence of viral antigens, development of T cell exhaustion and increased risk of secondary infections set SARS - CoV-2 infection apart from other viral respiratory infections.

CLIMATIC INFLUENCE ON THE MAGNITUDE OF COVID-19 OUTBREAK: A STOCHASTIC MODEL-BASED GLOBAL ANALYSIS

Pramanik M, Chowdhury K, Rana MJ, Bisht P, Pal R, Szabo S, Pal I, Behera B, Liang Q, Padmadas SS, Udmale P.. Int J Environ Health Res. 2020 Oct 22:1-16. doi: 10.1080/09603123.2020.1831446. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

Researchers from multiple institutes, including Asian Institute of Technology (Thailand) and Jawaharlal Nehru University (India), evaluated the effect of climates on COVID-19 transmission in 228 cities across 3 climatic zones (Figure 1). They found that the temperature and humidity may be major contributors to COVID-19 transmission: average temperatures and relative humidity were the primary contributors in Europe, diurnal temperatures were most important for India, and temperature seasonality was most important for Brazil (Table 2, Figure 4). These findings highlight the relationship between climates and COVID-19 spread and provide more insight into COVID-19 transmission.

ABSTRACT

We investigate the climatic influence on COVID-19 transmission risks in 228 cities globally across three climatic zones. The results, based on the application of a Boosted Regression Tree algorithm method, show that average temperature and average relative humidity explain significant variations in COVID-19 transmission across temperate and subtropical regions, whereas in the tropical region, the average diurnal temperature range and temperature seasonality significantly predict the infection outbreak. The number of positive cases showed a decrease sharply above an average temperature of 10 C in the cities of France, Turkey, the US, the UK, and Germany. Among the tropical countries, COVID-19 in Indian cities is most affected by mean diurnal temperature, and those in Brazil by temperature seasonality. The findings have implications on public health interventions, and contribute to the ongoing scientific and policy discourse on the complex interplay of climatic factors determining the risks of COVID-19 transmission.

FIGURES

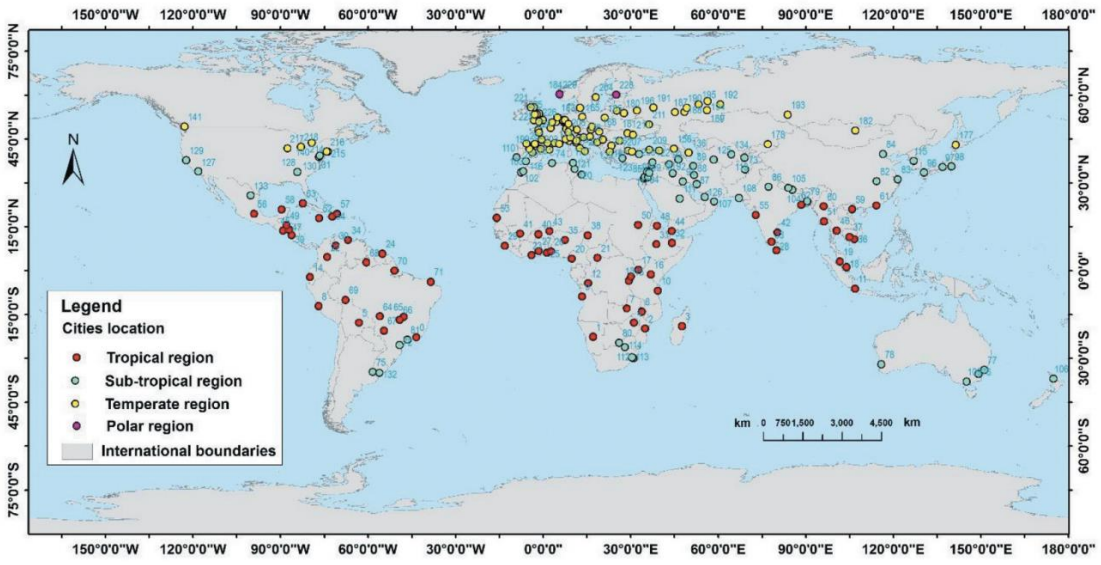

Figure 1. Shows the location of tropical, subtropical, and temperate cities considered for the present study.

Table 2. Relative importance of predictors (climatic, bioclimatic variables) in percent (±SD) and goodness of fit of the model.

	Predictors importance (%) to the COVID-19 cases				
Countries	Avg. Temperature (° C)	Temperature seasonality (%)	Avg. Relative Humidity (%)	Mean Diurnal range (° C)	R^2
The countries with the highest number of COVID-19 cases					
USA	56.3 ± 3.1	20.5 ± 0.6	7.40 ± 0.3	5.80 ± 0.01	0.831
Spain	25.70 ± 1.2	6.83 ± 0.8	51.0 ± 2.4	6.30 ± 0.01	0.921
Italy	12.02 ± 0.3	46.3 ± 1.8	32.2 ± 1.1	0.30 ± 0.01	0.890
Germany	35.4 ± 1.7	1.01 ± 0.01	4.40 ± 0.3	49.2 ± 2.4	0.820
UK	34.6 ± 2.1	3.20 ± 0.02	51.6 ± 0.5	3.00 ± 0.2	0.911
Russia	2.80 ± 0.1	56.5 ± 3.06	4.30 ± 0.1	26.40 ± 0.3	0.798
Turkey	58.4 ± 3.5	11.90 ± 0.6	14.60 ± 0.1	5.10 ± 0.7	0.823
France	58.72 ± 3.2	7.15 ± 0.01	16.03 ± 0.3	8.10 ± 0.4	0.865
Brazil	11.7 ± 0.3	38.4 ± 0.9	12.8 ± 0.3	27.1 ± 0.3	0.870
India	16.3 ± 0.4	11.70 ± 0.01	2.30 ± 0.01	58.7 ± 0.9	0.907
Climatic zones					
Tropical	8.60 ± 0.3	30.8 ± 1.1	8.90 ± 0.3	52.2 ± 2.1	0.876
Sub-tropical	61.7 ± 2.6	5.90 ± 0.2	17.5 ± 0.7	5.50 ± 0.2	0.913
Temperate	42.9 ± 1.6	12.3 ± 0.3	25.9 ± 0.9	9.20 ± 0.1	0.865

Table 2. Relative importance of predictors (climatic, bioclimatic variables) in percent (±SD) and goodness of fit of the model.

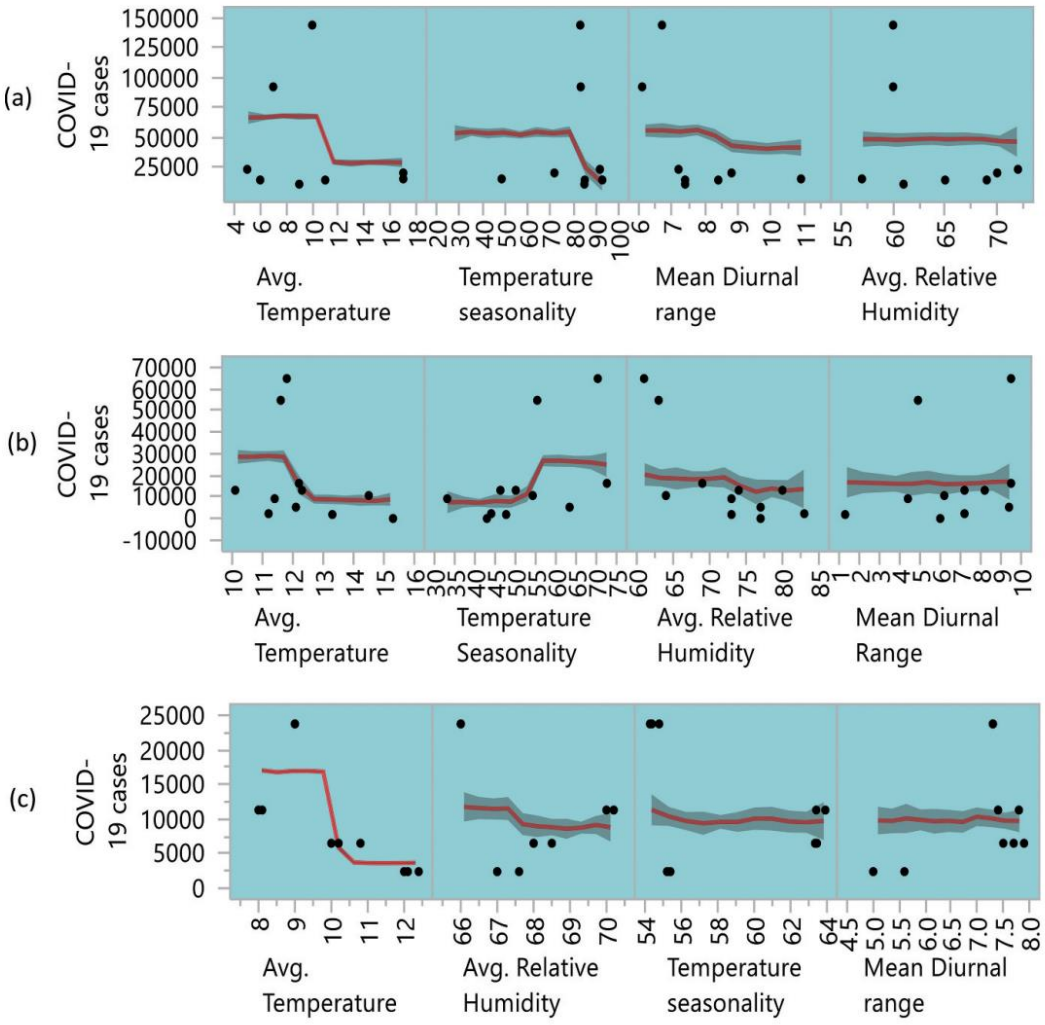

Figure 4. Marginal dependence graphs for the four most influential predictors in the model for COVID-19 disease in the USA (a), Spain (b), Italy (c), France (d), Germany (e),

PRECLINICAL VALIDATION OF OCCUPATIONAL AND ENVIRONMENTAL SAFETY OF AN ISOLATION SYSTEM FOR NON-INVASIVE VENTILATION IN COVID-19 AND OTHER AEROSOL-TRANSMITTED INFECTIONS

Quadros CA, Leal MCBDM, Baptista-Sobrinho CA, Nonaka CKV, Souza BSF, Milan-Mattos JC, Catai AM, Pires Di Lorenzo VA, Ferreira AG.. Expert Rev Med Devices. 2020 Oct 26. doi: 10.1080/17434440.2020.1842190. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Investigators from multiple institutes in Brazil, including Bahia State University, test the efficacy of the proposed Isolation System for Aerosol Transmitted Infections (ISATI) in ICU settings as a means of containment for viral particles. Using multiple sensors (Figure 2) and caffeine particles to mimic viral particles, the ISATI, which was hooked up to hospital ventilation systems, effectively contained microparticles in simulated scenarios of continuous positive airway pressure (CPAP), high flow nasal oxygen (HFNO), and mechanical ventilation. This finding suggests that the ISATI may protect hospital staff from contamination when providing CPAP or HFNO to virally infected patients.

ABSTRACT

BACKGROUND: Current SARS-CoV-2 pandemic has provoked the collapse of some health systems due to insufficient intensive care unit capacity. The use of continuous positive airway pressure (CPAP) and high-flow nasal oxygen (HFNO) therapies have been limited in consideration of the risk of occupational infection in healthcare professionals. AIMS: In preclinical experimental simulations, evaluate occupational and environmental safety of the newly developed isolation system for aerosol transmitted infections (ISATI). METHOD: Simulations were conducted to test ISATI's capability to isolate aerosolized molecular (caffeine), and biological (SARS-CoV-2 synthetic RNA) markers. Caffeine deposition was analyzed on nitrocellulose sensor discs by proton nuclear magnetic resonance spectroscopy. Synthetic SARS-CoV-2 detection was performed by reverse transcription polymerase chain reaction. RESULTS: ISATI demonstrated efficacy in isolating molecular and biological markers within the enclosed environment in simulated conditions of CPAP, HFNO and mechanical ventilation therapy. Neither the molecular marker nor substantial amounts of synthetic SARS-CoV-2 RNA were detected in the surrounding environment, outside ISATI, indicating appropriate occupational safety for healthcare professionals. CONCLUSION: Aerosolized markers were successfully contained within ISATI in all experimental simulations, offering occupational and environmental protection against the dissemination of aerosolized microparticles under CPAP or HFNO therapy conditions, which are indicated for patients with acute respiratory infections.

Figure 2. Positioning of nitrocellulose sensor discs. Position 1: entrance of multi parameter patient monitoring cables and respiratory tubes; position 2: entrance of intravenous therapy tube; position 3: on a health professional's chest; position 4 : inside the ISATI.

DIAGNOSTIC RADIOLOGY

DYNAMIC EVALUATION OF LUNG INVOLVEMENT DURING CORONAVIRUS DISEASE-2019 (COVID-19) WITH QUANTITATIVE LUNG CT

Ma C, Wang XL, Xie DM, Li YD, Zheng YJ, Zhang HB, Ming B.. Emerg Radiol. 2020 Oct 10. doi: 10.1007/s10140-020-01856-4. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A case series of 18 COVID-19 patients (4 mild, 10 moderate, 10 severe, 0 critical) conducted at People's Hospital of Deyang City in China from January 26 - June 15, 2020 found that lung abnormalities peaked at 8.8 ± 4.1 days (average number of CT scans was 3.9 ± 1.6), in addition to the initial CT typically revealing ground glass opacities as more common than consolidated opacities (Z = 2.229, P = 0.026), although no difference was observed at peak disease as read by an artificial intelligence software. This study highlights AI's ability to characterize progression of CT lung findings during COVID-19 illness, which may aid in clinical decision-making, especially in high volume settings where AI could maximize efficiency.

ABSTRACT

PURPOSE: To identify and quantify lung changes associated with coronavirus disease-2019 (COVID-19) with quantitative lung CT during the disease. METHODS: This retrospective study reviewed COVID-19 patients who underwent multiple chest CT scans during their disease course. Quantitative lung CT was used to determine the nature and volume of lung involvement. A semi-quantitative scoring system was also used to evaluate lung lesions. RESULTS: This study included eighteen cases (4 cases in mild type, 10 cases in moderate type, 4 cases in severe type, and without critical type cases) with confirmed COVID-19. Patients had a mean hospitalized period of 24.1 +- 7.1 days (range: 14-38 days) and underwent an average CT scans of 3.9 +- 1.6 (range: 2-8). The total volumes of lung abnormalities reached a peak of 8.8 +- 4.1 days (range: 2-14 days). The ground-glass opacity (GGO) volume percentage was higher than the consolidative opacity (CO) volume percentage on the first CT examination (Z = 2.229, P = 0.026), and there was no significant difference between the GGO volume percentage and that of CO at the peak stage (Z = - 0.628, P = 0.53). The volume percentage of lung involvement identified by AI demonstrated a strong correlation with the total CT scores at each stage (r = 0.873, P = 0.0001). CONCLUSIONS: Quantitative lung CT can automatically identify the nature of lung involvement and quantify the dynamic changes of lung lesions on CT during COVID-19. For patients who recovered from COVID-19, GGO was the predominant imaging feature on the initial CT scan, while GGO and CO were the main appearances at peak stage.

RECENT ADVANCES IN THE NUCLEIC ACID-BASED DIAGNOSTIC TOOL FOR CORONAVIRUS

Prabhakar PK, Lakhanpal J.. Mol Biol Rep. 2020 Oct 6. doi: 10.1007/s11033-020-05889-3. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review by members from the Department of Medical Laboratory Sciences, Lovely Professional University in India compiled the various different nucleic acid-based techniques (including advantages and disadvantages) which are currently used to detect SARS-CoV-2 for COVID-19 diagnosis (Table 1). They emphasize the continued need for quicker and cost-effective diagnostic methods with high sensitivity/specificity as the pandemic wears on.

ABSTRACT

Recently in China, a novel coronavirus outbreak took place which caused pneumonia-like symptoms. This coronavirus belongs to the family of SARS and MERS and causes respiratory system disease known as COVID-19. At present we use polymerase chain reaction (PCR) based molecular biology methods for the detection of coronavirus. Other than these PCR based methods, some improved methods also exist such as microarray-based techniques, Real time-quantitative PCR, CRISPR-Cas13 based tools but almost all of the available methods have advantages and disadvantages. There are many limitations associated with this method and hence there is a need for a fast, more sensitive, and specific diagnostic tool which can detect a greater number of samples in less time. Here we have summarised currently available nucleic acid-based diagnostic methods for the detection of coronavirus and the need for developing a better technique for a fast and sensitive detection of coronavirus infections. Nucleic acid based detection tool for SARS-CoV-2.

FIGURES

Table 1 Comparison of various detection techniques for SARS-CoV2

Detection methods	Detecting material	Advantages	Disadvantages
A. Nucleic acid detection-based technology			
High throughput sequencing	Nucleic acid	• Precise and sensitive • Not subject to cross-hybridization, and hence high accuracy • Larger dynamic range (> 10^5)	• High cost • Require sequencer
PCR based methods (RT-PCR; RT-qPCR)	Viral RNA/mRNA	• Detect virus directly • Highly accurate and sensitive • RT-qPCR is gold standard (96–100% specificity) • Time reuired: 2–4 h	• High cost • False positive result possible
B. Microarrays based methodologies			
Microarray		• Relatively low cost • Well defined protocol and SOP	• Small dynamic range (10^2) • Relies on hybridization which is non specific
C. Isothermal nucleic acid-based amplification			
Regular loop-mediated isothermal amplification-based methods	DNA/RNA	• High amount of DNA produced compared to PCR • Simple, Low cost • No requirement of thermocyclers • 99% specificity, Time required 15–60 min	• Detect total DNA amplification in a reaction and thus limited to detection in a single target
Sequence-specific loop-mediated isothermal amplification methods	DNA/RNA	• High amount of DNA produced compared to PCR • Simple, Low cost • High sensitive • No requirement of thermocyclers	• Detect total DNA amplification in a reaction and thus limited to detection in a single target
D. CRISPR based methods			
CRISPR based technology	ssDNA/ssRNA	• Rapid and quantitative detection of SARS-CoV2	• Off target effect and imprecise effect
E. Antigen–antibody based methods			
Rapid antigen test (RAT)	Nucleocapsid protein as antigen	• Sensitive and specific • Easy handling • No requirement of any sophisticated instruments • Rapid detection efficacy • Cost-effective	• Can be detected only after 7–9 days of infection • Antigenic variations make it difficult to generate similar antibodies
F. CT scan and other diagnostic methodology			
CT scan	NA	• Detect the severity of the COVID-19	• Not specific but sensitive • Not a confirmatory test • Can be auxillary test

Table 1: Comparison of various detection techniques for SARS-CoV2

COMPARING TWO SAMPLE POOLING STRATEGIES FOR SARS-COV-2 RNA DETECTION FOR EFFICIENT SCREENING OF COVID-19

Chen F, Geng Z, Wang J, Liuchang W, Huang D, Xu Y, Wang Z, Wang L.. J Med Virol. 2020 Oct 27. doi: 10.1002/jmv.26632. Online ahead of print.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

Members of the Huazhong University of Science and Technology Department of Clinical Laboratory in Wuhan, China investigated whether pooling RT-PCR testing for SARS-CoV-2 could increase testing capacity. Using 23 pools each containing 1 positive sample and either 5 or 9 negatives, authors demonstrated a similar diagnostic sensitivity to individual test ($p<0.005$; Figure 2) but pooling viral transport medium resulted in a false negative while pooling swabs resulted in diagnosis without loss of sensitivity (Tables 2,3). Authors suggests pooling swabs may facilitate testing in higher quantities at lower costs (which could be used where resources are limited), however this strategy would require collecting double swab samples for individual re-testing should a pool test positive.

ABSTRACT

The emerging pandemic of coronavirus disease 2019 (COVID-19) has affected over 200 countries and resulted in a shortage of diagnostic resources globally. Rapid diagnosis of COVID-19 is vital to control the spreading of the disease, which however is challenged by limited detection capacity and low detection efficiency in many parts of the world. The pooling test may offer an economical and effective approach to increase virus testing capacity of medical laboratories without requiring more laboratory resources such as laboratory workers, testing reagents and equipment. In this study, the sample pools of 6 and 10 were detected by a real-time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) assay targeting ORF1ab and N genes of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Each pool consisted of 5 or 9 negative SARS-CoV-2 samples and 1 positive counterpart with varying viral loads. Two different strategies of sample pooling were investigated and the results were compared comprehensively. One approach was to pool viral transport medium (VTM) of the samples in the laboratory, and the other was to pool swab samples during collection process. For swab pooling strategy, qualitative results of SARS-CoV-2 RNA, specific tests of ORF1ab and N genes, remained stable over the different pool sizes. Together, this study demonstrates that the swab pooling strategy may serve as an effective and economical approach for screening SARS-CoV-2 infections in large populations, especially in countries and regions where medical resources are limited during the pandemic and may thus be potential for clinical laboratory applications. This article is protected by copyright. All rights reserved.

FIGURES

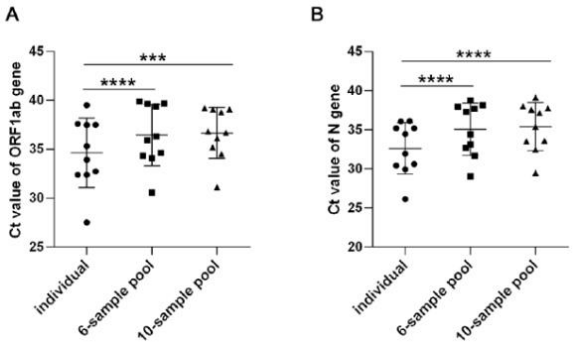

Figure 2. Comparison of Ct value of VTM pooling strategy in different pool sizes. (A) Mean Ct value of ORF1ab gene. (B) Mean Ct value of N gene. ***, $P < 0.005$; *****, $P < 0.001$; ANOVA.

Table 2. Comparison of cycle threshold (Ct) between the original and 6-swab pooling samples in 3 mL of VTM (n=3).

Sample No.	Ct value of ORF1ab (Mean, SD)			Ct value of N (Mean, SD)		
	Individual	6- swab minipool	M.D.	Individual	6- swab minipool	M.D.
1	38.59(0.96)	38.04(0.24)*	-0.55	37.95(0.51)	37.99(0.74)	0.04
2	38.07(0.90)	38.52(1.41)	0.45	37.47(0.81)	37.42(1.24)	-0.05
3	36.13(0.38)	36.62(0.59)	0.49	35.41(1.33)	35.82(0.85)	0.41

*: one of three replicates did not yield detectable RNA for the target; M.D.: mean difference.

Table 3. Comparison of cycle threshold (Ct) between the original and 10-swab pooling samples (n=3).

Sample No.	Volume (mL)	Ct value of ORF1ab (Mean, SD)			Ct value of N (Mean, SD)		
		Individual	10-swab minipool	M.D.	Individual	10-swab minipool	M.D.
1	3.00	36.27(0.07)	36.11(0.34)	-0.16	32.93(0.21)	33.22(0.21)	0.29
2	3.00	36.58(0.26)	37.26(0.18)	0.68	34.43(0.10)	35.08(0.36)	0.65
3	3.00	36.47(0.38)	36.96(0.91)	0.49	36.70(0.54)	36.84(0.49)	0.14
4	6.00	36.46(0.56)	35.66(0.37)	-0.8	35.35(0.93)	35.28(0.59)	-0.07
5	6.00	35.02(0.32)	38.00(1.52)	2.98	33.90(0.26)	35.68(0.66)	1.78
6	6.00	31.48(0.08)	38.53(0.63)	7.05	31.98(0.10)	37.13(0.96)	5.15

M.D.: mean difference.

ACCURACY OF SEROLOGICAL TESTING FOR SARS-COV-2 ANTIBODIES: FIRST RESULTS OF A LARGE MIXED-METHOD EVALUATION STUDY

Brigger D, Horn MP, Pennington LF, Powell AE, Siegrist D, Weber B, Engler O, Piezzi V, Damonti L, Iseli P, Hauser C, Froehlich TK, Villiger PM, Bachmann MF, Leib SL, Bittel P, Fiedler M, Largiadèr C, Marschall J, Stalder H, Kim PS, Jardetzky TS, Eggel A, Nagler M.. Allergy. 2020 Sep 30. doi: 10.1111/all.14608. Online ahead of print.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

A mixed-method study (Figure 1) by a multidisciplinary team from Inselspital University Hospital in Switzerland evaluated 3 ELISAs for accuracy: nucleoprotein (N), S1 domain of spike protein (S1), and Lateral Flow Immunoassay (LFI) for the full-length spike protein. From 1477 patient samples, 112 of which were COVID-19 positive by RT-PCR, they found specificities exceeded 94% for all 3 assays, with varying sensitivities (88.4% for RBD, 89.3% for S1, and 72.9% for N protein). Within one month follow-up, 52/54 COVID-19 positive samples of tested sera at serum dilutions ≥1:16 were indicative of protective immunity (Figure 3). The authors argue that ELISAs that target the RBD and S1 protein are good candidates for detecting protective immunity from the COVID-19 virus, and thus require further investigation.

ABSTRACT

BACKGROUND: Serological immunoassays that can identify protective immunity against SARS-CoV-2 are needed to adapt quarantine measures, assess vaccination responses, and evaluate donor plasma. To date, however, the utility of such immunoassays remains unclear. In a mixed-design evaluation study, we compared the diagnostic accuracy of serological immunoassays that are based on various SARS-CoV-2 proteins and assessed the neutralizing activity of antibodies in patient sera. METHODS: Consecutive patients admitted with confirmed SARS-CoV-2 infection were prospectively followed alongside medical staff and biobank samples from winter 2018/2019. An in-house enzyme-linked immunosorbent assay utilizing recombinant receptor-binding domain (RBD) of the SARS-CoV-2 spike protein was developed and compared to three commercially available enzyme-linked immunosorbent assays (ELISAs) targeting the nucleoprotein (N), the S1 domain of the spike protein (S1) and a lateral flow immunoassay (LFI) based on full-length spike protein. Neutralization assays with live SARS-CoV-2 were performed. RESULTS: One-thousand four-hundred and seventy-seven individuals were included comprising 112 SARS-CoV-2 positives (defined as a positive real-time PCR result; prevalence 7.6%). IgG seroconversion occurred between day 0 and day 21. While the ELISAs showed sensitivities of 88.4% for RBD, 89.3% for S1, and 72.9% for N protein, the specificity was above 94% for all tests. Out of 54 SARS-CoV-2 positive individuals, 96.3% showed full neutralization of live SARS-CoV-2 at serum dilutions >=1:16, while none of the 6 SARS-CoV-2 negative sera revealed neutralizing activity. CONCLUSIONS: ELISAs targeting RBD and S1 protein of SARS-CoV-2 are promising immunoassays which shall be further evaluated in studies verifying diagnostic accuracy and protective immunity against SARS-CoV-2.

FIGURES

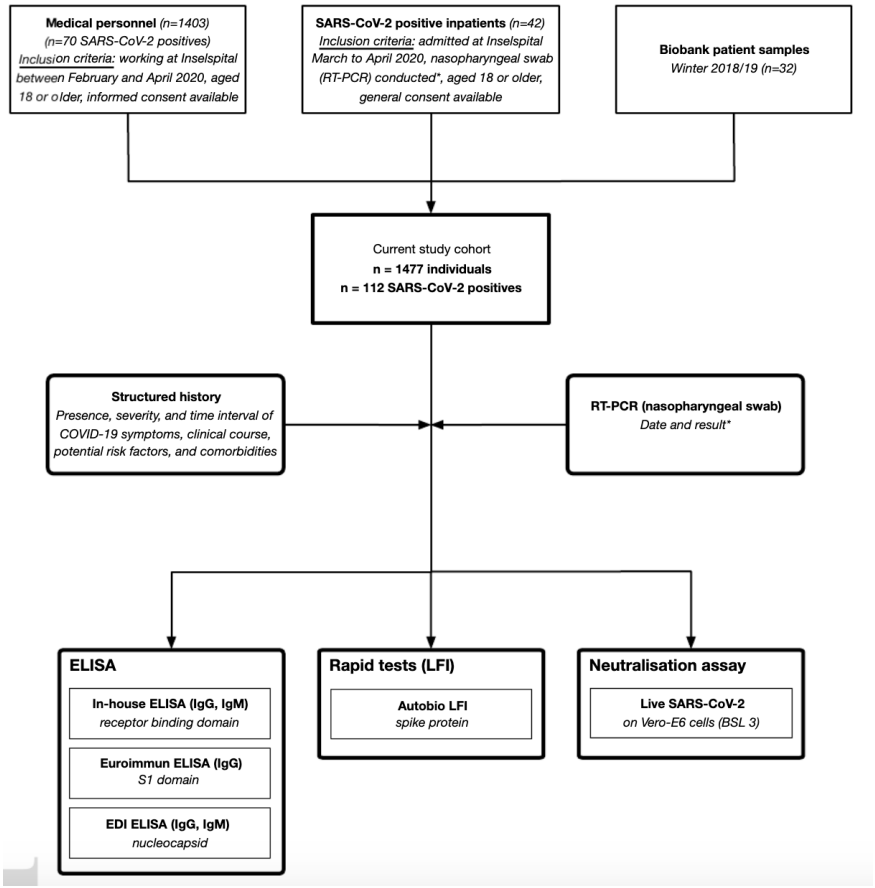

Figure 1: Flowchart of study cohort and study design. Only RT-PCR positive inpatients were considered in the current phase of the study (*). Consecutive patients admitted with confirmed SARS-CoV-2 infection were prospectively followed alongside medical staff and biobank samples from winter 2018/2019 (pooled data were used for calculation of diagnostic accuracy). Boxes with a dashed outline are not yet completed. RT-PCR, real-time PCR; ELISA, enzyme linked immunosorbent assay; LFI, lateral flow immunoassay

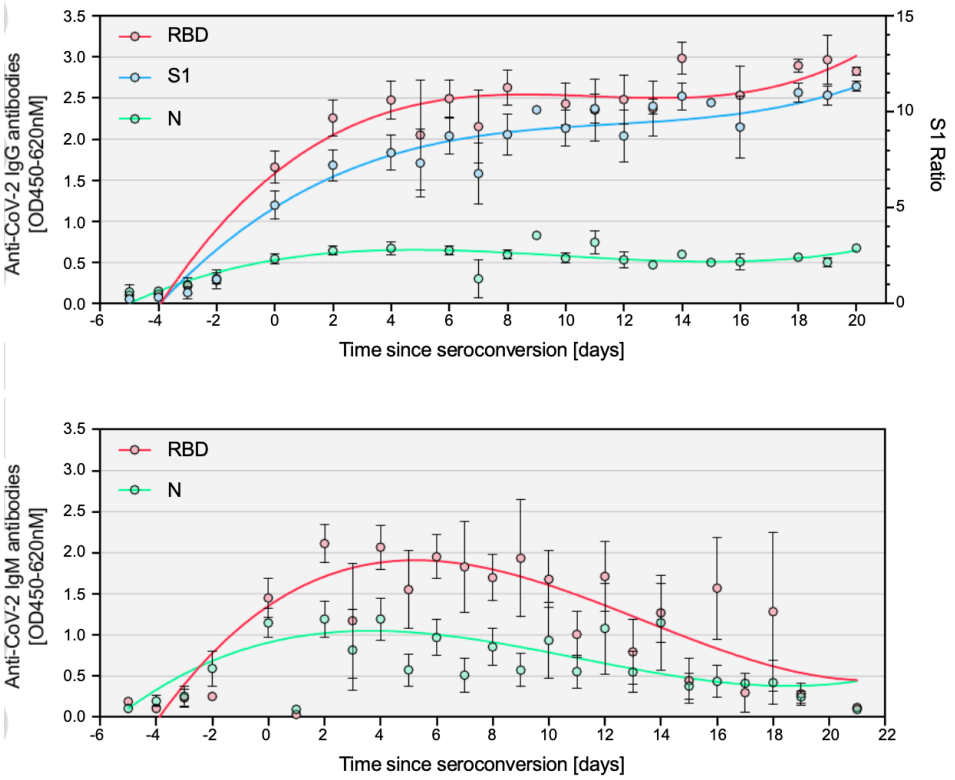

Figure 2: Temporal pattern of antibody responses against SARS-CoV-2 since seroconversion. IgG and IgM antibody responses of consecutive patients (n = 25) as measured by three ELISAs targeting different proteins of SARS-CoV-2: (a) IgG against the receptor binding domain (RBD), the S1 domain of the spike protein (S1) and the nucleoprotein (N); (b) IgM against the receptor binding domain (RBD) and the nucleoprotein (N). Data is shown as mean ± SEM. Curves were calculated using non-linear fitting

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