

The Daily COVID-19 Literature Surveillance Summary

November 13, 2020



DISCLAIMER

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

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

NOW LIVE!

Daily audio summaries of the literature in 10 minutes or less.

<https://www.covid19lst.org/podcast/>



COVID-19 Daily Literature Surveillance

COVID19LST



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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>

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

EXECUTIVE SUMMARY

Understanding the Pathology

- A literature review on thromboembolic events in COVID-19 patients identified [each element of Virchow's Triad in the context of COVID-19](#): endothelial cell disruption due to SARS-CoV-2 binding to angiotensin-converting enzyme 2 receptors, hypercoagulability due to subsequent over-expression of neutrophil extracellular traps, and blood stasis from illness-related immobilization and extended bed rest.

Adjusting Practice During COVID-19

- A prospective survey study of 66 patients who had undergone image-guided corticosteroid injections for pain management by musculoskeletal imaging specialists at Massachusetts General Hospital in Boston found [no significant difference in rates of new COVID-19 cases between patients who received corticosteroid injections](#) ($n=1/66$, 25 year-old male, 19 days following injection) and the general population ($p=0.44$), suggesting that corticosteroid injections are safe to perform during the COVID-19 pandemic.

R&D: Diagnosis & Treatments

- A primarily retrospective cohort study conducted at Johns Hopkins University analyzed specimens from 2,194 patients that completed multiple RT-PCR tests for SARS-CoV-2 and found a correlation between cycle threshold (Ct) values (used to determine positivity) and SARS-CoV-2 growth on cell culture, though some high Ct samples produced viral growth. Droplet digital PCR on samples from individuals with multiple negative RT-PCR tests found multiple samples positive. Generally, these results indicate [correlation between ability to culture the virus and Ct values from RT-PCR tests](#), though some variability in these tests demonstrates the need to continue CDC protocols for isolation by symptoms rather than cessation of isolation after a negative RT-PCR test.
- A multidisciplinary team affiliated with the Rwanda Joint Task Force on COVID-19 proposes an algorithm for [pooled testing of SARS-CoV-2 that is "based on the geometry of a hypercube"](#) currently being trialed in Rwanda and South Africa. Proof of concept experiments demonstrated that positive specimens can be detected even after 100-fold dilution, suggesting this pooled testing strategy could reduce costs, maximize speed of large-scale testing to monitor and reduce further spread of infection, and repeated group testing could be performed to address the loss of sensitivity due to dilution.

TABLE OF CONTENTS

DISCLAIMER.....	2
NOW LIVE!.....	2
LEVEL OF EVIDENCE.....	3
EXECUTIVE SUMMARY.....	4
TABLE OF CONTENTS.....	5
CLIMATE.....	6
AFFECTING THE HEALTHCARE WORKFORCE	6
Dutch cardiology residents and the COVID-19 pandemic: Every little thing counts in a crisis	6
UNDERSTANDING THE PATHOLOGY	7
COVID-19, thromboembolic risk, and Virchow's triad: Lesson from the past.....	7
Can immunological manipulation defeat SARS-CoV-2? Why G-CSF induced neutrophil expansion is worth a clinical trial: G-CSF treatment against COVID-19	8
Possible auto-antigens that may explain the post-infection autoimmune manifestations in COVID-19 patients displaying neurological conditions	9
MANAGEMENT	10
ACUTE CARE	10
<i>Critical Care</i>	10
Impact of tocilizumab administration on mortality in severe COVID-19	10
ADJUSTING PRACTICE DURING COVID-19	12
MEDICAL SUBSPECIALTIES	12
Symptomatic COVID-19 infections in outpatient image-guided corticosteroid injection patients during the lockdown phase.....	12
R&D: DIAGNOSIS & TREATMENTS.....	14
DEVELOPMENTS IN DIAGNOSTICS.....	14
Repeat COVID-19 Molecular Testing: Correlation of SARS-CoV-2 Culture with Molecular Assays and Cycle Thresholds	14
A pooled testing strategy for identifying SARS-CoV-2 at low prevalence	15
ACKNOWLEDGEMENTS	17

CLIMATE

AFFECTING THE HEALTHCARE WORKFORCE

DUTCH CARDIOLOGY RESIDENTS AND THE COVID-19 PANDEMIC: EVERY LITTLE THING COUNTS IN A CRISIS

Berger WR, Baggen V, Vorselaars VMM, van der Heijden AC, van Hout GPJ, Kapel GFL, Woudstra P; Junior Board (Juniorkamer) of the Netherlands Society of Cardiology (NVVC).. Neth Heart J. 2020 Nov 3. doi: 10.1007/s12471-020-01519-6. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

Dutch cardiologists review a nationwide survey of Dutch cardiology residents (n=122) and found 63% of survey respondents reported an interruption in their training due to the COVID-19 pandemic as trainees were re-allocated to staff COVID-19 units (Figure 1). Authors suggest lessons regarding pandemic response and compassionate care are invaluable (Table 1), however, inevitable knowledge gaps from interrupted training may require individualized education plans utilizing virtual learning to prevent knowledge gaps.

ABSTRACT

The COVID-19 pandemic has overwhelmed healthcare systems worldwide, and a large part of regular cardiology care came to a quick halt. A Dutch nationwide survey showed that 41% of cardiology residents suspended their training and worked at COVID-19 cohort units for up to 3 months. With tremendous flexibility, on-call schedules were altered and additional training was provided in order for residents to be directly available where needed most. These unprecedented times have taught them important lessons on crisis management. The momentum is used to incorporate novel tools for patient care. Moreover, their experience of pandemic and crisis management has provided future cardiologists with unique skills. This crisis will not be wasted; however, several challenges have to be overcome in the near future including, but not limited to, a second pandemic wave, a difficult labour market due to an economic recession, and limitations in educational opportunities.

FIGURES

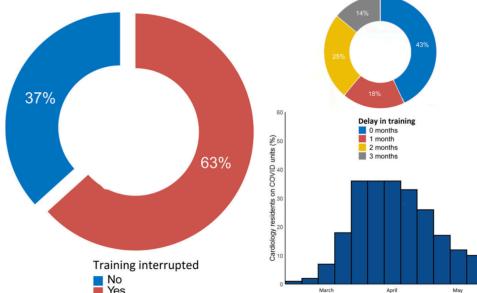


Figure 1. Results of nationwide survey among 122 Dutch cardiology residents during COVID-19 pandemic

Knowledge
- Pandemic and disease control measures
- Development of novel disease characteristics and treatment protocols
- Respiratory care on COVID-19 cohort units and intensive care units
Management
- Crisis management structures
- Opportunities for and limitations of a healthcare system
- Multidisciplinary improvement of care
Innovation
- Implementation of eHealth solutions
- Implementation of virtual learning
Communication and collaboration
- Teamwork and compassion are cornerstones of healthcare system
- Alternative (virtual) patient and family communication
- Importance of well-organized aftercare, such as peer support

Table 1. Lessons learned from COVID-19 healthcare crisis for cardiology residents

UNDERSTANDING THE PATHOLOGY

COVID-19, THROMBOEMBOLIC RISK, AND VIRCHOW'S TRIAD: LESSON FROM THE PAST

Mehta JL, Calcaterra G, Bassareo PP.. Clin Cardiol. 2020 Nov 11. doi: 10.1002/clc.23460. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Physicians in the United States, Italy, and Ireland review literature on thromboembolic events in COVID-19 patients (Table 1). They identify each element of Virchow's Triad (Figure 1) in the context of COVID-19: endothelial cell disrupting due to SARS-CoV-2 binding to angiotensin-converting enzyme 2 receptors, hypercoagulability due to subsequent over-expression of neutrophil extracellular traps, and blood stasis from illness-related immobilization and extended bed rest. Authors suggest the classic teachings from Virchow's Triad explains SARS-CoV-2 related thrombosis and interventions targeting each element (hypercoagulability, blood stasis, endothelial cell damage) should be studied.

FIGURES

Virchow's Triad in COVID-19

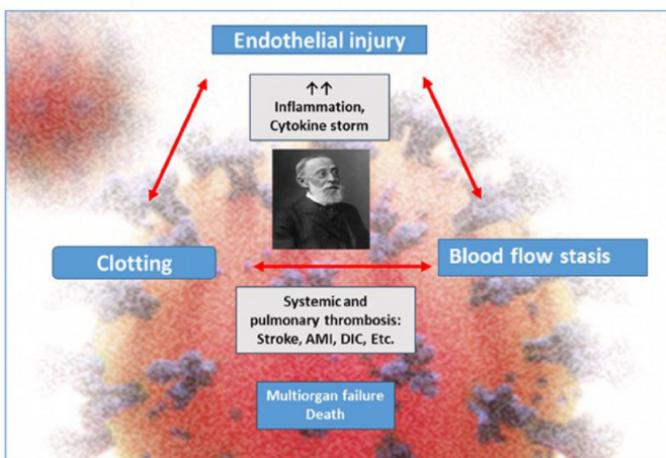


FIGURE 1 Virchow's Triad and COVID-19. Three cardinal component of Virchow's Triad—endothelial injury, clotting and blood flow stasis—are often observed in COVID-19 resulting in systemic and venous thrombosis and their manifestations—such as stroke, acute myocardial infarction (AMI), primary thrombosis, and disseminated intravascular coagulation (DIC)

TABLE 1 COVID-19-related thromboembolic events

Author	n	Mean age	Gender	Thromboembolic event(s)	Death
Oxley et al ²	5	40.4	80% male	Ischemic stroke (100%)	None
Klok et al ³	184	64	76% male	Venous thromboembolism (27%) Arterial thrombosis (3.7%)	13%
Kollia et al ⁴	1,563	52.2	57% male	venous thrombosis (0-54%)	NR
Akel et al ⁵	6	53.1	66.6% male	Pulmonary embolism (100%)	None
Paterson et al ⁶	43	62.5	75% male	Ischemic stroke (18.6%) Concomitant pulmonary embolism (9.3%)	12.5%
Middeldorp et al ⁷	198	61	66% male	Venous thromboembolism (20%)	19%
Helms et al ⁸	150	63	81.3% male	Arterial/venous thrombosis (42.6%) Pulmonary embolism (16.7%)	NR
Ackermann et al ⁹	7	74	71.4% male	Pulmonary embolism (100%)	100%
Fox et al ¹⁰	10	63	NR	Pulmonary embolism (100%)	100%
Wichmann et al ¹¹	12	73	75% male	Venous thromboembolism (58%)	100%
Bellotta et al ¹²	20	75	90% male	Acute limb ischaemia (100%)	40%
Stefanini et al ¹⁴	28	68	71.4% male	Intracoronary thrombus (100%)	39.3%
Bangalore et al ¹⁵	18	63	83% male	Intracoronary thrombus (100%)	72%
Mulvey et al ¹⁶	5	32	0% male	Placental thrombosis (100%)	0%

Abbreviation: NR, not reported.

CAN IMMUNOLOGICAL MANIPULATION DEFEAT SARS-COV-2? WHY G-CSF INDUCED NEUTROPHIL EXPANSION IS WORTH A CLINICAL TRIAL: G-CSF TREATMENT AGAINST COVID-19

Katayama H.. Bioessays. 2020 Nov 9:e2000232. doi: 10.1002/bies.202000232. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

This opinion piece by Hiroshi Katayama from Katayama Dermatology Clinic in Gunma, Japan discusses an intrinsic immunological mechanism of recovery from SARS-CoV-2 infection via accumulation of Th17 cells at the infection site (Figure 1), while proposing administration of granulocyte-colony stimulating factor (G-CSF, a growth factor promoting neutrophil egress from bone marrow) as treatment for patients with severe COVID-19. He speculates that patients with severe COVID-19 have impaired natural Th17 cells (nTh17) production, leading to decreased ability to fight SARS-CoV-2 infection in lung epithelium. The author advocates for further research on G-CSF as a treatment for COVID-19, suggesting it may stimulate the intrinsic immune system to recruit nTh17 cells to the infection site for improved immunity against SARS-CoV-2.

ABSTRACT

Immunity against SARS-CoV-2 that is acquired by convalescent COVID-19 patients is examined in reference to (A) the Th17 cell generation system in psoriatic epidermis and (B) a recently discovered phenomenon in which Th17 cells are converted into tissue-resident memory T (TRM) cells with Th1 phenotype. Neutrophils that are attracted to the site of infection secrete IL-17A, which stimulates lung epithelial cells to express CCL20. Natural Th17 (nTh17) cells are recruited to the infection site by CCL20 and expand in the presence of IL-23. These nTh17 cells are converted to TRM cells upon encounter with SARS-CoV-2 and continue to exist as ex-Th17 cells, which exert Th1-like immunity during a memory response. G-CSF can induce nTh17 cell accumulation at the infection site because it promotes neutrophil egress from the bone marrow. Hence, G-CSF may be effective against COVID-19. Administration of G-CSF to patients infected with SARS-CoV-2 is worth a clinical trial.

FIGURES

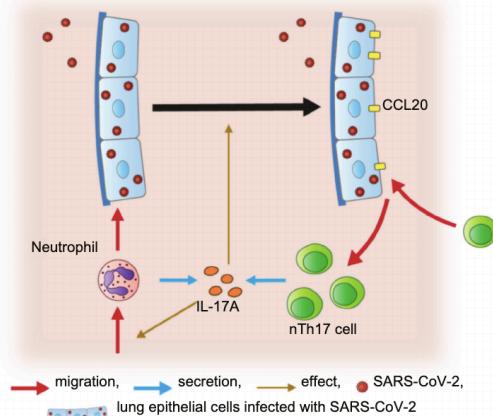


Figure 1. The process by which nTh17 cells are recruited to SARS-CoV-2 infection sites. Neutrophils, attracted by pathogen-derived chemoattractants and host chemokines expressed on the lung epithelium, secrete IL-17A. IL-17A stimulates lung epithelial cells to express CCL20, which in turn attracts nTh17 cells. nTh17 cells recruited to the infection site expand in the presence of IL-23 and IL-1 β and secrete IL-17A, establishing a positive feedback loop, beginning with IL-17A production by neutrophils and ending in IL-17A production by Th17 cells. As Th17 cells recruit neutrophils, this loop can also be regarded as a neutrophil supply system.

POSSIBLE AUTO-ANTIGENS THAT MAY EXPLAIN THE POST-INFECTION AUTOIMMUNE MANIFESTATIONS IN COVID-19 PATIENTS DISPLAYING NEUROLOGICAL CONDITIONS

Mohkhedkar M, Venigalla SSK, Janakiraman V.. J Infect Dis. 2020 Nov 7:jiaa703. doi: 10.1093/infdis/jiaa703. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

In a letter to the editor, biotech researchers affiliated with the Indian Institute of Technology Madras in India screened for shared B-cell epitopes between humans and SARS-CoV-2 to identify four human proteins (HSP90AB1, HSPA5/GRP78, titin, and RYR2; Table 1) that could potentially behave as autoreactive antigens in COVID-19 patients with neurological conditions. Study findings imply that SARS-CoV-2 infection may trigger molecular mimicry via these autoantigens, leading to increased autoimmunity and ultimately manifesting as post-infectious multi-organ (i.e. neurological) complications.

SUMMARY

This letter was published in response to the following: Schiaffino MT, Natale M Di, García-Martínez E, et al. Immunoserologic Detection and Diagnostic Relevance of Cross-Reactive Autoantibodies in Coronavirus Disease 2019 Patients. J Infect Dis. 2020; XX:1–5.

FIGURES

Table 1. Possible self-antigens in neurological conditions arising due to autoimmunity via molecular mimicry triggered by SARS-CoV-2 infection.

SARS-CoV-2 Protein	Sequence in SARS-CoV-2 (Homologous sequences in red)	Homologous human protein	Autoimmune condition
Spike protein	NFNGLTGTGVLTESNKFLPFQQFG[9]	HSPA5 ^a	Neuromyelitis optica
Spike protein	SALEPLVDLPIGINITRFQTLALH[9]	TTN ^b	Myasthenia gravis
Spike protein	SALEPLVDLPIGINITRFQTLALH[9]	RYR2 ^c	Myasthenia gravis
Nucleocapsid phosphoprotein	KDKKKK [5]	HSP90AB1 ^d	GBS

Table Footnote: superscripts indicate subcellular location as obtained from the Human Protein Atlas (<http://www.proteinatlas.org>) [10] a – cytosol, b – predicted to be intracellular and membrane for different isoforms, c – nucleoplasm, plasma membrane, cytosol, d – cytosol. Abbreviations: GBS: Guillain Barre Syndrome, HSPA5: heat shock protein family A (Hsp70) member 5, HSP90AB1: Heat Shock Protein 90 alpha family class B member 1, RYR2: ryanodine receptor 2, TTN: titin.

MANAGEMENT

ACUTE CARE

CRITICAL CARE

IMPACT OF TOCILIZUMAB ADMINISTRATION ON MORTALITY IN SEVERE COVID-19

Tsai A, Diawara O, Nahass RG, Brunetti L.. Sci Rep. 2020 Nov 5;10(1):19131. doi: 10.1038/s41598-020-76187-y.

Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

This single-center retrospective cohort study conducted by pharmacists from Robert Wood Johnson University Hospital, New Jersey evaluated use of tocilizumab for cytokine storm in patients admitted with COVID-19 from March 1 to May 5, 2020 and found no mortality reduction in those who received tocilizumab (n=66) compared to a control group (n=66), but advanced age and comorbidities (history of myocardial infarction, dementia, chronic pulmonary disease, heart failure, and malignancy) were more commonly present in patients who died (Table 2). Authors do not endorse use of tocilizumab for cytokine storm in patients with COVID-19 but acknowledge the observational nature of this study warrants further investigation.

ABSTRACT

The novel coronavirus disease 2019 (COVID-19) worldwide pandemic has placed a significant burden on hospitals and healthcare providers. The immune response to this disease is thought to lead to an aberrant inflammatory response or cytokine storm, which contributes to the severity of illness. There is an urgent need to confirm whether the use of tocilizumab provides a benefit in individuals with COVID-19. A single-center propensity-score matched cohort study, including all consecutive COVID-19 patients, admitted to the medical center who were either discharged from the medical center or expired between March 1, 2020, and May 5, 2020, was performed. Patients were stratified according to the receipt of tocilizumab for cytokine storm and matched to controls using propensity scores. The primary outcome was in-hospital mortality. A total of 274 patients meeting inclusion and exclusion criteria were identified and 132 patients were included in the matched dataset (tocilizumab = 66; no tocilizumab = 66). Approximately 73% of the patients were male. Hypertension (55%), diabetes mellitus (31%), and chronic pulmonary disease (15%) were the most common comorbidities present. There were 18 deaths (27.3%) in the tocilizumab group and 18 deaths (27.3%) in the no tocilizumab group (odds ratio, 1.0; 95% confidence interval, 0.465 - 2.151; p = 1.00). Advanced age, history of myocardial infarction, dementia, chronic pulmonary disease, heart failure, and malignancy were significantly more common in patients who died. The current analysis does not support the use of tocilizumab for the management of cytokine storm in patients with COVID-19. Use of this therapeutic agent should be limited to the context of a clinical trial until more evidence is available.

FIGURES

	Death (n = 36)	Survivor (n = 96)	p-value
Age (years, mean ± SD)	73.06 ± 12.03	57.67 ± 13.54	< 0.001
Female (n, %)	10 (27.8)	26 (27.1)	0.936
LDH (U/L, mean ± SD)	419.56 ± 178.38	383.10 ± 139.66	0.219
Lactic acid (mg/dL, mean ± SD)	2.40 ± 1.43	1.61 ± 0.56	0.002
C-reactive protein (mg/dL, mean ± SD)	13.93 ± 7.60	10.90 ± 5.82	0.035
Procalcitonin (ng/mL, mean ± SD)	2.15 ± 8.83	0.34 ± 0.65	0.227
Ferritin (ng/mL, mean ± SD)	1220.86 ± 813.77	1189.35 ± 1020.13	0.868
Serum creatinine (mg/dL, mean ± SD)	1.53 ± 1.68	1.19 ± 1.78	0.324
Oxygen saturation (%), mean ± SD)	85.58 ± 13.06	90.70 ± 5.45	0.028
Body mass index (kg/m ² , mean ± SD)	30.33 ± 8.25	30.20 ± 5.70	0.934
Ventilator use (n, %)	22 (61.1)	15 (15.6)	< 0.001
Comorbidity index score (mean ± SD)	2.39 ± 2.72	1.06 ± 1.76	0.009
Hypertension (n, %)	24 (66.7)	48 (50.0)	0.087
Myocardial infarction (n, %)	7 (19.4)	6 (6.7)	0.023
Heart failure (n, %)	5 (13.9)	2 (2.1)	0.016
Cerebrovascular disease (n, %)	6 (16.7)	6 (6.3)	0.064
Peripheral vascular disease (n, %)	3 (8.3)	5 (5.2)	0.683
Dementia (n, %)	6 (16.7)	2 (2.1)	0.005
Chronic pulmonary disease (n, %)	11 (30.6)	9 (9.4)	0.003
Rheumatic disease (n, %)	2 (5.6)	2 (2.1)	0.299
Peptic ulcer disease (n, %)	0 (0)	3 (9.4)	0.562
Liver disease (n, %)	1 (2.8)	1 (1.0)	0.473
Diabetes (n, %)	13 (33.3)	28 (29.2)	0.443
Hemiplegia/paraplegia (n, %)	1 (2.8)	1 (1.0)	0.473
Renal disease (n, %)	4 (11.1)	3 (3.1)	0.088
Any malignancy (n, %)	3 (8.3)	0 (0)	0.019
Metastatic solid tumor (n, %)	2 (5.6)	3 (3.1)	0.613

Table 2. Comparison of patient characteristics between patients surviving and those expiring in the overall population.

ADJUSTING PRACTICE DURING COVID-19

MEDICAL SUBSPECIALTIES

SYMPTOMATIC COVID-19 INFECTIONS IN OUTPATIENT IMAGE-GUIDED CORTICOSTEROID INJECTION PATIENTS DURING THE LOCKDOWN PHASE

Chang CY, Prabhakar A, Staffa SJ, Husseini JS, Kheterpal AB, Simeone FJ, Bredella MA.. Skeletal Radiol. 2020 Oct 27. doi: 10.1007/s00256-020-03656-w. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

A prospective survey study of patients who had undergone image-guided corticosteroid injections for pain management (n=66; Figures 1,2) conducted from April 15 to May 22, 2020 by musculoskeletal imaging specialists at Massachusetts General Hospital in Boston found no significant difference in rates of new COVID-19 cases between patients who received corticosteroid injections (n=1/66, 25 year-old male, 19 days following injection) and the general population ($p=0.44$), suggesting that corticosteroid injections are safe to perform during the COVID-19 pandemic. This study may be limited by its small sample size, but authors hope these results can inform clinical practice management in the midst of the COVID-19 pandemic.

ABSTRACT

BACKGROUND: Musculoskeletal pain is a debilitating problem treated with image-guided corticosteroid injections. During the COVID-19 pandemic, multiple societies issued caution statements because of the unknown effect of corticosteroids on the patient's immune system. The purpose is to determine if image-guided corticosteroid injections administered during the COVID-19 lockdown phase were associated with a higher infection rate compared to the general population. **MATERIALS AND METHODS:** In a prospective study, patients undergoing image-guided corticosteroid injections for pain management during the lockdown phase between April 15 and May 22, 2020, were enrolled. One month after the injection, patients were surveyed by telephone for any COVID-19-related symptoms, and the electronic medical record (EMR) was reviewed for symptoms and test results. **RESULTS:** Seventy-one subjects were recruited, 31 (44%) females, 40 (56%) males, ages 58 +- 17 (20-92) years. Follow-up was available in 66 (93%) of subjects, 60 (91%) by phone survey and EMR, 6 (9%) by EMR only, 45 +- 22 (19-83) days after injection. One (1/66, 1.52%; 95% CI 0.04-8.2%) 25-year-old male subject developed symptomatic infection 19 days after a tibiotalar injection. The prevalence of COVID-19 cases in the state of Massachusetts was 0.91% (62,726/6,892,503) during the study period. There was no significant difference in the rate of occurrence of new cases of COVID-19 infection between the corticosteroid injection group and the general population ($p = 0.44$). **CONCLUSION:** Image-guided corticosteroid injections for pain management performed during the lockdown phase of the COVID-19 pandemic were not associated with a higher infection rate compared to the general population.

FIGURES

Have you experienced any of the following symptoms in the past month, since your injection?

- Fever or feeling feverish
- Sore throat
- New cough (not related to chronic condition)
- New nasal congestion or new runny nose (not related to seasonal allergies)
- Muscle aches
- New loss of smell
- New loss of taste
- New shortness of breath
- Dizziness
- Headache
- Nausea/vomiting
- Diarrhea
- Abdominal pain
- Changes in your toes
- Other? (fill in) _____
- No symptoms

Have you had a COVID-19 test? Yes/No

If yes, what kind of test? Virus/Antibodies? What were the results?

Figure 1: Post-procedure survey

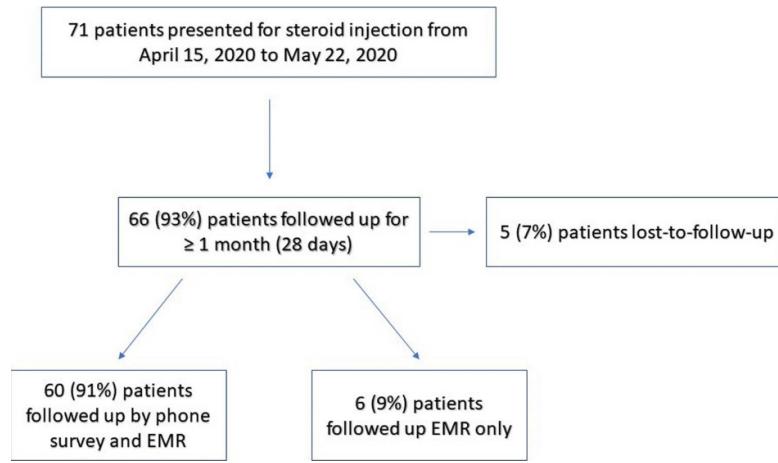


Figure 2: Flowchart depicting image-guided corticosteroid patient population

R&D: DIAGNOSIS & TREATMENTS

DEVELOPMENTS IN DIAGNOSTICS

REPEAT COVID-19 MOLECULAR TESTING: CORRELATION OF SARS-COV-2 CULTURE WITH MOLECULAR ASSAYS AND CYCLE THRESHOLDS

Gniazdowski V, Morris CP, Wohl S, Mehoke T, Ramakrishnan S, Thielen P, Powell H, Smith B, Armstrong DT, Herrera M, Reifsnyder C, Sevdali M, Carroll KC, Pekosz A, Mostafa HH. Clin Infect Dis. 2020 Oct 27:ciaa1616. doi: 10.1093/cid/ciaa1616. Online ahead of print.

Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A primarily retrospective cohort study, conducted at Johns Hopkins University (U.S.), analyzed specimens from 2,194 patients that completed multiple RT-PCR tests for SARS-CoV-2. There was a correlation between cycle threshold (Ct) values (used to determine positivity) and SARS-CoV-2 growth on cell culture, though some high Ct samples produced viral growth (Figure 2). Furthermore, droplet digital PCR on samples from individuals with multiple negative RT-PCR tests found multiple samples positive (Figure 5). Generally, these results indicate correlation between ability to culture the virus and Ct values from RT-PCR tests, though some variability in these tests demonstrates the need to continue CDC protocols for isolation by symptoms rather than cessation of isolation after a negative RT-PCR test.

ABSTRACT

BACKGROUND: Repeat COVID-19 molecular testing can lead to positive test results after negative tests and to multiple positive test results over time. The association between positive tests and infectious virus is important to quantify. **METHODS:** A two months cohort of retrospective data and consecutively collected specimens from COVID-19 patients or patients under investigation were used to understand the correlation between prolonged viral RNA positive test results, cycle threshold (Ct) values and growth of SARS-CoV-2 in cell culture. Whole genome sequencing was used to confirm virus genotype in patients with prolonged viral RNA detection. Droplet digital PCR (ddPCR) was used to assess the rate of false negative COVID-19 diagnostic tests. **RESULTS:** In two months, 29,686 specimens were tested and 2,194 patients received repeated testing. Virus recovery in cell culture was noted in specimens with SARS-CoV-2 target genes' Ct value average of 18.8 +- 3.4. Prolonged viral RNA shedding was associated with positive virus growth in culture in specimens collected up to 20 days after the first positive result but mostly in individuals symptomatic at time of sample collection. Whole genome sequencing provided evidence the same virus was carried over time. Positive tests following negative tests had Ct values higher than 29.5 and were not associated with virus culture. ddPCR was positive in 5.6% of negative specimens collected from COVID-19 confirmed or clinically suspected patients. **CONCLUSIONS:** Low Ct values in SARS-CoV-2 diagnostic tests were associated with virus growth in cell culture. Symptomatic patients with prolonged viral RNA shedding can also be infectious.

FIGURES

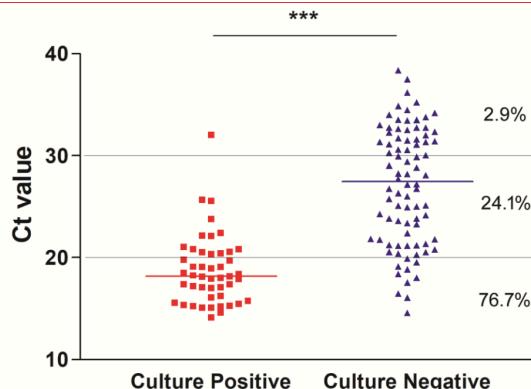


Figure 2. Correlation between SARS-CoV-2 growth on cell culture and Ct values. Nasopharyngeal specimens were cultured on VeroE6 cells and the recovery of virus and the development of cytopathic effect were monitored for up to 4 days post infection.

The percent viral growth positive samples with the given Ct values is shown on the right. Viral growth was confirmed by antigen staining or PCR. *** paired t test, $P<0.0001$

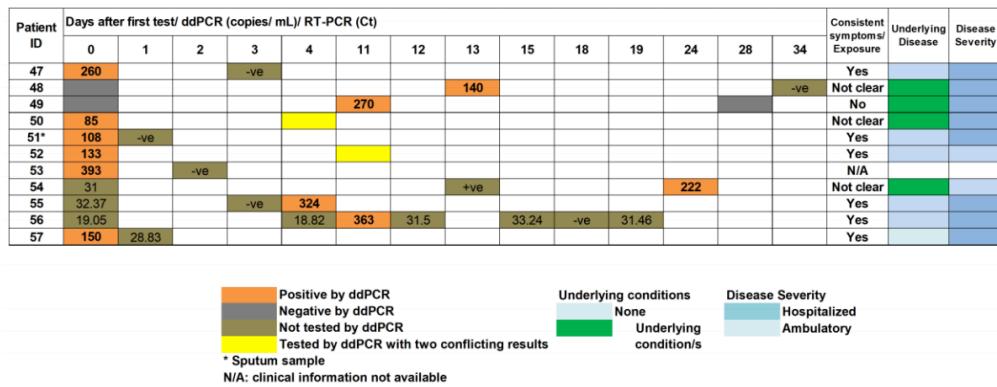


Figure 5. ddPCR sensitivity of detection in patients with consecutive negative results (47- 53) and negative specimens collected from known positive patients (54-57). ddPCR copies shown for the N1 target. -ve: negative result by the standard of care RT-PCR. +ve: positive results by the standard of care RT-PCR with no available Ct value

A POOLED TESTING STRATEGY FOR IDENTIFYING SARS-COV-2 AT LOW PREVALENCE

Mutesa L, Ndishimye P, Butera Y, Souopgui J, Uwineza A, Rutayisire R, Ndoricimpaye EL, Musoni E, Rujeni N, Nyatanyi T, Ntagwabira E, Semakula M, Musanabaganwa C, Nyamwasa D, Ndashimye M, Ujeneza E, Mwikarago IE, Muvunyi CM, Mazarati JB, Nsanzimana S, Turok N, Ndifon W.. Nature. 2020 Oct 21. doi: 10.1038/s41586-020-2885-5. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A multidisciplinary team affiliated with the Rwanda Joint Task Force on COVID-19 proposes an algorithm for pooled testing of SARS-CoV-2 that is "based on the geometry of a hypercube" (Figure 1) currently being trialed in Rwanda and South Africa. Proof of concept experiments demonstrated that positive specimens can be detected even after 100-fold dilution (Figure 2). Authors suggest this pooled testing strategy could reduce costs and maximize speed of large-scale testing to monitor and reduce further spread of infection, and repeated group testing could be performed to address the loss of sensitivity due to dilution.

ABSTRACT

Suppressing SARS-CoV-2 will likely require the rapid identification and isolation of infected individuals on an ongoing basis. Reverse transcription polymerase chain reaction (RT-PCR) tests are accurate but costly, making regular testing of every individual expensive. The costs are a challenge for all countries and particularly for developing countries. Cost reductions can be achieved by pooling (or combining) subsamples and testing them in groups 1-7. A balance must be struck between increasing the group size and retaining test sensitivity, since sample dilution increases the likelihood of false negatives for individuals with low viral load in the sampled region at the time of the test. Likewise, minimising the number of tests to reduce costs must be balanced against minimising the time testing takes to reduce the spread of infection. Here we propose an algorithm for pooling subsamples based on the geometry of a hypercube that, at low prevalence, accurately identifies infected individuals in a small number of tests and rounds of testing. We discuss the optimal group size and explain why, given the highly infectious nature of the disease, largely parallel searches are preferred. We report proof of concept experiments in which a positive subsample was detected even when diluted 100-fold with negative subsamples (cf. 30-fold to 48-fold dilution in Refs. 9-11). We quantify the loss of sensitivity due to dilution and discuss how it may be mitigated by frequent re-testing of groups, for example. With the use of these methods, the cost of mass testing could be reduced by a large factor which, furthermore, increases as the prevalence falls. Field trials of our approach are under way in Rwanda and South Africa. The use of group testing on a massive scale to closely and continually monitor infection in a population, along with rapid and effective isolation of infected people, provides a promising pathway to the longterm control of COVID-19.

FIGURES

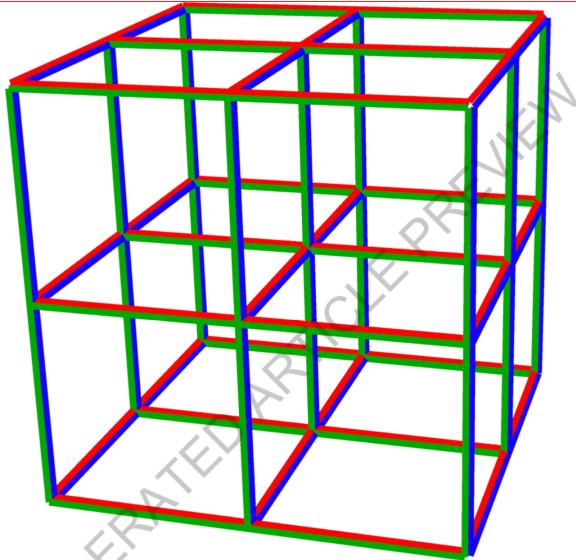


Figure 1. Subsample pooling in the hypercube algorithm. shown here for $D = L = 3$ and $N = 27 = 33$. Each vertex represents an individual. The hypercube is sliced into L slices, in each of the D principal directions. Samples from N/L individuals are pooled into a sample for each slice. For this example, the 3 sets of slices are shown in blue, red and green. If one infected individual is present, tests on each set of slices identify their coordinate in that direction. Hence only 9 tests uniquely identify them. As the viral prevalence p falls, the optimal group size N , the dimension D and the efficiency gain increase.

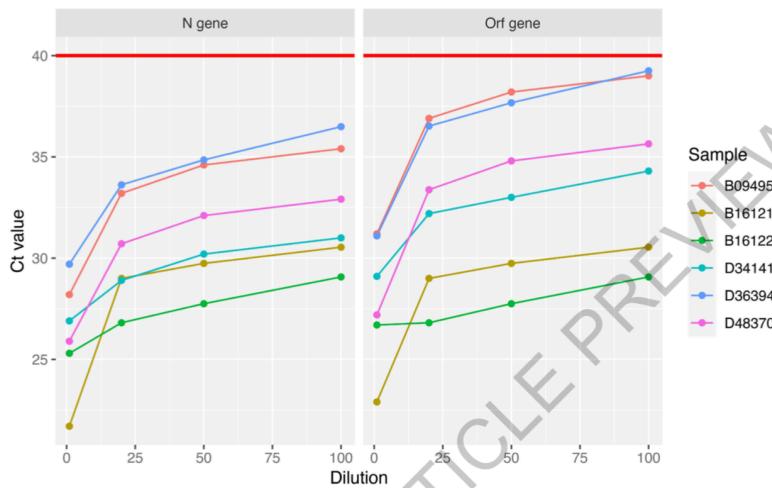


Figure 2. Positive specimens are detected after a 100-fold dilution. Each of six typical SARS-CoV-2-positive specimens was diluted through pooling with 19, 49, or 99 negative specimens. A Ct value (i.e., the PCR cycle at which the fluorescence signal generated by a specimen exceeds the baseline signal) was determined for each pool through RT-PCR amplification of the N and Orflab genes of SARS-CoV-2. For each gene, the Ct values are plotted against the dilution factor. The red horizontal lines indicate the Ct value (40) at or below which a specimen is considered positive. All Ct curves stay below the red lines even as the positive specimens are diluted 100-fold. (See Extended Data Figure 1 and Extended Data Table 2).

ACKNOWLEDGEMENTS

CONTRIBUTORS

Ankita Dharmendran
Ashley Kern
Danika Scott
Diep Nguyen
Julia Ghering
Sokena Zaidi
Veronica Graham

EDITORS

Alvin Rafou
Maggie Donovan
Maresa Woodfield

SENIOR EDITORS

Allison Hansen
Cameron Richards
Kyle Ellingsen

SENIOR EXECUTIVE EDITOR

Ann Staudinger Knoll

CHIEF EDITOR

Brennan Enright

ADVISOR

Will Smith