The Daily COVID-19 Literature Surveillance Summary

September 10, 2020

DISCLAIMER

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

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

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

EXECUTIVE SUMMARY

Epidemiology

- Researchers affiliated with Guangdong Provincial Center for Disease Control and Prevention conducted an epidemiological study of a COVID-19 outbreak in a Guangzhou high-rise apartment building that involved throat swab COVID-19 testing via RT-PCR (n=9 confirmed COVID-19 patients,193 residents, 24 staff employees), surface/air sampling from flats, public areas, and drainage systems, and tracer gas testing in restrooms. They found that COVID-19 transmission between the 9 infected residents, who were living in 3 vertically assembled flats with connecting drainage systems, was through fecal aerosol route, as confirmed by the environmental samples and dispersion measurements of airflow drainage gases. Based on these findings, the authors advocate for stronger hygiene practices, more secure drainage systems, and further studies into fecal aerosol spread of COVID-19.

Understanding the Pathology

- An observational study of 67 COVID-19 non-ICU patients (45 male, 22 female) admitted to COVID Hospital of Policlinico of Bari, Italy investigating the role of IL-6 levels in loss of taste/smell found a statistically significant correlation between decreased IL-6 and improvement in smell ($p<0.05$) and taste ($p=0.047$) (Table 3). The authors believe these results highlight the local inflammatory actions of IL-6 on chemosensory receptors, resulting in taste and smell disorders in COVID-19.

- A neuropathology research group affiliated with Harvard Medical School in Boston report on autopsy and clinical neurologic findings in 18 patients who died within 32 days of COVID-19 symptom onset. All patients had confusion and decreased arousal prior to death, and all brains showed signs of acute hypoxic injury with loss of neurons in cerebral cortex, hippocampus, and cerebellar Purkinje cells, but without thrombi, vasculitis, or viral staining on immunohistochemistry. Authors suggest these findings indicate neuropathological damage associated with COVID-19 cannot be specifically attributed to the virus alone.

Adjusting Practice During COVID-19

- Researchers from the Radiology department at University Hospitals Cleveland Medical Center/Case Western Reserve University conducted a retrospective study to assess imaging utilization in the emergency departments of a multicenter health system. They found a 46% reduction in imaging utilization (p less than 0.0001) with the exception to non-contrast chest CT (increased during this period, $p = 0.0053$), and non-trauma chest/abdomen/pelvis CT (largely unchanged in imaging use, $p = 0.0633$). The authors suggest that their findings shed light on how the pandemic has influenced ED imaging utilization, encouraging other institutions to publish data on their imaging practices for a comprehensive picture of the pandemic's impact.

- Healthcare professionals affiliated with the Universidade Federal de São Paulo in Brazil performed a comparative cohort study at their institution of pregnant women admitted in spontaneous labor (n=41 in 2019; n=40 in 2020). They found that in 2020 there were more deliveries within 3 hours of admission (11/41 or 26.8% in 2019; 16/40 or 40% in 2020), more nulliparous women (9% in 2019; 12.5% in 2020), fewer women with multiple pregnancies (54.5% vs 43.7%), and a lower percentage of newborns weighing less than 2500g (18.1% vs 12.5%). The authors suggest that gravid patients are presenting to the hospital in advanced stages of labor due to decreased public transportation and fear of COVID-19 infection and urge hospitals to encourage these patients to seek care.

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EPIDEMIOLOGY

PROBABLE EVIDENCE OF FECAL AEROSOL TRANSMISSION OF SARS-COV-2 IN A HIGH-RISE BUILDING

Kang M, Wei J, Yuan J, Guo J, Zhang Y, Hang J, Qu Y, Qian H, Zhuang Y, Chen X, Peng X, Shi T, Wang J, Wu J, Song T, He J, Li Y, Zhong N.. Ann Intern Med. 2020 Sep 1. doi: 10.7326/M20-0928. Online ahead of print.
Level of Evidence: 4 - Mechanism-based reasoning

BLUF

Researchers affiliated with Guangdong Provincial Center for Disease Control and Prevention conducted an epidemiological study of a COVID-19 outbreak in a Guangzhou high-rise apartment building from January 26 to February 13, 2020 that involved throat swab COVID-19 testing via RT-PCR (n=9 confirmed COVID-19 patients,193 residents, 24 staff employees), surface/air sampling from flats, public areas, and drainage systems, and tracer gas testing in restrooms (Figure 1). They found that COVID-19 transmission between the 9 infected residents, who were living in 3 vertically assembled flats with connecting drainage systems, was through fecal aerosol route, as confirmed by the environmental samples and dispersion measurements of airflow drainage gases (Figure 2; Table 1). Based on these findings, the authors advocate for stronger hygiene practices, more secure drainage systems, and further studies into fecal aerosol spread of COVID-19.

ABSTRACT

BACKGROUND: The role of fecal aerosols in the transmission of severe acute respiratory syndrome coronavirus 2 has been suspected. OBJECTIVE: To investigate the temporal and spatial distributions of 3 infected families in a high-rise apartment building and examine the associated environment variables to verify the role of fecal aerosols. DESIGN: Epidemiologic survey and quantitative reverse transcriptase polymerase chain reaction analyses on throat swabs from the participants; 237 surface and air samples from 11 of the 83 flats in the building, public areas, and building drainage systems; and tracer gas released into bathrooms as a surrogate for virus-laden aerosols in the drainage system. SETTING: A high-rise apartment building in Guangzhou, China. PARTICIPANTS: 9 infected patients, 193 other residents of the building, and 24 members of the building's management staff. MEASUREMENTS: Locations of infected flats and positive environmental samples, and spread of virus-laden aerosols. RESULTS: 9 infected patients in 3 families were identified. The first family had a history of travel to the coronavirus disease 2019 (COVID-19) epicenter Wuhan, whereas the other 2 families had no travel history and a later onset of symptoms. No evidence was found for transmission via the elevator or elsewhere. The families lived in 3 vertically aligned flats connected by drainage pipes in the master bathrooms. Both the observed infections and the locations of positive environmental samples are consistent with the vertical spread of virus-laden aerosols via these stacks and vents. LIMITATION: Inability to determine whether the water seals were dried out in the flats of the infected families. CONCLUSION: On the basis of circumstantial evidence, fecal aerosol transmission may have caused the community outbreak of COVID-19 in this high-rise building. PRIMARY FUNDING SOURCE: Key-Area Research and Development Program of Guangdong Province and the Research Grants Council of Hong Kong.

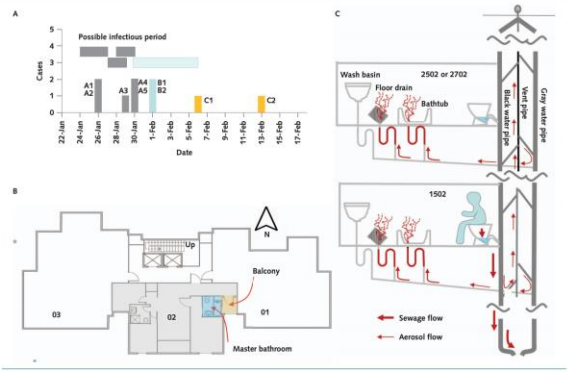
FIGURES

Table. Summary of the Infected Family and Other Families in Block X*

Flat Number	Family Members, *n*	Infected Members, *n*	Positive/Total Throat Swab Specimens, *n/n*	Positive/Total Environmental Samples (Date), *n/n*
1502	5	5	5/5	4/27 (12 February†) 1/1 (19 February‡)
2502	2	2	2/2	0/2 (14 February)
2702	2	2	2/2	0/9 (14 February)
Other flats	217 (including 24 staff)	0	0/217	1/134 (13–14 February§)

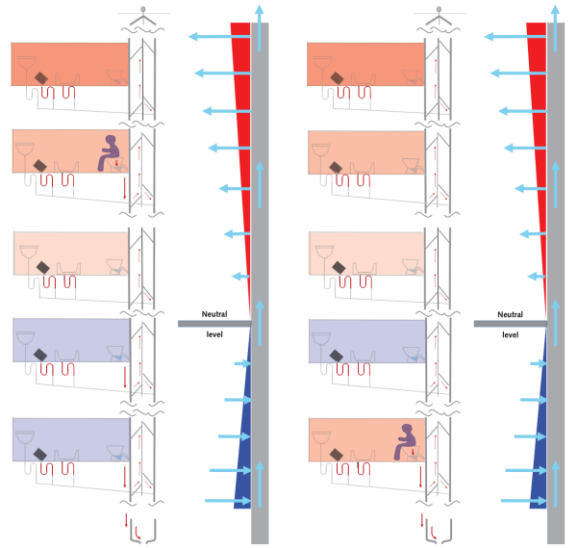
* Five samples from flat 1502 and 1 sample from flat 1602 were positive, and 5 of the 6 positive environmental samples were found in 2 master bathrooms.
† For 12 February, the 4 positive samples were as follows: 1 from the master bedroom with door handle, light switch, and air-conditioning remote control combined, and 3 from the master bathroom, including 1 from the mouthwash cup; 1 from the rubbish bin button; and 1 from the bathroom door handle, bathroom emergency phone, and tissue box cover (by the toilet) combined.
‡ For 19 February, the 1 positive sample was from the wash basin U-trap inner surface in the master bathroom.
§ For 13 February, the 1 positive sample was combined from the wash basin, faucet, and shower switch of flat 1602's master bathroom.

Figure 1. The block X outbreak and suggested transmission route.



A. Epidemiologic curve with patients from the same family shown in the same color. The possible infectious period for each group of patients with the same symptom onset date is estimated to be from 2 days before onset to their hospitalization dates. B. Floor plan for the second through 28th floors of block X, showing locations of bathrooms in -02 flats. C. Suggested transmission route from toilet flushing to the escape of gas in the drainage system containing bioaerosols into the master bathrooms of the -02 flats on the second to 29th floors. The dried-out water seals are shown with U-traps in red; escaped gas flow in the drainage system into a bathroom is shown by a red plume. Drawing is not to scale.

Figure 2. Illustration of the buoyancy (chimney) effect, with inflows into the vent at lower stories and outflows into the bathrooms at upper stories when the source bathroom is above (*left*) and below (*right*) the neutral level.



The red and blue chimney arrows indicate the flow of contaminated air in the drainage vents and branch pipes. Red shading of bathrooms indicates the infection risk for the occupants; the darker the shade, the higher the risk. Blue shading means no risk. The two drawings assume that all floor drain water seals were dried out. Left. Spatial infection pattern of the outbreak in the present study; the Heng Tai House outbreak (18), in which a 59-year-old man in flat 13 on the 34th floor was probably infected by 2 persons with confirmed COVID-19 who lived in flat 13 on the 32nd floor; the Luk Chuen House outbreak (19), in which 4 flats—710, 810, 1012, and 1112 on the seventh, eighth, 10th, and 11th floors, respectively— housing a total of 6 persons with secondary infection, were all linked to the index patient's flat— 812 on the 8th floor—by interconnected vertical drainage pipes; and the Amoy Gardens outbreak (spread in flat 7, block E) (16). Right. No outbreak has been identified so far.

TASTE AND SMELL DISORDERS IN COVID-19 PATIENTS: ROLE OF INTERLEUKIN-6

Cazzolla AP, Lovero R, Lo Muzio L, Testa NF, Schirinzi A, Palmieri G, Pozzessere P, Procacci V, Di Comite M, Ciavarella D, Pepe M, De Ruvo C, Crincoli V, Di Serio F, Santacroce L.. ACS Chem Neurosci. 2020 Sep 2;11(17):2774-2781. doi: 10.1021/acschemneuro.0c00447. Epub 2020 Aug 19.
Level of Evidence: 3 - Local non-random sample

BLUF

An observational study of 67 COVID-19 non-ICU patients (45 male, 22 female) admitted to COVID Hospital of Policlinico of Bari, Italy from March-May 2020 investigating the role of IL-6 levels in loss of taste/smell found a statistically significant correlation between decreased IL-6 and improvement in smell ($p<0.05$) and taste ($p=0.047$) (Table 3). The authors believe these results highlight the local inflammatory actions of IL-6 on chemosensory receptors, resulting in taste and smell disorders in COVID-19.

SUMMARY

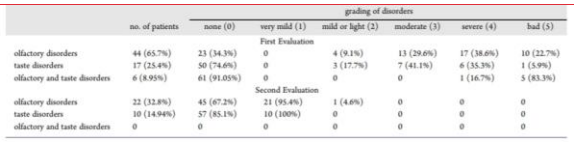
An observational study including 67 COVID-19 patients (45 male, 22 female) was conducted to establish a correlation between IL-6 levels and taste and smell disorders in COVID-19 patients (non-ICU) admitted to the Hospital of Bari. IL-6 assay and a survey to assess the dysfunctions were performed at the time of admission and again at swab negativization. The "Sinonasal outcome test (SNOT-22) for olfactory function, Taste, and Smell Questionnaire Section of the US NHANES 2011–2014 protocol (CDC 2013b) was used for gustatory assessment."

On evaluation at swab negativization, they found the following (Table 2):
- 35 patients reported complete recovery of the smell/taste disorder.
- 32 patients reported very mild disorder, 21 reported very mild smell disorder, 1 reported mild smell disorder, and 10 reported very mild taste disorder.

ABSTRACT

The rapid recovery of smell and/or taste functions in COVID-19 patients could be attributed to a decrease in Interleukin-6 levels rather than central nervous system ischemic injury or viral damage to neuronal cells. To correlate Interleukin-6 levels in COVID-19 patients with olfactory and/or gustatory dysfunctions and to investigate the role of IL-6 in the onset of these disorders. This observational study investigated 67 COVID-19 patients with taste and/or smell disorders, who did not require intensive care admission, admitted at COVID Hospital of Policlinico of Bari from March to May 2020. Interleukin-6 was assayed to COVID-19 patients with taste and/or smell disturbances at the time of admission and at the time of swab negativization. At the same time, patients have been given a specific survey to evaluate the severity of taste and/or smell disturbances. Of 125 patients with smell and/or taste dysfunctions at onset of disease, 67 fulfilled the inclusion criteria, while 58 were excluded because 35 of them required intensive care admission, 5 were unable to answer, 5 deceased, 7 had finished chemotherapy recently and 5 refused. The evaluation of taste and/or smell disorders was carried out using a survey performed at the time of admission and at the time of swab negativization. Sino-nasal outcome test 22 (SNOT-22) was used as a reference for olfactory function assessment and Taste and Smell Questionnaire Section of the US NHANES 2011-2014 protocol (CDC 2013b) was used as reference for gustatory function assessment. A venous blood sample was taken for each patient to measure IL-6 levels upon entry and at swab negativization. Interleukin-6 levels in COVID-19 patients in relation with olfactory and/or gustatory disorders from the time of their admission to the time of swab negativization. Statistically significant correlations were obtained between the decrease of Interleukin-6 levels and the improvement of smell (p value<0,05) and taste (p=0,047) functions at swab negativization. The acquired results demonstrate the key role of Interleukin-6 in the pathogenesis of chemosensitive disorders in COVID-19 patients.

FIGURES



		grading of disorders					
	no. of patients	none (0)	very mild (1)	mild or light (2)	moderate (3)	severe (4)	bad (5)
			First Evaluation				
olfactory disorders	44 (65.7%)	23 (34.3%)	0	4 (9.1%)	13 (29.6%)	17 (38.6%)	10 (22.7%)
taste disorders	17 (25.4%)	50 (74.6%)	0	3 (17.7%)	7 (41.1%)	6 (35.3%)	1 (5.9%)
olfactory and taste disorders	6 (8.95%)	61 (91.05%)	0	0	0	1 (16.7%)	5 (83.3%)
			Second Evaluation				
olfactory disorders	22 (32.8%)	45 (67.2%)	21 (95.4%)	1 (4.6%)	0	0	0
taste disorders	10 (14.94%)	57 (85.1%)	10 (100%)	0	0	0	0
olfactory and taste disorders	0	0	0	0	0	0	0

Table 2: "Characteristics of Smell or Taste Disorders in 67 COVID-19 Patients at the First and Second Evaluation (Grading of Disorders)".

(a) Wilcoxon Signed-Rank Test

variable	Wilcoxon test	*p* value
IL-6 level (first evaluation) vs IL-6 level (second evaluation)	2278	<0.05
score smell dysfunction (first evaluation) vs score smell dysfunction (second evaluation)	1225	<0.05
score taste dysfunction (first evaluation) vs score taste dysfunction (second evaluation)	325	<0.05

(b) Pearson's Linear Correlation Coefficients

variable	Pearson coefficient (*r*)	95% confidence intervals	*p* value
delta IL-6 vs delta score smell	0.58	0.33 to 0.68	<0.05
delta IL-6 vs delta score taste	0.24	0.003 to 0.45	0.047
delta score taste vs delta score smell	−0.38	−0.567 to −0.15	<0.05

Table 3: "Values of the (a) Wilcoxon Test and (b) Pearson's Correlation Coefficients between All the Variables of the Dataset Considered".

NEUROPATHOLOGICAL FEATURES OF COVID-19

Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, Adams G, Hornick JL, Padera RF Jr, Sabeti P.. N Engl J Med. 2020 Sep 3;383(10):989-992. doi: 10.1056/NEJMc2019373. Epub 2020 Jun 12.
Level of Evidence: 4 - Case-series

BLUF

A neuropathology research group affiliated with Harvard Medical School in Boston report on autopsy and clinical neurologic findings in 18 patients who died within 32 days of COVID-19 symptom onset between April 14 and April 29, 2020. All patients had confusion and decreased arousal prior to death, and all brains showed signs of acute hypoxic injury with loss of neurons in cerebral cortex, hippocampus, and cerebellar Purkinje cells, but without thrombi, vasculitis, or viral staining on immunohistochemistry (Table 1). Authors suggest these findings indicate neuropathological damage associated with COVID-19 cannot be specifically attributed to the virus alone.

FIGURES

Table 1. Gross Findings and Results of Histologic Analysis to Detect SARS-CoV-2.*

Patient No.	Days from Symptom Onset to Death	Hours from Death to Autopsy	Gross Inspection		Histologic Analysis
			Brain Volume	Observations	
			grams		
1	20	52	1290	No gross abnormalities	Acute hypoxic ischemic damage, mild arteriolosclerosis
2	6	32	1460	Moderate atherosclerosis	Acute hypoxic ischemic damage
3	12	21	1210	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, mild arteriolosclerosis
4	6	36	1150	Moderate-to-severe atherosclerosis, pale substantia nigra and locus coeruleus	Acute hypoxic ischemic damage, moderate arteriolosclerosis, pathological features of Lewy body disease and Alzheimer's disease
5	9	40	1460	No gross abnormalities	Acute hypoxic ischemic damage
6	0	77	1330	Mild atherosclerosis	Acute hypoxic ischemic damage, moderate arteriolosclerosis, focal leptomeningeal chronic inflammation
7	2	54	1300	Moderate atherosclerosis, cortical atrophy	Acute hypoxic ischemic damage, mild arteriolosclerosis, pathological features of Alzheimer's disease
8	2	32	1350	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, moderate arteriolosclerosis
9	23	23	1330	Mild atherosclerosis	Acute hypoxic ischemic damage, mild arteriolosclerosis
10	7	21	1120	Moderate atherosclerosis, anaplastic astrocytoma tumor resection cavity	Acute hypoxic ischemic damage, recurrent or residual anaplastic astrocytoma
11	26	41	1090	No gross abnormalities	Acute hypoxic ischemic damage, Alzheimer's type II astrocytosis
12	6	45	1130	Mild atherosclerosis, pale substantia nigra	Acute hypoxic ischemic damage, mild arteriolosclerosis, pathological features of Lewy body disease and Alzheimer's disease
13	12	61	1300	No gross abnormalities	Acute hypoxic ischemic damage, mild arteriolosclerosis, focal perivascular chronic inflammation, Alzheimer's type II astrocytosis
14	0	102	1650	Moderate atherosclerosis	Acute hypoxic ischemic damage, moderate arteriolosclerosis
15	8	20	1530	Moderate atherosclerosis	Acute hypoxic ischemic damage, mild arteriolosclerosis, Alzheimer's type II astrocytosis
16	32	31	1150	Moderate atherosclerosis, chronic infarcts	Acute hypoxic ischemic damage, chronic infarcts, mild arteriolosclerosis
17	7	25	1300	Moderate atherosclerosis	Acute hypoxic ischemic damage, moderate arteriolosclerosis, focal perivascular chronic inflammation, pathological features of Alzheimer's disease
18	9	26	1350	Mild atherosclerosis	Acute hypoxic ischemic damage, single microglial nodule, Alzheimer's type II astrocytosis

* The results of immunohistochemical analysis to detect SARS-CoV-2 were negative in all the patients.

RIFAMPICIN-INDUCED PNEUMONITIS MIMICKING SEVERE COVID-19 PNEUMONIA INFECTION

Ata F, Shaher Mousa Hussein M, Mismar AY, Sharma R, Bozom IAM, Alsiddig Ali Ibrahim Z, Ibrahim WH.. Am J Case Rep. 2020 Aug 25;21:e927586. doi: 10.12659/AJCR.927586.
Level of Evidence: Other - Case Report

BLUF

Physicians affiliated with Hamad General Hospital, Detroit Medical Center, and Weill-Cornell Medical College describe a case of a 43-year old man taking anti-tuberculosis (TB) treatment who presented to the ED with new-onset fever, fatigue, hypoxemic respiratory failure, and bilateral pulmonary opacities. Chest X-ray, CT (Figure 2), and clinical features resembled both SARS-CoV-2 infection and rifampicin-induced pneumonitis, however negative results for SARS-CoV-2 via RT-PCR and lung biopsy (Figure 3) confirmed the diagnosis for drug-induced pneumonitis. The authors believe that this case highlights the importance of accurate and timely COVID-19 testing so that curable lung diseases do not progress to permanent lung damage.

ABSTRACT

BACKGROUND Rifampicin-induced pneumonitis is an infrequent occurrence, with only a few cases reported in the literature. Furthermore, this condition constitutes a diagnostic challenge, particularly in the era of COVID-19 infection. Here, we report a case of rifampicin-induced pneumonitis with clinical, imaging, and histological features of acute respiratory distress syndrome (ARDS), which required severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing to exclude a diagnosis of coronavirus disease 2019 (COVID-19) pneumonia. CASE REPORT A 43-year-old man on anti-TB treatment for TB meningitis developed new-onset fever, fatigue, hypoxemic respiratory failure, and bilateral pulmonary opacities. His clinical, chest X-ray, and CT thorax findings of ARDS were similar to both rifampicin-induced pneumonitis and severe COVID-19 pneumonia. However, reverse transcription polymerase chain reaction (RT-PCR) testing from a nasopharyngeal swab and bronchoalveolar lavage (BAL) via the GeneXpert system was negative for SARS-CoV-2. A detailed workup, including lung biopsy, revealed drug-induced pneumonitis as the cause of his presentation. His pneumonitis improved after discontinuation of rifampicin and recurred following the rifampicin challenge. CONCLUSIONS This case highlights the importance of early, rapid, and accurate testing for SARS-CoV-2 during the COVID-19 pandemic for patients presenting with acute respiratory symptoms, so that accurate diagnosis and early patient management are not delayed for patients with treatable causes of acute and severe lung diseases. Timely identification of rifampicin-induced pneumonitis via a high clinical suspicion, detailed workup, and histopathological analysis is required to avoid permanent damage to the lungs.

FIGURES

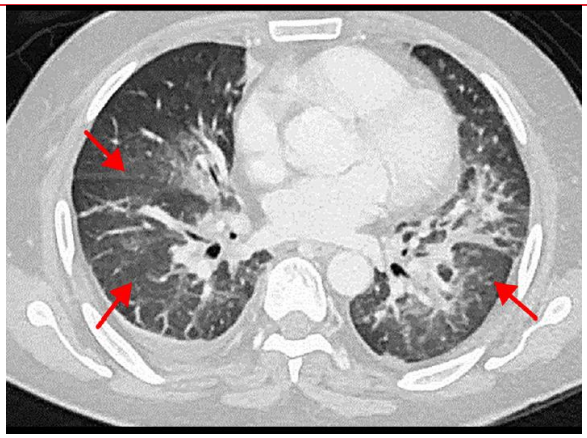


Figure 2. Computed tomography (CT) scan Thorax (Red arrows: Patchy consolidation and air bronchograms consistent with ARDS).

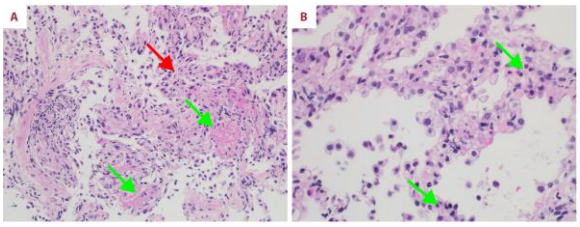


Figure 3. Photomicrographs of the histology of the lung biopsies (day 5 of admission) in a 43-year-old man with a history of tuberculous meningitis and rifampicin pneumonitis who presented with symptoms that mimicked severe COVID-19 pneumonia with negative test results for SARS-CoV-2 infection. (A) Histology of the lung shows thickening of the alveolar walls (Red arrow) with an increase in mononuclear cells and pink hyaline membranes (Green arrows), consistent with diffuse alveolar damage (DAD) and with acute respiratory distress syndrome (ARDS) and also with rifampicin-induced pneumonitis. Hematoxylin and eosin (H&E) ×200. (B) Histology of the lung shows some residual thickening of the alveolar walls and type II pneumocyte hyperplasia without hyaline membranes. H&E ×400.

EMERGENCY MEDICINE

QUANTIFYING THE DECREASE IN EMERGENCY DEPARTMENT IMAGING UTILIZATION DURING THE COVID-19 PANDEMIC AT A MULTICENTER HEALTHCARE SYSTEM IN OHIO

Parikh KD, Ramaiya NH, Kikano EG, Tirumani SH, Pierce J, Butcher C, Sunshine JL, Plecha DM.. Emerg Radiol. 2020 Sep 1. doi: 10.1007/s10140-020-01848-4. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Researchers from the Radiology department at University Hospitals Cleveland Medical Center/Case Western Reserve University conducted a retrospective study to assess imaging utilization in the emergency departments of a multicenter health system between March 1 to May 11, 2020 (Table 1). They found a 46% reduction in imaging utilization (p less than 0.0001) with the exception to non-contrast chest CT (increased during this period, p = 0.0053), and non-trauma chest/abdomen/pelvis CT (largely unchanged in imaging use, p = 0.0633; Figure 2, 4). The authors suggest that their findings shed light on how the pandemic has influenced ED imaging utilization, encouraging other institutions to publish data on their imaging practices for a comprehensive picture of the pandemic's impact.

ABSTRACT

PURPOSE: To illustrate the change in emergency department (ED) imaging utilization at a multicenter health system in the state of Ohio during the COVID-19 pandemic. METHODS: A retrospective observational study was conducted assessing ED imaging volumes between March 1, 2020, and May 11, 2020, during the COVID-19 crisis. A rolling 7-day total value was used for volume tracking and comparison. Total imaging utilization in the ED was compared with new COVID-19 cases in our region. Utilization was first categorized by modality and then by plain films and computed tomography (CT) scans grouped by body part. CT imaging of the chest was specifically investigated by assessing both CT chest only exams and CT chest, abdomen, and pelvis (C/A/P) exams. Ultimately, matching pair-wise statistical analysis of exam volumes was performed to assess significance of volume change. RESULTS: Our multicenter health system experienced a 46% drop in imaging utilization (p < 0.0001) during the pandemic. Matching pair-wise analysis showed a statistically significant volume decrease by each modality and body part. The exceptions were non-contrast chest CT, which increased (p = 0.0053), and non-trauma C/A/P CT, which did not show a statistically significant volume change (p = 0.0633). CONCLUSION: ED imaging utilization trends revealed through actual health system data will help inform evidence-based decisions for more accurate volume predictions and therefore institutional preparedness for current and future pandemics.

FIGURES

	Normal volume (%)	Volume during COVID-19 pandemic (%)	Mean difference ± SE	% Change from normal	95% CI	*p* value
Overall ED imaging	6296 (100)	3421 (100)	2875 ± 47	46%	2983, 2767	< 0.0001*
Modality						
Plain films	3680 (58)	1901 (56)	− 1779 ± 34	− 48%	− 1858, − 1699	< 0.0001*
CT	2232 (35)	1307 (38)	− 925 ± 14	− 41%	− 958, − 892	< 0.0001*
Ultrasound	305 (5)	181 (5)	− 122 ± 2	− 40%	− 126, − 118	< 0.0001*
MRI	64 (1)	30 (1)	− 34 ± 2	− 53%	− 39, − 29	< 0.0001*
Nuclear medicine	12 (0)	0 (0)	− 12 ± 1	− 100%	− 14, − 11	< 0.0001*
Plain films by body part						
Chest	2066 (56)	1138 (60)	− 928 ± 25	− 45%	− 986, − 871	< 0.0001*
Spine and extremities	1406 (38)	677 (36)	− 729 ± 15	− 52%	− 763, − 695	< 0.0001*
Abdomen and/or pelvis	177 (5)	74 (4)	− 103 ± 3	− 58%	− 110, − 97	< 0.0001*
Head and/or neck	19 (1)	8 (0)	− 11 ± 1	− 58%	− 12, − 9	< 0.0001*
CT by body part						
Head and/or neck	862 (39)	484 (37)	− 378 ± 11	− 44%	− 402, − 353	< 0.0001*
Abdomen and/or pelvis	633 (28)	363 (28)	− 270 ± 5	− 43%	− 281, − 258	< 0.0001*
Spine and extremities	437 (20)	248 (19)	− 189 ± 5	− 43%	− 200, − 176	< 0.0001*
Chest only	253 (11)	168 (13)	− 84 ± 6	− 34%	− 98, − 71	< 0.0001*
C/A/P	47 (2)	43 (3)	− 4 ± 2	− 9%	− 9, 1	0.0857
CT chest imaging						
CT chest angio	210 (77)	125 (67)	− 85 ± 5	− 40%	− 96, − 74	< 0.0001*
CT chest IV	16 (6)	8 (4)	− 9 ± 1	− 50%	− 12, − 5	< 0.0002*
CT chest WO	26 (10)	35 (19)	9 ± 2	+ 35%	3, 14	0.0053*
CT C/A/P non-trauma	8 (3)	12 (6)	4 ± 2	+ 50%	0, 8	0.0633
CT C/A/P trauma	12 (4)	7 (4)	− 5 ± 1	− 42%	− 7, − 2	0.002*

A negative sign indicates decrease in volume. An asterisk (*) indicates a statistically significant two-tailed *p* value < 0.05. *SE*, standard error; *CI*, confidence interval; *Angio*, angiography; *IV*, with intravenous contrast; *WO*, without intravenous contrast; *C/A/P*, chest, abdomen, and pelvis

Table 1: Matching pair-wise analysis results assessing statistical significance of change in ED imaging volumes are provided. "Normal volume" denotes the normalized mean system-wide ED imaging volume before the state of emergency was declared in Ohio on March 9, 2020. The proportions within each subsection are provided in parentheses. "Volume during COVID-19 pandemic" denotes the mean volume during the system-wide trough of imaging utilization amidst the crisis (April 11, 2020–April 19, 2020). The proportions within each subsection are again provided in parentheses. The calculated "Mean difference" between these two columns is provided along with the lower and upper limits of the 95% confidence interval. "% Change from normal" indicates the percentage by which the volume dropped during COVID-19 compared with normal

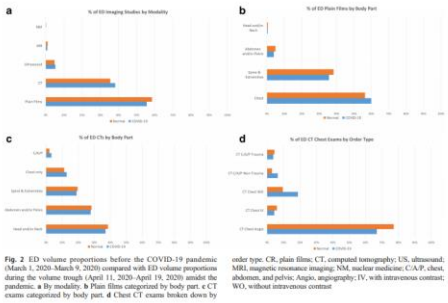


Figure 2: ED volume proportions before the COVID-19 pandemic (March 1, 2020–March 9, 2020) compared with ED volume proportions during the volume trough (April 11, 2020–April 19, 2020) amidst the pandemic. a By modality. b Plain films categorized by body part. c CT
exams categorized by body part. d Chest CT exams broken down by order type. CR, plain films; CT, computed tomography; US, ultrasound; MRI, magnetic resonance imaging; NM, nuclear medicine; C/A/P, chest, abdomen, and pelvis; Angio, angiography; IV, with intravenous contrast; WO, without intravenous contrast

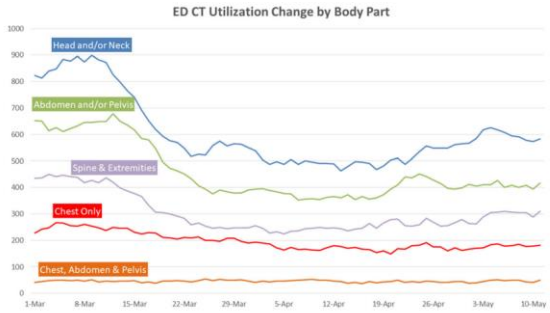


Fig. 4 Actual 7-day total ED CT volume between March 1, 2020, and May 11, 2020 split by the five highest volume body part exams: head and/or neck; abdomen and/ or pelvis; spine and extremities; chest only; and chest, abdomen, and pelvis.

OBGYN

EFFECT OF DELAYED OBSTETRIC LABOR CARE DURING THE COVID-19 PANDEMIC ON PERINATAL OUTCOMES

Sun SY, Guazzelli CAF, de Morais LR, Dittmer FP, Augusto MN, Soares AC, Coutinho da Silva PM, de Sá Vieira Abuchaim E, Mattar R.. Int J Gynaecol Obstet. 2020 Aug 29. doi: 10.1002/ijgo.13357. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

Healthcare professionals affiliated with the Universidade Federal de São Paulo in Brazil performed a comparative cohort study at their institution between March 11 through June 11, 2019 and March 11 through June 11, 2020 of pregnant women admitted in spontaneous labor (n=41 in 2019; n=40 in 2020). They found that in 2020 there were more deliveries within 3 hours of admission (11/41 or 26.8% in 2019; 16/40 or 40% in 2020), more nulliparous women (9% in 2019; 12.5% in 2020), fewer women with multiple pregnancies (54.5% vs 43.7%), and a lower percentage of newborns weighing less than 2500g (18.1% vs 12.5%; Table 1). The authors suggest that gravid patients are presenting to the hospital in advanced stages of labor due to decreased public transportation and fear of COVID-19 infection and urge hospitals to encourage these patients to seek care.

ABSTRACT

Since the beginning of the COVID-19 quarantine in Sao Paulo, Brazil, our institution has noticed that some pregnant women, particularly those that were recommended elective cesarean sections for reasons such as repeated cesarean deliveries or abnormal fetal presentation, were admitted to Sao Paulo Hospital in the second stage of labor and then went on to have vaginal deliveries. Therefore, we conducted a comparative cohort study between March 11-June 11, 2019 and March 11-June 11, 2020 in order to evaluate whether the quarantine period led to pregnant women with spontaneous labor arriving at our

hospital in a more advanced phase of labor. The Institutional Review Board of UNIFESP provided ethical approval for this study (No. 33734620.7.0000.5505).

FIGURES

	0-3 h *		>3h*	
Year, n	2019, 11 (26.8)	2020, 16 (40)	2019, 30 (73)	2020, 24 (60)
Maternal age				
< 20	0	1 (6.2)	3 (10)	0
20 - 34	8 (72.7)	10 (62.5)	21 (70)	19 (79.1)
≥35	3 (27.2)	5 (31.2)	6 (20)	5 (20.8)
Média(years)	32.45	31.75	28.37	28.63
Robson				
1 and 3	7 (63.6)	9 (56.2)	24 (80)	15 (62.5)
5	3 (27.2)	3 (18.7)	3 (10)	6 (25)
6 to 10	1 (9)	4 (25)	3 (10)	3 (12.5)
Gestational age				
<37	2 (18.1)	3 (18.7)	4 (13.3)	21 (87.5)
≥ 37	9 (81.8)	13 (81.2)	26 (86.6)	3 (12.5)
Parity				
Nulliparous	1 (9)	2 (12.5)	12 (40)	11 (45.8)
1	4 (36.4)	7 (43.7)	8 (26.6)	10 (41.6)
≥2	6 (54.5)	7 (43.7)	10 (33.3)	3 (12.5)
Delivery type				
Vaginal	10 (90.9)	15 (93,7)	21 (70)	18 (75)
Forceps	0	0	0	1 (4.1)
Cesarean section	1 (9)	1 (6.3)	9 (30)	5 (20.8)
Newborn's weight (g)				
< 2500	2 (18.1)	2 (12.5)	1 (3.3)	0
2500-<4000	8 (72.7)	14 (87.5)	28 (93.3)	24 (100)
≥4000	1 (9)	0	1 (3.3)	0
Perineal laceration				
no	3 (30)	7 (43)	9 (30)	3 (12.5)
1°	4 (40)	6 (37.5)	4 (13)	9 (37.5)
2°	2 (20)	2 (12.5)	7 (23)	7 (29)
3°	1 (10)	0	1 (3)	0
Prenatal care				
None	2 (18.1)	1 (6.2)	5 (16.6)	0
Elsewhere	3 (27.3)	3 (18.7)	1 (3.3)	1 (4.1)
SPH	6 (54.5)	12 (75)	24 (80)	23 (95.8)
Apgar score				
<7	2 (18.1)	1 (6.25)	0	1 (4.1)
≥7	9 (81.8)	15 (93.7)	30 (100)	23 (95.8)

*Time between the arrival at the hospital and the delivery

[a] Values shown as number (percentage.)

Abbreviations: SPH, São Paulo Hospital.

Table 1. Characteristics of pregnant women admitted at Sao Paulo Hospital (SPH) in spontaneous labor from 11 March, 2019–11 June, 2019, and from 11 March, 2020–11 June, 2020a

COVID-19: NANOMEDICINE UNCOVERS BLOOD-CLOT MYSTERY

Saei AA, Sharifi S, Mahmoudi M.. J Proteome Res. 2020 Aug 31. doi: 10.1021/acs.jproteome.0c00425. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Investigators affiliated with departments of Medical Biochemistry and Biophysics and Radiology at the Karolinska Institutet, Sweden and Michigan State University, USA review the role of nanotechnology in understanding and addressing the pathogenesis and severity of blood clotting in COVID-19-positive individuals. Based on their findings (illustrated below), the authors believe that using nanotechnology in point-of-care tools for blood clotting risk/severity assessment can assist physicians in making informed decisions on optimal treatment and management for this population.

SUMMARY

The main observations of this review include, but are not limited to, the following:

1. The presence of the ACE2 receptor on the surface of the endothelial cells that line the blood and lymph vessel may be instrumental to SARS-CoV-2 induced blood clotting formation.

2. The authors believe that it is the interplay and imbalance between the complement system, inflammation, and the coagulation system influences thrombosis formation in patients infected by SARS-CoV-2 (Table 1).

3. Nanotechnology has been combined with proteomics techniques (mass spectrometry (MS)-based proteomics) to create plasma protein and biomarker detection both for disease identification and in deciphering disease mechanism.

4. Theragnostic nanotechnologies have been used to diagnose thrombosis early and deliver thrombolytics/thrombosis inhibitors to the affected area by targeting biomarkers (P-selectin, D-dimer, and E-selectin molecules) in thrombi (Figure 1).

5. Nanotechnology has potential in the point-of-care diagnosis of COVID-19 infection in patients at high risk of blood clotting in determining appropriate treatment options.

6. Thrombosis treatment via nanomedicine involves delivering nanoparticles loaded with antithrombotic agents to the thrombus sites through one or several proteins involved in coagulation (e.g., fibrin, thrombin, or hydrogen peroxide (H_2O_2), in the coagulation process (activated platelets, via cell-binding ligands).

7. Multiple other techniques involving the use of H_2O_2-responsive boronate antioxidant polymer (BAP), iron oxide nanoparticle micelles and liposome nanoparticles surface-modified with cyclic Arg-Gly-Asp (RGD) have been used with some success. (Table 2)

8. Limitations to nanomedicine approaches have included:
a. biomolecular/protein corona formation, which causes shielding of targeting species on the surface of nanoparticles and creates an additional barrier at the surface of drug-loaded nanocarriers
b. the inherent thrombogenicity of nanoparticles, such as TiO_2 nanoparticles causing platelet aggregation and exacerbation of thrombosis risk

9. Challenges with mass spectrometry (MS)-based proteomics include:
a. preservation of proteome coverage in larger sample cohorts
b. the presence of highly abundant proteins such as albumin (55% of the total protein mass in plasma) which hinders comprehensive profiling of the plasma proteome and makes in-depth analysis of plasma cohorts challenging.

10. Though it can interfere with analysis, the presence of the biomolecular/protein corona can be utilised to mitigate the above limitations by detecting disease specific biomarkers via MS-based proteomics.

11. Biomolecular/protein corona are unique from the biofluids in which they are submerged. The corona pattern (e.g., liposomes with various surface chemistries) acts as a "fingerprint" under the nanoparticle sensor can aid in rapid diagnosis of blood clotting and its severity.

12. To further aid MS-based proteomic techniques, biofluids (serum, plasma) can be used:
a. to probe biomarkers in healthy versus patient samples
b. to develop nanoparticle-based assays that can adsorb proteins of interest on the surface of nanoparticles and make identifiable detection signals through color changes, electric signals etc.

13. Ezzat et al (2019) showed that respiratory syncytial virus (RSV) and herpes simplex virus type 1 (HSV-1) are covered by rich and unique biomolecular/ protein coronas in different biofluids. They suggest that the viral corona is a critical factor dictating virus–host interactions, affecting viral infectivity and induction of immunity through its interaction with biological markers.

14. Nanomedicine can help in selecting the best treatment strategy (e.g., appropriate dosing of blood-thinning medications) and in monitoring and drug adjustment (eg. aggressiveness of treatment to prevent the lethal consequences of massive blood clotting such as heart and/or brain strokes).

15. Analysis of the biomolecular/protein corona profiles of many nanoparticles (e.g., silica, polystyrene and gold) has shown that the corona has a role in absorption of complement proteins, immunoglobulins, and/or coagulants, which can be extremely helpful for detection of sudden increases in the abundance of these proteins in blood plasma.

16. Pre-coating nanoparticles with clot-related proteins such as fibrinogen, fibrin, factor VIII, factor XIII, tissue plasminogen activator or protein Z could aid the recruitment of similar proteins into the corona, leading to rapid identification of subtle signs of clotting in plasma.

17. Well-developed colorimetric sensing platforms, including smartphone-readable systems for detection and discrimination of multiple proteins, may identify changes in the secretion of blood-clotting proteins by generating colored solutions detectable by the naked eye or point-of-care devices. For example, via the use of the protein corona in combination with the enzyme-mimetic activity of gold nanoparticles (i.e., polyhedral oligomeric silsesquioxane polymer-caged), a colorimetric analysis was developed to identify metallothioneins, which are important biomarkers for heavy-metal poisoning

18. Thermal proteome profiling (TPP) which allows the binding of a protein to a molecule can change its thermal stability, thus utilizing protein stability and structural change as structural disease biomarkers.

ABSTRACT

Further complications associated with infection by severe acute respiratory syndrome coronavirus 2 (a.k.a. SARS-CoV-2) continue to be reported. Very recent findings reveal that 20-30% of patients at high risk of mortality from COVID-19 infection experience blood clotting that leads to stroke and sudden death. Timely assessment of the severity of blood clotting will be of enormous help to clinicians in determining the right blood-thinning medications to prevent stroke or other life-threatening consequences. Therefore, rapid identification of blood clotting-related proteins in the plasma of COVID-19 patients would save many lives. Several nanotechnology-based approaches are being developed to diagnose patients at high risk of death due to the complications of COVID-19 infections, including blood clots. This perspective outlines the significant potential of nanomedicine i) in assessing the risk of blood clotting and its severity in SARS-CoV-2 infected patients, and ii) its synergistic roles with advanced mass spectrometry (MS)-based proteomics approaches in identifying the important protein patterns that are involved in the disease occurrence and progression. The combination of such powerful tools might help us understand the clotting phenomenon and pave the way for development of new diagnostics and therapeutics in the fight against COVID-19.

FIGURES

Table 1. Possible Mechanisms by Which Some Viruses Interfere with the Coagulation Cascade, Causing Bleeding Disorders or Thrombosis

mechanism	description	usual pathological outcome	example(s)	ref(s)
reduced platelet numbers or changes in their function	increased adherence or activation of platelets or change in platelet number due to secretion of autoimmune antibodies against platelets	hemorrhage	• avian influenza (H5N1) • SARS	39, 40
damage to endothelial cells	• inhibits the anticoagulation properties of endothelial cells by reducing heparan sulfate anticoagulant synthesis • affects the production of coagulation regulatory substances such as protein C, a coagulation inhibitor • enhances the procoagulant properties of endothelial cells by production of tissue factor or Von Willebrand factor (vWF) • through attachment of inflammatory cells such as platelets or granulocytes, may reverse the antithrombogenic properties of endothelial cells toward procoagulation	thrombus formation	herpes viruses	41, 42
alteration of coagulation proteins	decrease or increase the level of coagulation factor: e.g., increased fibrinogen or factor VII may favor thrombosis, whereas decreased factors IX and X may lead to hemorrhage	either thrombus formation or hemorrhage	ebola virus	43
disruption of the function of natural anticoagulant	viral infection can decrease anticoagulant substances such as protein C, protein S, or antithrombin through either decreased synthesis or degradation by the host immune system	thrombus formation	hantavirus	44
alteration in fibrinolysis	decreased fibrinolysis due to increased serpin E1, an inhibitor of tissue plasminogen activator (tPA), or decreased tPA, leading to hyperfibrinolysis	either thrombus formation or hemorrhage	SARS	45

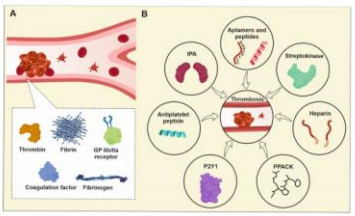


Figure 1. Examples of (A) thrombosis-specific biomarkers and (B) different types of biomolecules that are used in targeted nanoparticles for diagnosis and treatment of thrombosis. Abbreviations: tPA, tissue plasminogen activator; PPACK, D-phenylalanyl-L-prolyl-L-arginyl chloromethylketone. Adapted with permission from ref 75. Copyright 2020 Elsevier. Some features were created with BioRender (www.BioRender.com).

Table 2. Representative Examples of Targeted Nanocarriers for Treatment of Thrombosis with Efficacy Validations in Rat or Mouse Models

mechanism of action	payloads	nanocarriers	refs
delivery of clot-busting drugs	tissue plasminogen activator (tPA), hirulog, heparin, and streptokinase	iron oxide; micelle; carbon capsule; liposome; and copper	66−74
thrombin inhibitors	D-phenylalanyl-L-prolyl-L-arginyl chloromethylketone (PPACK) and aspirin		
platelet aggregation inhibitors	antiplatelet peptides, heparin, and P2Y1 agonist		

CURRENT DIAGNOSTICS

CAUTIONARY NOTE ON CONTAMINATION OF REAGENTS USED FOR MOLECULAR DETECTION OF SARS-COV-2

Huggett JF, Benes V, Bustin SA, Garson JA, Harris K, Kammel M, Kubista M, McHugh TD, Moran-Gilad J, Nolan T, Pfaffl MW, Salit M, Shipley G, Vallone PM, Vandesompele J, Wittwer C, Zeichhardt H.. Clin Chem. 2020 Sep 7:hvaa214. doi: 10.1093/clinchem/hvaa214. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

An expert opinion by microbiologists from Germany, UK, USA, Belgium, and Israel discusses how false positives in PCR assays detecting SARS-CoV-2 occur due to cross-contamination between specimens or through synthesis of billions/trillions of copies of nucleic acid targets of interest in PCR assays (Figure 1). The authors suggest ways to monitor and limit contamination (Box 1), enabling higher test specificity for SARS-CoV-2 detection, in addition to allowing for improved planning and preparedness in future pandemics.

ABSTRACT

Reverse transcription (RT)-PCR, the principal diagnostic method applied in the world-wide struggle against COVID-19, is capable of detecting a single molecule of a viral genome. Correctly designed and practiced RT-PCR assays for SARS-CoV-2 should not cross react with similar but distinct viral pathogens, such as the coronaviruses associated with the common cold, and should perform with very high analytical sensitivity. This analytical performance is predicated on the ability of the method to detect the presence of the selected nucleic acid target, without detection of a false positive signal.

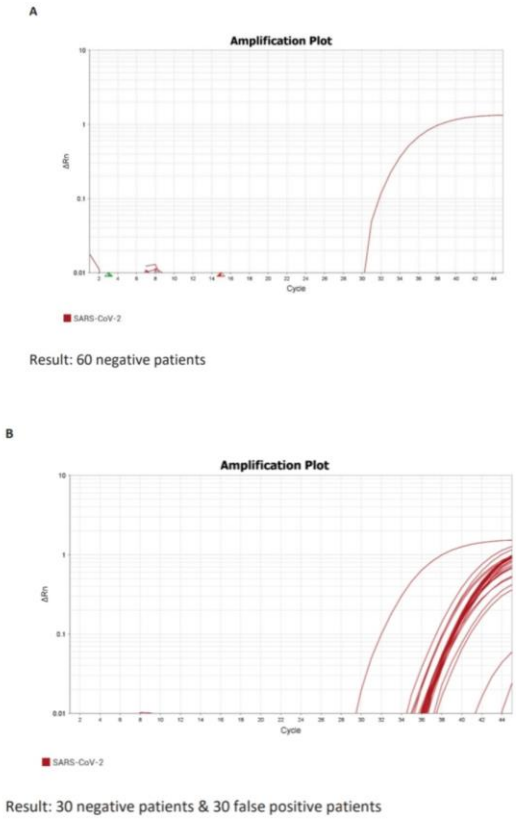
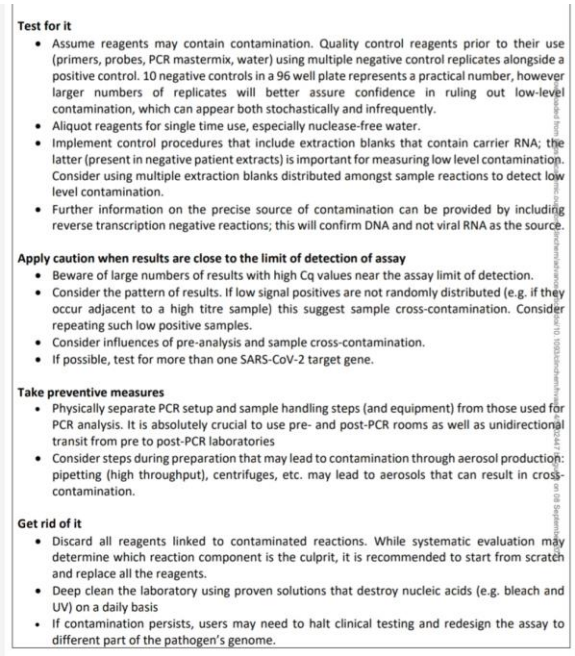


Figure 1: RNA extracts from 60 SARS-CoV-2 negative clinical samples (nasopharyngeal swabs and aspirates) and a positive control (RNA transcript of the SARS-CoV-2 nucleocapsid (N) gene) were amplified in parallel in two multiplexed reactions: A) amplification plot showing SARSCoV-2 fluorescence from a duplex reaction that contains SARS-CoV-2 and RNaseP primers and probes. B) amplification plot of SARS-CoV-2 fluorescence in a triplex PCR assay including the targets SARS-CoV-2, RNaseP, and an internal spike positive control (phocine distemper virus, PDV). This illustrates SARS-CoV-2 target contamination from a non SARS-CoV-2 assay, in this case PDV: half of the negative patient samples now test positive for SARS-CoV-2. The real-time amplification plots for SARS-CoV-2 (N2) were performed on a QuantStudio 5 thermal cycler (Thermo Fisher) using the One Step PrimeScript III RT-PCR Kit (Takara). X axis = PCR cycles, Y axis = Fluorescence, curved lines = plots of amplified SARS-CoV-2 target.



Test for it

- Assume reagents may contain contamination. Quality control reagents prior to their use (primers, probes, PCR mastermix, water) using multiple negative control replicates alongside a positive control. 10 negative controls in a 96 well plate represents a practical number, however larger numbers of replicates will better assure confidence in ruling out low-level contamination, which can appear both stochastically and infrequently.
- Aliquot reagents for single time use, especially nuclease-free water.
- Implement control procedures that include extraction blanks that contain carrier RNA; the latter (present in negative patient extracts) is important for measuring low level contamination. Consider using multiple extraction blanks distributed amongst sample reactions to detect low level contamination.
- Further information on the precise source of contamination can be provided by including reverse transcription negative reactions; this will confirm DNA and not viral RNA as the source.

Apply caution when results are close to the limit of detection of assay

- Beware of large numbers of results with high Cq values near the assay limit of detection.
- Consider the pattern of results. If low signal positives are not randomly distributed (e.g. if they occur adjacent to a high titre sample) this suggest sample cross-contamination. Consider repeating such low positive samples.
- Consider influences of pre-analysis and sample cross-contamination.
- If possible, test for more than one SARS-CoV-2 target gene.

Take preventive measures

- Physically separate PCR setup and sample handling steps (and equipment) from those used for PCR analysis. It is absolutely crucial to use pre- and post-PCR rooms as well as unidirectional transit from pre to post-PCR laboratories
- Consider steps during preparation that may lead to contamination through aerosol production: pipetting (high throughput), centrifuges, etc. may lead to aerosols that can result in cross-contamination.

Get rid of it

- Discard all reagents linked to contaminated reactions. While systematic evaluation may determine which reaction component is the culprit, it is recommended to start from scratch and replace all the reagents.
- Deep clean the laboratory using proven solutions that destroy nucleic acids (e.g. bleach and UV) on a daily basis
- If contamination persists, users may need to halt clinical testing and redesign the assay to different part of the pathogen's genome.

Box 1: How to be confident your SARS-CoV-2 results are not corrupted with contamination.

DEVELOPMENTS IN DIAGNOSTICS

WHEN SHOULD CLINICIANS REPEAT SARS-COV-2 RT-PCR?: REPEAT PCR TESTING TARGETING PATIENTS WITH PULMONARY CT FINDINGS SUGGESTIVE OF COVID-19

Yamamoto K, Saito S, Hayakawa K, Hashimoto M, Takasaki J, Ohmagari N.. Jpn J Infect Dis. 2020 Aug 31. doi: 10.7883/yoken.JJID.2020.531. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Investigators affiliated with the National Center for Global Health and Medicine in Japan performed a retrospective observational study of medical records and rRT-PCR test results of 1803 patients collected between March 9 to April 24, 2020. Of 45 patients who retested after initial negative rRT-PCR results, COVID-19 was verified in 4 patients with typical chest CT findings of SARS-CoV-2 infection and 1 patient with normal CT findings whose test result was thought to be a false positive (1 positive out of 5 rRT-PCR tests within 7 days). The authors recommend that in patients with persistent COVID-19 symptoms and a negative rRT-PCR test, pulmonary CT scans may be more useful than continued rRT-PCR testing to rule out COVID-19.

ABSTRACT

Real-time reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 is sometimes repeated when clinicians suspect a false-negative result, but the conditions under which repeated RT-PCR testing is warranted remain unclear. We evaluated the practice of repeat RT-PCR testing for SARS-CoV-2 in 45 patients who retested after an initial negative PCR test. Of these, the diagnosis of coronavirus disease (COVID-19) was confirmed in four patients with typical chest computed tomography (CT) findings, and one patient without typical CT findings in whom the test result was strongly suspected to be false positive. We recommend repeat RT-PCR only for patients with typical CT findings of COVID-19.

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