

The Daily COVID-19 Literature Surveillance Summary

September 21, 2020



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<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

Epidemiology

- A meta-analysis of 15 peer-reviewed articles found [recurrent COVID-19 infections](#) (confirmed via RT-PCR) were reported at a mean of 34 ± 10.5 days after full clinical recovery from an initial infection, but these patients also had persistent positive RT-PCR tests for a mean of 39 ± 9 days following their initial infection. Furthermore, a persistent positive test could be detected in patients without clinical relapse for 54 ± 24 days following initial infection.

Understanding the Pathology

- Investigators describe [post-mortem neuropathological findings in 2 patients with COVID-19 and neurological decompensation](#). Case 1 showed widespread multi-focal cortical infarcts, and case 2 showed brainstem encephalitis. Since viral RNA was not detected in the post mortem brain tissue in either case, these pathologies may not be a direct consequence of viral invasion.

Transmission & Prevention

- Researchers argue that [hurricane protection measures](#), such as evacuation and sheltering, cause people to gather together and is the paramount reason for the 3.7x increase in COVID-19 cases between May 1 and July 24, 2020. They suggest that during hurricanes, 1) people at risk should social distance, 2) officials should provide better communications for guidance on safe evacuation and sheltering, and that 3) we should "learn from each 2020 storm and refine operations."

Adjusting Practice During COVID-19

- Pharmacists and epidemiologists in Denmark conducted a population-based cohort study of 9,236 patients who tested positive for SARS-CoV-2 via PCR and found [no significant difference between NSAID users \(n=248\) and non-NSAID users \(n=8,988\)](#) regarding 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy. Authors suggest NSAID use during COVID-19 infection may have minimal effect on risk of mortality or adverse outcomes.
- A survey of 414 interventional cardiologists and cardiac catheterization laboratory (CCL) directors in the United States found a [55% decrease in percutaneous coronary interventions \(PCI\) and a 64% decrease in transcatheter aortic valve replacements](#) during March 15 to April 15, 2020 compared to 2019. Additionally, procedure deferral for angiogram/PCI for unstable angina, NSTEMI, and STEMI increased with greater inpatient COVID-19 burden and 40% of CCL directors reported increased cases of late presenting STEMIs. These findings suggest that patient fears due to the pandemic may be influencing their decisions to delay seeking urgent cardiac care.

R&D: Diagnosis & Treatments

- Editors from the New England Journal of Medicine had an audio discussion to discuss guidelines for [deployment of a COVID-19 vaccine](#) and discussed:
 - The recent pause of testing for one vaccine due to a participant contracting transverse myelitis shows that the safety protocols in place for vaccine development are functioning as planned.
 - The public does not need to apply causality hastily in these situations where an adverse effect comes to light in a trial.
 - Deployment guidelines, including prioritized groups, is not COVID-19 exceptionalism but standard for medical practice worldwide.
 - Public trust should be gained by transparency and honesty about vaccine development.

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EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

CURRENT META-ANALYSIS DOES NOT SUPPORT THE POSSIBILITY OF COVID-19 REINFECTIONS

Arafkas M, Khosrawipour T, Kocbach P, Zielinski K, Schubert J, Mikolajczyk A, Celinska M, Khosrawipour V.. J Med Virol. 2020 Sep 8. doi: 10.1002/jmv.26496. Online ahead of print.

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

BLUF

A meta-analysis of 15 peer-reviewed articles from the United States National Library of Medicine at the National Institutes of Health (Table 1) by physicians in the U.S. and Europe found recurrent COVID-19 infections (confirmed via RT-PCR) were reported at a mean of 34 ± 10.5 days after full clinical recovery from an initial infection, but these patients also had persistent positive RT-PCR tests for a mean of 39 ± 9 days following their initial infection; furthermore, a persistent positive test could be detected in patients without clinical relapse for 54 ± 24 days following initial infection (Figure 1). Authors highlight the complexity of differentiating prolonged infection versus reinfection with COVID-19, suggesting these findings may be useful for advancements in vaccine development.

ABSTRACT

BACKGROUND: COVID-19 reinfections could be a major aggravating factor in this current pandemic, as this would further complicate potential vaccine development and help to maintain worldwide virus pockets. To investigate this critical question, we conducted a clinical meta-analysis including all available currently reported cases of potential COVID-19 reinfections.

METHODS: We searched for all peer-reviewed articles in the search engine of the National Center for Biotechnology Information. While there are over 30.000 publications on COVID-19, only about 15 specifically target the subject of COVID-19 reinfections. Available patient data in these reports was analyzed for age, gender, time of reported relapse after initial infection and persistent COVID-19 positive PCR results. **RESULTS:** Following the first episode of infection, cases of clinical relapse are reported at 34 (mean) ± 10.5 days after full recovery. Patients with clinical relapse have persisting positive COVID-19 PCR testing results until 39 ± 9 days following initial positive testing. For patients without clinical relapse, positive testing was reported up to 54 ± 24 days. There were no reports of any clinical reinfections after a 70-day period following initial infection. **CONCLUSIONS:** Reports of COVID-19 reinfections all appear within a vulnerable timeframe, where affected patients are still tested positive for COVID-19 via PCR. According to our data, it is most likely that all reported cases of COVID-19 reinfections are in fact protracted initial infections. To diagnose a true COVID-19 reinfection, positive COVID-19 testing combined with recurrent clinical symptoms occurring outside of this timeframe is required. This article is protected by copyright. All rights reserved.

FIGURES

Cases [references in parenthesis]	Patients	Time of clinical relapse	Diagnostic confirmation	Outcome	Important Observations
Case Report, USA [11] (1 Patient)	82y, male, discharged	day 48 after initial presentation	Positive RT-PCR	cured	
Case Report, France [12]	84y, female	day 41 after initial presentation	positive RT-PCR	fatal	relapse during in- clinic rehabilitation
(3 Patients)			Negative COVID- 19 antibodies at relapse		
	90y, female, discharged	6-7 weeks after initial presentation	Positive RT-PCR	fatal	
	84y, female	day 22	CAT scan positive nasopharyngeal sample twice negative	fatal	relapse during in- clinic rehabilitation
Cumulative Case Report, France [13] (11 Patients)	P1 19y, female P2 32y, female P3 33y, female P4 43y, female P5 85y, male P6 54y, male P7 91y, female P8 55y, male P9 72y, male P10 73y, male P11 84y, female	day 26 day 37 day 27 day 24 day 44 day 45 day 25 day 27 day 27 day 24 day 49	positive RT- PCR tests both initially and during relapse; All patients showed typical signs of acute COVID-19 infection in CAT- scan during relapse	cured cured cured cured cured fatal cured cured fatal cured fatal	
Case report, China [14] (1 patient)	34y, male, discharged	No relapse	RT- PCR positive 59 days after initial symptoms	cured	RT- PCT positive after 59 days
Clinical study, China [15] (8 Patients)	All patients were asymptomatic CAT-scans showed no abnormalities		Readmission due to positive RT- PCR	cured	Patients were cleared after three consecutive tests were negative. In two cases positive results persisted for >90 days
In-vivo study [16]	Study specimen were macaques				Study suggests formation of neutralizing antibodies after COVID-19 infection
Clinical study on coronavirus family, USA [17] (191 patients)	Beta- coronaviruses HKU1 and OC43	34 weeks after enrollment/fir st infection [2]		No significant association between testing positive at least once and relapse of betacoronavirus	

Table 1. Available research data extracted from the United States National Library of Medicine at the National Institutes of Health; (y) indicates years, Reverse transcription polymerase chain reaction (RT-PCR).

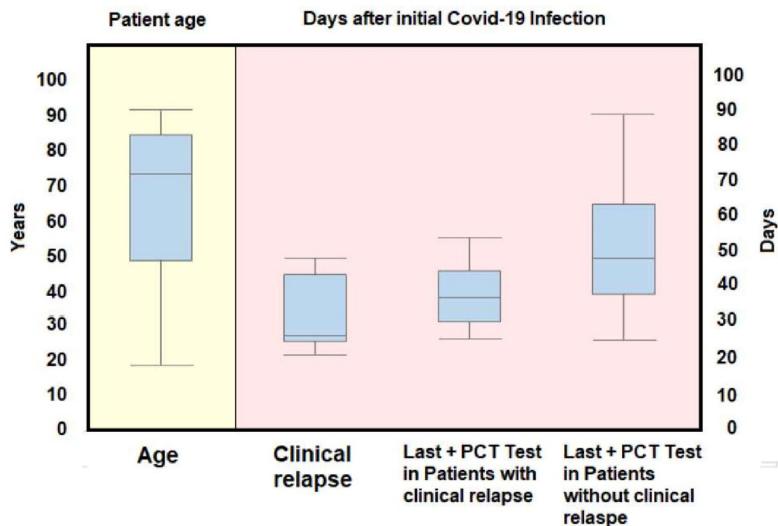


Figure 1. Meta-analysis of patients with clinical relapse and persisting COVID-19 positive test results. Age distribution is presented on the left side. Distribution of beginning of clinical relapse as well as last time of positive COVID-19 testing after initial diagnosis is shown on the right. Box-plot model including minimum value, first quartile, median value, third quartile, and maximum value.

UNDERSTANDING THE PATHOLOGY

NEUROPATHOLOGICAL FINDINGS IN TWO PATIENTS WITH FATAL COVID-19

Jensen MP, Le Quesne J, Officer-Jones L, Teodòsio A, Thaventhiran J, Ficken C, Goddard M, Smith C, Menon D, Allinson KSJ.. Neuropathol Appl Neurobiol. 2020 Sep 8. doi: 10.1111/nan.12662. Online ahead of print.

Level of Evidence: 5 - Case report

BLUF

Investigators affiliated with the Barts Health NHS Trust, the University of Cambridge, and the University of Glasgow describe post-mortem neuropathological findings in 2 patients with COVID-19 and neurological decompensation. Case 1 showed widespread multi-focal cortical infarcts and case 2 showed brainstem encephalitis. Since viral RNA was not detected in the post mortem brain tissue in either case, these pathologies may not be a direct consequence of viral invasion. These findings contribute information to the spectrum of neuropathology associated with COVID-19, although further research into the mechanisms behind such neuropathological findings is needed.

SUMMARY

Details on each case is provided below:

Case 1: 71 year-old male with a 2 week history of COVID-19 had diffuse bilateral gyral calcification without hemorrhage or mass lesions on CT imaging. Patient died about one month into admission. Post-mortem exam showed widespread multi-focal cortical infarcts containing extra-medullary megakaryocytes, associated with extensive perivascular calcification and cerebral amyloid angiopathy (Figure 1).

Case 2: 66 year-old male presented with multi-organ failure and neurological decline. MRI showed evidence of old subarachnoid hemorrhage. Patient died about one month into admission. Post-mortem exam showed a focus of extravasated blood over right lateral cerebellar hemisphere, a brainstem encephalitis centered on the dorsal medulla and a subacute regional infarct involving the cerebellar cortex (Figure 2).

ABSTRACT

AIMS: To describe the neuropathological findings in two cases of fatal Coronavirus Disease 2019 (COVID-19) with neurological decline. **METHODS:** Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection was confirmed in both patients by reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swabs antemortem. Coronial autopsies were performed on both patients and histological sampling of the brain was undertaken with a variety of histochemical and immunohistochemical stains. RNAscope *in situ* hybridisation (ISH) using the V-nCoV2019-S probe and RT-PCR SARS-CoV-2 ribonucleic acid (RNA) was performed in paraffin-embedded brain tissue sampled from areas of pathology. **RESULTS:** Case 1 demonstrated severe multifocal cortical infarction with extensive perivascular calcification and numerous megakaryocytes, consistent with a severe multi-territorial cerebral vascular injury. There was associated cerebral thrombotic microangiopathy. Case 2 demonstrated a brainstem encephalitis centred on the dorsal medulla and a subacute regional infarct involving the cerebellar cortex. In both cases ISH and RT-PCR for SARS-CoV-2 RNA were negative in tissue sampled from the area of pathology. **CONCLUSIONS:** Our case series adds calcifying cerebral cortical infarction with associated megakaryocytes and brainstem encephalitis to the spectrum of neuropathological findings that may contribute to the neurological decompensation seen in some COVID-19 patients. Viral RNA was not detected in post-mortem brain tissue, suggesting that these pathologies may not be a direct consequence of viral neuroinvasion and may represent para-infectious phenomena, relating to the systemic hyperinflammatory and hypercoagulable syndromes that both patients suffered.

FIGURES

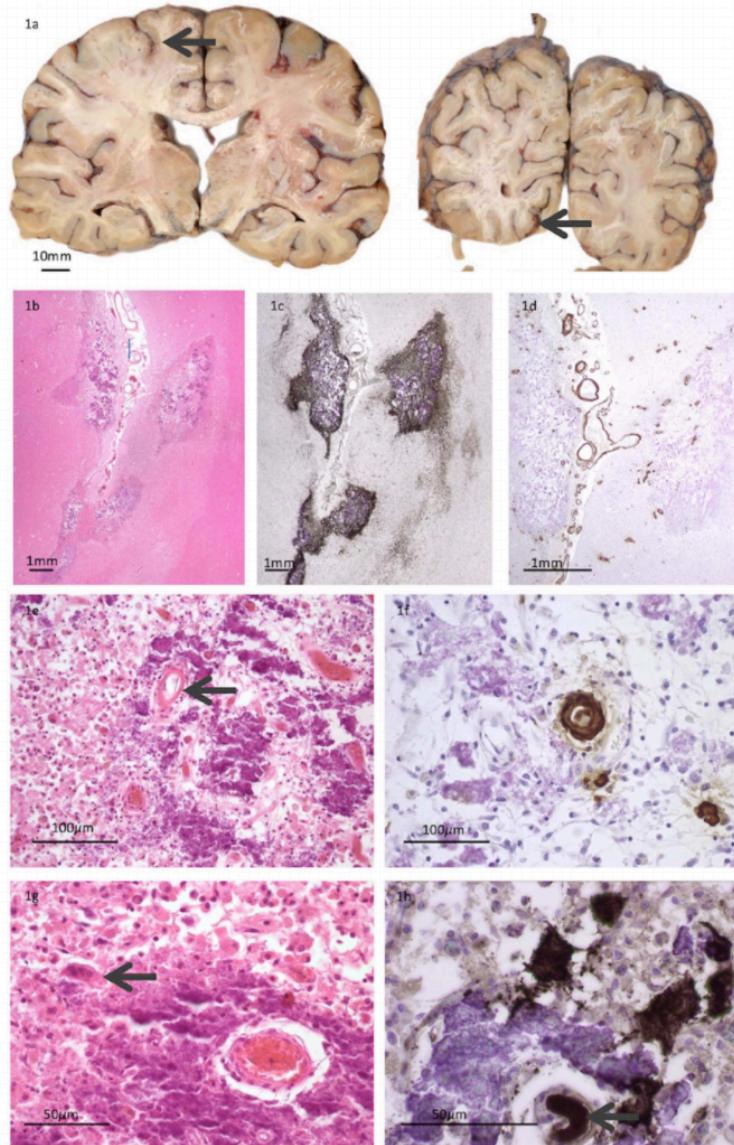


Figure 1. Coronal sections through the cerebrum showing thinning and calcification of the frontal and occipital cortices (scale bar 10mm) (1a) Multiple foci of calcified necrosis in cerebral cortex shown with H&E (1b) and CD68 immunostaining (1c) with beta-amyloid immunostaining demonstrating a background cerebral amyloid angiopathy (1d) (scale bar 1mm).Cerebral cortical necrosis with perivascular calcification and background amyloid angiopathy (arrow) (1e) confirmed with beta-amyloid immunostaining (1f). Perivascular megakaryocytes (1g), immunostained for CD61, also showing platelet microthrombi (arrow) (1h).Scale bars: 1a 10mm; 1b-d 1mm; 1e-f 100um; 1g-h 50um.

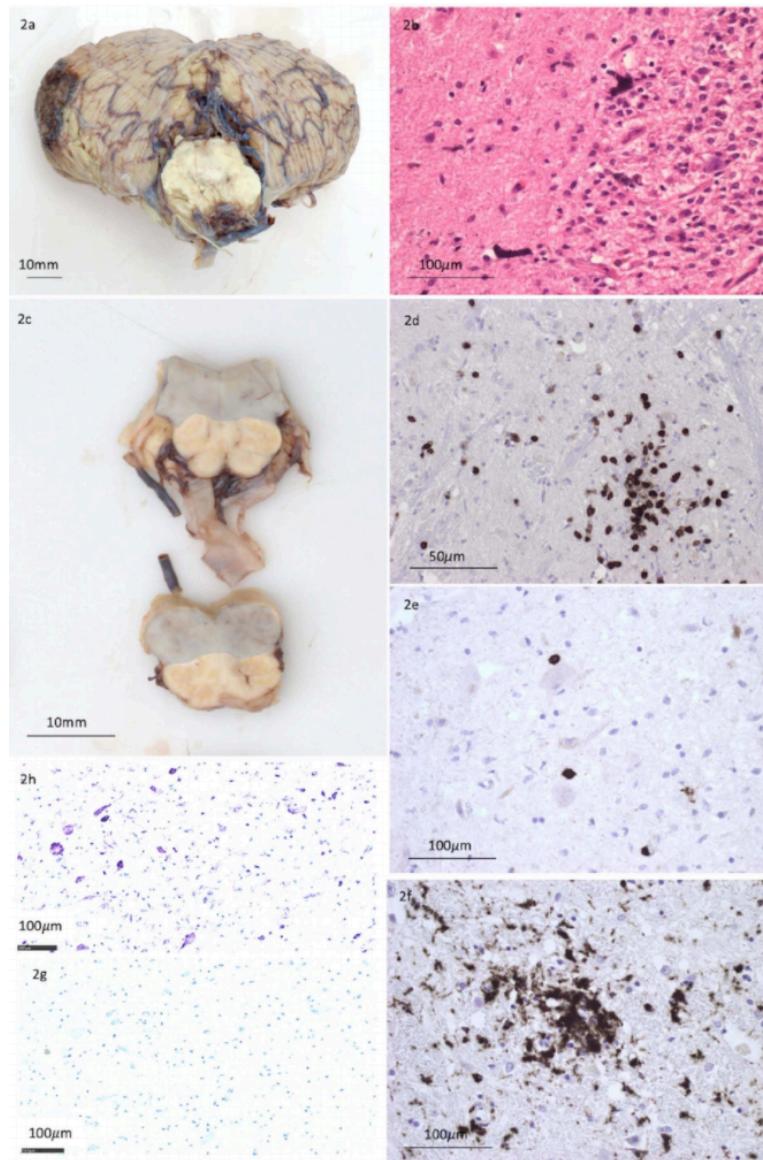


Figure 2. Brainstem and cerebellum showing haemorrhage over the right cerebellar hemisphere (2a). Histology of the cerebellar infarct showing calcification of Purkinje cells (2b). Axial sections of the medulla. The shaded area corresponds to the inflammation seen microscopically (2c). CD3 immunohistochemistry showing a moderate parenchymal infiltrate of T-lymphocytes (2d). CD3 immunohistochemistry showing T-cell neuronophagia (2e). CD68 immunohistochemistry showing microgliosis with microglial nodules (2f). ISH (RNAscope®) for SARS-CoV-2 genomic RNA showing no reactivity (2g). ISH for the mRNA encoding ubiquitin C demonstrating preservation of RNA (2h)

GENDER SUSCEPTIBILITY TO COVID-19: A REVIEW OF THE PUTATIVE ROLE OF SEX HORMONES AND X CHROMOSOME

Foresta C, Rocca MS, Di Nisio A.. J Endocrinol Invest. 2020 Sep 16. doi: 10.1007/s40618-020-01383-6. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review conducted by andrology experts at University of Padova in Italy proposes two mechanisms (Figure 1), in addition to differences in comorbidities, that could explain why COVID-19 may be less lethal in females vs males (analysis of 239,709 patients in Italy: 17.7% lethality in males and 10.8% in females): (1) females may have a larger reservoir of ACE2 expression due to increased estrogen or skewed X chromosome inactivation, and thus are able to better maintain their RAS-regulatory axis after viral infection, as well as (2) having low TMPRSS2 levels (protease used for SARS-CoV-2 cell entry) due to low baseline androgen levels. These two hypotheses could contribute to why morbidity and mortality are greater in males than in females.

ABSTRACT

BACKGROUND: The recent emergence of COVID-19 poses a global health emergency. One of the most frequently reported data is sex-related severity and mortality: according to the last available analysis on 239,709 patients in Italy, lethality is 17.7% in men and 10.8% in women, with 59% of total deaths being men. Interestingly, the infection rate is lower in males than in females, with 45.8% and 54.2% of positive cases, respectively, suggesting that gender-related factor may worsen disease evolution. A tentative hypothesis to explain these findings is the role of angiotensin-converting enzyme 2 (ACE2) and serine protease TMPRSS2 involved in viral infection. **PURPOSE:** In this review, we summarize the available evidence pointing to gender-related differences in ACE2 and TMPRSS2 expression, from both genetic and endocrine points of view. **RESULTS:** Altogether, available evidence points toward two not-mutually exclusive mechanisms in gender susceptibility to COVID-19 by sex hormonal regulation of ACE2 and TMPRSS2. On one hand, ACE2 expression could be increased in women, either by estrogens or constitutively by X chromosome inactivation escape or by reduced methylation, providing a larger reservoir of ACE2 to maintain the fundamental equilibrium of RAS regulatory axis. On the other, low levels of androgens in women may keep at low levels TMPRSS2 expression, representing a further protective factor for the development of COVID-19 infection, despite the increased expression of ACE2, which represents the Trojan horse for SARS-CoV-2 entry. **CONCLUSIONS:** Both mechanisms consistently point to the role of sex hormones and sex chromosomes in the differential severity and lethality of COVID-19 in men and women.

FIGURES

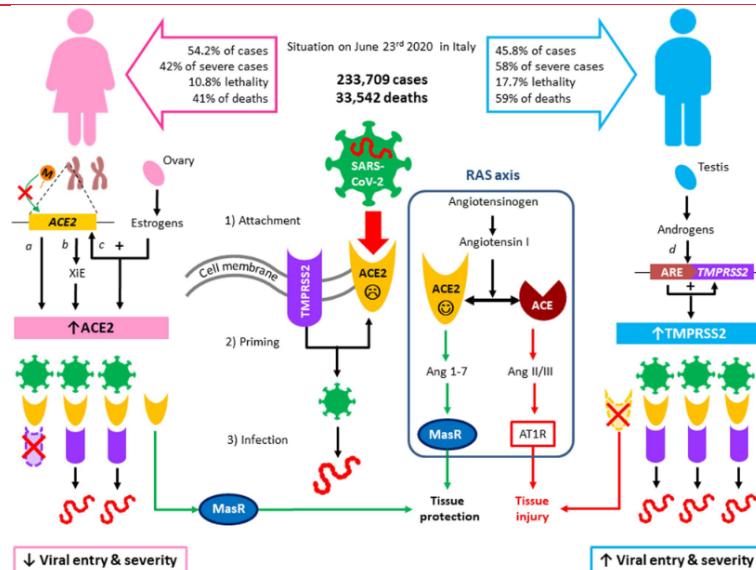


Figure 1. Proposed mechanisms of sex-related susceptibility to COVID-19. On the top of the figure, epidemiological data from the Italian Ministry of Health are reported, with respective gender distribution of cases and deaths. A schematic representation of SARS-CoV-2 mechanism of infection is reported: after binding of viral spike proteins to angiotensin-converting enzyme 2 (ACE2) (1), transmembrane serine protease-2 (TMPRSS2) primes S protein (2), favoring viral entry and infection (3). ACE2 is also crucial in tissue response to viral infection, as it is typically involved in the renin-angiotensin system (RAS), where it converts angiotensin I into angiotensin 1-7 (Ang 1-7), which binds to Mas receptor (MasR) and favors tissue protection, mainly by hypotensive and anti-inflammatory pathways. Conversely, ACE converts angiotensin I into angiotensin II/III (Ang II/III) that binds to angiotensin II type 1 receptor (AT1R), favoring tissue injury. On the left, the main mechanisms involved in reduced COVID-19 severity and mortality in women are proposed: (a) ACE2 methylation (M, orange dot) is reduced in women, resulting in higher ACE2 expression; (b) ACE2 is located on the X chromosome, which in females is present in two copies, in a region of the short arm where 15–30% of genes undergoes X inactivation Escape (XiE); (c) estrogens, produced by the ovary, promote ACE2 expression. Increased levels of ACE2 would provide a larger pool for tissue protection (green arrows) after viral entry. On the right, mechanisms involved in male increased susceptibility: (d) androgens, produced by testes, bind to the androgen receptor and are recognized by androgen-responsive elements (ARE) in the promoter of TMPRSS2, leading to increased expression, which in turn favors viral entry in males, whereas low levels of androgens in women may keep at low levels TMPRSS2 expression, representing a further protective factor for the development of COVID-19 infection. The lack of increased ACE2 pool in men due to low estrogens would favor the ACE pathway (red arrows) in the RAS axis, which further promotes tissue injury and disease severity in men, compared with women with the same viral load.

TRANSMISSION & PREVENTION

PREVENTION IN THE COMMUNITY

MASS EVENTS TRIGGER MALTA'S SECOND PEAK AFTER INITIAL SUCCESSFUL PANDEMIC SUPPRESSION

Cuschieri S, Balzan M, Gauci C, Aguis S, Grech V.. J Community Health. 2020 Sep 16. doi: 10.1007/s10900-020-00925-6.
Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

A review article by medical professionals and public health experts from Malta discusses how the island's initial success in handling the first wave of COVID-19 has now deteriorated to rapidly increasing case numbers after loosening tourism restrictions beginning July 1st, with two mass events illustrated in Figures 1 & 2. These events have led to re-implementation of restrictions with social gathering limits, mandatory mask wearing, swabbing, and contact-tracing to decrease the high community transmission and active cases, further highlighting the need for public restrictions to protect the health of the population hand-in-hand with cooperation from the public to curb resurgences in the form of a second COVID-19 wave.

ABSTRACT

The second COVID-19 wave is sweeping the globe as restrictions are lifted. Malta, the 'poster child of Europe's COVID-19 first wave success' also fell victim shortly after it welcomed the first tourists on 1st of July 2020. Only four positive cases were reported over the successive 15 days. Stability was disrupted when two major mass events were organized despite various health professional warnings. In a matter of few just days, daily cases rose to two-digit figures, with high community transmission, a drastic rise in active cases, and a rate per hundred thousand in Europe second only to Spain. Frontliners were swamped with swabbing requests while trying to sustain robust case management, contact tracing and follow-up. Indeed, the number of hospitalizations and the need for intensive ventilation increased. Despite the initial cases were among young adults, within weeks a small spill off on the more elderly population was observed. Restrictions were re-introduced including mandatory mask wearing in specific locations and capping of the total number of people in a single gathering. Malta is an island and the potential for containment would have been relatively simple and effective and permitting mass gatherings was unwise. Protecting the health of the population should take centre stage while carrying out extensive testing, contact tracing and surveillance. Containment and mitigation along with public cooperation is the key to curbing resurgences especially with the influenza season around the corner.

FIGURES

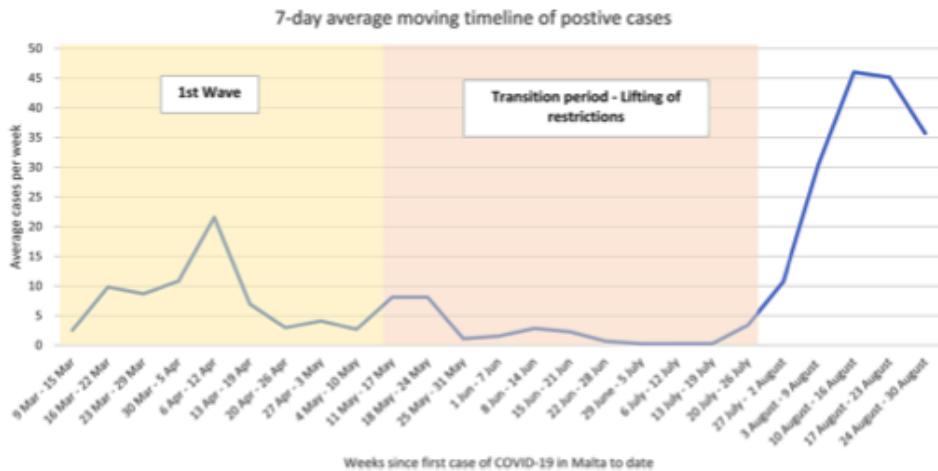


Fig. 1 Distribution of the 7-day average moving timeline of the positive cases since March 2020

Fig 1: Distribution of the 7-day average moving timeline of the positive cases since March 2020.

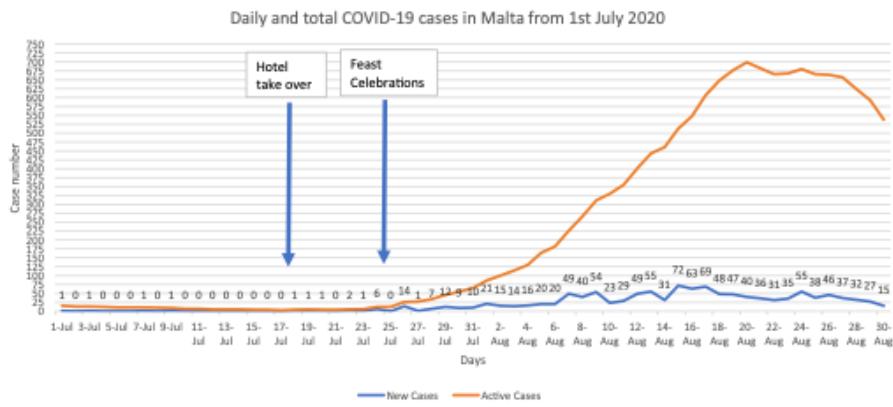


Fig. 2 Distribution of the daily and total active COVID-19 cases in Malta as of 1st July 2020 [35]. *As reported by the official COVID-19 figures by Ministry of Health. The reminder clusters are as reported during the weekly COVID-19 Media Briefing

Fig 2: Distribution of the daily and total active COVID-19 cases in Malta as of 1st July 2020. *As reported by the official COVID-19 figures by Ministry of Health. The reminder clusters are as reported during the weekly COVID-19 Media Briefing.

CASCADING RISKS OF COVID-19 RESURGENCE DURING AN ACTIVE 2020 ATLANTIC HURRICANE SEASON

Shultz JM, Fugate C, Galea S. JAMA. 2020 Sep 8;324(10):935-936. doi: 10.1001/jama.2020.15398.

Level of Evidence: Other - Expert Opinion

BLUF

Researchers affiliated with University of Miami, Craig Fugate Consulting LLC, and, Boston University argue that hurricane protection measures, such as evacuation and sheltering, cause people to gather together and is the paramount reason for the 3.7x increase in COVID-19 cases between May 1 and July 24, 2020. They suggest that during hurricanes, 1) people at risk should social distance, 2) officials should provide better communications for guidance on safe evacuation and sheltering, and that 3) we should "learn from each 2020 storm and refine operations."

ADJUSTING PRACTICE DURING COVID-19

ADVERSE OUTCOMES AND MORTALITY IN USERS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS WHO TESTED POSITIVE FOR SARS-COV-2: A DANISH NATIONWIDE COHORT STUDY

Lund LC, Kristensen KB, Reilev M, Christensen S, Thomsen RW, Christiansen CF, Støvring H, Johansen NB, Brun NC, Hallas J, Pottegård A.. PLoS Med. 2020 Sep 8;17(9):e1003308. doi: 10.1371/journal.pmed.1003308. eCollection 2020 Sep.

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

BLUF

Pharmacists and epidemiologists in Denmark conducted a population-based cohort study of 9,236 patients (Table 1) who tested positive for SARS-CoV-2 via PCR from February 27 to April 29, 2020 and found no significant difference between NSAID users ($n=248$) and non-NSAID users ($n=8,988$) regarding 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy (Tables 2, 3). Authors suggest NSAID use during COVID-19 infection may have minimal effect on risk of mortality or adverse outcomes.

ABSTRACT

BACKGROUND: Concerns over the safety of non-steroidal anti-inflammatory drug (NSAID) use during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been raised. We studied whether use of NSAIDs was associated with adverse outcomes and mortality during SARS-CoV-2 infection. **METHODS AND FINDINGS:** We conducted a population-based cohort study using Danish administrative and health registries. We included individuals who tested positive for SARS-CoV-2 during the period 27 February 2020 to 29 April 2020. NSAID users (defined as individuals having filled a prescription for NSAIDs up to 30 days before the SARS-CoV-2 test) were matched to up to 4 non-users on calendar week of the test date and propensity scores based on age, sex, relevant comorbidities, and use of selected prescription drugs. The main outcome was 30-day mortality, and NSAID users were compared to non-users using risk ratios (RRs) and risk differences (RDs). Secondary outcomes included hospitalization, intensive care unit (ICU) admission, mechanical ventilation, and acute renal replacement therapy. A total of 9,236 SARS-CoV-2 PCR-positive individuals were eligible for inclusion. The median age in the study cohort was 50 years, and 58% were female. Of these, 248 (2.7%) had filled a prescription for NSAIDs, and 535 (5.8%) died within 30 days. In the matched analyses, treatment with NSAIDs was not associated with 30-day mortality (RR 1.02, 95% CI 0.57 to 1.82, $p = 0.95$; RD 0.1%, 95% CI -3.5% to 3.7%, $p = 0.95$), risk of hospitalization (RR 1.16, 95% CI 0.87 to 1.53, $p = 0.31$; RD 3.3%, 95% CI -3.4% to 10%, $p = 0.33$), ICU admission (RR 1.04, 95% CI 0.54 to 2.02, $p = 0.90$; RD 0.2%, 95% CI -3.0% to 3.4%, $p = 0.90$), mechanical ventilation (RR 1.14, 95% CI 0.56 to 2.30, $p = 0.72$; RD 0.5%, 95% CI -2.5% to 3.6%, $p = 0.73$), or renal replacement therapy (RR 0.86, 95% CI 0.24 to 3.09, $p = 0.81$; RD -0.2%, 95% CI -2.0% to 1.6%, $p = 0.81$). The main limitations of the study are possible exposure misclassification, as not all individuals who fill an NSAID prescription use the drug continuously, and possible residual confounding by indication, as NSAIDs may generally be prescribed to healthier individuals due to their side effects, but on the other hand may also be prescribed for early symptoms of severe COVID-19. **CONCLUSIONS:** Use of NSAIDs was not associated with 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy in Danish individuals who tested positive for SARS-CoV-2. **TRIAL REGISTRATION:** The European Union electronic Register of Post-Authorisation Studies EUPAS34734.

FIGURES

Characteristic	Unmatched			Matched		
	NSAID users (n = 248)	Non-users (n = 8,988)	SMD	NSAID users (n = 224)	Non-users (n = 896)	SMD
Age in years, median (IQR)	55 (43–64)	49 (35–63)	0.24	54 (43–64)	54 (41–66)	0.00
Sex male	99 (39.9)	3,793 (42.2)	0.05	90 (40.2)	375 (41.9)	0.03
Prescription drugs*						
Antihypertensive	72 (29.0)	2,221 (24.7)	0.10	62 (27.7)	233 (26.0)	0.04
Antidiabetic drug	26 (10.5)	680 (7.6)	0.10	21 (9.4)	78 (8.7)	0.02
Low-dose aspirin	16 (6.5)	532 (5.9)	0.02	15 (6.7)	47 (5.2)	0.06
Immunosuppressant	(n < 5)	63 (0.7)	0.05	(n < 5)	6 (0.7)	0.07
Opioid	59 (23.8)	950 (10.6)	0.36	46 (20.5)	172 (19.2)	0.03
Z-drug	8 (3.2)	279 (3.1)	0.01	7 (3.1)	28 (3.1)	0.00
Benzodiazepine	10 (4.0)	378 (4.2)	0.01	10 (4.5)	38 (4.2)	0.01
First generation antipsychotic	(n < 5)	58 (0.6)	0.03	(n < 5)	(n < 5)	0.02
Second generation antipsychotic	(n < 5)	224 (2.5)	0.10	(n < 5)	11 (1.2)	0.03
Systemic glucocorticoid	19 (7.7)	431 (4.8)	0.12	15 (6.7)	65 (7.3)	0.02
Inhaled corticosteroid	27 (10.9)	625 (7.0)	0.14	21 (9.4)	92 (10.3)	0.03
Prior diagnoses**						
Asthma	16 (6.5)	613 (6.8)	0.01	13 (5.8)	47 (5.2)	0.02
COPD	11 (4.4)	368 (4.1)	0.02	9 (4.0)	35 (3.9)	0.01
Cardiovascular disease	28 (11.3)	1,238 (13.8)	0.08	23 (10.3)	91 (10.2)	0.00
Ischemic stroke	9 (3.6)	376 (4.2)	0.03	8 (3.6)	30 (3.3)	0.01
Chronic kidney failure	(n < 5)	126 (1.4)	0.11	(n < 5)	(n < 5)	0.06
Liver disease	(n < 5)	125 (1.4)	0.02	(n < 5)	10 (1.1)	0.06
Alcohol-related disorders	5 (2.0)	239 (2.7)	0.04	(n < 5)	12 (1.3)	0.04
Dementia	(n < 5)	154 (1.7)	0.08	(n < 5)	10 (1.1)	0.02
Cancer	21 (8.5)	646 (7.2)	0.05	16 (7.1)	64 (7.1)	0.00
Overweight or obesity	33 (13.3)	765 (8.5)	0.15	29 (12.9)	111 (12.4)	0.02
Hemiplegia and paraplegia	(n < 5)	35 (0.4)	0.00	(n < 5)	(n < 5)	0.02
Osteoarthritis	47 (19.0)	1,054 (11.7)	0.20	37 (16.5)	143 (16.0)	0.02
Rheumatoid arthritis	17 (6.9)	308 (3.4)	0.16	13 (5.8)	51 (5.7)	0.00
Dysmenorrhea	7 (2.8)	62 (0.7)	0.16	(n < 5)	8 (0.9)	0.00

Data are given as number (percent) unless otherwise indicated.

*Defined as 1 or more prescription fills during the period 365 days to 1 day prior to cohort entry.

**Defined as 1 or more discharge diagnoses assigned up to 1 day prior to cohort entry.

COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; SMD, standardized mean difference.

Table 1. Baseline characteristics in the unmatched and propensity-score-matched cohorts.

Outcome	NSAID users		Non-users		Comparison			
	Number of events/ sample size	Risk (%) (95% CI)	Number of events/ sample size	Risk (%) (95% CI)	Risk difference (%) (95% CI)	p- Value	Risk ratio (95% CI)	p- Value
Unmatched cohort								
Death	14/248	5.6 (2.8, 8.5)	521/8,988	5.8 (5.3, 6.3)	-0.2 (-3.1, 2.8)	0.92	0.97 (0.58, 1.63)	0.92
Hospitalization*	56/228	24.6 (19.0, 30.2)	1,456/8,414	17.3 (16.5, 18.1)	7.3 (1.6, 12.9)	0.01	1.42 (1.13, 1.79)	<0.01
ICU admission*	11/247	4.5 (1.9, 7.0)	279/8,956	3.1 (2.8, 3.5)	1.3 (-1.3, 3.9)	0.31	1.43 (0.79, 2.58)	0.23
Mechanical ventilation*	10/248	4.0 (1.6, 6.5)	225/8,970	2.5 (2.2, 2.8)	1.5 (-0.9, 4.0)	0.23	1.61 (0.86, 2.99)	0.13
Renal replacement therapy*	n < 5/248	—**	—**	—**	0.6 (-0.8, 1.9)	0.42	1.87 (0.59, 5.94)	0.29
Matched cohort								
Death	14/224	6.3 (3.1, 9.4)	55/896	6.1 (4.4, 7.8)	0.1 (-3.5, 3.7)	0.95	1.02 (0.57, 1.82)	0.95
Hospitalization*	50/204	24.5 (18.6, 30.4)	175/826	21.2 (18.1, 24.3)	3.3 (-3.4, 10.0)	0.33	1.16 (0.87, 1.53)	0.31
ICU admission*	11/223	4.9 (2.1, 7.8)	42/889	4.7 (3.2, 6.2)	0.2 (-3.0, 3.4)	0.90	1.04 (0.54, 2.02)	0.90
Mechanical ventilation*	10/224	4.5 (1.8, 7.2)	35/891	3.9 (2.5, 5.3)	0.5 (-2.5, 3.6)	0.73	1.14 (0.56, 2.30)	0.72
Renal replacement therapy*	n < 5/224	—**	—**	—**	-0.2 (-2.0, 1.6)	0.81	0.86 (0.24, 3.09)	0.81

NSAID use was defined as having an NSAID prescription filled within 30 days prior to the date of cohort entry.

*Patients with a secondary outcome occurring during the exclusion assessment window were excluded, resulting in exclusion of n = 594 patients for hospitalization, n = 33 for ICU admission, n = 18 for mechanical ventilation, and n = 6 for renal replacement therapy in unmatched cohorts, and n = 90, n = 8, n = 5, and n < 5, respectively, in matched cohorts.

**Censored to preserve anonymity for counts n < 5.

ICU, intensive care unit; NSAID, non-steroidal anti-inflammatory drug.

Table 2. Association between current NSAID use and 30-day mortality, hospitalization, ICU admission, mechanical ventilation, and renal replacement therapy in unmatched and propensity-score-matched cohorts.

Subgroup	Outcome	Risk (%) (95% CI)		Comparison			
		NSAID users	Non-users	Risk difference (%) (95% CI)	p-Value	Risk ratio (95% CI)	p-Value
Age < 65 years	Death	1.2 (-0.4, 2.8)	0.3 (-0.1, 0.7)	0.8 (-0.8, 2.5)	0.31	3.76 (0.53, 26.56)	0.18
	Hospitalization	16.3 (10.6, 21.9)	11.2 (8.5, 13.9)	5.1 (-1.2, 11.3)	0.11	1.45 (0.95, 2.22)	0.08
	ICU admission	1.2 (-0.4, 2.8)	2.5 (1.1, 3.8)	-1.3 (-3.4, 0.8)	0.22	0.47 (0.11, 2.07)	0.43
	Mechanical ventilation	1.2 (-0.4, 2.8)	1.8 (0.7, 3.0)	-0.7 (-2.7, 1.3)	0.50	0.63 (0.14, 2.87)	0.55
	Renal replacement therapy	0.6 (-0.6, 1.7)	1.1 (0.1, 2.1)	-0.5 (-2.0, 1.0)	0.52	0.54 (0.06, 4.67)	0.57
Age 65+ years	Death	23.5 (11.8, 35.3)	21.6 (16.0, 27.3)	1.9 (-11.1, 14.9)	0.77	1.09 (0.62, 1.91)	0.77
	Hospitalization	60.5 (44.8, 76.3)	54.2 (46.0, 62.3)	6.4 (-11.2, 23.9)	0.48	1.12 (0.83, 1.51)	0.47
	ICU admission	18.0 (7.2, 28.8)	10.9 (6.6, 15.2)	7.1 (-4.4, 18.6)	0.22	1.65 (0.81, 3.37)	0.17
	Mechanical ventilation	15.7 (5.6, 25.8)	9.5 (5.5, 13.6)	6.1 (-4.6, 16.9)	0.26	1.64 (0.76, 3.53)	0.20
	Renal replacement therapy	3.9 (-1.5, 9.3)	2.9 (0.5, 5.2)	1.1 (-4.8, 6.9)	0.72	1.37 (0.28, 6.73)	0.70
Female	Death	4.5 (1.0, 8.0)	4.8 (2.8, 6.8)	-0.3 (-4.4, 3.7)	0.88	0.93 (0.38, 2.27)	0.88
	Hospitalization	21.7 (14.6, 28.8)	14.0 (10.5, 17.4)	7.7 (-0.2, 15.6)	0.05	1.55 (1.03, 2.34)	0.03
	ICU admission	1.5 (-0.6, 3.6)	1.3 (0.4, 2.3)	0.1 (-2.1, 2.4)	0.90	1.11 (0.23, 5.29)	0.90
	Mechanical ventilation	1.5 (-0.6, 3.6)	0.6 (-0.1, 1.2)	0.9 (-1.2, 3.1)	0.41	2.59 (0.44, 15.36)	0.30
	Renal replacement therapy	—	0.8 (0.0, 1.5)	—	—	—	—
Male	Death	8.9 (3.0, 14.8)	8.0 (5.1, 10.9)	0.9 (-5.7, 7.5)	0.79	1.11 (0.52, 2.37)	0.79
	Hospitalization	29.3 (19.0, 39.7)	31.9 (26.3, 37.5)	-2.6 (-14.3, 9.2)	0.67	0.92 (0.62, 1.36)	0.67
	ICU admission	10.1 (3.8, 16.4)	9.5 (6.2, 12.8)	0.6 (-6.5, 7.7)	0.86	1.07 (0.52, 2.17)	0.86
	Mechanical ventilation	8.9 (3.0, 14.8)	8.6 (5.4, 11.8)	0.3 (-6.4, 7.0)	0.94	1.03 (0.48, 2.20)	0.94
	Renal replacement therapy	3.3 (-0.4, 7.1)	2.7 (0.6, 4.7)	0.7 (-3.6, 4.9)	0.76	1.25 (0.32, 4.83)	0.75
No history of cardiovascular disease	Death	4.5 (1.6, 7.3)	3.5 (2.2, 4.8)	1.0 (-2.1, 4.1)	0.53	1.29 (0.62, 2.69)	0.50
	Hospitalization	23.9 (17.8, 30.1)	19.3 (16.2, 22.5)	4.6 (-2.3, 11.5)	0.19	1.24 (0.91, 1.68)	0.17
	ICU admission	4.5 (1.6, 7.3)	4.1 (2.6, 5.7)	0.4 (-2.9, 3.6)	0.83	1.09 (0.52, 2.28)	0.83
	Mechanical ventilation	4.0 (1.3, 6.7)	3.5 (2.1, 4.9)	0.5 (-2.6, 3.6)	0.75	1.14 (0.51, 2.52)	0.75
	Renal replacement therapy	1.0 (-0.4, 2.4)	1.2 (0.3, 2.2)	-0.2 (-1.9, 1.4)	0.77	0.80 (0.16, 3.90)	0.78
History of cardiovascular disease	Death	21.7 (4.5, 39.0)	29.7 (19.0, 40.4)	-7.9 (-28.0, 12.1)	0.44	0.73 (0.31, 1.73)	0.48
	Hospitalization	31.3 (7.8, 54.7)	42.4 (29.2, 55.7)	-11.2 (-37.6, 15.2)	0.41	0.74 (0.33, 1.63)	0.45
	ICU admission	9.1 (-3.2, 21.4)	10.2 (3.8, 16.7)	-1.1 (-14.8, 12.5)	0.87	0.89 (0.20, 3.86)	0.88
	Mechanical ventilation	8.7 (-3.1, 20.5)	7.9 (2.2, 13.5)	0.8 (-12.1, 13.7)	0.90	1.11 (0.24, 5.02)	0.90
	Renal replacement therapy	4.3 (-4.2, 12.9)	4.4 (0.1, 8.7)	-0.1 (-9.5, 9.3)	0.98	0.98 (0.11, 8.44)	0.98
Not healthcare professional	Death	7.0 (3.3, 10.7)	8.0 (5.7, 10.2)	-0.9 (-5.3, 3.4)	0.67	0.88 (0.49, 1.60)	0.68
	Hospitalization	27.9 (21.0, 34.7)	26.4 (22.5, 30.4)	1.4 (-6.5, 9.3)	0.72	1.05 (0.79, 1.41)	0.72
	ICU admission	5.4 (2.2, 8.7)	6.1 (4.1, 8.1)	-0.7 (-4.5, 3.1)	0.73	0.89 (0.45, 1.76)	0.73
	Mechanical ventilation	4.9 (1.8, 8.0)	5.1 (3.2, 6.9)	-0.2 (-3.8, 3.4)	0.92	0.96 (0.46, 2.00)	0.92
	Renal replacement therapy	1.1 (-0.4, 2.6)	2.1 (0.8, 3.4)	-1.0 (-3.0, 1.0)	0.32	0.52 (0.12, 2.37)	0.40

NSAID use was defined as a filled prescription within 30 days prior to the date of cohort entry.

ICU, intensive care unit; NSAID, non-steroidal anti-inflammatory drug.

Table 3. Association between current NSAID use and 30-day mortality, hospitalization, ICU admission, mechanical ventilation, and renal replacement therapy in propensity-score-matched cohorts according to subgroups of interest.

MEDICAL SUBSPECIALTIES

CARDIOLOGY

CARDIAC PROCEDURAL DEFERRAL DURING THE CORONAVIRUS (COVID-19) PANDEMIC

Yong CM, Ang L, Welt FGP, Gummidipundi S, Henry TD, Pinto DS, Cox D, Wang P, Asch S, Mahmud E, Fearon WF; Society for Cardiovascular Angiography and Interventions (SCAI) and the American College of Cardiology (ACC) Interventional Council... Catheter Cardiovasc Interv. 2020 Sep 3. doi: 10.1002/ccd.29262. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Investigators within the field of cardiology performed a survey distributed in May, 2020 of 414 interventional cardiologists and cardiac catheterization laboratory (CCL) directors in the United States. They found a 55% decrease in percutaneous coronary interventions (PCI) and a 64% decrease in transcatheter aortic valve replacements during March 15 to April 15, 2020 compared to 2019. Additionally, procedure deferral for angiogram/PCI for unstable angina, NSTEMI, and STEMI increased with greater inpatient COVID-19 burden (Figures 1-2) and 40% of CCL directors reported increased cases of late presenting STEMIs (Figure 3). These findings suggest that patient fears due to the pandemic may be influencing their decisions to delay seeking urgent cardiac care.

ABSTRACT

We aimed to examine factors impacting variability in cardiac procedural deferral during the COVID-19 pandemic and assess cardiologists' perspectives regarding its implications. Unprecedented cardiac procedural deferral was implemented nationwide during the COVID-19 pandemic. A web-based survey was administered by Society for Cardiovascular Angiography and Interventions and the American College of Cardiology Interventional Council to cardiac catheterization laboratory (CCL) directors and interventional cardiologists across the United States during the COVID-19 pandemic. Among 414 total responses, 48 states and 360 unique cardiac catheterization laboratories were represented, with mean inpatient COVID-19 burden 16.4 \pm 21.9%. There was a spectrum of deferral by procedure type, varying by both severity of COVID-19 burden and procedural urgency ($p < .001$). Percutaneous coronary intervention volumes dropped by 55% ($p < .0001$) and transcatheter aortic valve replacement volumes dropped by 64% ($p = .004$), with cardiologists reporting an increase in late presenting ST-elevation myocardial infarctions and deaths among patients waiting for transcatheter aortic valve replacement. Almost 1/3 of catheterization laboratories had at least one interventionalist testing positive for COVID-19. Salary reductions did not influence procedural deferral or speed of reinstituting normal volumes. Pandemic preparedness improved significantly over time, with the most pressing current problems focused on inadequate testing and staff health risks. During the COVID-19 pandemic, cardiac procedural deferrals were associated with procedural urgency and severity of hospital COVID-19 burden. Yet patients did not appear to be similarly influenced, with cardiologists reporting increases in late presenting ST-elevation myocardial infarctions independent of local COVID-19 burden. The safety and importance of seeking healthcare during this pandemic deserves emphasis.

FIGURES

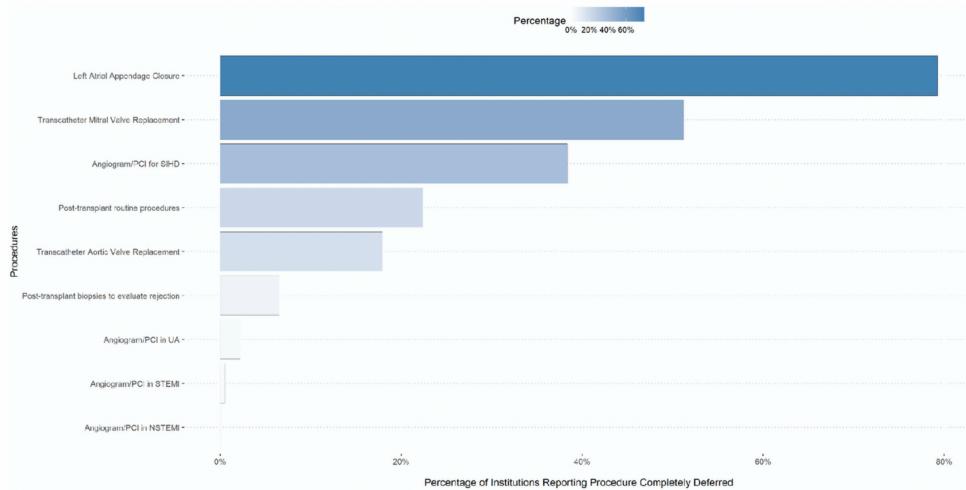


Figure 1. Procedural deferral across the spectrum of catheterization laboratory procedures. Percentage of institutions reporting 100% deferral of each procedure type [Color figure can be viewed at wileyonlinelibrary.com]

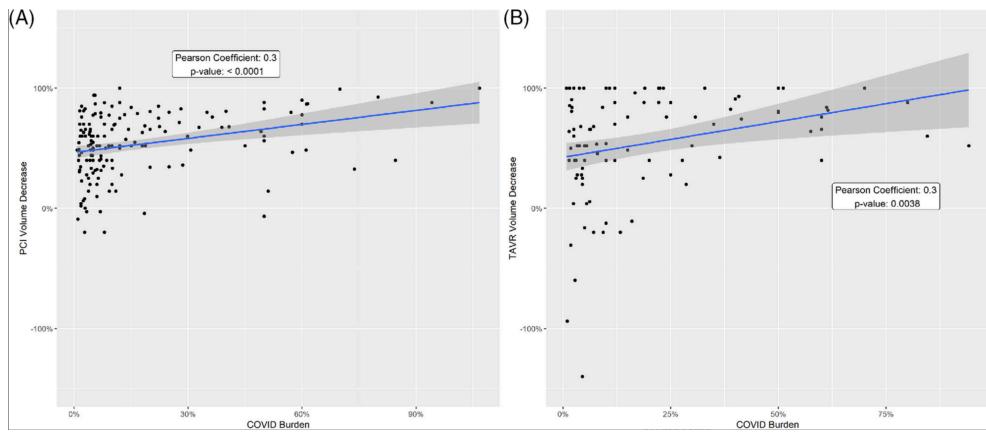


Figure 2. Relationship between procedural volume changes and inpatient COVID-19 disease burden (a) changes in PCI volume (b) changes in TAVR volume. Magnitude of volume reductions increased as COVID-19 burden increased [Color figure can be viewed at [wileyonlinelibrary.com](#)]

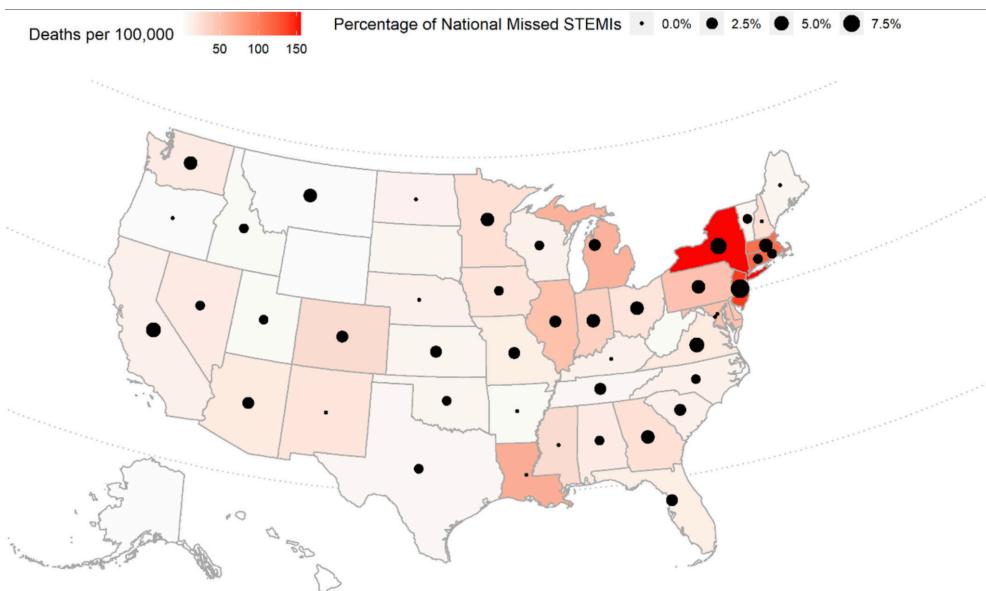


Figure 3. Increase in late presenting STEMIs in relationship to geographic COVID-19 mortality burden. Late presenting STEMIs increased nationwide regardless of regional COVID-19 burden [Color figure can be viewed at [wileyonlinelibrary.com](#)]

FIGURE 4
Relationship between deferral of angiograms by clinical indication and salary reductions (wRVU and base pay) (a) SIHD (b) UA. Differences in procedural deferral are not related to severity of salary reductions [Color figure can be viewed at [wileyonlinelibrary.com](#)]

YONG ET AL. 5

R&D: DIAGNOSIS & TREATMENTS

AUDIO INTERVIEW: GUIDELINES FOR COVID-19 VACCINE DEVELOPMENT

Rubin EJ, Baden LR, Morrissey S.. N Engl J Med. 2020 Sep 10;383(11):e88. doi: 10.1056/NEJMMe2029435.

Level of Evidence: Other - Guidelines and Recommendations

BLUF

Editors from the New England Journal of Medicine had an audio discussion on September 9, 2020 to discuss guidelines for deployment of a COVID-19 vaccine. The editors opined that:

- The recent pause of testing for one vaccine due to a participant contracting transverse myelitis shows that the safety protocols in place for vaccine development are functioning as planned
- The public does not need to apply causality hastily in these situations where an adverse effect comes to light in a trial
- Deployment guidelines, including prioritized groups, is not COVID-19 exceptionalism but standard for medical practice worldwide
- Public trust should be gained by transparency and honesty about vaccine development

While the COVID-19 pandemic is a new phenomenon, rapid development and deployment of vaccines is not unique, and these aforementioned discussion points may be useful in helping educate the public on this topic.

SUMMARY

In this audio interview the authors discussed deployment guidelines for a COVID-19 vaccine and also the recent state of two in-trial vaccines. Highlights include:

- AstraZeneca vaccine trial paused due to patient contracting transverse myelitis
- A new Russian vaccine under trial is a recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector
- CDC cursory guidelines for COVID-19 vaccine distribution includes 4 main groups as prioritized, including: healthcare workers, essential workers, national security and residents and staff of long-term care facilities
- COVID-19 vaccine development timeframe and public distrust mirrors that of the Ebola vaccine development in recent years

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CONTRIBUTORS

Alisa Malyavko
Ashley Kern
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Eva Shelton
Jonathan Baker
Renate Meckl
Sara Rutz

EDITORS

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