# The Daily COVID-19 Literature Surveillance Summary

## October 27, 2020

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# 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**

- Association of ABO blood group with indices of disease severity and multiorgan dysfunction in COVID-19 were evaluated in one study by looking at the potential protective effect of anti-A antibodies in SARS-CoV-2 infection on consecutively admitted ICU patients across 6 metropolitan Vancouver hospitals. While national and provincial ABO blood group distributions did not differ from the cohort analyzed, higher proportions of COVID-19 patients with blood group A or AB needed mechanical ventilation, continuous renal replacement therapy (CRRT), and a longer ICU stay compared to patients with blood types O or B. This correlation remained significant after adjusting for sex, age, and presence of one or more co-morbidities. These findings suggest that A or AB blood group is associated with higher disease severity in patients with severe COVID-19, though there is no known mechanism by which this may occur.

- Proteins associated with neutrophil degranulation are upregulated in nasopharyngeal swabs from SARS-CoV-2 patients according to 15 SARS-CoV-2 positive and 15 negative naso-oropharyngeal samples, specifically 17 significantly altered proteins were found in the positive samples. Notable proteins include neutrophil elastase (ELANE), azurocidin (AZU1), myeloperoxidase (MPO), myeloblastin (PRTN3), cathepsin G (CTSG), and transcobalamine-1 (TCN1). Presence of these altered proteins in the positive samples suggest their importance in the host immune response to SARS-CoV-2, particularly for their roles in neutrophil degranulation and NETosis. The authors recommend further research into these proteins as prognostic markers and targets for therapeutics.

**Transmission & Prevention**

- SARS-CoV-2 presence was found in the saliva, tears, and cerumen of COVID-19 patients according to analyzed samples from 38 patients with RT-PCR confirmed SARS-CoV-2 within 72 hours of the first positive result. 76.3% of saliva samples, 55.3% of tear samples, and 39.5% of cerumen samples tested positive for SARS-CoV-2 RNA. Notably, half of the samples from asymptomatic patients (n=2/4) contained SARS-CoV-2 RNA. Authors suggest that SARS-CoV-2 viral RNA can be found in different bodily secretions and that personal protective equipment should be utilized when contact with patient saliva, tears, or cerumen is possible.

**R&D: Diagnosis & Treatments**

- Effect of tocilizumab vs usual care in 131 adults hospitalized with COVID-19 and moderate or severe pneumonia was investigated in a randomized-controlled trial with 63 receiving Tocilizumab (TCZ) and 67 receiving usual care (UC). Authors found the TCZ cohort did not have improved WHO-clinical progression scores (CPS) by day 4 compared to the UC cohort, and there was no significant difference in deaths between the groups at day 28 despite ventilation rates being lower in TCZ group at day 14. These results suggest marginal benefit from TCZ treatment in moderate to severe COVID-19 pneumonia, but authors acknowledged a need for further research to determine its effect on clinical outcomes.

**Mental Health & Resilience Needs**

- Psychological impact of mass quarantine on population during pandemics were seen based on a cross-sectional survey study conducted during the 2nd and 3rd weeks of strict quarantine in India showing prevalence of depression, anxiety, and stress to be 30.5%, 22.4%, and 10.8%, respectively, with significantly higher incidence in the 3rd week compared to the 2nd. This data showed an 8-10 fold increase in depression and anxiety compared to baseline statistics in the Indian population as a result of the quarantine period, suggesting a detrimental psychological impact, which authors hope can assist in future consideration of coping strategies for those required to quarantine for prolonged periods of time.

# TABLE OF CONTENTS

## THE ASSOCIATION OF ABO BLOOD GROUP WITH INDICES OF DISEASE SEVERITY AND MULTIORGAN DYSFUNCTION IN COVID-19

Hoiland RL, Fergusson NA, Mitra AR, Griesdale DEG, Devine DV, Stukas S, Cooper J, Thiara S, Foster D, Chen LYC, Lee AYY, Conway EM, Wellington CL, Sekhon MS.. Blood Adv. 2020 Oct 27;4(20):4981-4989. doi: 10.1182/bloodadvances.2020002623.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

### BLUF

Investigators from the University of British Columbia retrospectively investigated the potential protective effect of anti-A antibodies in SARS-CoV-2 infection on consecutively admitted ICU patients across 6 metropolitan Vancouver hospitals (February 21 and April 28, 2020). While national and provincial ABO blood group distributions did not differ from the cohort analyzed (Table 2), higher proportions of COVID-19 patients with blood group A or AB needed mechanical ventilation, continuous renal replacement therapy (CRRT), and a longer ICU stay compared to patients with blood types O or B (Table 3). This correlation remained significant after adjusting for sex, age, and presence of one or more co-morbidities. These findings suggest that A or AB blood group is associated with higher disease severity in patients with severe COVID-19, though there is no known mechanism by which this may occur.

### ABSTRACT

Studies on severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) suggest a protective effect of anti-A antibodies against viral cell entry that may hold relevance for SARS-CoV-2 infection. Therefore, we aimed to determine whether ABO blood groups are associated with different severities of COVID-19. We conducted a multicenter retrospective analysis and nested prospective observational substudy of critically ill patients with COVID-19. We collected data pertaining to age, sex, comorbidities, dates of symptom onset, hospital admission, intensive care unit (ICU) admission, mechanical ventilation, continuous renal replacement therapy (CRRT), standard laboratory parameters, and serum inflammatory cytokines. National (N = 398 671; P = .38) and provincial (n = 62 246; P = .60) ABO blood group distributions did not differ from our cohort (n = 95). A higher proportion of COVID-19 patients with blood group A or AB required mechanical ventilation (P = .02) and CRRT (P = .004) and had a longer ICU stay (P = .03) compared with patients with blood group O or B. Blood group A or AB also had an increased probability of requiring mechanical ventilation and CRRT after adjusting for age, sex, and presence of >=1 comorbidity. Inflammatory cytokines did not differ between patients with blood group A or AB (n = 11) vs O or B (n = 14; P > .10 for all cytokines). Collectively, our data indicate that critically ill COVID-19 patients with blood group A or AB are at increased risk for requiring mechanical ventilation, CRRT, and prolonged ICU admission compared with patients with blood group O or B. Further work is needed to understand the underlying mechanisms.

### FIGURES

| Blood group | National (N = 398 671), % | Provincial (n = 62 246), % | ICU sample (n = 95), % (n) | ICU vs national, *P* | ICU vs provincial, *P* |
|---|---|---|---|---|---|
| A | 34.7 | 34.1 | 37 (35) | .38 | .60 |
| B | 11.8 | 13.3 | 17 (16) | | |
| AB | 3.9 | 4.2 | 3 (3) | | |
| O | 49.6 | 48.4 | 43 (41) | | |

Ninety-fine of 125 ICU patients had ABO data available. The *P* values were determined using the $\chi^2$ goodness of fit test.

Table 2. Comparison of blood group distributions between national and provincial blood donor data and ICU-admitted patients with COVID-19

| | | | | Competing risks regression model | | |
|---|---|---|---|---|---|---|
| | Groups O/B, n = 57 | Groups A/AB, n = 38 | P | Adjusted sHR* | 95% CI | P |
| **Overall** | | | | | | |
| Mechanical ventilation, n (%) | 35 (61) | 32 (84) | .02 | 1.76 | 1.17-2.65 | .007 |
| CRRT, n (%) | 5 (9) | 12 (32) | .01 | 3.75 | 1.28-10.9 | .004 |
| Extubation, n (%) | 24 (42) | 21 (55) | .21 | 0.92 | 0.52-1.62 | .78 |
| Discharged from ICU, n (%) | 43 (75) | 24 (63) | .20 | 0.63 | 0.39-1.03 | .06 |
| Ventilator-free days, median (IQR) | 13 (0-21) | 7 (0-19) | .50 | — | — | — |
| ICU LOS, median (IQR), d | 9 (5-18) | 13.5 (7-26) | .03 | — | — | — |
| Hospital LOS, median (IQR), d | 16 (11-29) | 21 (13-36) | .13 | — | — | — |
| Remaining in ICU, n (%) | 6 (11) | 5 (13) | .77 | — | — | — |
| Remaining in hospital, n (%) | 10 (18) | 6 (16) | .80 | — | — | — |
| Discharged home alive, n (%) | 33 (58) | 18 (47) | .31 | — | — | — |
| Died in hospital, n (%) | 8 (14) | 9 (24) | .23 | 1.22† | 0.47-3.21 | .68 |
| **Discharged from ICU, median (IQR)** | | | | | | |
| Ventilator-free days | 18 (13-24) | 18 (9-22) | .54 | — | — | — |
| ICU LOS, d | 7 (3-13) | 12 (7.5-22.5) | .03 | — | — | — |
| Hospital LOS, d | 15 (10-29) | 22 (16-37.5) | .08 | — | — | — |

LOS, length-of-stay.
*Adjusted for age, sex, and the presence of ≥1 comorbidity (binary, yes/no). sHR >1 indicates an increased probability of an event occurring during the study period in blood groups A/AB vs O/B, whereas a ratio <1 indicates a decreased probability in blood groups A/AB vs O/B.
†Hazard ratio for overall survival.

Table 3. Clinical outcomes between groups O/B and groups A/AB

# IN VITRO

## PROTEINS ASSOCIATED WITH NEUTROPHIL DEGRANULATION ARE UPREGULATED IN NASOPHARYNGEAL SWABS FROM SARS-COV-2 PATIENTS

Akgun E, Tuzuner MB, Sahin B, Kilercik M, Kulah C, Cakiroglu HN, Serteser M, Unsal I, Baykal AT.. PLoS One. 2020 Oct 20;15(10):e0240012. doi: 10.1371/journal.pone.0240012. eCollection 2020.
Level of Evidence: Other - Mechanism-based reasoning

### BLUF

Investigators at Acibadem University in Turkey analyzed 15 SARS-CoV-2 positive and 15 negative naso-oropharyngeal samples and found 17 significantly altered proteins in the positive samples (Table 1; Figure 1). Notable proteins include neutrophil elastase (ELANE), azurocidin (AZU1), myeloperoxidase (MPO), myeloblastin (PRTN3), cathepsin G (CTSG), and transcobalamine-1 (TCN1). Presence of these altered proteins in the positive samples suggest their importance in the host immune response to SARS-CoV-2, particularly for their roles in neutrophil degranulation and NETosis. The authors recommend further research into these proteins as prognostic markers and targets for therapeutics.

### ABSTRACT

COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared throughout the World and currently affected more than 9 million people and caused the death of around 470,000 patients. The novel strain of the coronavirus disease is transmittable at a devastating rate with a high rate of severe hospitalization even more so for the elderly population. Naso-oro-pharyngeal swab samples as the first step towards detecting suspected infection of SARS-CoV-2 provides a non-invasive method for PCR testing at a high confidence rate. Furthermore, proteomics analysis of PCR positive and negative naso-oropharyngeal samples provides information on the molecular level which highlights disease pathology. Samples from 15 PCR positive cases and 15 PCR negative cases were analyzed with nanoLC-MS/MS to identify the differentially expressed proteins. Proteomic analyses identified 207 proteins across the sample set and 17 of them were statistically significant. Protein-protein interaction analyses emphasized pathways like Neutrophil degranulation, Innate Immune System, Antimicrobial Peptides. Neutrophil Elastase (ELANE), Azurocidin (AZU1), Myeloperoxidase (MPO), Myeloblastin (PRTN3), Cathepsin G (CTSG) and Transcobalamine-1 (TCN1) were found to be significantly altered in naso-oropharyngeal samples of SARS-CoV-2 patients. The identified proteins are linked to alteration in the innate immune system specifically via neutrophil degranulation and NETosis.

## FIGURES

| Accession | Unique peptides | *P value* | Fold change (Pos/Neg) | Description |
|---|---|---|---|---|
| **Q9BQE3** | 2 | 0.0234 | 0.41 | Tubulin alpha-1C chain |
| **P20160** | 4 | 0.0413 | 2.03 | Azurocidin |
| **P01876** | 12 | 0.0073 | 2.04 | Immunoglobulin heavy constant alpha 1 |
| **P29401** | 2 | 0.0337 | 2.10 | Transketolase |
| **P09104** | 2 | 0.0075 | 2.11 | Gamma-enolase |
| **P20061** | 3 | 0.0294 | 2.48 | Transcobalamin-1 |
| **P04004** | 2 | 0.0001 | 2.65 | Vitronectin |
| **P02790** | 7 | 0.0000 | 2.71 | Hemopexin |
| **P0DOX7** | 3 | 0.0127 | 2.83 | Immunoglobulin kappa light chain |
| **P08246** | 2 | 0.0035 | 2.91 | Neutrophil elastase |
| **Q9UKL4** | 2 | 0.0011 | 3.18 | Gap junction delta-2 protein |
| **Q16695** | 2 | 0.0003 | 3.20 | Histone H3.1t |
| **P01871** | 2 | 0.0003 | 3.44 | Immunoglobulin heavy constant mu |
| **P08311** | 3 | 0.0097 | 3.67 | Cathepsin G |
| **P05164** | 9 | 0.0050 | 3.72 | Myeloperoxidase |
| **P00450** | 4 | 0.0020 | 5.06 | Ceruloplasmin |
| **P24158** | 2 | 0.0023 | 29.42 | Myeloblastin |

Table 1. Significantly altered protein identification list

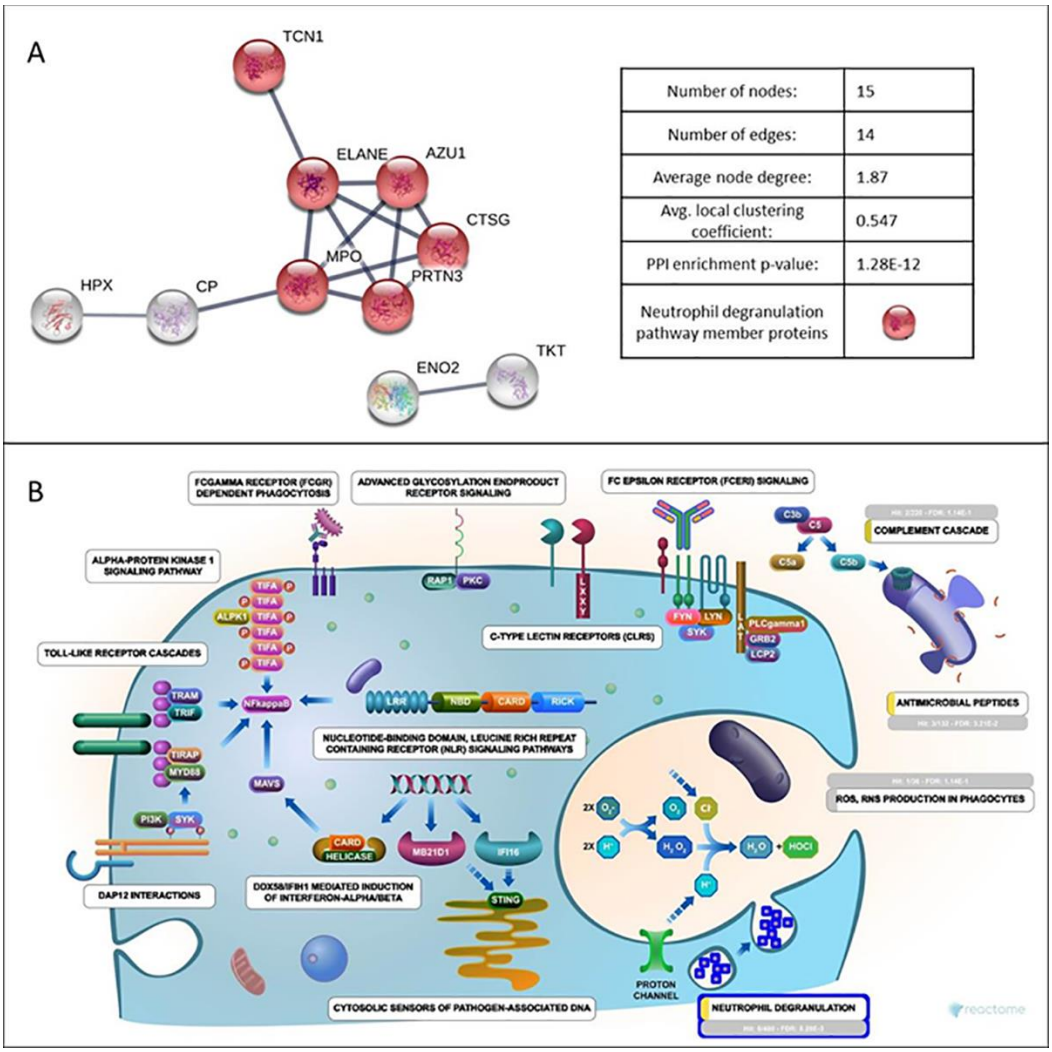


Figure 1. STRING and Reactome analysis of identified proteins. A-Protein-protein interaction network. B-Diagram of Initiate Immune System pathway (HSA-168249, FDR = 2.3E-5) from Reactome, showing a significant enrichment for neutrophil degranulation pathway (HSA-6798695, FDR = 2.01E-7) having the most hits.

## SARS-COV-2 PRESENCE IN THE SALIVA, TEARS AND CERUMEN OF COVID-19 PATIENTS

Hanege FM, Kocoglu E, Kalcioglu MT, Celik S, Cag Y, Esen F, Bayindir E, Pence S, Alp Mese E, Agalar C.. Laryngoscope. 2020 Oct 23. doi: 10.1002/lary.29218. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

### BLUF

Turkish otolaryngologists and clinical microbiologists from Istanbul Medeniyet University analyzed samples from 38 patients with RT-PCR confirmed SARS-CoV-2 (Table 1) within 72 hours of the first positive result and found 76.3% of saliva samples, 55.3% of tear samples, and 39.5% of cerumen samples tested positive for SARS-CoV-2 RNA (Table 2). Notably, half of the samples from asymptomatic patients (n=2/4) contained SARS-CoV-2 RNA. Authors suggest that SARS-CoV-2 viral RNA can be found in different bodily secretions and that personal protective equipment should be utilized when contact with patient saliva, tears, or cerumen is possible.

### ABSTRACT

OBJECTIVES: The emergence of a new coronavirus strain (SARS-CoV-2) in December 2019 from China led to a global pandemic. The lack of herd immunity against this virus and the possibility of viral spread from asymptomatic individuals is still a major challenge for the prevention of viral transmission. The aim of this study was to evaluate the presence of the virus in different bodily secretions as a potential source of viral spread among patients infected with SARS-CoV-2. METHODS: The study included 38 COVID-19 patients with a positive real time polymerase chain reaction (RT-PCR) test result for SARS-CoV-2, obtained from the combined nasopharyngeal-oropharyngeal swab samples. Saliva, tear and cerumen samples were taken from the patients within 72 hours of the first RT-PCR test. SARS-CoV-2 N1 and N2 gene regions were studied with single-step RT-PCR in all samples. RESULTS: Among the studied samples, the highest positivity rate was in saliva (76.3%) followed by tears (55.3%) and cerumen (39.5%). Viral load in saliva was also significantly higher compared to tears and cerumen ($p<0.001$), while there was no significant difference between tears and cerumen. Higher viral load in combined nasopharyngeal-oropharyngeal swab samples was associated with higher viral load in tears, but not in saliva or cerumen. Half of the saliva, tear and cerumen samples obtained from asymptomatic patients contained SARS-CoV-2 genome. CONCLUSION: The virus was detected in the saliva, tears and cerumen samples of both symptomatic and asymptomatic patients. The potential role of these bodily fluids on viral spread needs to be studied.

**Table 1. The demographic and clinical characteristics of the patients**

| | |
|---|---|
| Gender | |
| - female, % (n) | 63,2 (24) |
| - male, % (n) | 36,8 (14) |
| Mean age, years ±SD | 48.8 ±22.8 |
| Symptoms | |
| - fever, % (n) | 52,6 (20) |
| - fatigue, % (n) | 57,9 (22) |
| - cough, % (n) | 47,4 (18) |
| - dyspnea, % (n) | 26,3 (10) |
| - sore throat, % (n) | 21,1 (8) |
| - headache, % (n) | 21,1 (8) |
| - smell/taste disturbance, % (n) | 13,2 (5) |
| - nausea, % (n) | 13,2 (5) |
| - asymptomatic, % (n) | 10,5 (1) |
| - diarrhea, % (n) | 5,3 (2) |
| - loos of appetite, % (n) | 2,6 (1) |
| - conjunctivitis, % (n) | 0 (0) |

SD, standard deviation

**Table 2. RT-PCR positivity rates and viral load in different bodily secretions**

| | Positivity rate, %(n) | Ct value (mean ±SD) | Ct value (95% CI) |
|---|---|---|---|
| Nazo/oropharynx | 100 (38) | 27.98 ±4.29 | 26.57-29.39 |
| Saliva | 76.3 (29) | 30.97±1.56 | 30.37-31.56 |
| Tears | 55.3 (21) | 35.39 ±1.01 | 34.93-35.85 |
| Cerumen | 39.5 (15) | 35.14 ±1.03 | 34.57-35.71 |

RT-PCR, real time polymerase chain reaction; Ct, threshold cycle; SD, standard deviation; CI, confidence interval

Table 3. The factors that influence viral presence and viral load in different body secretions

| | Saliva | | | | Tear | | | | Cerumen | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Test positivity rate, % (n) | p value | Ct value (median, IQR) | p value | Test positivity rate, % (n) | p value | Ct value (median, IQR) | p value | Test positivity rate, % (n) | p value | Ct value (median, IQR) | p value |
| Age | | | | | | | | | | | | |
| - Below 50 (n=19) | 78.9 (15) | 1.0 | 31.4 (29.7-32.7) | 0.78 | 57.8 (11) | 0.74 | 35.0 (34.5-36.0) | 0.42 | 42.1 (8) | 0.11 | 34.5 (34.3-35.8) | 0.23 |
| - Above 50 (n=19) | 73.6 (14) | | 30.9 (30.2-31.9) | | 52.6 (10) | | 35.8 (34.8-36.0) | | 36.8 (7) | | 35.1 (34.7-36.2) | |
| Gender | | | | | | | | | | | | |
| - Female (n=24) | 70.8 (17) | 0.43 | 30.9 (30.2-31.9) | 0.71 | 54.2 (13) | 0.72 | 35.8 (35.0-35.9) | 0.37 | 45.8 (11) | 0.32 | 34.9 (34.3-36.2) | 0.75 |
| - Male (n=14) | 85.7 (12) | | 31.4 (29.9-32.6) | | 57.1 (8) | | 35.0 (34.6-36.0) | | 28.6 (4) | | 34.6 (34.2-36.4) | |
| Oro/nasopharynx viral load | | | | | | | | | | | | |
| - Low (Ct>27.7) (n=19) | 68.4 (13) | 0.44 | 31.0 (29.9-32.5) | 0.77 | 57.9 (11) | 1.0 | 35.8 (35.0-36.3) | 0.036 | 31.6 (6) | 0.99 | 34.8 (34.6-36.4) | 0.53 |
| - High (Ct<27.7) (n=19) | 84.2 (16) | | 30.9 (30.2-31.8) | | 52.6 (10) | | 34.9 (34.0-35.8) | | 47.3 (9) | | 34.7 (34.2-35.9) | |
| Pulmonary involvement | | | | | | | | | | | | |
| - Yes (n=20) | 75.0 (15) | 1.0 | 31.4 (30.5-32.0) | 0.15 | 50.0 (10) | 0.55 | 35.7 (35.0-36.0) | 0.39 | 30.0 (6) | 0.20 | 35.0 (34.7-35.8) | 0.27 |
| - No (n=18) | 77.7 (14) | | 30.4 (29.7-31.6) | | 61.1 (11) | | 35.0 (34.6-36.0) | | 50.0 (9) | | 34.5 (34.2-36.6) | |
| Hospitalization | | | | | | | | | | | | |
| - Yes (n=11) | 63.6 (7) | 0.40 | 31.8 (30.9-32.8) | 0.15 | 45.5 (5) | 0.49 | 35.7 (34.4-36.3) | 0.84 | 36.4 (4) | 1.0 | 35.3 (34.7-36.1) | 0.34 |
| - No (n=27) | 81.5 (22) | | 30.6 (30.0-31.7) | | 59.2 (16) | | 35.3 (34.6-35.9) | | 40.7 (11) | | 34.6 (34.3-36.2) | |

Ct, threshold circle; IQR, interquartile range

# DEVELOPMENTS IN TRANSMISSION & PREVENTION

## SEGMENTING AREAS OF POTENTIAL CONTAMINATION FOR ADAPTIVE ROBOTIC DISINFECTION IN BUILT ENVIRONMENTS

Hu D, Zhong H, Li S, Tan J, He Q.. Build Environ. 2020 Oct 15;184:107226. doi: 10.1016/j.buildenv.2020.107226. Epub 2020 Aug 26.
Level of Evidence: Other - Modeling

### BLUF

A modeling study conducted by engineers from the University of Cambridge and University of Tennessee proposes a potential use for robotic disinfection using simultaneous localization and mapping techniques for navigation, along with the object affordance concept (Figure 1, Figure 12, Figure 17). This is achieved by using deep-learning methods to determine potential areas of contamination and short UV light waves to adapt to the geometries of these areas to allow for complete and safe disinfection. These findings suggest potential for extrapolation and application of intelligent robotic disinfection in mass-gathering built environments to reduce infection risks and prevent COVID-19 outbreaks.

### ABSTRACT

Mass-gathering built environments such as hospitals, schools, and airports can become hot spots for pathogen transmission and exposure. Disinfection is critical for reducing infection risks and preventing outbreaks of infectious diseases. However, cleaning and disinfection are labor-intensive, time-consuming, and health-undermining, particularly during the pandemic of the coronavirus disease in 2019. To address the challenge, a novel framework is proposed in this study to enable robotic disinfection in built environments to reduce pathogen transmission and exposure. First, a simultaneous localization and mapping technique is exploited for robot navigation in built environments. Second, a deep-learning method is developed to segment and map areas of potential contamination in three dimensions based on the object affordance concept. Third, with short-wavelength ultraviolet light, the trajectories of robotic disinfection are generated to adapt to the geometries of areas of potential contamination to ensure complete and safe disinfection. Both simulations and physical experiments were conducted to validate the proposed methods, which demonstrated the feasibility of intelligent robotic disinfection and highlighted the applicability in mass-gathering built environments.

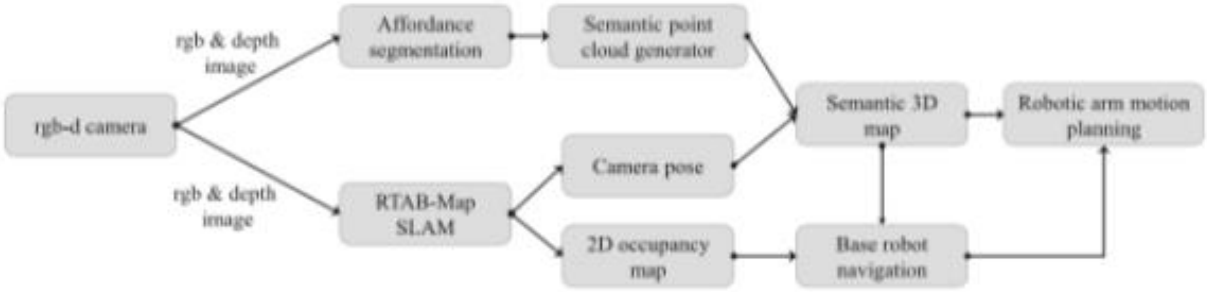


**Fig. 1.** Methodology overview.

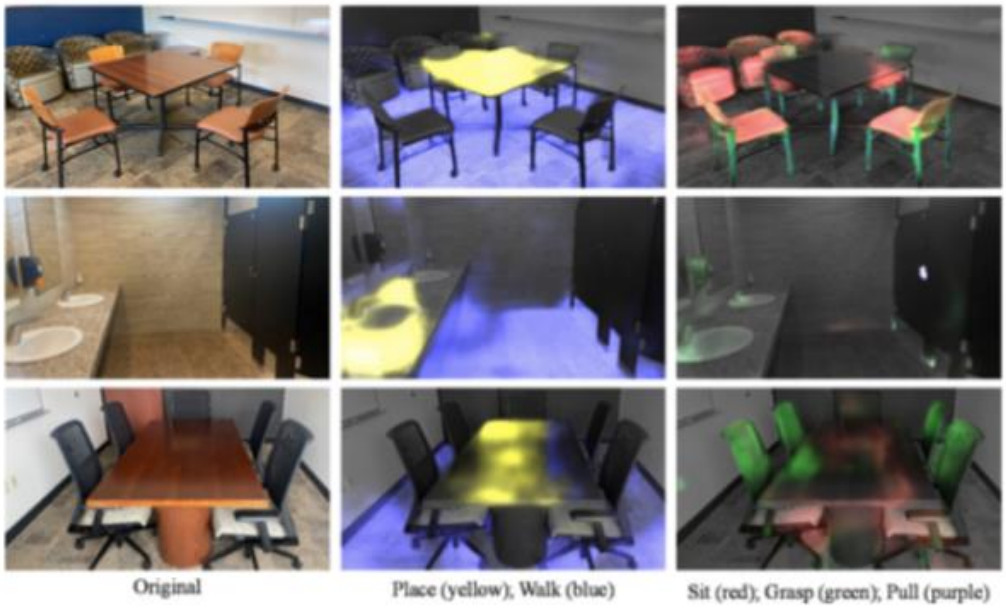


**Fig. 12.** Results of affordance segmentation.

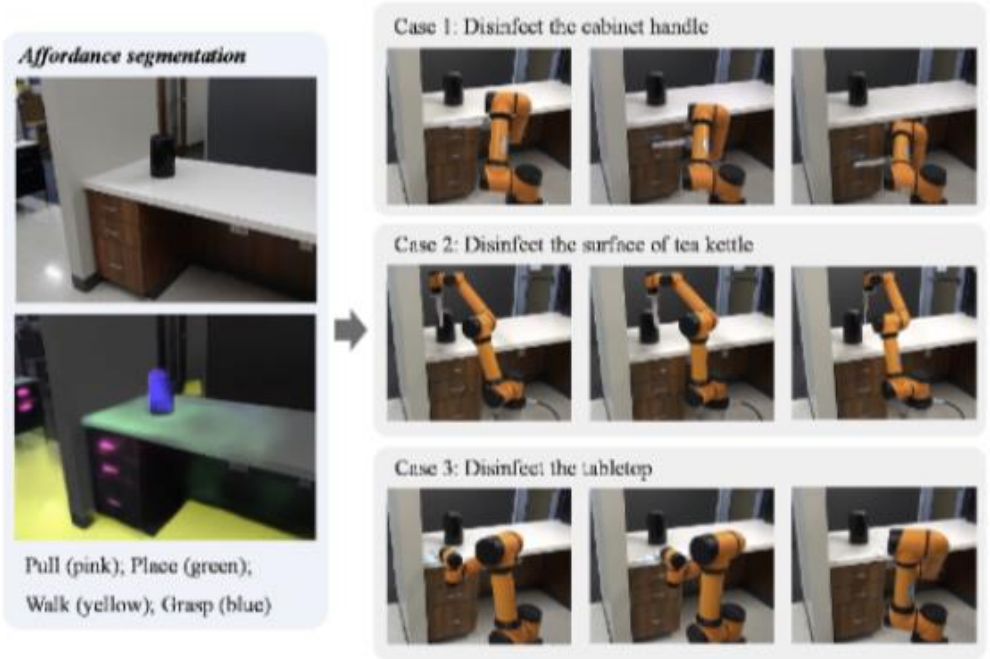


**Fig. 17.** Results of robotic disinfection based on affordance map.

# PROLONGED NUCLEIC ACID CONVERSION AND FALSE-NEGATIVE RT-PCR RESULTS IN PATIENTS WITH COVID-19: A CASE SERIES

Trisnawati I, El Khair R, Puspitarani DA, Fauzi AR, Gunadi.. Ann Med Surg (Lond). 2020 Nov;59:224-228. doi: 10.1016/j.amsu.2020.09.040. Epub 2020 Oct 6.
Level of Evidence: 4 - Case-series

## BLUF

A case series presented by physicians from Universitas Gadjah Mada/Dr. Sardjito Hospital in Yogyakarta, Indonesia describes 4 patients with false negative RT-PCR results in addition to the WHO recommendation of two negative RT-PCR results on sequential samples at least 24 hours apart (Table 1; see summary). They suggest careful clinical analysis of SARS-CoV-2 RT-PCR results as prolonged nucleic acid conversion (>24 days after onset of COVID-19 symptoms) may contribute to false RT-PCR results rather than infection recurrence, and positive RT-PCR results may not indicate an infectious or transmissive state.

## SUMMARY

Summary of each case detailed as follows:
- Case 1: A 36 year-old male with a positive COVID-19 sick contact on 3/13/20 presented with productive cough and tested positive for COVID-19 via nasopharyngeal swab on 3/24/20 and 3/25/20. He had normal vital signs aside from elevated blood pressure (187/94 mmHg) and lung auscultation was normal. Chest x-ray showed mild right pneumonia and blood tests revealed elevated neutrophil-lymphocyte ratio (NLR) and C-reactive protein (CRP). Treatment regimen during hospital admission consisted of azithromycin, hydroxychloroquine, oseltamivir, lopinavir-ritonavir, and umifenovir. 2 out of 9 swabs (number 6 and 8) were false negatives prior to number 10 and 11 being consecutively negative. The patient was discharged after 31 days.
- Case 2: A 54 year-old male with a history of diabetes mellitus and a positive COVID-19 sick contact reported shortness of breath with fever for 9 days and cough with phlegm for 3 days. After admission his vital signs included a blood pressure of 131/72 mmHg, heart rate of 96 bpm, 24 respirations/min, temperature of 38 degrees C, and 97% O2 sat on 2L nasal cannula. Rapid SARS-CoV-2 antibody showed non-reactive results. Imaging showed findings typical of viral pneumonia secondary to COVID-19 and labs revealed elevated NLR and CRP levels. Treatment regimen involved azithromycin, hydroxychloroquine, oseltamivir, and lopinavir-ritonavir. 1 out of 6 swabs (number 5) was a false negative prior to number 7 and 8 being consecutively negative. He was discharged after 29 days.
- Case 3: A 47 year-old male with a history of asthma and ventricular extra systole presented with fever, cough, sore throat, and diarrhea for 10 days prior to admission. Vital signs were within normal limits and lung auscultation revealed bilateral crackles. Rapid diagnostic SARS-CoV-2 antibodies were reactive. Chest x-ray showed bilateral pneumonia and labs showed NLR and CRP being elevated. Treatment regimen included azithromycin, hydroxychloroquine, umifenovir, and lopinavir-ritonavir. 2 out of 9 swabs (number 4 and 6) were false negatives prior to number 10 and 11 being consecutively negative. The patient was discharged after 52 days of treatment.
- Case 4: A 56 year-old female with hyperthyroidism presented with worsening lethargy for 6 days before admission and >10 episodes of diarrhea daily. Vital signs were within normal limits and lung auscultation was normal. Rapid diagnostic SARS-CoV-2 antibodies were non-reactive. Chest x-ray revealed bilateral pneumonia and labs showed evidence of pancytopenia. Her husband was later found to have reactive SARS-CoV-2 antibodies and COVID-19 exposure was confirmed. Treatment regimen included azithromycin, hydroxychloroquine, umifenovir and lopinavir-ritonavir. 2 out of 12 swabs were false negatives (number 2 and 10) prior to number 13 and 14 being consecutively negative. The patient was discharged after 70 days of treatment.

## ABSTRACT

Background: Prolonged nucleic acid conversion and false-negative real-time polymerase chain reaction (RT-PCR) results might occur in COVID-19 patients rather than infection recurrence. Presentation of cases: We reported four cases who had negative RT-PCR results, in addition to the last two consecutive negative results. Patient-1 had negative RT-PCR results twice (the 6th and 8th) from a total of 11 swabs. Patient-2 had negative RT-PCR results once (the 5th) from a total of 8 swabs. Patient-3 showed negative results of RT-PCR twice (the 4th and 6th) from a total of 11 swabs. Patient-4 had negative RT-PCR results twice (the 2nd and 10th) from a total of 14 swabs. Discussion: The fluctuating trend of our RT-PCR results in our cases might be due to insufficient viral material in the specimen, laboratory errors during sampling, restrictions on sample

transportation, or mutations in the primary and probe target regions in the SARS-CoV-2 genome. Several factors might affect the occurrence of prolonged nucleic acid conversion, including older age, comorbidities, such as diabetes and hypertension, and impaired immune function. Conclusion: Here, we confirmed the occurrence of prolonged nucleic acid conversion and the possibility of false negative RT-PCR results in COVID-19 patients.

## FIGURES

Table 1. RT-PCR findings in COVID-19 patients treated in Dr. Sardjito Hospital, Indonesia.

| Patients | Age | Gender | RT-PCR 1 | Test days, after onset | RT-PCR 2 | Test days, after onset | RT-PCR 3 | Test days, after onset | RT-PCR 4 | Test days, after onset | RT-PCR 5 | Test days, after onset | RT-PCR 6 | Test days, after onset | R P 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case 1 | 36 | Male | + | 1 | + | 2 | + | 8 | + | 10 | + | 14 | - | 16 | + |
| Case 2 | 54 | Male | + | 2 | + | 6 | + | 10 | + | 14 | - | 18 | + | 20 | - |
| Case 3 | 47 | Male | + | 10 | + | 15 | + | 22 | - | 28 | + | 32 | - | 37 | + |
| Case 4 | 56 | Female | + | 15 | - | 16 | + | 22 | + | 27 | + | 32 | + | 37 | + |

# DEVELOPMENTS IN DIAGNOSTICS

## ULTRASENSITIVE DETECTION OF PATHOGENIC VIRUSES WITH ELECTROCHEMICAL BIOSENSOR: STATE OF THE ART

Khan MZH, Hasan MR, Hossain SI, Ahommed MS, Daizy M.. Biosens Bioelectron. 2020 Oct 15;166:112431. doi: 10.1016/j.bios.2020.112431. Epub 2020 Jul 16.
Level of Evidence: Other - Review / Literature Review

## BLUF

A review by a group of chemical engineers summarizes current electrochemical detection methods for various pathogenic viruses in the context of the COVID-19 pandemic (Figures 1,4, & 6). Optimizing the immobilization method and assay lifetime are two obstacles that need to be overcome before the various potential electrochemical biosensors can be used for very rapid detection of the SARS-CoV-2 virus.

## SUMMARY

The authors review the following:
1. Electrochemical Impedence Biosensor: This cost-effective and label-free detection method has been studied for Dengue RNA virus and the authors hypothesize that assay modifications can lead to potential usage for the COVID-19 virus.

2. Electrochemical Immunosensors: This method has recently been applied to various viruses (e.g. Fig mosaic virus, human enterovirus 71, avian leukosis virus subgroup J). In Mar 2020, there have been experiments with ELISA and colloidal gold-immunochromatographic assay to detect the COVID-19 virus.

3. DNA-based sensors: This method has been studied recently for various viruses (e.g. Dengue virus, influenza A,B). A dual-functional plasmonic photothermal biosensor has been proposed as a potential method to detect the COVID-19 virus. The authors hypothesize that this method will soon be adaptable for the COVID-19 virus.

## ABSTRACT

Last few decades, viruses are a real menace to human safety. Therefore, the rapid identification of viruses should be one of the best ways to prevent an outbreak and important implications for medical healthcare. The recent outbreak of coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus which belongs to the single-stranded, positive-strand RNA viruses. The pandemic dimension spread of COVID-19 poses a severe threat to the health and lives of seven billion people worldwide. There is a growing urgency worldwide to establish a point-of-care device for the rapid detection of COVID-19 to prevent subsequent secondary spread. Therefore, the need for sensitive, selective, and rapid diagnostic devices plays a vital role in selecting appropriate treatments and to prevent the epidemics. During the last decade, electrochemical biosensors have emerged as reliable analytical devices and represent a new promising tool for the detection of different pathogenic viruses. This review summarizes the state of the art of different virus detection with currently available electrochemical detection methods. Moreover, this review discusses different fabrication techniques, detection principles, and applications of various virus biosensors. Future research also looks at the use of electrochemical biosensors regarding a potential detection kit for the rapid identification of the COVID-19.

## FIGURES

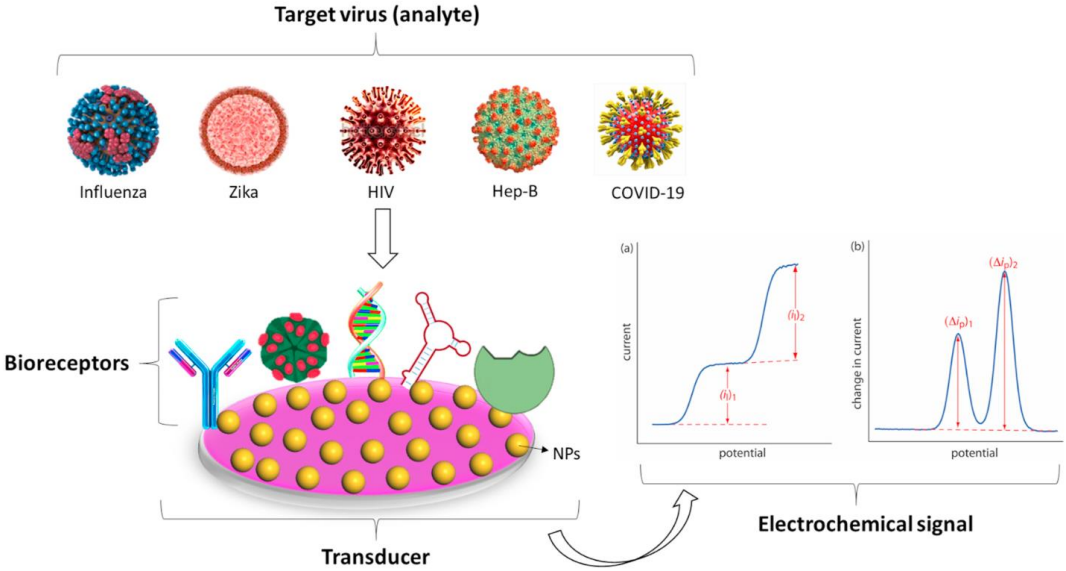


Figure 1. Potential electrochemical biosensor platforms for the detection of various pathogenic viruses including COVID-19. M.Z.H. Khan et al.

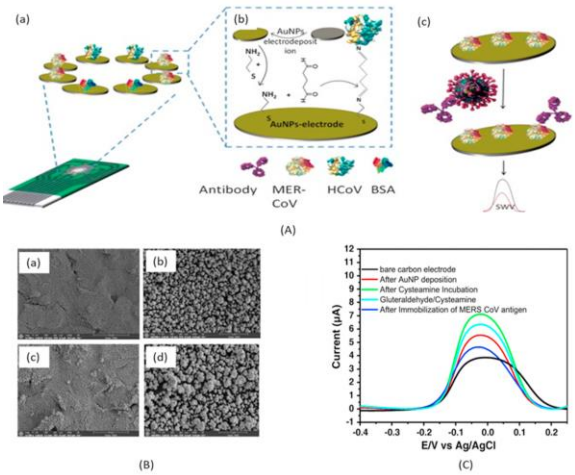


Figure 4. A) Schematic drawing of COV immunosensor array chip (a), the fabrication steps of the immunosensor (b), application of the immunosensor for the virus detection (c). (B) SEM images of, AuNPs deposited on electrodes using 20 CV scans at 12000x (a) and 100,000 xmagnification (b); the AuNPs deposited using 30 CV scans at 12000x (c) and 100,000x magnification (d). (C) SWV in ferro/ferrocyanide redox couple of the bare carbon array electrodes (black), after AuNPs electrodeposition using 20 CV scans (red), after cysteamine attachment (green), after glutaraldehyde activation (cyan) and after immobilization of MERS-CoV (blue) antibody (Layqah and Eissa, 2019).

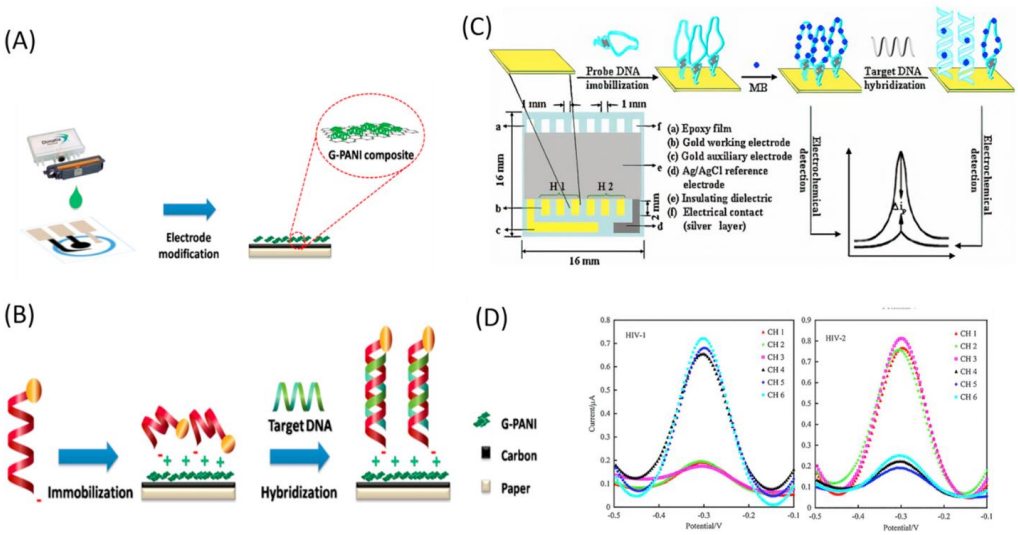


Figure 6. A) Schematic illustration of electrode modification with G-PANI. (B) immobilization and hybridization procedures of target DNA. (C) Cross-interference assays of the biosensor array for HIV-1 and HIV-2 detection. (D) Simultaneous detection of the biosensor array in the 100 µL of electrolyte buffer solution (CH1~CH3 with sample solution & CH4~CH6 in immobilized condition).

# DEVELOPMENTS IN TREATMENTS

## EFFECT OF TOCILIZUMAB VS USUAL CARE IN ADULTS HOSPITALIZED WITH COVID-19 AND MODERATE OR SEVERE PNEUMONIA: A RANDOMIZED CLINICAL TRIAL

Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P; CORIMUNO-19 Collaborative Group.. JAMA Intern Med. 2020 Oct 20. doi: 10.1001/jamainternmed.2020.6820. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

### BLUF

A randomized-controlled trial by interdisciplinary researchers conducted at 9 French hospitals from March 31 to April 18, 2020 included 131 hospitalized COVID-19 patients with moderate to severe pneumonia (Figure 1) randomized to receive Tocilizumab (TCZ; n=63) or usual care (UC; n=67). Authors found the TCZ cohort did not have improved WHO-clinical progression scores (CPS) by day 4 compared to the UC cohort, and there was no significant difference in deaths between the groups at day 28 (Table 2, Figure 2) despite ventilation rates being lower in TCZ group at day 14. These results suggest marginal benefit from TCZ treatment in moderate to severe COVID-19 pneumonia, but author acknowledge a need for further research to determine its effect on clinical outcomes.

### SUMMARY

Further details of the multicenter clinical trial as follows:
- 131 hospitalized COVID-19 patients with moderate to severe pneumonia (required 3L/min supplemental oxygen but no ICU admission) and WHO-CPS >5 were included in the study (Figure 1).
- Participants were randomized to the TCZ cohort (n=63) and received 8mg/kg TCZ on day 1 plus usual care, or to the UC cohort (n=67) and received antibiotics, antivirals, corticosteroids, anticoagulants, and vasopressors.
- Primary outcomes such as WHO-CPS >5 at day 4, mechanical ventilation, non-invasive ventilation, high-flow oxygen, and deaths at day 14 were analyzed (Table 2, Figure 2). These were overall lower in the TCZ group than UC group at day 14.
- Secondary outcomes included deaths by day 28 (Table 2), incidence of oxygen weaning, and discharge on day 28. There was no significant difference between groups regarding mortality by day 28 but the TCZ cohort had higher rate of oxygen weaning and discharge at day 28.

## ABSTRACT

Importance: Severe pneumonia with hyperinflammation and elevated interleukin-6 is a common presentation of coronavirus disease 2019 (COVID-19). Objective: To determine whether tocilizumab (TCZ) improves outcomes of patients hospitalized with moderate-to-severe COVID-19 pneumonia. Design, Setting, and Particpants: This cohort-embedded, investigator-initiated, multicenter, open-label, bayesian randomized clinical trial investigating patients with COVID-19 and moderate or severe pneumonia requiring at least 3 L/min of oxygen but without ventilation or admission to the intensive care unit was conducted between March 31, 2020, to April 18, 2020, with follow-up through 28 days. Patients were recruited from 9 university hospitals in France. Analyses were performed on an intention-to-treat basis with no correction for multiplicity for secondary outcomes. Interventions: Patients were randomly assigned to receive TCZ, 8 mg/kg, intravenously plus usual care on day 1 and on day 3 if clinically indicated (TCZ group) or to receive usual care alone (UC group). Usual care included antibiotic agents, antiviral agents, corticosteroids, vasopressor support, and anticoagulants. Main Outcomes and Measures: Primary outcomes were scores higher than 5 on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS) on day 4 and survival without need of ventilation (including noninvasive ventilation) at day 14. Secondary outcomes were clinical status assessed with the WHO-CPS scores at day 7 and day 14, overall survival, time to discharge, time to oxygen supply independency, biological factors such as C-reactive protein level, and adverse events. Results: Of 131 patients, 64 patients were randomly assigned to the TCZ group and 67 to UC group; 1 patient in the TCZ group withdrew consent and was not included in the analysis. Of the 130 patients, 42 were women (32%), and median (interquartile range) age was 64 (57.1-74.3) years. In the TCZ group, 12 patients had a WHO-CPS score greater than 5 at day 4 vs 19 in the UC group (median posterior absolute risk difference [ARD] -9.0%; 90% credible interval [CrI], -21.0 to 3.1), with a posterior probability of negative ARD of 89.0% not achieving the 95% predefined efficacy threshold. At day 14, 12% (95% CI -28% to 4%) fewer patients needed noninvasive ventilation (NIV) or mechanical ventilation (MV) or died in the TCZ group than in the UC group (24% vs 36%, median posterior hazard ratio [HR] 0.58; 90% CrI, 0.33-1.00), with a posterior probability of HR less than 1 of 95.0%, achieving the predefined efficacy threshold. The HR for MV or death was 0.58 (90% CrI, 0.30 to 1.09). At day 28, 7 patients had died in the TCZ group and 8 in the UC group (adjusted HR, 0.92; 95% CI 0.33-2.53). Serious adverse events occurred in 20 (32%) patients in the TCZ group and 29 (43%) in the UC group (P = .21). Conclusions and Relevance: In this randomized clinical trial of patients with COVID-19 and pneumonia requiring oxygen support but not admitted to the intensive care unit, TCZ did not reduce WHO-CPS scores lower than 5 at day 4 but might have reduced the risk of NIV, MV, or death by day 14. No difference on day 28 mortality was found. Further studies are necessary for confirming these preliminary results. Trial Registration: ClinicalTrials.gov Identifier: NCT04331808.


## FIGURES

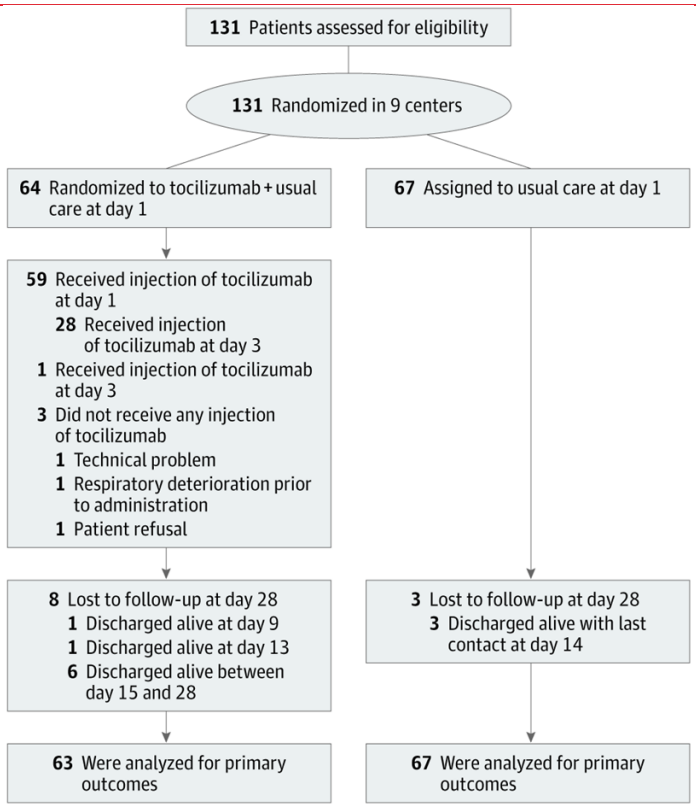


Figure 1: Study Flowchart.

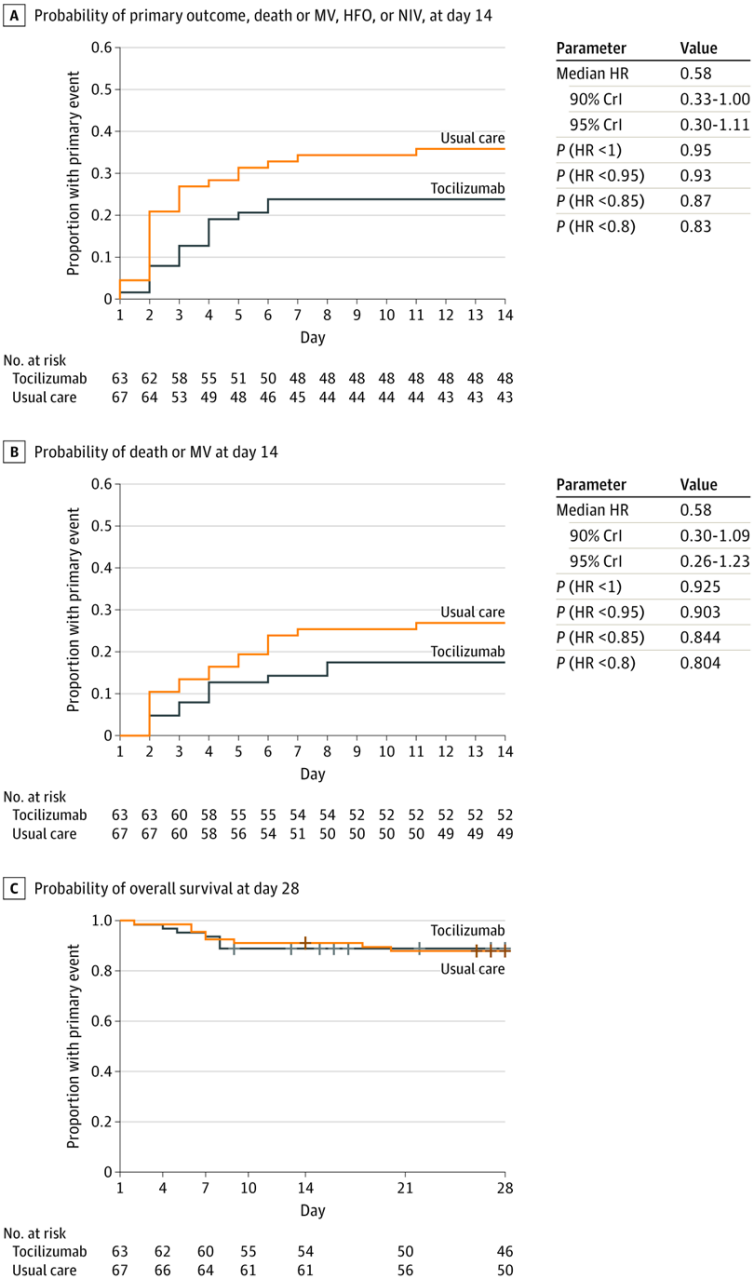


Figure 2: Occurrence of Primary Outcome Events During Follow-up.

**Table 2. Number of Patients With Noninvasive Ventilation or High-Flow Oxygen, Mechanical Ventilation, or Death**

| Variable | Tocilizumab (n = 63) | UC (n = 67) | Difference (95% CI) |
|---|---|---|---|
| Primary outcome by day 14, No. | 15 | 24 | |
| Cumulative incidence, % (95% CI) | 24 (13 to 34) | 36 (23 to 46) | −12 (−28 to 4) |
| First event, No. | | | |
| NIV/HFO | 8 | 13 | |
| MV | 3 | 8 | |
| Death/DNR order | 4 | 3 | |
| MV or death by day 14, No. | | | |
| % (95% CI) | 17 (8 to 26) | 27 (15 to 37) | −9 (−24 to 5) |
| First event, No. | | | |
| MV | 5 | 14 | |
| Death/DNR order | 6 | 4 | |
| Deaths | | | |
| Day 14, No. | 7 | 6 | |
| Survival, % (95% CI) | 89 (81 to 97) | 91 (84 to 98) | |
| Day 28, No. | 7 | 8 | |
| Survival, % (95% CI) | 89 (81 to 97) | 88 (80 to 96) | |

Abbreviations: DNR, do not resuscitate; HFO, high-flow oxygen; MV, mechanical ventilation; NIV, noninvasive ventilation.

Table 2: Number of Patients With Noninvasive Ventilation or High-Flow Oxygen, Mechanical Ventilation, or Death.

# PSYCHOLOGICAL IMPACT OF MASS QUARANTINE ON POPULATION DURING PANDEMICS-THE COVID-19 LOCK-DOWN (COLD) STUDY

Pandey D, Bansal S, Goyal S, Garg A, Sethi N, Pothiyill DI, Sreelakshmi ES, Sayyad MG, Sethi R.. PLoS One. 2020 Oct 22;15(10):e0240501. doi: 10.1371/journal.pone.0240501. eCollection 2020.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

## BLUF

A cross-sectional survey study conducted during the 2nd and 3rd weeks of strict quarantine starting March 24, 2020 by various medical institutions in India found prevalence of depression, anxiety, and stress to be 30.5%, 22.4%, and 10.8%, respectively, with significantly higher incidence in the 3rd week compared to the 2nd (Table 3, Figure 1). This data showed an 8-10 fold increase in depression and anxiety compared to baseline statistics in the Indian population as a result of the quarantine period, suggesting a detrimental psychological impact, which authors hope can assist in future consideration of coping strategies for those required to quarantine for prolonged periods of time.

## ABSTRACT

BACKGROUND: Quarantine often is an unpleasant experience. The aim of this study is to explore the degree of psychological distress in terms of-Depression, Anxiety and Stress among the adult population in India during the strict 21 days mandatory lockdown. We hypothesize that quantification of psychological impact of current situation will help us to modify the policies and implementation strategies. This assessment might also help in future to keep targeted services in place, to cope up with the psychological distress of the quarantined population. METHOD: A cross sectional survey design was adopted to assess the psychological state of general population in India, during the COVID-19 mandatory lockdown period, with the help of a validated questionnaire. FINDINGS: The reported prevalence of depression was around 30.5%, which was the highest among the variables of psychological health. Anxiety was reported by 22.4%, followed by stress which was seen in 10.8% of respondents. In the third week the incidence of depression (37.8% versus 23.4%; p<0.001), anxiety (26.6% versus 18.2%; p<0.001) and stress (12.2% versus 9.3%; p<0.045) was reported to be significantly higher as compared to second week. INTERPRETATION: Our results suggest a progressively detrimental impact of lockdown on various aspects of psychological health. We noticed around eight to ten fold increase in the prevalence of depression (30.5%) and anxiety (22.4%) during lockdown, as compared to baseline statistics in Indian population (3 1-3 6% for depressive disorders and 3 0-3 5% for anxiety disorders).

## FIGURES

**Table 3. Distribution of level of depression, anxiety and stress according to duration of lockdown among the respondents participated in the study (n = 1395).**

| | | Duration of Lockdown | | | | |
|---|---|---|---|---|---|---|
| | | Week 2 (n = 708) | | Week 3 (n = 687) | | P-value |
| | | n | % | n | % | |
| Depression | Normal | 542 | 76.6 | 427 | 62.2 | 0.001*** |
| | Mild | 87 | 12.3 | 107 | 15.6 | |
| | Moderate | 69 | 9.7 | 139 | 20.2 | |
| | Severe | 10 | 1.4 | 14 | 2.0 | |
| Anxiety | Normal | 579 | 81.8 | 504 | 73.4 | 0.001*** |
| | Mild | 55 | 7.8 | 58 | 8.4 | |
| | Moderate | 54 | 7.6 | 105 | 15.3 | |
| | Severe | 11 | 1.6 | 19 | 2.8 | |
| | Extremely severe | 9 | 1.3 | 1 | 0.1 | |
| Stress | Normal | 642 | 90.7 | 603 | 87.8 | 0.045* |
| | Mild | 47 | 6.6 | 70 | 10.2 | |
| | Moderate | 19 | 2.7 | 14 | 2.0 | |

P-value by Chi-Square test, P-value<0.05 is considered to be statistically significant.
*P-value<0.05,
***P-value<0.001.

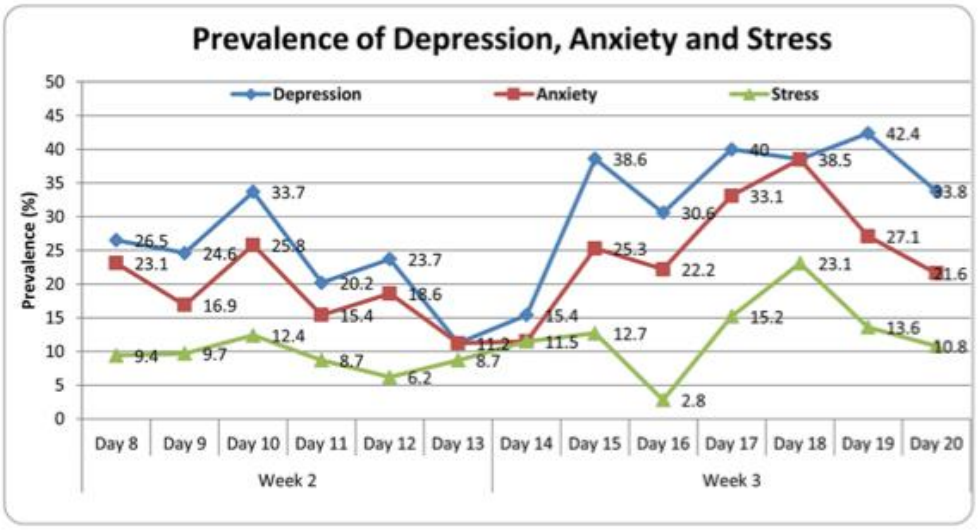


**Fig 1. Impact of duration of lockdown on psychological health.** This graph depicts day wise prevalence of depression, anxiety and stress in our study cohort.

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