

The Daily COVID-19 Literature Surveillance Summary

October 09, 2020



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COVID-19 Daily Literature Surveillance

COVID19LST



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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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EXECUTIVE SUMMARY

Epidemiology

- Computer scientists evaluated [Italian, Swiss, and German COVID-19 contact tracing apps](#) based on Google/Apple exposure notification (GAEN) and Bluetooth signals in 108 pairs of handsets and found that Swiss and German app detection rules triggered no exposure notifications, while the Italian app's detection rules triggered notifications at a 50% true positive rate and 50% false positive rate, suggesting that while contact tracing apps are innovative, many limitations exist before they can be used for epidemiological data collection.
- A case report describes a previously healthy 20 year old male with fever and odynophagia who was admitted 2 weeks later for [bilateral facial weakness](#), at which time neurological examination revealed severe neuropathy of the facial nerve bilaterally and discrete signs of active denervation. SARS-CoV-2 and Epstein-Barr virus (EBV) were subsequently detected, which may have contributed to this patient's clinical presentation (either via immune mediated or direct viral damage).

Understanding the Pathology

- An in vitro study found that 15/15 ex vivo thyroid specimens (removed due to the presence of benign thyroid nodules) expressed [abundant levels of mRNA encoding for the ACE-2 receptor in thyroid follicular cells](#), making them a potential target for SARS-CoV-2 entry and suggesting that COVID-19-related subacute thyroiditis may potentially be due to direct viral infection of the thyroid gland.

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MEASUREMENT-BASED EVALUATION OF GOOGLE/APPLE EXPOSURE NOTIFICATION API FOR PROXIMITY DETECTION IN A LIGHT-RAIL TRAM

Leith DJ, Farrell S.. PLoS One. 2020 Sep 30;15(9):e0239943. doi: 10.1371/journal.pone.0239943. eCollection 2020.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

Irish computer scientists evaluated Italian, Swiss, and German COVID-19 contact tracing apps based on Google/Apple exposure notification (GAEN) and Bluetooth signals in 108 pairs of handsets on a tram in Dublin, Ireland (Figure 1). Authors found Swiss and German app detection rules triggered no exposure notifications, while the Italian app's detection rules triggered notifications at a 50% true positive rate and 50% false positive rate (Figures 3,4). They conclude that contact tracing apps are innovative, but many limitations exist so significant improvements will be required to increase their accuracy before they can be used for epidemiological data collection.

ABSTRACT

We report on the results of a Covid-19 contact tracing app measurement study carried out on a standard design of European commuter tram. Our measurements indicate that in the tram there is little correlation between Bluetooth received signal strength and distance between handsets. We applied the detection rules used by the Italian, Swiss and German apps to our measurement data and also characterised the impact on performance of changes in the parameters used in these detection rules. We find that the Swiss and German detection rules trigger no exposure notifications on our data, while the Italian detection rule generates a true positive rate of 50% and a false positive rate of 50%. Our analysis indicates that the performance of such detection rules is similar to that of triggering notifications by randomly selecting from the participants in our experiments, regardless of proximity.

FIGURES

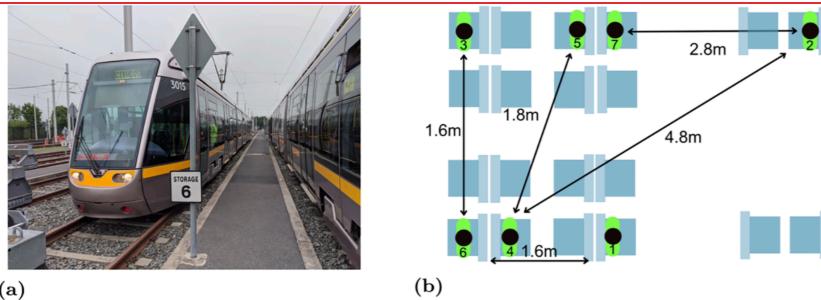


Figure 1. (a) Tram on which measurements were collected. (b) Relative positions of participants during tests.

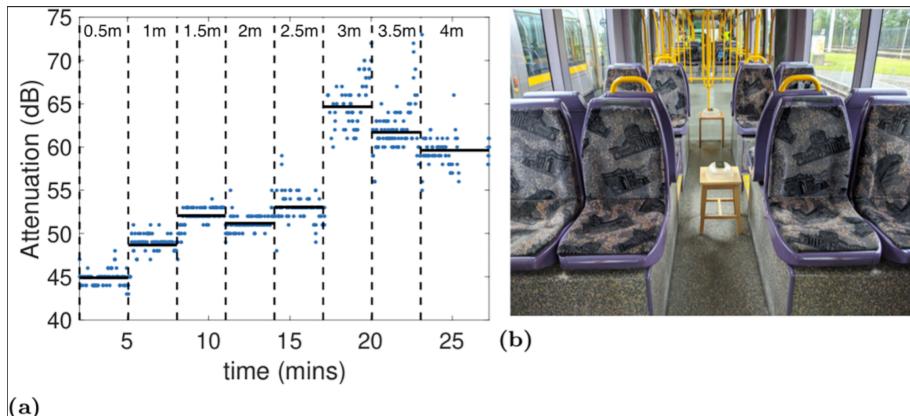


Figure 3. (a) Measurements of attenuation between two handsets as the distance between them is varied along the centre aisle in the tram carriage, (b) shows the setup used. The vertical dashed lines indicate when the distance between the handsets was changed, starting at 0.5m and then increasing by 0.5m at each step. The solid horizontal lines indicate the mean attenuation level at each distance. Measurements taken using the standard Android Bluetooth LE scanner API.

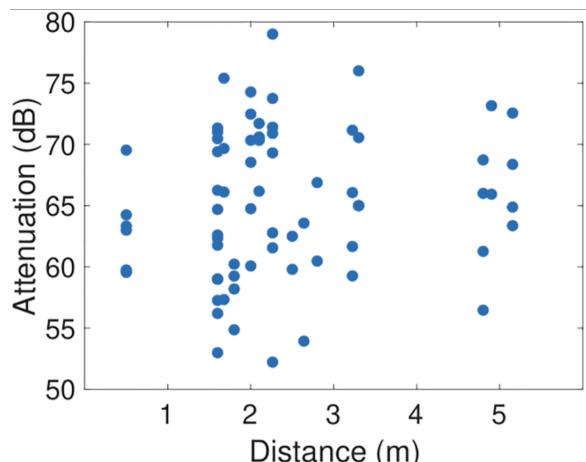


Figure 4. Mean attenuation level vs distance between handsets.

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

BILATERAL FACIAL NERVE PALSY ASSOCIATED WITH COVID-19 AND EPSTEIN-BARR VIRUS CO-INFECTION

Cabrera Muras A, Carmona-Abellán MDM, Collía Fernández A, Uterga Valiente JM, Antón Méndez L, García-Moncó JC.. Eur J Neurol. 2020 Sep 30. doi: 10.1111/ene.14561. Online ahead of print.

Level of Evidence: 5 - Case Report

BLUF

This case report conducted at the Hospital Universitario de Basurto in Bilbao, Spain by neurologists and radiologists describes a 20 year old male with no significant medical history who had fever and odynophagia and was admitted 2 weeks later for bilateral facial weakness, at which time neurological examination revealed severe neuropathy of the facial nerve bilaterally and discrete signs of active denervation (Figure 1). SARS-CoV-2 was subsequently detected via RT-PCR and Epstein-Barr virus (EBV) was also detected via heterophile antibody test. Authors suggest both SARS-CoV-2 and EBV may have contributed to this patient's clinical presentation (either immune mediated or direct viral damage) and COVID-19 should be considered in patients with facial palsy and mild respiratory symptoms.

ABSTRACT

A 20-year-old male, with no relevant previous medical history, was admitted due to bilateral facial weakness. Two weeks before, he noticed odynophagia and fever of 39°C without cough. He associated significant asthenia with headache, myalgia, nausea, and vomiting and he was treated with levofloxacin 500mg qd for 7 days. One week after, during an initial improvement of the respiratory symptoms, he presented acute right facial weakness. He was diagnosed with right peripheral facial palsy and was treated with prednisone 60 mg/24h with a tapering schedule.

FIGURES

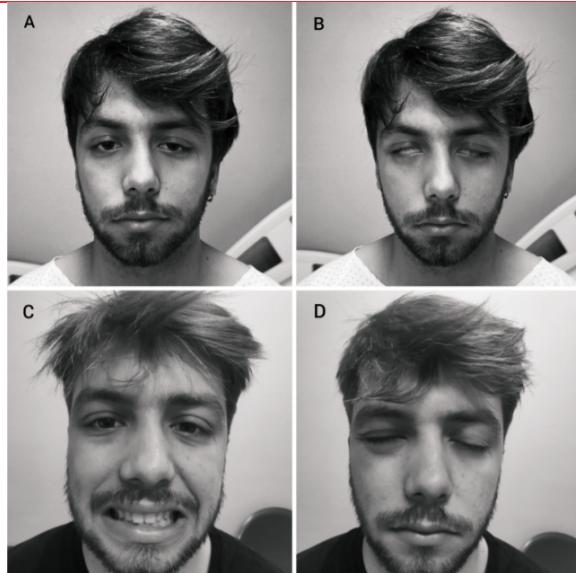


Figure 1. Patient with acute bilateral facial nerve paresis trying to smile (A) and closing eyes (B). The pictures (C) and (D) correspond with the same gestures 3 weeks after discharge with a significant spontaneous improvement. Informed consent of publication was obtained from the patient.

UNDERSTANDING THE PATHOLOGY

IN VITRO

DETECTION OF SARS-COV-2 RECEPTOR ACE-2 mRNA IN THYROID CELLS: A CLUE FOR COVID-19-RELATED SUBACUTE THYROIDITIS

Rotondi M, Coperchini F, Ricci G, Denegri M, Croce L, Ngnitejeu ST, Villani L, Magri F, Latrofa F, Chiovato L. J Endocrinol Invest. 2020 Oct 6. doi: 10.1007/s40618-020-01436-w. Online ahead of print.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

An in vitro study conducted by a multidisciplinary team of physicians in Italy found that 15/15 ex vivo thyroid specimens (removed due to the presence of benign thyroid nodules) expressed abundant levels of mRNA encoding for the ACE-2 receptor in thyroid follicular cells, making them a potential target for SARS-COV-2 entry. This study suggests that COVID-19 related subacute thyroiditis may potentially be due to direct viral infection of the thyroid gland.

ABSTRACT

PURPOSE: SARS-CoV-2 is a pathogenic agent belonging to the coronavirus family, responsible for the current global world pandemic. Angiotensin-converting enzyme 2 (ACE-2) is the receptor for cellular entry of SARS-CoV-2. ACE-2 is a type I transmembrane metallo-carboxypeptidase involved in the Renin-Angiotensin pathway. By analyzing two independent databases, ACE-2 was identified in several human tissues including the thyroid. Although some cases of COVID-19-related subacute thyroiditis were recently described, direct proof for the expression of the ACE-2 mRNA in thyroid cells is still lacking. Aim of the present study was to investigate by RT-PCR whether the mRNA encoding for ACE-2 is present in human thyroid cells. **METHODS:** RT-PCR was performed on in vitro ex vivo study on thyroid tissue samples (15 patients undergoing thyroidectomy for benign thyroid nodules) and primary thyroid cell cultures. **RESULTS:** The ACE-2 mRNA was detected in all surgical thyroid tissue samples ($n = 15$). Compared with two reporter genes (GAPDH: 0.052 ± 0.0026 Cycles-1; beta-actin: 0.044 ± 0.0025 Cycles-1; ACE-2: 0.035 ± 0.0024 Cycles-1), the mean level of transcript expression for ACE-2 mRNA was abundant. The expression of ACE-2 mRNA in follicular cells was confirmed by analyzing primary cultures of thyroid cells, which expressed the ACE-2 mRNA at levels similar to tissues. **CONCLUSIONS:** The results of the present study demonstrate that the mRNA encoding for the ACE-2 receptor is expressed in thyroid follicular cells, making them a potential target for SARS-CoV-2 entry. Future clinical studies in patients with COVID-19 will be required for increase our understanding of the thyroid repercussions of SARS-CoV-2 infection.

MANAGEMENT

MEDICAL SUBSPECIALTIES

HEMATOLOGY AND ONCOLOGY

THE COMPLEX MANAGEMENT OF ATRIAL FIBRILLATION AND CANCER IN THE COVID-19 ERA: DRUG INTERACTIONS, THROMBOEMBOLIC RISK, AND PROARRHYTHMIA

Gatti M, Raschi E, Poluzzi E, Martignani C, Salvagni S, Ardizzone A, Diemberger I.. Curr Heart Fail Rep. 2020 Oct 6. doi: 10.1007/s11897-020-00485-9. Online ahead of print.

Level of Evidence: Other - Guidelines and Recommendations

BLUF

A review conducted by a multidisciplinary team from Bologna, Italy addresses the diagnostic and management challenges of oncologic therapies due to onset and worsening of preexisting atrial fibrillation, leading to increased bleeding risk and arrhythmia susceptibility, especially in the presence of COVID-19 (Figure 1). They suggest optimized treatment regimens, antithrombotic management, review of medications, and close monitoring for high-risk individuals with COVID-19 due to additional drug/drug interactions with COVID-19 treatment to avoid potential harm in this vulnerable patient population.

ABSTRACT

PURPOSE OF REVIEW: Cardiotoxicity by anticancer agents has emerged as a multifaceted issue and is expected to affect both mortality and morbidity. This review summarizes clinical challenges in the management of oncological patients requiring anticoagulants for atrial fibrillation (AF) also considering the current outbreak of the COVID-19 (coronavirus disease 2019) pandemic, since this infection can add challenges to the management of both conditions. Specifically, the aims are manyfold: (1) describe the evolving use of direct oral anticoagulants (DOACs) in AF patients with cancer; (2) critically appraise the risk of clinically important drug-drug interactions (DDIs) between DOACs and oral targeted anticancer agents; (3) address expected DDIs between DOACs and candidate anti-COVID drugs, with implications on management of the underlying thrombotic risk; and (4) characterize the proarrhythmic liability in cardio-oncology in the setting of COVID-19, focusing on QT prolongation.

RECENT FINDINGS: AF in cardio-oncology poses diagnostic and management challenges, also due to the number of anticancer drugs recently associated with AF onset/worsening. Oral targeted drugs can potentially interact with DOACs, with increased bleeding risk mainly due to pharmacokinetic DDIs. Moreover, the vast majority of oral anticancer agents cause QT prolongation with direct and indirect mechanisms, potentially resulting in the occurrence of torsade de pointes, especially in susceptible patients with COVID-19 receiving additional drugs with QT liability. Oncologists and cardiologists must be aware of the increased bleeding risk and arrhythmic susceptibility of patients with AF and cancer due to DDIs. High-risk individuals with COVID-19 should be prioritized to target preventive strategies, including optimal antithrombotic management, medication review, and stringent monitoring.

FIGURES

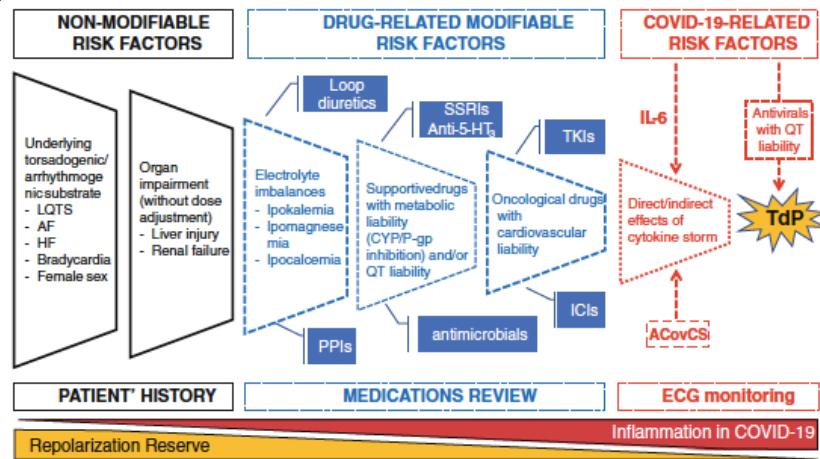


Fig. 1 Revisiting the concept of the reduced repolarization reserve in cardio-oncology during the COVID-19 era. ACovCS, acute COVID cardiovascular syndrome; ICIs, immune checkpoint inhibitors; PPIs, proton pump inhibitors; SSRIs, selective serotonin re-uptake inhibitors; TKIs, tyrosine kinase inhibitors; LQTS, long QT syndrome; AF, atrial fibrillation; HF, heart failure; ECG, Electrocardiography

Fig. 1 Revisiting the concept of the reduced repolarization reserve in cardio-oncology during the COVID-19 era. ACovCS, acute COVID cardiovascular syndrome; ICIs, immune checkpoint inhibitors; PPIs, proton pump inhibitors; SSRIs, selective serotonin re-uptake inhibitors; TKIs, tyrosine kinase inhibitors; LQTS, long QT syndrome; AF, atrial fibrillation; HF, heart failure; ECG, Electrocardiography

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