The Daily COVID-19 Literature Surveillance Summary

June 24, 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

** 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

Climate

- The director of the World Health Organization Collaborating Center on Public Health Law and Human Rights recommend using the current COVID-19 pandemic to rebuild the World Health Organization (WHO) as a more responsive international agency by:
    - allocating more funding
    - ensuring member state compliance with WHO's recommendations
    - increasing WHO's freedom to act without political influence.
- Researchers in Ahmedabad, India predict that this will affect 26 million couples in India and result in 2.4 million unintended pregnancies, 1.45 million abortions, and 1,700 maternal deaths.
    - Lack of PPE, interruption of public transport, and reallocation of healthcare workers to treatment of COVID-19 patients has led to a decrease in provision of:
        - injectable contraceptives (down 36%),
        - abortions (down 28%),
        - condom kits (down 23%),
        - IUD insertion (down 21%),
        - oral contraceptives (down 15%).
- Approximately 33% of rural counties, 29% of semi-rural counties, and 19% of micropolitan counties fall into the high-risk category based on 11 susceptibility and resiliency indicators created by an author at Iowa State University. This was thought to be a result of lack of health care, social services, and high-speed internet access, making telemedicine nearly impossible. Thus, the author suggests that many rural and semi-rural communities may be underprepared for a COVID-19 outbreak.

Epidemiology

- Descriptive analyses conducted by researchers affiliated with the Centers for Disease Control (CDC) COVID-19 Emergency Response assessed the demographic characteristics, underlying health conditions, symptoms, and outcomes of 1,320,488 confirmed United States cases of COVID-19 from January 22 to May 30, 2020 (Figure). Their results depict the state of the ongoing public health crisis due to COVID-19 and highlight the need for mitigation strategies to slow transmission, especially for vulnerable populations.
    - Major findings included:
        - The cumulative incidence was 403.6 cases per 100,000 persons, incidence was similar between males and females, and the highest incidence was in persons aged 80 year or older at 902 per 100,000 persons.
        - Among positive cases that reported race and ethnicity, 33% were Hispanic patients, 22% were black, and 1.3% were American Indian or Alaska Native, suggesting that these groups were disproportionately affected by COVID-19.
        - Among cases that reported underlying health conditions, 32% of COVID-19 patients had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease.
        - Hospitalizations and deaths were higher in patients with reported underlying health conditions.

Understanding the pathology

- A single-cell RNA sequencing (scRNAseq) study conducted in multiple centers in Shanghai, China focused on the expression of ACE2 as a model for SARS-CoV-2 virulence and found:
    - ACE2 was expressed in arterial vascular cells of fibrotic lungs (compared to alveolar type 2 [AT2] cells of normal lungs), which authors suggest may allow the virus to spread hematogenously by transporting across the lung-blood interface.
    - Both TMPRSS2 and FURIN were expressed in AT2 cells of normal lungs, but only FURIN was found in fibrotic lungs, suggesting that FURIN alone is sufficient for SARS-CoV-2 viral entry into cells of fibrotic lungs.
    - Higher ACE2-positive rates in failed heart cells, which authors suggest may allow the virus to spread to the heart from the lungs and play a role in multi-organ involvement and cardiac injury.
    - Lower ACE2 expression in arterial vascular cells of failed hearts, which could correlate with weak infectability of the heart.
    - Normal hearts showed expression of viral response genes compared to failed hearts which expressed more inflammatory markers.
    - ACE2 lung expression in human carcinoma and mice tissue was upregulated in response to viral infection and LPS inflammation, respectively, suggesting that previous viral infection or inflammatory states may make patients more susceptible to COVID-19.

Management

- Obstetricians at four academic medical centers in New York City found significant changes to their labor and delivery policies when mothers were known or suspected to have COVID-19.
- Notable changes included the following:
    - Requiring staff to wear surgical masks.
    - Screening patients for COVID-19 using history and temperature.
    - Performing deliveries in a negative pressure room when available.
    - Medication usage: most of the sites reported using corticosteroids for fetal lung maturity, magnesium sulfate for COVID-19 patients experiencing preterm labor or preeclampsia, and no use of carboprost.
    - Thromboprophylaxis was initiated at three of the four sites (rationale for this was not stated, but was likely due to presumed increased risk in COVID-19).
    - There were significant differences in the sites' policies for checking the fetus in a hospitalized pregnant patient who tested positive for SARS-CoV-2, with one site starting to check a daily fetal heartbeat at 24 weeks and another site starting at 34 weeks. Half the sites performed daily non-stress tests in addition to fetal heartbeat checks.

Adjusting the practice

- COVID-19 pandemic to include strategies to help patients' families cope with being separated from their loved ones during ICU stays and potentially end-of-life processes.
- The authors specifically say that ICU providers must:
    - acknowledge the uniqueness of the situation with families,
    - initiate video conferencing early in treatment when possible and if desired by the family,
    - allow themselves to display their emotions when talking with families, and
    - address potential mental health issues and trauma responses directly.
- Authors from the Washington University in St. Louis School of Medicine and Mayo Clinic in Rochester recommend the following:
    - A combination of all of these should be considered the "Gold Standard" for this diagnosis (Table 2).
        - Known exposure history.
        - Symptoms and clinical exam:
        - Fever is the most common symptom of COVID-19 seen in 84%-87%.
        - Hyposmia ([LR+] 5.3, [LR-] 0.61) and hypogeusia (LR+ 7.1, LR- 0.38) are better to rule-in COVID-19; less helpful to rule out.
        - Routine Labs:
          -Lymphopenia is seen in over 50% of COVID-19 patients.
          -Elevated prothrombin time, ferritin, D-dimer, or IL-6 seen in severe COVID-19.
        - Imaging:
          -Single view Chest X-ray has sensitivity range from 33-60%.
          -CT may increase diagnostic sensitivity in conjunction with rRT-PCR; ~97% sensitivity.
        - Serology:
          -May identify past SARS-CoV-2 infection.
          -High false-positive rate; test specificity ranges 87-100%.
        - Viral culture with rRT-PCR (real-time RT-PCR):
          -rRT-PCR is the standard criterion for diagnosis.
          -High false-negativity rate; test sensitivity ranges 60-78% (Table 1 for common causes).
          -Blood and urine samples for rRT-PCR are inadequate due to limited virus in body fluids.

R&D Diagnosis and Treatments

- This retrospective case-control study conducted at Maimonides Medical Center, New York evaluates mortality differences in severe and critical COVID-19 patients treated with tocilizumab, an interleukin-6 inhibitor. While there was no significant difference in mortality between the tocilizumab-treated cohort (n=96) and the control patients (n=97; 52% vs. 62.1% P= 0.09), exclusion of intubated patients revealed a significantly decreased mortality rate in the treated cohort (6% vs. 27% P= 0.024; Table 3). Given limitations in exact matching of the cohorts, the authors urge for randomized control trials to evaluate tocilizumab's role in controlling the cytokine storm linked to high mortality in COVID-19 patients.
- Iranian authors performed a review of in vivo and in vitro studies from the last 50 years to document Ivermectin's antiviral activities against a wide variety of DNA and RNA viruses, including SARS-CoV-2 (Table 1). Although an in vitro study has shown Ivermectin's antiviral activity against COVID-19, the authors warn against immediately using Ivermectin as a therapy, which is consistent with Food and Drug Administration (FDA) recommendations as well; the

lack of in vivo studies available support the need for more clinical trials and safer formulations of Ivermectin prior to its establishment as a treatment for COVID-19.

TABLE OF CONTENTS

DATA ON CORONA-VIRUS READINESS STRATEGIES INFLUENCING CUSTOMER SATISFACTION AND CUSTOMER BEHAVIOURAL INTENTIONS IN SOUTH AFRICAN RETAIL STORES

Rukuni TF, Maziriri ET.. Data Brief. 2020 Aug;31:105818. doi: 10.1016/j.dib.2020.105818. Epub 2020 Jun 5.
Level of Evidence: 3 - Local non-random sample

BLUF

A survey conducted in Bloemfontein, South Africa by University of the Free State that received responses from 344 individuals shopping at ten different retail stores analyzed data using the the "Statistical Packages for Social Sciences (SPSS) and the Smart PLS software for structural equation modelling (SEM) technique" (Table 1) and found a statistically significant positive impact of retail stores that sanitized shelves and sanitized counters on customer satisfaction and a statistically insignificant effect of sanitized retail entrances, social distancing, and senior citizen shopping hours on customer satisfaction (Table 3), suggesting that the former safety measures are important to customers and should be emphasized by retail marketers.

ABSTRACT

This article presents raw inferential statistical data that determined the coronavirus readiness strategies at retail stores in South Africa and their consequences for consumer behavioural intentions. The data was collected from customers within the metropolitan area of Bloemfontein. The data were analysed using a quantitative approach. Structured questionnaires were provided to customers throughout South Africa's Bloemfontein metropolitan area. Reliability and validity were confirmed. The data was presented using Structural Equation modelling (SEM) using the Smart PLS program. The analysis of the SEM path shows estimates of the interconnectivity of the major constructs in the data. The findings from this dataset show that sanitised retail entrances, sanitised retail counters and sanitised retail shelves had a statistically significant effect on customer satisfaction with covid-19 readiness in retail stores. Furthermore, the data reveals that retail social distancing and senior citizens shopping hours had a statistically insignificant effect on customer satisfaction with covid-19 readiness. Moreover, the data reveals that customer satisfaction with covid-19 readiness strategies of retail stores also had a positive and statistically significant effect on customer behavioural intentions.

FIGURES

Table 1
Measurement accuracy assessment.

Research constructs	PLS code item	Scale item		Cronbach's alpha value	Composite reliability	Average variance extracted (AVE)	Factor loadings
		Mean	SD				
Sanitised retail entrances	SRE1	3.178	1.181	0.858	0.904	0.702	0.806
	SRE2	3.930	0.932				0.836
	SRE3	3.439	0.986				0.877
	SRE4	3.159	1.154				0.830
Sanitised retail shelves	SRS1	3.159	1.115	0.679	0.824	0.611	0.696
	SRS2	3.064	1.032				0.864
	SRS3	3.471	1.032				0.776
Sanitised retail counters	SRC1	3.274	1.104	0.856	0.902	0.698	0.761
	SRC2	3.140	1.202				0.870
	SRC3	3.873	0.949				0.843
	SRC4	3.535	1.080				0.864
Retail social distancing	RSD1	3.395	1.081	0.838	0.892	0.674	0.796
	RSD2	3.541	1.056				0.838
	RSD3	3.497	0.988				0.861
	RSD4	3.025	1.094				0.787
Senior citizens shopping hours	SCSH1	3.013	1.041	0.873	0.912	0.723	0.849
	SCSH2	3.025	1.022				0.868
	SCSH3	3.274	1.104				0.857
	SCSH4	3.140	1.202				0.826
Customer satisfaction	CSC1	3.331	0.967	0.799	0.882	0.713	0.847
	CSC2	3.089	1.055				0.876
	CSC3	3.140	1.202				0.809
Customer behavioural intentions	CBI1	3.873	0.949	0.888	0.922	0.748	0.823
	CBI2	3.535	1.080				0.895
	CBI3	3.395	1.081				0.886
	CBI4	3.541	1.056				0.854

Table 3
Outcomes of structural equation model analysis.

Path	Hypothesis	Path coefficients (β)	T- Statistics	Decision
Sanitised retail entrances -> Customer satisfaction with retail covid-19 readiness	H1(+)	0.157	2.382	Positive and insignificant
Sanitised retail shelves -> Customer satisfaction with retail covid-19 readiness	H2(+)	0.365	5.592	Positive and significant
Sanitised retail counters -> Customer satisfaction with retail covid-19 readiness	H3(+)	0.149	2.251	Positive and significant
Retail social distancing -> Customer satisfaction with retail covid-19 readiness	H4 (-)	0.095	1.505	Positive and insignificant
Senior citizens shopping hours -> Customer satisfaction with retail covid-19 readiness	H5 (+)	−0.041	0.688	Negative and insignificant
Customer satisfaction with retail covid-19 readiness -> Customer behavioural intentions	H6 (+)	0.454	9.444	Positive and significant

AFTER COVID-19: THINKING DIFFERENTLY ABOUT RUNNING THE HEALTH CARE SYSTEM

Butler SM.. JAMA. 2020 Jun 23;323(24):2450-2451. doi: 10.1001/jama.2020.8484.
Level of Evidence: Other - Expert Opinion

BLUF

An expert opinion piece written by an author from Brookings Institution discusses innovative strategies that should be emphasized to improve the US healthcare system post-COVID-19:
- using waivers to boost federalism
- rethinking healthcare access hubs and the role of hospitals
- expanding telehealth
- consolidating public funds so that cooperation is facilitated among different departments of the state

GLOBAL

COVID-19 REVEALS URGENT NEED TO STRENGTHEN THE WORLD HEALTH ORGANIZATION

Gostin LO.. JAMA. 2020 Jun 16;323(23):2361-2362. doi: 10.1001/jama.2020.8486.
Level of Evidence: Other - Expert Opinion

BLUF

The director of the World Health Organization Collaborating Center on Public Health Law and Human Rights outlines the contributions made by the World Health Organization (WHO) in controlling a variety of global health threats, including tuberculosis, malaria, small pox, polio, Zika, Ebola, etc. They recommend using the current COVID-19 pandemic to rebuild WHO as a more responsive international agency by allocating more funding, ensuring member state compliance with WHO's recommendations, and increasing WHO's freedom to act without political influence.

AFFECTING THE HEALTHCARE WORKFORCE

TOWARD BETTER PREPAREDNESS FOR THE NEXT PANDEMIC

Shapiro LI, Kajita GR, Arnsten JH, Tomer Y.. J Clin Invest. 2020 Jun 23:140296. doi: 10.1172/JCI140296. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A literature review conducted by physicians of the Albert Einstein College of Medicine focused on survey results regarding resident physician experiences with PPE and COVID-19 exposure in New York City, NY from March 2020 through April 2020. Results showed that there is a serious need to prepare PPE stockpiles and create distribution plans to keep the healthcare workforce from becoming infected, particularly during aerosolizing procedures such as intubation.

IMPACT OF COVID-19 ON FAMILY PLANNING SERVICES IN INDIA

32552622. Impact of COVID-19 on family planning services in India
Level of Evidence: Other - Expert Opinion

BLUF

Researchers in Ahmedabad, India discuss the impacts of COVID-19 on access to and availability of contraceptive products. Lack of PPE, interruption of public transport, and reallocation of healthcare workers to treatment of COVID-19 patients has led to a decrease in provision of injectable contraceptives (down 36%), abortions (down 28%), condom kits (down 23%), IUD insertion (down 21%), and oral contraceptives (down 15%). Authors predict that this will affect 26 million couples in India and result in 2.4 million unintended pregnancies, 1.45 million abortions, and 1,700 maternal deaths. Thus, they advocate for Indian health care systems to address family planning services provisions during the COVID-19 pandemic.

COVID-19 AS A RISK FACTOR FOR OBSTETRIC VIOLENCE

Sadler M, Leiva G, Olza I.. Sex Reprod Health Matters. 2020 Jun 19:1-4. doi: 10.1080/26410397.2020.1785379. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A commentary by several authors from Spain and Chile highlights the adverse impact that the COVID-19 pandemic is having on maternal care and the rights of women and newborns. The "prohibition of companionship" during labor and after birth (i.e. skin-to-skin contact between mother and newborn), unnecessary inductions of labor, and unjustified Cesarean sections have been noted in webinars and reports; these practices are contradictory to those advocated by the World Health Organization. The authors argue that these practices are not evidence-based and suggest such practices could potentially lead to poorer outcomes.

COMMUNITY SUSCEPTIBILITY AND RESILIENCY TO COVID-19 ACROSS THE RURAL-URBAN CONTINUUM IN THE UNITED STATES

Peters DJ.. J Rural Health. 2020 Jun 16. doi: 10.1111/jrh.12477. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

An author at Iowa State University created a model to determine the susceptibility and resiliency of counties across the United States. Using data from 11 susceptibility indicators and exploratory factor analysis, a susceptibility scale was created and every county was given a score (Table 1). The results showed that nonmetropolitan counties are more susceptible to COVID-19 than large urban counties (Figure 3). Approximately 33% of rural counties, 29% of semi-rural counties, and 19% of micropolitan counties fall into the high-risk category. Assessing resiliency of each high-risk county showed that rural communities are more vulnerable, likely due to a lack of health care, social services, and high-speed internet access, making telemedicine nearly impossible. Thus, the author suggests that many rural and semi-rural communities may be underprepared for a COVID-19 outbreak.

ABSTRACT

PURPOSE: This study creates a COVID-19 susceptibility scale at the county level, describes its components, and then assesses the health and socioeconomic resiliency of susceptible places across the rural-urban continuum. METHODS: Factor analysis grouped 11 indicators into 7 distinct susceptibility factors for 3,079 counties in the conterminous United States. Unconditional mean differences are assessed using a multivariate general linear model. Data from 2018 are primarily taken from the US Census Bureau and CDC. RESULTS: About 33% of rural counties are highly susceptible to COVID-19, driven by older and health-compromised populations, and care facilities for the elderly. Major vulnerabilities in rural counties include fewer physicians, lack of mental health services, higher disability, and more uninsured. Poor Internet access limits telemedicine. Lack of social capital and social services may hinder local pandemic recovery. Meat processing facilities drive risk in micropolitan counties. Although metropolitan counties are less susceptible due to healthier and younger populations, about 6% are at risk due to community spread from dense populations. Metropolitan vulnerabilities include minorities at higher health and

diabetes risk, language barriers, being a transportation hub that helps spread infection, and acute housing distress. CONCLUSIONS: There is an immediate need to know specific types of susceptibilities and vulnerabilities ahead of time to allow local and state health officials to plan and allocate resources accordingly. In rural areas it is essential to shelter-in-place vulnerable populations, whereas in large metropolitan areas general closure orders are needed to stop community spread. Pandemic response plans should address vulnerabilities.

FIGURES

Table 1 COVID-19 Susceptibility Scale Factor Analysis for N = 3,079 Counties in the Conterminous United States

	Factors							
	1	2	3	4	5	6	7	h^2
Factor Loadings and Variance								
Population density (sq. mi)	−0.06	−0.07	−0.01	−0.02	**0.99**	−0.02	−0.03	0.99
Group quarters (%)	0.09	−0.11	0.07	−0.05	−0.02	**0.96**	0.00	0.95
Age 65-84 (%)	0.06	**0.88**	0.05	−0.08	−0.08	−0.13	−0.12	0.83
Age 85 and older (%)	−0.13	**0.67**	**0.59**	−0.01	−0.01	−0.01	0.01	0.81
Elderly and nursing care jobs (10k)†	0.01	0.10	**0.88**	0.08	0.00	0.08	0.05	0.80
Cancer mortality (100k)†	**0.78**	0.06	0.01	0.00	0.02	0.07	0.26	0.69
Cardiovascular mortality (100k)†	**0.82**	−0.08	0.00	0.06	0.02	0.04	0.05	0.68
Lower respiratory mortality (100k)†	**0.77**	0.06	−0.09	0.03	−0.11	0.04	0.10	0.63
Diabetes mortality (100k)†	0.27	−0.11	0.05	−0.02	−0.03	−0.01	**0.92**	0.94
Flu and pneumonia mortality (100k)†	**0.57**	−0.36	0.36	−0.22	−0.06	−0.21	−0.13	0.69
Meat processing jobs (10k)†	0.04	−0.07	0.07	**0.97**	−0.02	−0.05	−0.02	0.96
Eigenvalue	2.55	1.72	1.08	1.04	0.99	0.80	0.78	n.a.
Variance explained (%)	23.19	15.64	9.83	9.42	9.01	7.28	7.10	n.a.
Parallel Test								
Random eigenvalue	0.88	0.86	0.83	0.82	0.81	0.80	0.79	n.a.
Parallel test (model–random eigenvalue)	1.67	0.86	0.25	0.21	0.18	0.01	−0.01	n.a.

Notes: † = rate per population, bold indicates high factor loading. Principal components extraction, varimax rotation; h2 = communality or variance explained by factors. Sampling adequacy KMO = 0.67, root mean square residual RMSR = 0.07.

Table 1. COVID-19 Susceptibility Scale Factor Analysis for N=3,079 Counties in the Conterminous United States.

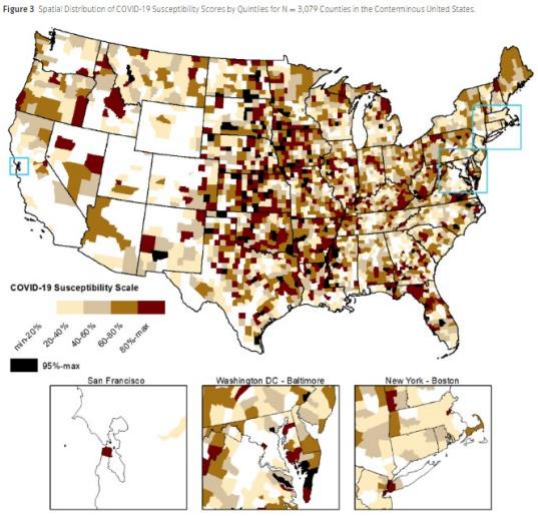


Figure 3. Spatial Distribution of COVID-19 Susceptibility Scores by Quintiles for N = 3,079 Counties in the Conterminous United States.

EPIDEMIOLOGY

CORONAVIRUS DISEASE 2019 CASE SURVEILLANCE - UNITED STATES, JANUARY 22-MAY 30, 2020

32555134. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020
Level of Evidence: 3 - Local non-random sample

BLUF

Descriptive analyses conducted by researchers affiliated with the Centers for Disease Control (CDC) COVID-19 Emergency Response assessed the demographic characteristics, underlying health conditions, symptoms, and outcomes of 1,320,488 confirmed United States cases of COVID-19 from January 22 to May 30, 2020 (Figure). Their results depict the state of the ongoing public health crisis due to COVID-19 and highlight the need for mitigation strategies to slow transmission, especially for vulnerable populations.

SUMMARY

Major findings included:
1. The cumulative incidence was 403.6 cases per 100,000 persons, incidence was similar between males and females, and the highest incidence was in persons aged 80 year or older at 902 per 100,000 persons.
2. Among positive cases that reported race and ethnicity, 33% were Hispanic patients, 22% were black, and 1.3% were American Indian or Alaska Native, suggesting that these groups were disproportionately affected by COVID-19.
3. Among cases that reported underlying health conditions, 32% of COVID-19 patients had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease.
4. Hospitalizations and deaths were higher in patients with reported underlying health conditions.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic resulted in 5,817,385 reported cases and 362,705 deaths worldwide through May, 30, 2020, including 1,761,503 aggregated reported cases and 103,700 deaths in the United States. Previous analyses during February-early April 2020 indicated that age >=65 years and underlying health conditions were associated with a higher risk for severe outcomes, which were less common among children aged <18 years (1-3). This report describes demographic characteristics, underlying health conditions, symptoms, and outcomes among 1,320,488 laboratory-confirmed COVID-19 cases individually reported to CDC during January 22-May 30, 2020. Cumulative incidence, 403.6 cases per 100,000 persons, was similar among males (401.1) and females (406.0) and highest among persons aged >=80 years (902.0). Among 599,636 (45%) cases with known information, 33% of persons were Hispanic or Latino of any race (Hispanic), 22% were non-Hispanic black (black), and 1.3% were non-Hispanic American Indian or Alaska Native (AI/AN). Among 287,320 (22%) cases with sufficient data on underlying health conditions, the most common were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%). Overall, 184,673 (14%) patients were hospitalized, 29,837 (2%) were admitted to an intensive care unit (ICU), and 71,116 (5%) died. Hospitalizations were six times higher among patients with a reported underlying condition (45.4%) than those without reported underlying conditions (7.6%). Deaths were 12 times higher among patients with reported underlying conditions (19.5%) compared with those without reported underlying conditions (1.6%). The COVID-19 pandemic continues to be severe, particularly in certain population groups. These preliminary findings underscore the need to build on current efforts to collect and analyze case data, especially among those with underlying health conditions. These data are used to monitor trends in COVID-19 illness, identify and respond to localized incidence increase, and inform policies and practices designed to reduce transmission in the United States.

FIGURES

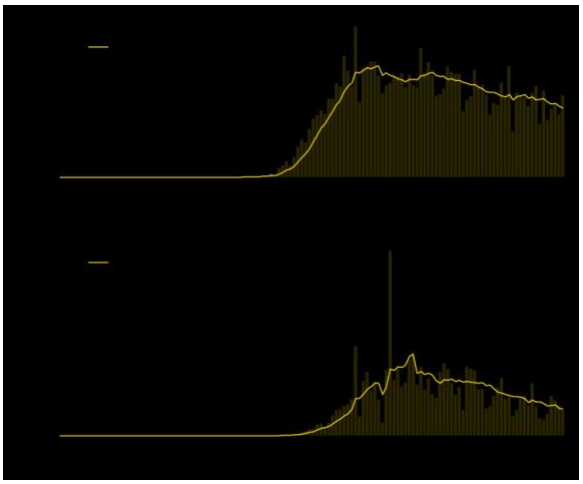


Figure. A combination histogram, epidemiologic curve, and line chart showing the daily number of COVID-19 cases (A) and COVID-19–associated deaths (B) reported to CDC, in the United States, during January 22–May 30, 2020.

MODELING

EVIDENCE FOR TRANSMISSION OF COVID-19 PRIOR TO SYMPTOM ONSET

Tindale LC, Stockdale JE, Coombe M, Garlock ES, Lau WYV, Saraswat M, Zhang L, Chen D, Wallinga J, Colijn C.. Elife. 2020 Jun 22;9:e57149. doi: 10.7554/eLife.57149. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

This retrospective cohort study conducted by the University of British Columbia evaluates contact tracing data from Singapore and Tianjin, China (Table 1) in order to explore the extent of pre-symptomatic transmission of COVID-19. Findings include that serial intervals are shorter than incubation periods (Figure 8), suggesting there is substantial transmission of SARS-CoV-2 prior to symptom onset. This study is limited by the uncertainty in timing of exposure and the identification of the infectors.

ABSTRACT

We collated contact tracing data from COVID-19 clusters in Singapore and Tianjin, China and estimated the extent of pre-symptomatic transmission by estimating incubation periods and serial intervals. The mean incubation periods accounting for intermediate cases were 4.91 days (95%CI 4.35, 5.69) and 7.54 (95%CI 6.76, 8.56) days for Singapore and Tianjin, respectively. The mean serial interval was 4.17 (95%CI 2.44, 5.89) and 4.31 (95%CI 2.91, 5.72) days (Singapore, Tianjin). The serial intervals are shorter than incubation periods, suggesting that pre-symptomatic transmission may occur in a large proportion of transmission events (0.4-0.5 in Singapore and 0.6-0.8 in Tianjin, in our analysis with intermediate cases, and more without intermediates). Given the evidence for pre-symptomatic transmission it is vital that even individuals who appear healthy abide by public health measures to control COVID-19.

FIGURES

Without intermediates	Incubation (days)	Serial interval (days)	Mean difference (days)	Portion pre-symptomatic (-)
Singapore (all)	5.99 (4.97, 7.14)	4.0 (2.73, 5.57)	1.99	0.74
Singapore (early)	5.91 (4.50,7.64)		1.91	0.742
Singapore (late)	6.06 (4.70, 7.67)		2.06	0.744
Tianjin (all)	8.68 (7.72, 9.7)	5.0 (3.82, 6.12)	3.68	0.81
Tianjin (early)	6.88 (5.97,7.87)		1.88	0.72
Tianjin (late)	12.4 (11.1,13.7)		7.4	0.96
Account for intermediates				
Singapore $r = 0.05$	4.91	4.17 (2.44, 5.89)	0.77	0.53
Singapore $r = 0.1$	4.43		0.26	0.46
Singapore $r = 0.15$	4.12		-0.05	0.41
Singapore $r = 0.2$	3.89		-0.28	0.38
Tianjin $r = 0.05$	7.54	4.31 (2.91, 5.72)	3.23	0.79
Tianjin $r = 0.1$	6.89		2.58	0.74
Tianjin $r = 0.15$	6.30		1.99	0.67
Tianjin $r = 0.2$	5.91		1.6	0.64

Table 1. Mean incubation period, serial interval and pre-symptomatic transmission. Incubation periods are based on the gamma estimates because these are the most convenient for taking the covariation of serial intervals and incubation periods into account (done throughout the table). 95% CIs are provided in brackets.

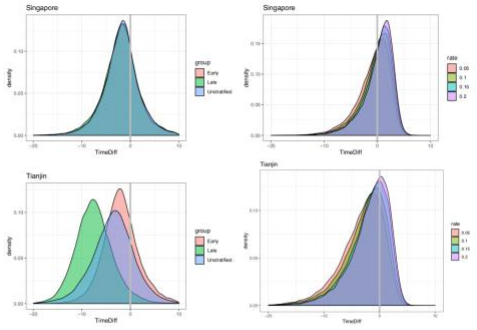


Figure 8. Pre-symptomatic infection as estimated by samples of (serial interval - incubation period), accounting for covariation. Top: Singapore. Bottom: Tianjin. Left: without intermediates. Right: accounting for intermediates. Grey vertical line: 0. Samples below zero indicate pre-symptomatic transmission. In all cases there is substantial pre-symptomatic transmission.

ESTIMATING THE PREVALENCE AND RISK OF COVID-19 AMONG INTERNATIONAL TRAVELERS AND EVACUEES OF WUHAN THROUGH MODELING AND CASE REPORTS

Luo G, McHenry ML, Letterio JJ.. PLoS One. 2020 Jun 23;15(6):e0234955. doi: 10.1371/journal.pone.0234955. eCollection 2020.
Level of Evidence: Other - Modeling

BLUF

A new model based on COVID-19 travel case reports from Japan, Singapore, and Korea created by Case Western Reserve University captured movement of Wuhan travelers before a quarantine/travel ban was announced on 23 January 2020. Their model estimates that the highest rate of infected travelers was seen from 19 January to 22 January with an average infection rate of 1.3% among those who traveled (Figure 2). This rate is higher than previously thought, which may indicate the need to re-examine initial spread to better model current and future pandemics.

FIGURES

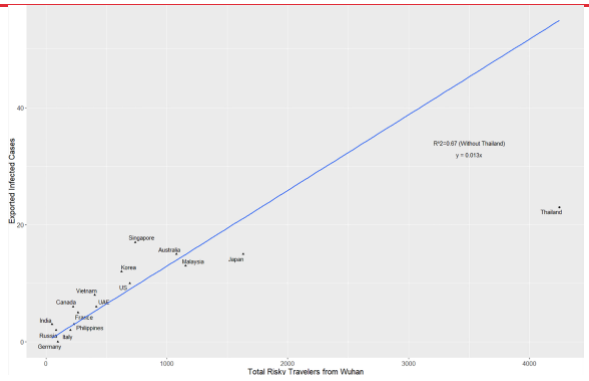


Figure 2. Exported infected cases and risky travelers. The number of confirmed exported cases were plotted against the number of estimated risky travelers from Wuhan from January 19th to 22nd, 2020. A line of best fit was used for countries besides Thailand. Infected evacuees were excluded from the exported infected cases.

ASSESSING FUNCTIONAL PROPAGATION PATTERNS IN COVID-19

Zanin M, Papo D.. Chaos Solitons Fractals. 2020 Sep;138:109993. doi: 10.1016/j.chaos.2020.109993. Epub 2020 Jun 12.
Level of Evidence: Other - Modeling

BLUF

Authors funded by the European Research Council (ERC) applied functional models to the spread of the COVID-19 pandemic in the six countries with the highest number of cases per capita (US, UK, Italy, France, Spain, and Belgium) and found that by using this methodology, researchers can predict the temporospatial spread of SARS-CoV-2 (Table 1 and Figure 3).

ABSTRACT

Among the many efforts done by the scientific community to help coping with the COVID-19 pandemic, one of the most important has been the creation of models to describe its propagation, as these are expected to guide the deployment of containment and health policies. These models are commonly based on exogenous information, as e.g. mobility data, whose limitedness always compromise the reliability of obtained results. In this contribution we propose a different approach, based on extracting relationships between the evolution of the disease in different regions through information theoretical metrics. In a way similar to what is commonly done in neuroscience, propagation is understood as information transfer, and the resulting propagation patterns are represented and studied as functional networks. By applying this methodology to the dynamics of COVID-19 in several countries and regions thereof, we were able to reconstruct static and time-varying propagation graphs. We further discuss the advantages, promises and open research questions associated with this functional approach.

FIGURES

Table 1

Cases *vs.* death peaks. This table reports the approximate date of the day with most daily confirmed cases (second column) and with most deaths (third column) for different countries. The first six countries correspond to those that had a higher density of cases (see also Fig. 2; while the last three are examples of countries that have limited the propagation of the disease.

Country	Date of peak, daily confirmed	Date of peak, daily deaths	Difference
Belgium	April 10th	April 12th	2
Spain	March 31st	April 2nd	2
United Kingdom	April 5th	April 9th	4
Italy	March 21st	27th March	6
France	March 31st	April 6th	6
US	April 24th	May 6th	12
Switzerland	March 23rd	March 31st	8
Germany	March 28th	April 16th	19
South Korea	March 1st	March 23rd	22

Table 1. Cases vs. death peaks. This table reports the approximate date of the day with most daily confirmed cases (second column) and with most deaths (third column) for different countries. The first six countries correspond to those that had a higher density of cases

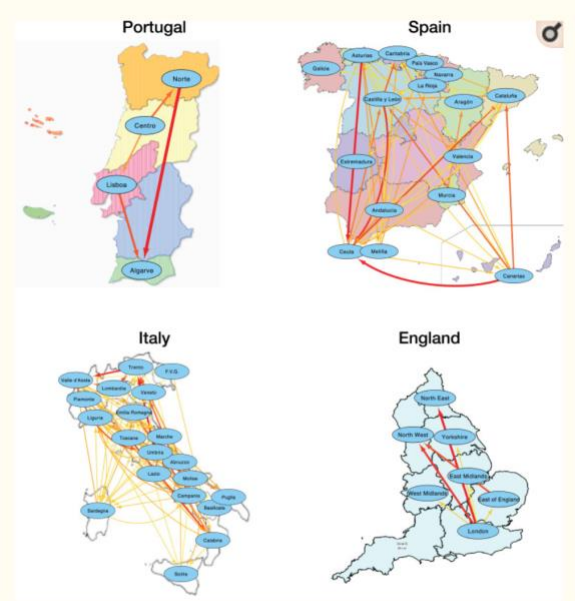


Fig. 3

Functional propagation networks for Portugal, Spain, Italy and England. Link's thickness and color indicates the strength of the causality link (from yellow for the weakest, to red for the strongest). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Figure 3. Functional propagation networks for Portugal, Spain, Italy and England. Link's thickness and color indicates the strength of the causality link (from yellow for the weakest, to red for the strongest).

ARE CO-INFECTIONS WITH COVID-19 AND INFLUENZA LOW OR UNDERREPORTED? AN OBSERVATIONAL STUDY EXAMINING CURRENT PUBLISHED LITERATURE INCLUDING THREE NEW UNPUBLISHED CASES

Antony SJ, Almaghlouth NK, Heydemann EL.. J Med Virol. 2020 Jun 12. doi: 10.1002/jmv.26167. Online ahead of print.
Level of Evidence: 4 - Review / Literature Review

BLUF

The authors reviewed the literature and found six studies based in China, Iran, USA, and Japan, and combined those results with data from three patients from El Paso, Texas, between December 2019 and May 2020 to study the occurrence of co-infections with SARS-CoV-2 and influenza in 16 patients (13 with influenza A, three with influenza B). All patients presented with the symptoms of fever, dyspnea, and cough, while leukopenia, lymphopenia, and elevated C-reactive protein were the most common lab findings. Thirteen patients presented with viral pneumonia and nine of these had ground-glass opacities. Overall, these findings may provide insight into the clinical features of influenza and SARS-CoV-2 co-infection as flu season approaches. The authors recommend further studies to better elucidate the characteristics and clinical prognosis associated with co-infection.

ABSTRACT

As the COVID-19 pandemic continues, one major point of uncertainty is the impact this novel pathogen will have during the upcoming 2020-2021 flu season. While the influenza virus is a known contributor to human morbidity and mortality, the question of how a coinfection between COVID-19 and influenza might manifest is of utmost concern. The aim of this study was to review the limited cases of COVID-19/influenza coinfection currently available in the literature, along with cases in the community of El Paso, Texas, to determine whether any patterns of clinical presentation and morbidity emerged. An international review of the literature was conducted. Six published articles describing COVID-19/influenza coinfection were identified, with a total of thirteen patients described therein. Three additional patients were identified from the El Paso, Texas data. The most common presenting symptoms were fever and cough. The most common laboratory findings were elevated C-reactive protein and lymphocytopenia. Thirteen patients presented with viral pneumonia findings on CT, and nine had findings of ground-glass opacity. Finally, complications were reported in six patients, with most common complication being acute respiratory distress syndrome (ARDS). The results of the review indicate that, due to the similarity in presentation between COVID-19 and influenza, further analysis will be required to understand the effects of coinfection on morbidity and mortality. However, the limited number of coinfection cases in the literature indicates that the implementation of COVID-19 control measures may continue to play a role in limiting the spread of these human respiratory pathogens. This article is protected by copyright. All rights reserved.

PATHOLOGICAL FINDINGS OF POSTMORTEM BIOPSIES FROM LUNG, HEART, AND LIVER OF 7 DECEASED COVID-19 PATIENTS

.

Level of Evidence: 4 - Case-series

BLUF

In this case series, Iranian researchers performed core needle biopsies of lung, heart, and liver tissue in 7 patients who died from COVID-19. The prepared tissue sections were reviewed by two expert pathologists, who reported lung specimens with diffuse alveolar damage (DAD) and evidence of histological organization in patients with longer hospitalizations, cardiac biopsies with inflammatory cells that did not meet criteria for myocarditis, and limited necrosis suggestive of ischemia in both cardiac and liver samples (Table 2, Figures 1 and 3). The authors conclude that, consistent with previous research on other strains of coronavirus, DAD is the primary histological feature in the lung and that disease duration is associated with histological organization.

ABSTRACT

Background. A novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been affecting almost all nations around the world. Most infected patients who have been admitted to intensive care units show SARS signs. In this study, we aimed to achieve a better understanding of pathological alterations that take place during the novel coronavirus infection in most presumed affected organs. Methods. We performed postmortem core needle biopsies from lung, heart, and liver on 7 deceased patients who had died of coronavirus disease 2019. Prepared tissue sections were observed by 2 expert pathologists. Results. Diffuse alveolar damage was the main pathologic finding in the lung tissue samples. Patients with hospitalization durations of more than 10 days showed evidence of organization. Multinucleated cells in alveolar spaces and alveolar walls, atypical enlarged cells, accumulation of macrophages in alveolar spaces, and congestion of vascular channels were the other histopathologic alteration of the lung. None of our heart biopsy samples met the criteria for myocarditis. Liver biopsies showed congestion, micro- and macro-vesicular changes, and minimal to mild portal inflammation, in the majority of cases. Conclusions. Similar to the previous coronavirus infection in 2003, the main pathologic finding in the lung was diffuse alveolar damage with a pattern of organization in prolonged cases. The SARS-CoV-2 infection does not cause myocarditis, and the ischemia of myocardium is the most probable justification of the observed pathologic changes in the heart. Liver tissue sections mostly showed nonspecific findings; however, ischemia of the liver can be identified in some cases.

FIGURES

Table 2. Pulmonary Pathologic Findings of Deceased COVID-19 Patients.

	Patient						
	1	2	3	4	5	6	7
Hyaline membrane formation	Present	Present	NI	Present	Present	NI	Present
Edema	Present	Present	Present	Present	Present	Present	Present
Fibrin exudation	NI	Present	Present	NI	Present	Present	Present
Multinucleation	Present	Present	Present	NI	Present	Present	NI
Inflammation intensity	Severe in 1 out of 4 cores but mild in other cores	Mild	Severe	Mild and focal	Moderate	Severe	Severe
Inflammation site	Alveolar walls	Alveolar walls	Alveolar spaces	Alveolar wall	Alveolar walls and alveolar spaces	Alveolar space and alveolar walls	Alveolar spaces and alveolar walls
Predominant type of inflammatory cells	Lymphocytes and plasma cells with few PMNs	Lymphocytes with occasional PMNs	PMNs and few lymphocytes	Lymphocyte and rare PMNs	Lymphocytes and few PMNs	PMNs and lypmhocytes	PMNs and lymphocytes
Pneumocyte type II hyperplasia	Present	NI	Present	NI	Present	Present	Present
Atypical enlarged cells	Present	Present	Present	Present	Present	Present	Present
Acute pneumonia pattern	NI	NI	Present	NI	NI	Present	Present with necrosis
Organization	NI	NI	Present	NI	Present	Present	NI
Accumulation of macrophages in alveolar spaces	Present	Present	Present	NI	Present (hemosiderin-laden macrophages are also seen)	Present	NI
Fresh hemorrhage	Present	NI	NI	NI	NI	Present	NI
Vessels	Fibrinoid material deposition in vessel walls	Fibrinoid material deposition in vessel walls	No obvious pathological finding	No obvious pathological finding	No obvious pathological finding	No obvious pathological finding	Fibrinoid material deposition in vessel walls
Squamous metaplasia	No obvious bronchioles	NI	NI	No obvious bronchioles	Present, associated with bronchiolitis	No obvious bronchioles	NI

Abbreviation: NI, not identified; PMN, polymorphonuclear neutrophils.

Table 2. Pulmonary Pathologic Findings of Deceased COVID-19 Patients.

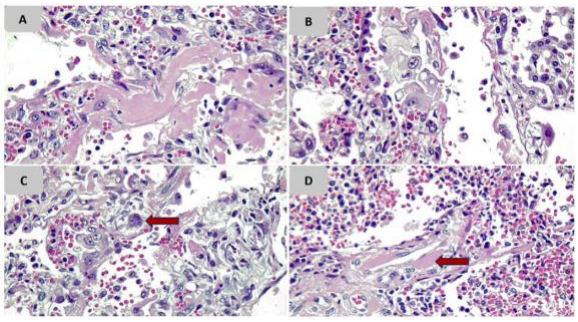


Figure 1. Pathologic findings of lung tissue of case 1. (A) Hyaline membrane formation; (B) intra-alveolar atypical enlarged cells; (C) multinucleated cells; (D) deposition of fibrinoid material in vessel walls.

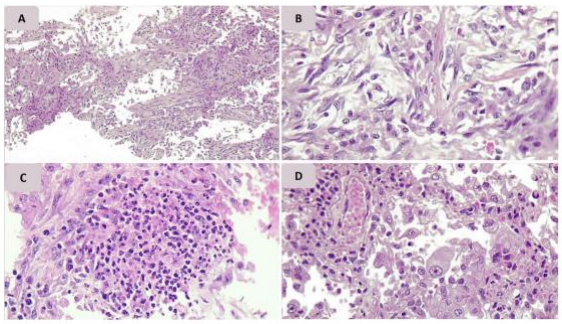


Figure 1. Pathologic findings of lung tissue of case 1. (A) Hyaline membrane formation; (B) intra-alveolar atypical enlarged cells; (C) multinucleated cells; (D) deposition of fibrinoid material in vessel walls.

IN SILICO

STRUCTURE-BASED VIRTUAL SCREENING AND MOLECULAR DYNAMICS SIMULATION OF SARS-COV-2 GUANINE-N7 METHYLTRANSFERASE (NSP14) FOR IDENTIFYING ANTIVIRAL INHIBITORS AGAINST COVID-19

Selvaraj C, Dinesh DC, Panwar U, Abhirami R, Boura E, Singh SK.. J Biomol Struct Dyn. 2020 Jun 22:1-12. doi: 10.1080/07391102.2020.1778535. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

This in silico homology modeling study examines the structure of SARS-CoV-2's Guanine-N7 methyltransferase enzyme and identifies compounds (Figure 7) that inhibit Asn306, Arg310, Trp395, and Asn388, which were identified as "important residues to inhibit the functional mechanism initiated by N7 methyltransferase enzyme" (Figure 1). The authors suggest these findings could be key to the development of therapeutic treatments that inhibit SARS-CoV-2 RNA proliferation.

ABSTRACT

The recent pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) calls the whole world into a medical emergency. For tackling Coronavirus Disease 2019 (COVID-19), researchers from around the world are swiftly working on designing and identifying inhibitors against all possible viral key protein targets. One of the attractive drug targets is guanine-N7 methyltransferase which plays the main role in capping the 5'-ends of viral genomic RNA and sub genomic RNAs, to escape the host's innate immunity. We performed homology modeling and molecular dynamic (MD) simulation, in order to understand the molecular architecture of Guanosine-P3-Adenosine-5',5'-Triphosphate (G3A) binding with C-terminal N7-MTase domain of nsp14 from SARS-CoV-2. The residue Asn388 is highly conserved in present both in N7-MTase from SARS-CoV and SARS-CoV-2 and displays a unique function in G3A binding. For an in-depth understanding of these substrate specificities, we tried to screen and identify inhibitors from the Traditional Chinese Medicine (TCM) database. The combination of several computational approaches, including screening, MM/GBSA, MD simulations, and PCA calculations, provides the screened compounds that readily interact with the G3A binding site of homology modeled N7-MTase domain. Compounds from this screening will have strong potency towards inhibiting the substrate-binding and efficiently hinder the

viral 5'-end RNA capping mechanism. We strongly believe the final compounds can become COVID-19 therapeutics, with huge international support.Communicated by Ramaswamy H. Sarma.

FIGURES

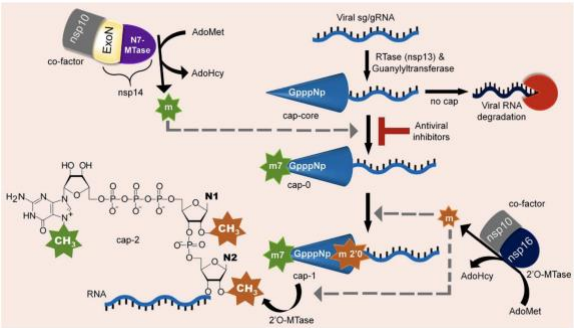


Figure 1. Schematic pathway representation of coronaviral (CoV) RNA capping mechanism of showing the target step for proposed antiviral inhibitors against the SARS-CoV-2 N7-MTase resulting in viral RNA degradation by the host immune response and chemical structure of a viral RNA cap-2 formed at the 5'-end of genomic and sub-genomic RNAs.

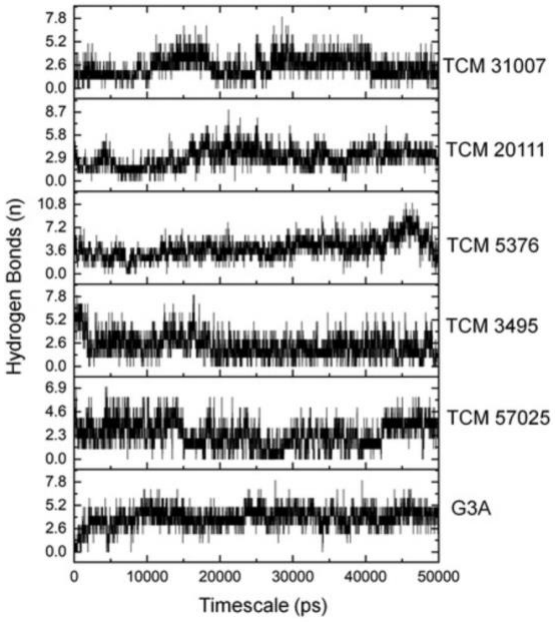


Figure 7. Overall hydrogen-bonding interaction plot of ligand-bound complexes with SARS-CoV-2 substrate-binding site of N7-MTase and its substrate G3A.

IN VITRO

SINGLE-CELL RNA ANALYSIS ON ACE2 EXPRESSION PROVIDES INSIGHTS INTO SARS-COV-2 POTENTIAL ENTRY INTO THE BLOODSTREAM AND HEART INJURY

Guo J, Wei X, Li Q, Li L, Yang Z, Shi Y, Qin Y, Zhang X, Wang X, Zhi X, Meng D.. J Cell Physiol. 2020 Jun 8. doi: 10.1002/jcp.29802. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

A single-cell RNA sequencing (scRNAseq) study conducted in multiple centers in Shanghai, China focused on the expression of ACE2 as a model for SARS-CoV-2 virulence and found:
-ACE2 was expressed in arterial vascular cells of fibrotic lungs (compared to alveolar type 2 [AT2] cells of normal lungs), which authors suggest may allow the virus to spread hematogenously by transporting across the lung-blood interface.
-Both TMPRSS2 and FURIN were expressed in AT2 cells of normal lungs, but only FURIN was found in fibrotic lungs,

suggesting that FURIN alone is sufficient for SARS-CoV-2 viral entry into cells of fibrotic lungs.
-Higher ACE2-positive rates in failed heart cells, which authors suggest may allow the virus to spread to the heart from the lungs and play a role in multi-organ involvement and cardiac injury.
-Lower ACE2 expression in arterial vascular cells of failed hearts, which could correlate with weak infectability of the heart.
-Normal hearts showed expression of viral response genes compared to failed hearts which expressed more inflammatory markers.
-ACE2 lung expression in human carcinoma and mice tissue was upregulated in response to viral infection and LPS inflammation, respectively, suggesting that previous viral infection or inflammatory states may make patients more susceptible to COVID-19.

SUMMARY

Authors discuss the following results:

Lungs:
-Authors found five major cell types in normal and fibrotic lung tissue (type I and type II alveolar cells (AT1, AT2), ciliated bronchial epithelial cells, immune cells, fibroblasts, and vascular cells) based on molecular features.
-In normal lung tissue, AT2 cells were found to express ACE2; in fibrotic lungs, ACE2 was expressed mainly in arterial vascular cells and rarely In AT2. Authors propose that this difference in ACE2 expression supports hematogenous spread of COVID-19 from the lungs.
-Chemokines (CCL2, CXCL12) and complement component (C1R) were highly expressed in ACE2-positive arterial vascular cells of fibrotic lungs and had lower expression of ACE2-positive AT2 cells of normal lungs, suggesting an association with the inflammatory response.
-Both TMPRSS2 and FURIN were expressed in AT2 cells of normal lungs, but only FURIN was expressed in arterial vascular cells of fibrotic lungs, suggesting that SARS-CoV-2 might depend on FURIN in fibrotic lungs.

Hearts:
-Authors identified four major cells types in normal hearts and heart failure hearts (cardiomyocytes, fibroblasts, vascular cells, and immune cells).
-Cells in failed hearts showed higher ACE2-positive rate than normal hearts (7.60% of all cells vs. 5.88% of all cells) and lower expression of ACE2 in arterial vascular cells of failed hearts compared to normal (7.93% of arterial vascular cells vs. 19.4% of arterial vascular cells).
-Gene ontology (GO) enrichment analysis of ACE2-expressing arterial vascular cells in normal hearts showed that highly expressed genes were associated with viral infection response. Failed heart cells expressed SOX4 and MEF2C (regulators of monocyte and B cell differentiation), possibly related to the inflammatory response.

RSV/MERS-CoV:
-Using RNA-seq data, ACE2 expression significantly was upregulated in lung carcinoma cells
infected with RSV and MERS-CoV. ACE2 expression in pulmonary endothelial cells of mice was upregulated after lipopolysaccharide (LPS) injection.
-From these results, authors conclude that viral infection or inflammation (LPS) may make the patient more susceptible to COVID-19.

ABSTRACT

Coronavirus disease-2019 (COVID-19) is a global pandemic with high infectivity and pathogenicity, accounting for tens of thousands of deaths worldwide. Recent studies have found that the pathogen of COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), shares the same cell receptor angiotensin converting enzyme II (ACE2) as SARS-CoV. The pathological investigation of COVID-19 deaths showed that the lungs had characteristics of pulmonary fibrosis. However, how SARS-CoV-2 spreads from the lungs to other organs has not yet been determined. Here, we performed an unbiased evaluation of cell-type-specific expression of ACE2 in healthy and fibrotic lungs, as well as in normal and failed adult human hearts, using published single-cell RNA-seq data. We found that ACE2 expression in fibrotic lungs mainly locates in arterial vascular cells, which might provide a route for bloodstream spreading of SARS-CoV-2. Failed human hearts have a higher percentage of ACE2-expressing cardiomyocytes, and SARS-CoV-2 might attack cardiomyocytes through the bloodstream in patients with heart failure. Moreover, ACE2 was highly expressed in cells infected by respiratory syncytial virus or Middle East respiratory syndrome coronavirus and in mice treated by lipopolysaccharide. Our findings indicate that patients with pulmonary fibrosis, heart failure, and virus infection have a higher risk and are more susceptible to SARS-CoV-2 infection. The SARS-CoV-2 might attack other organs by getting into the bloodstream. This study provides new insights into SARS-CoV-2 blood entry and heart injury and might propose a therapeutic strategy to prevent patients from developing severe complications.

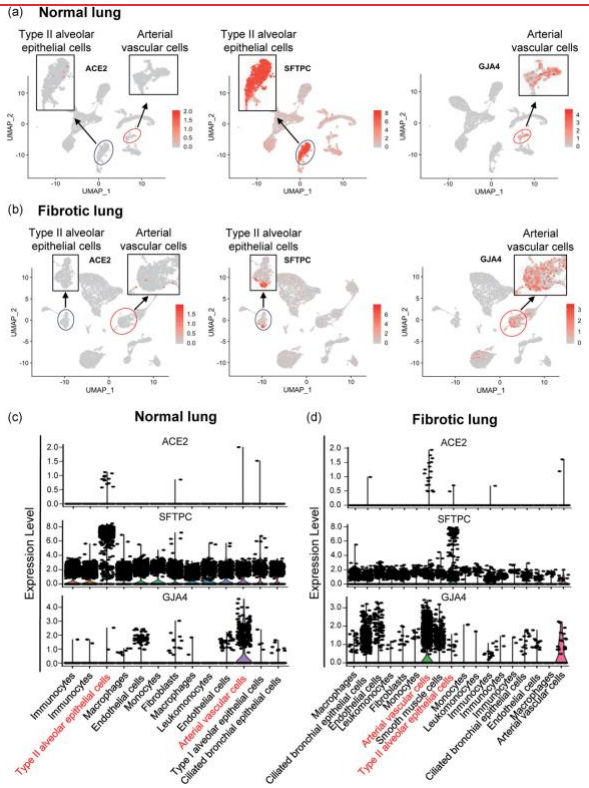


Figure 1: Different distribution pattern of angiotensin converting enzyme II (ACE2)-expressing cells in normal and fibrotic lungs. (a and b) Feature plot showing the distribution of ACE2 , SFTPC , and GJA4 expression levels in normal lungs (a) and in fibrotic lungs (b). (c and d) Violin plot showing the distribution of ACE2 , SFTPC , and GJA4 expression levels in normal lungs (c) and in fibrotic lungs (d)

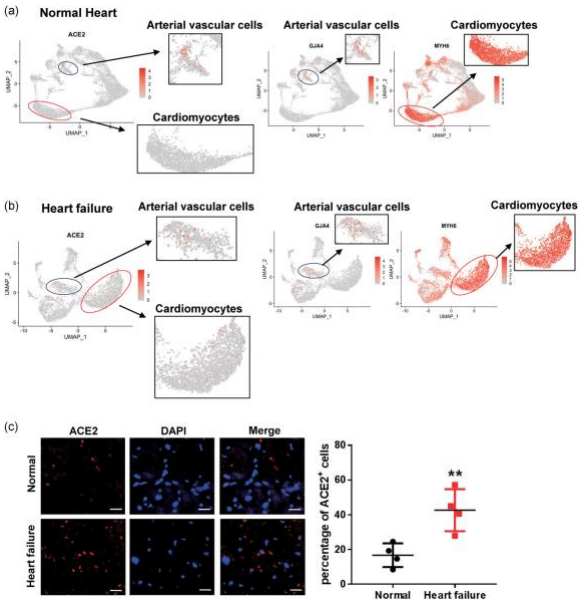


Figure 3: Different distribution of angiotensin converting enzyme II (ACE2)-expressing cells in normal and failed hearts. (a,b) Feature plot showing the distribution of ACE2 , GJA4 , and MYH6

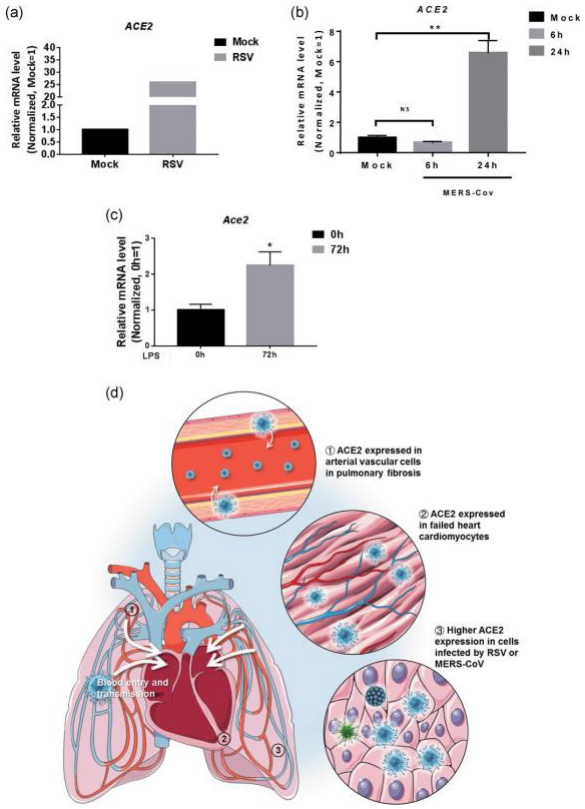


Figure 3: Different distribution of angiotensin converting enzyme II (ACE2)-expressing cells in normal and failed hearts. (a,b) Feature plot showing the distribution of ACE2 , GJA4 , and MYH6

OPERATING PROTOCOLS OF A COMMUNITY TREATMENT CENTER FOR ISOLATION OF PATIENTS WITH CORONAVIRUS DISEASE, SOUTH KOREA

Kang E, Lee SY, Jung H, Kim MS, Cho B, Kim YS.. Emerg Infect Dis. 2020 Jun 22;26(10). doi: 10.3201/eid2610.201460. Online ahead of print.

Level of Evidence: 4 - Case-series, case-control studies, or historically controlled studies

BLUF

Authors in affiliation with Seoul National University Hospital (SNUH) in South Korea present the design and outcomes of a community treatment center (CTC) functioning as an intermediate between hospitals and self-isolation at home for patients with mild COVID-19 symptoms (Figure 3). The researchers suggest CTCs or similar facilities may be an effective model to address resource shortages, observe disease progression, control disease transmission, and safely monitor patients during public health emergencies, as seen during the COVID-19 pandemic.

SUMMARY

Between March 5-26, 2020 there were 113 patients admitted to the Seoul National University Hospital community treatment center (SNUH-CTC). Each patient room was equipped with an automatic blood pressure monitor, digital thermometer, and pulse oximeter so that patients could check vital signs independently twice daily. Telemedicine was conducted via video consultations with a team of interprofessional medical staff including nurses, physicians, infectious disease specialists, radiologists, and psychiatrists (if needed). Of the 113 patients, 49 recovered and were discharged home (43.4%), 62 were classified as “not discharged” (54.8%), and 2 were transferred to a COVID-19 designated facility for hospitalization (1.8%). The average length of stay among the group that recovered and discharged home was 15.7 days (interquartile range [IQR] 5-21 days) and the interval from diagnosis to discharge was 19.5 days (interquartile range [IQR] 10-27 days). Discharge criteria was specified by negative results on two reverse-transcription PCR (RT-PCR) tests >24 hours apart for symptomatic patients or two negative RT-PCR tests >24 hours apart within 7 days of diagnosis for asymptomatic patients. The authors acknowledge CTC limitations, including potential lack of appropriate emergency response, no real-time patient monitoring to timely detect symptom progression or patient discomfort, as well as absence of negative pressure isolation functions.

ABSTRACT

Most persons with confirmed coronavirus disease (COVID-19) have no or mild symptoms. During the COVID-19 pandemic, communities need efficient methods to monitor asymptomatic patients to reduce transmission. We describe the structure and operating protocols of a community treatment center (CTC) run by Seoul National University Hospital (SNUH) in South Korea. SNUH converted an existing facility into a CTC to isolate patients who had confirmed COVID-19 but mild or no symptoms. Patients reported self-measured vital signs and symptoms twice a day by using a smartphone application. Medical staff in a remote monitoring center at SNUH reviewed patient vital signs and provided video consultation to patients twice daily. The CTC required few medical staff to perform medical tests, monitor patients, and respond to emergencies. During March 5-26, 2020, we admitted and treated 113 patients at this center. CTCs could be an alternative to hospital admission for isolating patients and preventing community transmission.

FIGURES

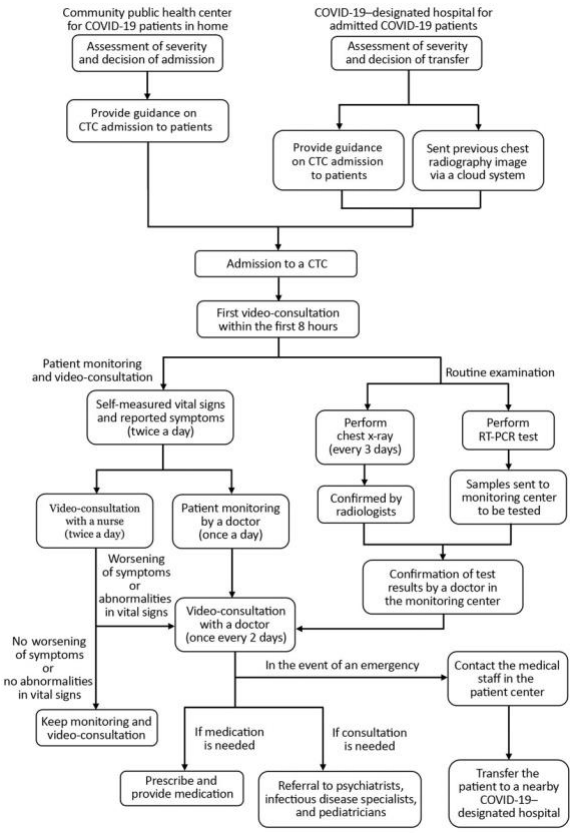


Figure 3. Flow chart of protocols for admission and management of mildly symptomatic or asymptomatic patients with coronavirus disease admitted to the Seoul National University Hospital community treatment center (SNUH-CTC) for isolation and monitoring, South Korea. COVID-19, coronavirus disease; CTC, community treatment center; RT-PCR, reverse transcription PCR.

PREVENTION IN THE HOSPITAL

N95 USAGE DURING THE COVID-19 PANDEMIC

DeLauro NM, Ghobrial N, Yu D.. J Am Podiatr Med Assoc. 2020 Jun 22. doi: 10.7547/20-101. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Authors from New Jersey review a list of FDA-approved respiratory mask manufacturing companies in China and various decontamination methods for safe re-use of personal protective equipment, namely N95 respirators, including hydrogen peroxide vaporization, ultraviolet germicidal irradiation, moist heat, dry heat, and 70% ethanol solution. The authors note that the choice of decontamination method is determined on a case-by-case basis and suggest this article as a resource for currently available methods.

ABSTRACT

Personal Protective Equipment (PPE), formerly ubiquitous and disposable in the hospital and healthcare environment, has become scarce during the COVID-19 pandemic. This shortage has precipitated creative solutions to re-use and/or extend the lifetime of PPE, most notably the N95 mask. This article attempts to summarize options regarding re-use of N95 respirators and is for informational purposes only.

COVID-19-ASSOCIATED COAGULOPATHY: AN EXPLORATION OF MECHANISMS

Colling ME, Kanthi Y.. Vasc Med. 2020 Jun 19:1358863X20932640. doi: 10.1177/1358863X20932640. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A review of clinical and lab findings of COVID-19-associated coagulopathy observed that a COVID-19 hypercoaguable state typically includes elevations in D-dimer and fibrinogen degradation products (FDPs), prolonged prothrombin time, and thrombocytopenia, in addition to increased neutrophil recruitment and neutrophil extracellular traps (NETs) propagation as seen via autopsy reports (Figure 1). In comparing sepsis-induced disseminated intravascular coagulation (DIC) to COVID-19-associated coagulopathy, the authors note that FDPs and D-dimer tend to be predictors of severity in COVID-19 disease, while platelet count and PT prolongation are related to sepsis severity and mortality in DIC. The authors also offer potential pharmaceutical candidates, namely dipyridamole, that may be able to reduce both the coagulation and inflammatory responses of COVID-19 infection. Based on these observations, the authors suggest a need for randomized controlled trials of anticoagulants in COVID-19 and further investigation into optimal management of COVID-19 associated coagulopathy.

ABSTRACT

An ongoing global pandemic of viral pneumonia (coronavirus disease [COVID-19]), due to the virus SARS-CoV-2, has infected millions of people and remains a threat to many more. Most critically ill patients have respiratory failure and there is an international effort to understand mechanisms and predictors of disease severity. Coagulopathy, characterized by elevations in D-dimer and fibrin(ogen) degradation products (FDPs), is associated with critical illness and mortality in patients with COVID-19. Furthermore, increasing reports of microvascular and macrovascular thrombi suggest that hemostatic imbalances may contribute to the pathophysiology of SARS-CoV-2 infection. We review the laboratory and clinical findings of patients with COVID-19-associated coagulopathy, and prior studies of hemostasis in other viral infections and acute respiratory distress syndrome. We hypothesize that an imbalance between coagulation and inflammation may result in a hypercoagulable state. Although thrombosis initiated by the innate immune system is hypothesized to limit SARS-CoV-2 dissemination, aberrant activation of this system can cause endothelial injury resulting in loss of thromboprotective mechanisms, excess thrombin generation, and dysregulation of fibrinolysis and thrombosis. The role various components including neutrophils, neutrophil extracellular traps, activated platelets, microparticles, clotting factors, inflammatory cytokines, and complement play in this process remains an area of active investigation and ongoing clinical trials target these different pathways in COVID-19.

FIGURES

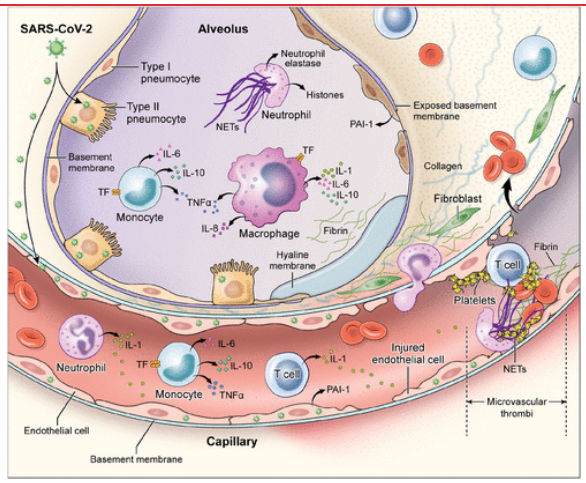


Figure 1. Immune activation and mechanisms of coagulopathy in patients with coronavirus disease 2019 (COVID-19). Multiple processes may contribute to COVID-19-associated coagulopathy including direct infection of type II pneumocytes and endothelial cells, leading to barrier dysfunction and increased permeability; inflammatory responses characterized by activation of T cells, neutrophils, monocytes, macrophages, and platelets resulting in exuberant inflammatory cytokine release (including IL-1, IL-6, IL-10, TNF-α), monocyte-derived TF and PAI-1 expression; and culminating in the development of microvascular and macrovascular thrombi composed of fibrin, NETs, and platelets.

IL, interleukin; NETs, neutrophil extracellular traps; PAI-1, plasminogen activator inhibitor-1; TF, tissue factor; TNF-α, tumor necrosis factor-alpha.

ACUTE CARE

FIBRINOLYSIS AND COVID-19: A PLASMIN PARADOX

Medcalf RL, Keragala CB, Myles PS.. J Thromb Haemost. 2020 Jun 16. doi: 10.1111/jth.14960. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Authors from Australia argue that although some studies have found the use of fibrinolytics (i.e., fibrinogen) for thromboembolism prophylaxis to be beneficial in COVID-19 patients, there is potential danger in this practice as viruses can use plasmin to enhance proliferation (Table 1) and plasmin can suppress the immune response. This could imply that study outcomes on the efficacy of fibrinolytic therapy may be depend on the timing of administration, as use of these therapies early in the course of disease could promote viral proliferation.

ABSTRACT

The COVID-19 pandemic has provided many challenges in the field of thrombosis and haemostasis. Among these is a novel form of coagulopathy that includes exceptionally high levels of D-dimer. D-dimer is a marker of poor prognosis, but does this also imply a causal relationship? These spectacularly raised D-dimer levels may actually signify the failing attempt of the fibrinolytic system to remove fibrin and necrotic tissue from the lung parenchyma, being consumed or overwhelmed in the process. Indeed, recent studies suggest that increasing fibrinolytic activity might offer hope for patients with critical disease and severe respiratory failure. However, the fibrinolytic system can also be harnessed by coronavirus to promote infectivity and where anti-fibrinolytic measures would also seem appropriate. Hence, there is a clinical paradox where plasmin formation can be either deleterious or beneficial in COVID-19, but not at the same time. Hence, it all comes down to timing.

FIGURES

Evolving COVID-19 clinical course	Pathology	Plasmin(ogen) activity	Potential role of antifibrinolytics
Stage 1 Presymptomatic or mild disease, without distressing symptoms and able to maintain oxygen saturation > 92% with up to 4 L/min oxygen via nasal prongs	SARS-Cov-2 harnesses extracellular proteases including plasmin to infect cells. Plasmin levels further increase in response to infection. Results in an immunosuppressive state.	++	Blocks plasmin activity – likely anti-inflammatory and immune enhancing; potentially therapeutic
Stage 2 Moderate or severe disease, with prostration, fever, persistent cough, and/or shortness of breath. Oxygen saturation typically ≤ 92% at rest, so requires supplemental oxygen, noninvasive ventilation, or tracheal intubation.	Plasmin levels continue to rise. Increase in cell permeability in lungs. Plasmin pro-inflammatory and immunosuppressive.	+++	As above. Consider heparin thromboprophylaxis.
Stage 3 Critical disease (ICU), respiratory failure with PaO_2/FiO_2 ratio < 200 (acute lung injury/ARDS), shock, DIC, and other organ failure. Mechanical ventilation, with or without prone positioning or extra-corporeal membrane oxygenation.	Large scale plasminogen activation to remove fibrin deposits and DIC. Hyperfibrinolytic state. D-dimer levels greatly elevated. Fibrinolytic system overwhelmed and fails to remove fibrin.	Relative deficiency	Fibrinolytic capacity needs to be enhanced. Exogenous plasmin(ogen) or plasminogen activators may be beneficial. Antifibrinolytics should not be trialled in critical disease. Heparin thromboprophylaxis/ anticoagulation recommended.

Table 1. The temporal opposing roles of plasmin in the pathogenesis of COVID-19.

MEDICAL SUBSPECIALTIES

HEMATOLOGY AND ONCOLOGY

COVID-19 COAGULOPATHY VS DISSEMINATED INTRAVASCULAR COAGULATION

Levi M.. Blood Adv. 2020 Jun 23;4(12):2850. doi: 10.1182/bloodadvances.2020002197.
Level of Evidence: Other - Expert Opinion

BLUF

In a peer-reviewed "Blood Advances Talk" podcast lecture, a UK physician reviews clinical manifestations of COVID-19 coagulopathy in comparison to disseminated intravascular coagulation (DIC) and thrombotic microangiopathy in critically ill patients with severe infections. COVID-19 appears to have unique features in comparison to other coagulopathies, including less profound thrombocytopenia, much higher levels of coagulation factors (II, V, VII, X) and physiological anticoagulants (antithrombin and protein C), no post-mortem evidence of systemic microvascular platelet-rich thrombi, and no overt intravascular hemolysis. The speaker advocates for new COVID-19 coagulopathy diagnostic criteria to significantly improve clinical outcomes via preventive or therapeutic management strategies.

OBGYN

A SURVEY OF LABOR AND DELIVERY PRACTICES IN NEW YORK CITY DURING THE COVID-19 PANDEMIC

Peña JA, Bianco AT, Simpson LL, Bernstein PS, Roman AS, Goffman D, Schweizer WE, Overbey J, Stone JL.. Am J Perinatol. 2020 Jun 9. doi: 10.1055/s-0040-1713120. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

The authors report the result of an online survey which was sent to obstetricians at four academic medical centers in New York City between April 14 and April 17. They found that all sites made significant changes to their labor and delivery policies when mothers were known or suspected to have COVID-19. Notable changes included the following:
- Requiring staff to wear surgical masks.
- Screening patients for COVID-19 using history and temperature.
- Performing deliveries in a negative pressure room when available.
- Medication usage: most of the sites reported using corticosteroids for fetal lung maturity, magnesium sulfate for COVID-19 patients experiencing preterm labor or preeclampsia, and no use of carboprost.
- Thromboprophylaxis was initiated at three of the four sites (rationale for this was not stated, but was likely due to presumed increased risk in COVID-19).
- For further details on the above and other policy changes, see Tables 2 and 3.
- There were significant differences in the sites' policies for checking the fetus in a hospitalized pregnant patient who tested positive for SARS-CoV-2, with one site starting to check a daily fetal heartbeat at 24 weeks and another site starting at 34 weeks. Half the sites performed daily non-stress tests in addition to fetal heartbeat checks.
-For further details on fetal monitoring, see Table 4.
These results suggest that, while guidelines may differ in certain aspects, facilities are taking increased precautions with updated COVID-19 guidelines.

ABSTRACT

Recently, a novel coronavirus, precisely severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), that causes the disease novel coronavirus disease 2019 (COVID-19) has been declared a worldwide pandemic. Over a million cases have been confirmed in the United States. As of May 5, 2020, New York State has had over 300,000 cases and 24,000 deaths with more than half of the cases and deaths occurring in New York City (NYC). Little is known, however, of how this virus impacts pregnancy. Given this lack of data and the risk for severe disease in this relatively immunocompromised population, further understanding of the obstetrical management of COVID-19, as well as hospital level preparation for its control, is crucial. Guidance has come from expert opinion, professional societies and public health agencies, but to date, there is no report on how obstetrical practices have adapted these recommendations to their local situations. We therefore developed an internet-based survey to elucidate the practices put into place to guide the care of obstetrical patients during the COVID-19 pandemic. We surveyed obstetrical leaders in four academic medical centers in NYC who were implementing and testing protocols at the height of the pandemic. We found that all sites made changes to their practices, and that there appeared to be agreement with screening and testing for COVID-19, as well as labor and delivery protocols, for SARS-CoV-2-positive patients. We found less consensus with respect to inpatient antepartum fetal surveillance. We hope that this experience is useful to other centers as they formulate their plans to face this pandemic. KEY POINTS: Practices changed to accommodate public health needs.. Most practices are screened for novel coronavirus disease 2019 (COVID-19) on admission.. Fetal testing in COVID-19 patients varied..

Table 2 Labor and delivery/postpartum practices and procedures for SARS-CoV-2 negative or person under investigation

Practices and procedures	Site 1	Site 2	Site 3	Site 4	All
Only one support person allowed	Yes	Yes	Yes	Yes	4/4
Early epidural recommended	Yes	Yes	Yes	Yes	4/4
Nitrous oxide suspended [a]	N/A	N/A	Yes	N/A	1/4
All cesareans performed in an AIIR OR	No	No	No	No	0/4
O2 for NRFHRT	No	No	No	No	0/4
carboprost for PPH	Yes[b]	Yes	Yes	Yes	4/4
NSAID used	Yes	Yes	Yes	Yes	4/4
Cohorting patients based on SARS-CoV-2 status	Yes	No	Yes	Yes	3/4
Offering early discharge to all patients.	Yes	No	Yes	Yes	3/4
Phone follow-up for patients discharged early	Yes	Yes	Yes	Yes	4/4

Abbreviations: AIIR, airborne infection isolation room (also known as negative pressure room); N/A, not available; NRFHRT, nonreassuring fetal heart rate tracing; NSAID, nonsteroidal anti-inflammatory drug; OR, operating room; PPH, postpartum hemorrhage; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.
[a]Nitrous oxide used in only one center.
[b]Only used in known negatives.

Table 2. Labor and delivery/postpartum practices and procedures for SARS-CoV-2 negative or person under investigation

Table 3 Labor and delivery/postpartum practices and procedures for SARS-CoV-2 PCR-positive patients

Practices and Procedures	Site 1	Site 2	Site 3	Site 4	All
If available, vaginal delivery performed in an AIIR room on L&D	Yes	Yes	Yes	Yes	4/4
Vaginal delivery performed in an AIIR room in the main OR	No	No	No	No	0/4
Cesarean performed in standard OR on L&D	Yes	Yes	Yes	Yes[a]	3/4
Cesarean performed in an AIIR room on L&D	No	No	No	No[a]	3/3
Cesarean performed in standard room in the main OR	No	Yes	No	No	1/4
Cesarean performed in an AIIR room in the main OR	No	No	No	Yes	1/4
Critically ill delivered in an AIIR in main OR	No	No	Yes	Yes	2/4
Cord blood banking collection suspended	No	N/A	Yes	Yes	2/3
Labor nurse in and out of room	Yes	Yes	Yes	Yes	4/4
IV pumps and tubing outside of room	Yes	No	Yes	No	2/4
Modified PPE procedure to accommodate urgent cesarean	Yes[b]	Yes	No	No	1/4
carboprost used	No	Yes	No	No	1/4
NSAID used	Yes[c]	Yes	Yes	Yes	3/4
Thromboprophylaxis for 2 weeks postpartum[e]	Yes	Yes[d]	Yes	No	3/4

Abbreviations: AIIR, airborne infection isolation room (also known as negative pressure room); IV, intravenous; L&D, labor and delivery; N/A, not applicable; NSAID, nonsteroidal anti-inflammatory drug; OR, operating room; PCR, polymerase chain reaction; PPE, personal protective equipment; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2; VTE, venous thromboembolism.
[a]Yes, only if negative pressure in main OR unavailable, then perform with HEPA filter.
[b]Case by case.
[c]Use caution in ordering NSAIDs for symptomatic postpartum patients with novel coronavirus disease 2019 (COVID-19) infection and/or asymptomatic COVID-19 with chronic kidney disease.
[d]Sometimes.
[e]Sites used either heparin or enoxaparin for thromboprophylaxis.

Table 3. Labor and delivery/postpartum practices and procedures for SARS-CoV-2 PCR-positive patients

Table 4 Comments on antepartum fetal surveillance for COVID-19 pregnant women

Clinical scenario	Site 1	Site 2	Site 3	Site 4
23–33^{6} weeks of GA: mother stable	N/A	<26 FH checks, >26 weeks daily NST	None until 34 weeks	Daily NST starting at 24 weeks
23–33^{6} weeks of GA: mother in the ICU, not intubated	Continuous	<26 weeks FH checks, >26 weeks daily NST	None until 34 weeks	Daily NST starting at 24 weeks
23–33^{6} weeks of GA: mother in the ICU, intubated	Continuous	<28 weeks FH checks, >28 weeks daily NST	None until 34 weeks	Daily NST starting at 28 weeks.
23–33^{6} weeks of GA: mother in the ICU, decompensating	Continuous	<28 weeks FH checks, >28 weeks daily NST	None until 34 weeks	Daily NST starting at 28 weeks
34+ weeks of GA: mother in the ICU, not intubated	Continuous	Deliver	Deliver	Deliver
34+ weeks of GA: mother in the ICU, intubated	Continuous	Deliver	Deliver	Deliver
34+ weeks of GA: mother in the ICU, decompensating	Continuous	Deliver	Deliver	Deliver

Abbreviations: COVID-19, novel coronavirus disease 2019; FH, fetal heart; GA, gestational age; ICU, intensive care unit; NST, non-stress test; N/A, not answered.

Table 3. Labor and delivery/postpartum practices and procedures for SARS-CoV-2 PCR-positive patients

EMERGENCY MEDICINE

CHEST X-RAY IN NEW CORONAVIRUS DISEASE 2019 (COVID-19) INFECTION: FINDINGS AND CORRELATION WITH CLINICAL OUTCOME

Cozzi D, Albanesi M, Cavigli E, Moroni C, Bindi A, Luvarà S, Lucarini S, Busoni S, Mazzoni LN, Miele V.. Radiol Med. 2020 Jun 9. doi: 10.1007/s11547-020-01232-9. Online ahead of print.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

A cross-sectional study conducted in Florence, Italy from 1 March to 31 March 2020 by University Hospital Careggi of 482 patients tested for COVID-19 via reverse transcriptase polymerase chain reaction (RT-PCR) who also received a chest radiograph (CXR) found that:

-234 (48.5%) patients (mean age 66) were positive for COVID-19, and all but 13 (5.6%) had radiographic findings suggestive of an infection.

-Reticular-nodular opacities (66.6%), ground glass opacifications (62.8%), and lung consolidations (57.7%) were common findings. Patients above 80 years old tended to have more advanced lung involvement on radiograph (Figure 1).

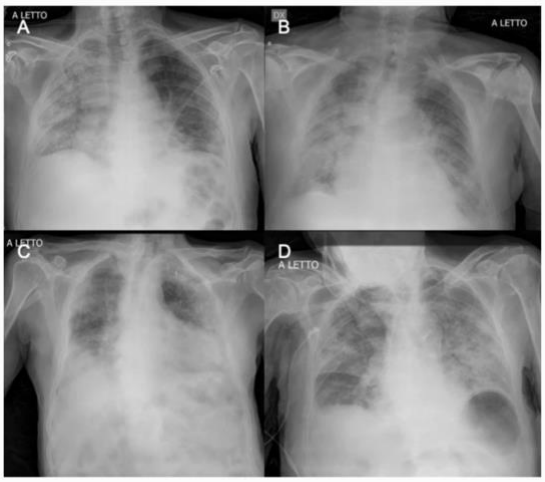
-There were significant differences in Radiographic Assessment of Lung Edema (RALE) scores for discharged patients (group 1) compared to ICU patients (group 3) ($p < 0.001$; Figure 2) and hospitalized patients (group 2) compared to ICU patients (group 3) ($p = 0.001$; Figure 2). RALE scores higher than 15 points correlated with an increased risk of being admitted to the ICU, indicating use of this scoring the emergency setting for identification of high risk patients.

-Baseline CXR was found to have a sensitivity of 67.1% for COVID-19, suggesting the use of this modality for COVID-19 diagnosis.

ABSTRACT

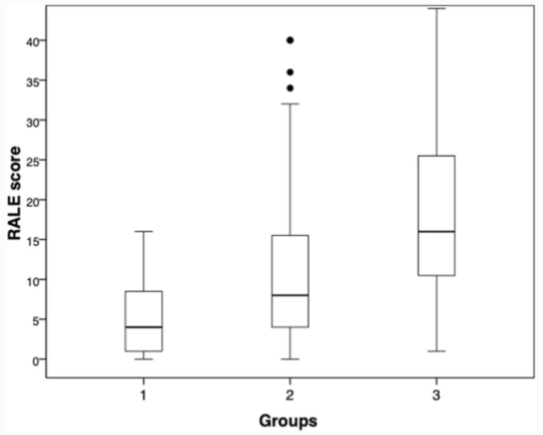
AIM: The purpose of this study is to describe the main chest radiological features (CXR) of COVID-19 and correlate them with clinical outcome.
MATERIALS AND METHODS: This is a retrospective study involving patients with clinical-epidemiological suspect of COVID-19 infection, who performed CXRs at the emergency department (ED) of our University Hospital from March 1 to March 31, 2020. All patients performed RT-PCR nasopharyngeal and throat swab, CXR at the ED and clinical-epidemiological data. RT-PCR results were considered the reference standard. The final outcome was expressed as discharged or hospitalized patients into a medicine department or intensive care unit (ICU).
RESULTS: Patients that had a RT-PCR positive for COVID-19 infection were 234 in total: 153 males (65.4%) and 81 females (34.6%), with a mean age of 66.04 years (range 18-97 years). Thirteen CXRs were negative for radiological thoracic involvement (5.6%). The following alterations were more commonly observed: 135 patients with lung consolidations (57.7%), 147 (62.8%) with GGO, 55 (23.5%) with nodules and 156 (66.6%) with reticular-nodular opacities. Patients with consolidations and GGO coexistent in the same radiography were 35.5% of total. Peripheral (57.7%) and lower zone distribution (58.5%) were the most common predominance. Moreover, bilateral involvement (69.2%) was most frequent than unilateral one. Baseline CXR sensitivity in our experience is about 67.1%. The most affected patients were especially males in the age group 60-79 years old (45.95%, of which 71.57% males). RALE score was slightly higher in male than in female patients. ANOVA with Games-Howell post hoc showed significant differences of RALE scores for group 1 vs 3 ($p < 0.001$) and 2 vs 3 ($p = 0.001$). Inter-reader agreement in assigning RALE score was very good (ICC: 0.92-with 95% confidence interval 0.88-0.95).
CONCLUSION: In COVID-19, CXR shows patchy or diffuse reticular-nodular opacities and consolidation, with basal, peripheral and bilateral predominance. In our experience, baseline CXR had a sensitivity of 68.1%. The RALE score can be used in the emergency setting as a quantitative method of the extent of SARS-CoV-2 pneumonia, correlating with an increased risk of ICU admission.

Fig. 1



Diffuse lung involvement in elderly patients. Four cases of advanced lung disease with diffuse consolidations and interstitial involvement of patients older than 80 years at the emergency department

Fig. 2



Box and Whisker plot of RALE score estimated in each group defined by outcome: discharged patients (group 1), hospitalized patients into a medicine department (group 2), hospitalized patients into an intensive care unit (group 3). RALE score showed statistically significant differences between group 1 vs 3 and 2 vs 3

COVID-19 Radiological features	N (%)
Normal baseline CXRs	13 (5.6)
Abnormal baseline CXRs	223 (94.4)
Reticular-nodular opacities	156 (66.6)
Ground glass opacities	147 (62.8)
Consolidation	135 (57.7)
Vascular congestion signs	92 (39.3)
Cardiomegaly	70 (29.9)
Nodules	55 (23.5)
Pleural effusion	39 (16.7)
Pneumothorax	5 (2.4)
Distribution:	
Peripheral	135 (57.7)
Perihilar	51 (20.7)
Diffuse	99 (41)
Basal predominance	137 (58.5)
Superior predominance	31 (13.1)
Right lung	29 (58)
Left lung	21 (42)
Bilateral	162 (69.2)

IMPACT OF THE COVID-19 PANDEMIC ON EMERGENCY DEPARTMENT VISITS - UNITED STATES, JANUARY 1, 2019-MAY 30, 2020

Hartnett KP, Kite-Powell A, DeVies J, Coletta MA, Boehmer TK, Adjemian J, Gundlapalli AV; National Syndromic Surveillance Program Community of Practice.. MMWR Morb Mortal Wkly Rep. 2020 Jun 12;69(23):699-704. doi: 10.15585/mmwr.mm6923e1.
Level of Evidence: 4 - Local and current random sample surveys (or censuses)

BLUF

A surveillance study conducted using the National Syndromic Surveillance Program (NSSP) in the United States during March 29 to April 25, 2020 by the Center for Disease Control and Prevention found a 42% decrease in the number of emergency department visits compared to the same time period in 2019 (Figure 1), suggesting fewer individuals are utilizing the Emergency Department (ED) in the wake of the COVID-19 pandemic. The authors note that female patients, children under the age of 14, and people living in the Northeast saw the sharpest decline in ED visits (Figure 2) and suggest that triage help lines and telemedicine visits be utilized when possible to prevent people from contracting COVID-19 during an ED visit.

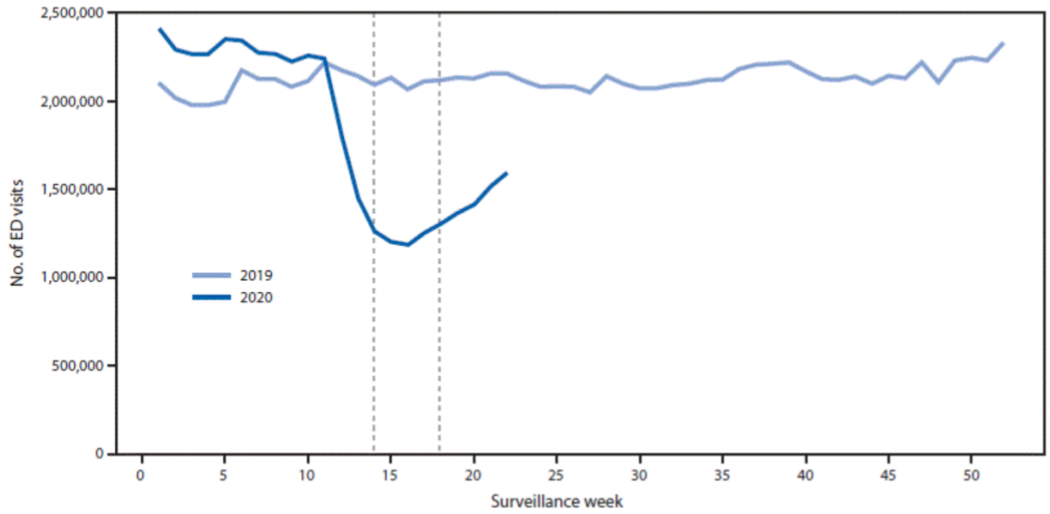
ABSTRACT

On March 13, 2020, the United States declared a national emergency to combat coronavirus disease 2019 (COVID-19). As the number of persons hospitalized with COVID-19 increased, early reports from Austria (1), Hong Kong (2), Italy (3), and California (4) suggested sharp drops in the numbers of persons seeking emergency medical care for other reasons. To quantify the effect of COVID-19 on U.S. emergency department (ED) visits, CDC compared the volume of ED visits during four weeks early in the pandemic March 29-April 25, 2020 (weeks 14 to 17; the early pandemic period) to that during March 31-April 27, 2019 (the comparison period). During the early pandemic period, the total number of U.S. ED visits was 42% lower than during the same period a year earlier, with the largest declines in visits in persons aged <=14 years, females, and the Northeast region. Health messages that reinforce the importance of immediately seeking care for symptoms of serious conditions, such as myocardial infarction, are needed. To minimize SARS-CoV-2, the virus that causes COVID-19, transmission risk and address public concerns about visiting the ED during the pandemic, CDC recommends continued use of virtual visits and triage help lines and adherence to CDC infection control guidance.

FIGURES

FIGURE 1. Weekly number of emergency department (ED) visits — National Syndromic Surveillance Program, United States,* January 1, 2019– May 30, 2020†

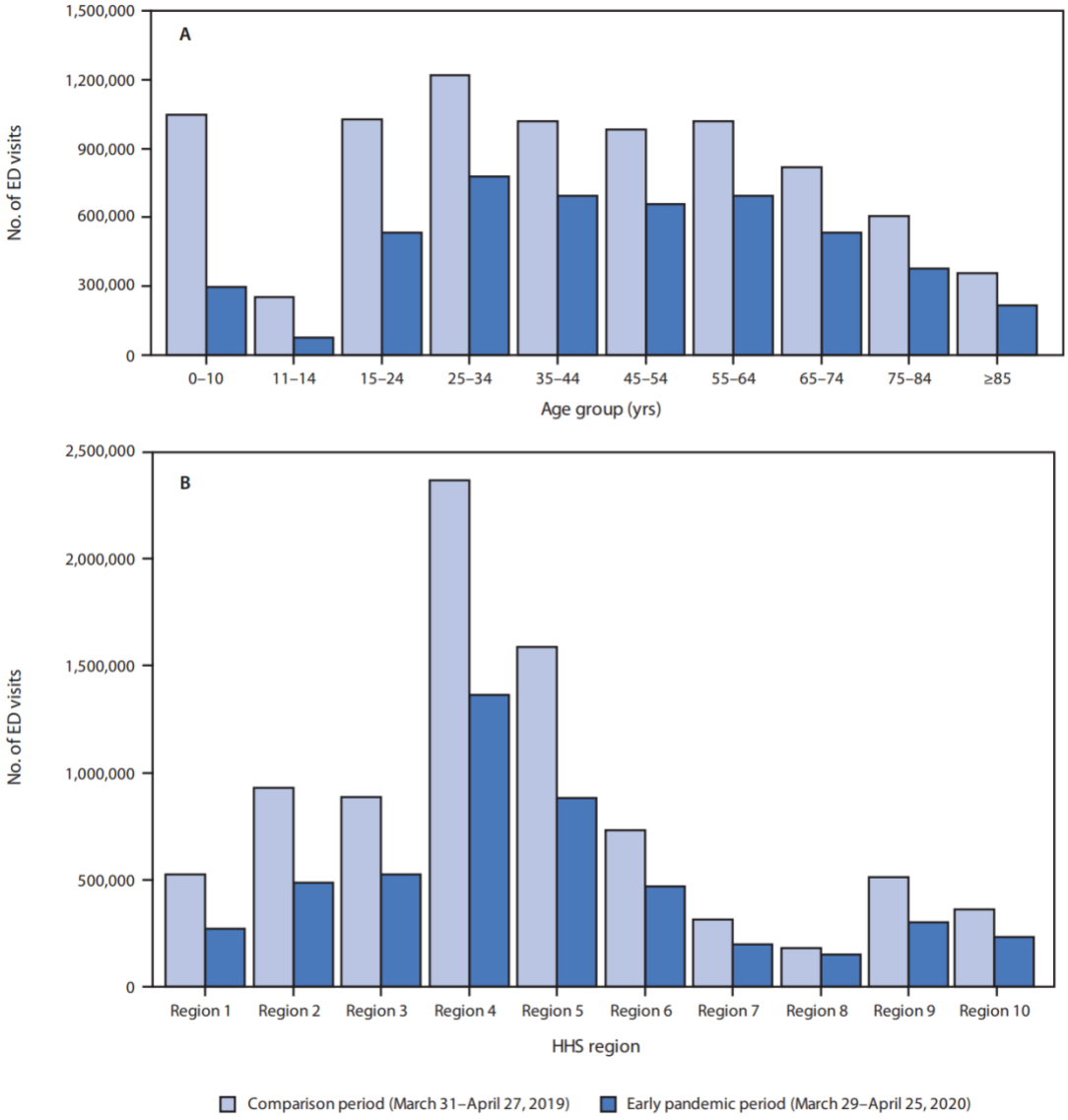
Return



* Hawaii, South Dakota, and Wyoming are not included.

† Vertical lines indicate the beginning and end of the 4-week coronavirus disease 2019 (COVID-19) early pandemic period (March 29–April 25, 2020) and the comparison period (March 31–April 27, 2019).

FIGURE 2. Emergency department (ED) visits, by age group (A) and U.S. Department of Health and Human Services (HHS) region* (B) — National Syndromic Surveillance Program, United States,† March 31–April 27, 2019 (comparison period) and March 29–April 25, 2020 (early pandemic period)



* *Region 1*: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont; *Region 2*: New Jersey and New York; *Region 3*: Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia; *Region 4*: Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, and Tennessee; *Region 5*: Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin; *Region 6*: Arkansas, Louisiana, New Mexico, Oklahoma, and Texas; *Region 7*: Iowa, Kansas, Missouri, and Nebraska; *Region 8*: Colorado, Montana, North Dakota, and Utah; *Region 9*: Arizona, California, and Nevada; *Region 10*: Alaska, Idaho, Oregon, and Washington.
† Hawaii, South Dakota, and Wyoming are not included.

CRITICAL CARE

COVID-RELATED FAMILY SEPARATION AND TRAUMA IN THE INTENSIVE CARE UNIT

Montauk TR, Kuhl EA.. Psychol Trauma. 2020 Jun 22. doi: 10.1037/tra0000839. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

American healthcare specialists argue that intensive care unit (ICU) healthcare providers must adjust their practice during the COVID-19 pandemic to include strategies to help patients' families cope with being separated from their loved ones during ICU

stays and potentially end-of-life processes. The authors specifically say that ICU providers must:
1) acknowledge the uniqueness of the situation with families,
2) initiate video conferencing early in treatment when possible and if desired by the family,
3) allow themselves to display their emotions when talking with families, and
4) address potential mental health issues and trauma responses directly.

ABSTRACT

Due to stringent but necessary infection control mandates, the COVID-19 pandemic is increasingly resulting in family separation from loved ones admitted to intensive care units (ICUs). Even in normal circumstances, ICU families frequently experience significant psychological dysfunction-including posttraumatic stress disorder and other trauma-related reactions, especially during the end of life period. The COVID pandemic likely will exacerbate these reactions as more and more families are being barred from the ICU. Consequently, ICU families are facing additional barriers in fully understanding the complex medical needs of their loved ones (and hence being able to make informed care decisions on their behalf); establishing rapport and bonding with nurses and other members of the ICU treatment team; and, in the event that a loved one passes, achieving closure. ICU health care providers can take steps to mitigate these outcomes by being mindful of the unique stressors ICU families are currently facing and tailoring their communication and behavior accordingly. (PsycInfo Database Record (c) 2020 APA, all rights reserved).

SURGICAL SUBSPECIALTIES

TRANSPLANT SURGERY

ETHICAL ISSUES IN THE COVID ERA: DOING THE RIGHT THING DEPENDS ON LOCATION, RESOURCES, AND DISEASE BURDEN

Stock PG, Wall A, Gardner J, Domínguez-Gil B, Chadban S, Muller E, Dittmer I, Tullius SG; TTS Ethics Committee..
Transplantation. 2020 Jul;104(7):1316-1320. doi: 10.1097/TP.0000000000003291.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

The Transplantation Society (TTS) Ethics Committee outlines ethically-guided transplantation recommendations that consider the severity of resource constraints and COVID-19 incidence at a given moment (Figure 1). These guidelines suggest that decisions on transplant and donor procedures may give more weight to certain ethical principles compared to others depending on the current position of a transplant center and the state of the pandemic.

SUMMARY

The Transplantation Society (TTS) Ethics Committee's ethically-guided recommendations include, but are not limited to, the following:
- "Current [transplantation] guidelines are insufficient to determine who should be transplanted under such conditions."
- "Uncertainty, lack of knowledge, and lack of prognostic ability about the pandemic" should be considered when determining risk-benefit of transplantation.
- Facilities in affected areas should consider essential resource availability (ICU beds, ventilators, blood products, PPE).
- The principle of distributive justice for determining which patients should be transplanted involves "[maximizing] benefits, [minimizing] resource utilization, and [treating] highest need patients first."
- The same ethical principles should be applied to guide transplantation, considering distributive justice, beneficence, and non-maleficence over autonomy, and reassessing these principles with increasing information/data on COVID-19 infection.
- Donor and recipient testing for COVID-19 should be performed prior to organ acceptance.
- Transparency and communication about guidelines and known/unknown risks of COVID-19 infection should be implemented.
- "The Transplantation Society (TTS) is currently providing an online dashboard of up-to-date global information and experience in response to the crisis."

FIGURES

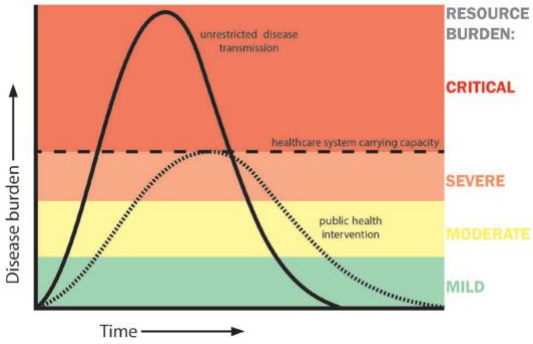


FIGURE 1. Responses on allocation, donor/recipient criteria, and transplant activities will largely depend on the position of centers on the slope of the incidence curve. Geographic and social characteristics will also determine the height of the curve, impacting risk-benefit assessments.

UROLOGY

SUMMARY AND CONSIDERATIONS IN GENITOURINARY CANCER PATIENT CARE DURING THE COVID-19 PANDEMIC

Rodríguez-Covarrubias F, Castillejos-Molina RA, Autrán-Gómez AM.. Int Braz J Urol. 2020 Jun 17;46. doi: 10.1590/S1677-5538.. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

The authors performed a literature review on May 8th 2020 to compile and summarize recommendations for managing urological cancers during the COVID-19 pandemic. In general, their findings highlight priority treatment of high-risk malignancies and usage of level-three personal protective equipment (PPE) during any invasive procedure; their recommendations (summarized below) can serve as a guide for urological centers during the pandemic.

SUMMARY

Observations and associated recommendations include, but are not limited to, the following:

Prostate Cancer
- Patients with COVID-19 are more likely to have poorer outcomes.
- Patients with low-risk features (e.g. low prostate specific antigen (PSA), normal digital rectal exam) may defer diagnostic testing during the pandemic's critical phase. Patients with high-risk features should be tested for prostate cancer, but they should first undergo testing for the COVID-19 virus.

Localized/Locally Advanced Prostate Cancer
- Patients with low risk disease can undergo active surveillance.
- Patients with high risk disease can delay radical prostatectomy up to 6 months without adverse outcomes (based on literature).
- Neoadjuvant Androgen Deprivation Therapy may be used to delay usage of External Radiation Therapy while hypofractionated radiation therapy can be used to reduce tumor burden.

Advanced Disease
- Minimize usage of glucocorticoids.
- Use androgen-receptor-axis therapies and androgen deprivation therapy.
- Radium-223 can be used for bone-only mets or metastatic castration-resistant disease.

Bladder Cancer
- Patients with low risk disease can delay cystoscopic surveillance.
- Recent literature has stated that transurethral resection of bladder tumor should be non-deferable for high-risk non-muscle invasive bladder cancer.

Non-muscle invasive bladder cancer
- Active surveillance is a viable option.
- Radical cystectomy is discouraged during the pandemic's acute phase.

Muscle invasive bladder cancer
- Bladder-sparing trimodality treatment should be an available option.
- Radical cystectomy should not be delayed for more than 90 days.

Advanced bladder cancer
- Management is individualized to patient needs and how high risk the bladder cancer is.

Upper tract urothelial cancer
- Urinary cytology and computed tomography urography should be the tools of diagnosis.
- Diagnostic ureteroscopy should not be used unless absolutely needed.
- Radical nephrouterectomy can be delayed up to 12 weeks.

Renal cell-carcinoma
- Diagnosis is based on imaging; biopsy may be delayed in small renal masses (<4cm).
- Patients with T3 renal cell-carcinoma should be prioritized.
- Small renal masses and T1 renal cell-carcinoma cases can undergo active surveillance.
- Tumors removable by nephrectomy can be delayed potentially from 3-6 months.
- Nephrectomy is reserved for symptomatic metastatic cases; otherwise, active surveillance may be used.

Testicular and penile cancer
- There are not many studies around this topic for delays in treatment. In general, high risk cases are prioritized.

ABSTRACT

PURPOSE: To provide a summary and recommendations for the set-up of strategies for cancer patients care in genitourinary oncology clinics during the pandemic and in the recovery period. MATERIAL AND METHODS: A non-systematic review of available literature on the management of urological malignancies during the COVID-19 pandemic was performed to summarize recommendations to improve the diagnosis and treatment of urological cancers during and after the contingence, including clinical and research aspects. RESULTS: Urological cancer diagnosis and management should be tailored according to the severity of the COVID-19 crisis in each region and the aggressiveness of each tumor. Clinicians should adhere to strict protocols in order to prioritize the attention of patients with high-risk malignancies while optimizing resources to avoid the saturation of critical care services. CONCLUSIONS: During the COVID-19 pandemic urological cancer care has been severely impaired. For proper patient management, multidisciplinary approach is encouraged tailoring therapy according to COVID-19 regional behavior and local institutional resources. Patients with high-risk malignancies should be prioritized.

VIRTUAL SCREENING AND DYNAMICS OF POTENTIAL INHIBITORS TARGETING RNA BINDING DOMAIN OF NUCLEOCAPSID PHOSPHOPROTEIN FROM SARS-COV-2

Yadav R, Imran M, Dhamija P, Suchal K, Handu S.. J Biomol Struct Dyn. 2020 Jun 22:1-16. doi: 10.1080/07391102.2020.1778536. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

This study uses virtual screening and molecular modeling to estimate binding potentials of various FDA approved drugs to the nucleocapsid protein (N protein) of SARS-CoV-2. The authors identified three FDA approved drugs as potentially effective inhibitors of the N protein, with Zidovudine having a stronger and more stable interaction (Table 7B). The authors recommend future experimental trials investigate the efficacy and safety of Zidovudine as a therapeutic option for COVID-19.

ABSTRACT

The emergence of the coronavirus disease-2019 pandemic has led to an outbreak in the world. The SARS-CoV-2 is seventh and latest in coronavirus family with unique exonucleases for repairing any mismatches in newly transcribed genetic material. Therefore, drugs with novel additional mechanisms are required to simultaneously target and eliminate the virus. Thus, a newly deciphered N protein is taken as a target that belongs to SARS-CoV-2. They play a vital role in RNA transcription, viral replication and new virion formation. This study used virtual screening, molecular modeling and docking of the 8987 ligands from Asinex and PubChem databases against this novel target protein. Three hotspot sites having DScore >=1 (Site 1, Site 2 and Site 3) for ligand binding were selected. Subsequently, high throughput screening, standard precision and extra precision docking process and molecular dynamics concluded three best drugs from two libraries. Two antiviral moieties from Asinex databases (5817 and 6799) have docking scores of -10.29 and -10.156; along with their respective free binding energies (DeltaG bind) of -51.96 and -64.36 on Site 3. The third drug, Zidovudine, is from PubChem database with docking scores of -9.75 with its binding free energies (DeltaG bind) of -59.43 on Site 3. The RMSD and RMSF were calculated for all the three drugs through molecular dynamics simulation studies for 50 ns. Zidovudine shows a very stable interaction with fluctuation starting at 2.4 A on 2 ns and remained stable at 3 A from 13 to 50 ns. Thus, paving the way for further biological validation as a potential treatment.Communicated by Ramaswamy H. Sarma.

FIGURES

Table 7B. Potential FDA approved drug molecules, their indication and mechanism of action.

S/no.	Name of drug molecules	PubChem Id	Indication	Mechanism of action
1	Zidovudine	72187	Antiviral drug used for the treatment of human immunodeficiency virus (HIV) infections	Nucleoside reverse transcriptase inhibitor (NRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1) (https://www.drugbank.ca/drugs/DB00495)
2	Valganciclovir	135413534	Antiviral drug used for the treatment of cytomegalovirus infections	Inhibition of viral DNA synthesis by incorporation with viral DNA& inhibits viral DNA polymerases (https://www.drugbank.ca/drugs/DB01610)
3	Ribavirin	37542	Used for the treatment of chronic Hepatitis C virus (HCV) infection	Inhibits of viral RNA and protein synthesis by inhibition of the enzyme RNA dependent RNA polymerase (https://www.drugbank.ca/drugs/DB00811)

DIAGNOSING COVID-19 IN THE EMERGENCY DEPARTMENT: A SCOPING REVIEW OF CLINICAL EXAM, LABS, IMAGING ACCURACY AND BIASES

Carpenter CR, Mudd P, West CP, Wilber E, Wilber ST.. Acad Emerg Med. 2020 Jun 16. doi: 10.1111/acem.14048. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Physicians at the Washington University in St. Louis School of Medicine and Mayo Clinic in Rochester, MN performed a literature search of 1,907 citations from April 23-May 5, 2020 and reviewed 87 primary studies related to COVID-19 diagnostic accuracy. Based on the identified studies, the authors proposed a number of guidelines to improve COVID-19 diagnosis and management in the ED (see summary for key findings).

SUMMARY

The authors recommend the following investigations for ED diagnosis of COVID-19 and suggest that the combination of all of these should be considered the "Gold Standard" for this diagnosis (Table 2).
1. Known exposure history.
2. Symptoms and clinical exam:
-Fever is the most common symptom of COVID-19 seen in 84%-87%.
-Hyposmia ([LR+] 5.3, [LR-] 0.61) and hypogeusia (LR+ 7.1, LR- 0.38) are better to rule-in COVID-19; less helpful to rule out.
3. Routine Labs:
-Lymphopenia is seen in over 50% of COVID-19 patients.
-Elevated prothrombin time, ferritin, D-dimer, or IL-6 seen in severe COVID-19.
4. Imaging:
-Single view Chest X-ray has sensitivity range from 33-60%.
-CT may increase diagnostic sensitivity in conjunction with rRT-PCR; ~97% sensitivity.
5. Serology:
-May identify past SARS-CoV-2 infection.
-High false-positive rate; test specificity ranges 87-100%.
6. Viral culture with rRT-PCR (real-time RT-PCR):
-rRT-PCR is the standard criterion for diagnosis.
-High false-negativity rate; test sensitivity ranges 60-78% (Table 1 for common causes).
-Blood and urine samples for rRT-PCR are inadequate due to limited virus in body fluids.

ABSTRACT

In December 2019 a novel viral respiratory pathogen emerged in China, ultimately named severe acute respiratory syndrome coronavirus 2 (SARS-Co-V-2) with the clinical illness dubbed coronavirus disease (COVID-19). COVID-19 became a global pandemic in early 2020 forcing governments worldwide to enact social isolation policies with dire economic ramifications. Emergency departments (ED) encountered decreased patient volumes before some in Seattle, New York City, New Orleans, and Detroit experienced waves of COVID-19 patients mixed with asymptomatic patients or those concerned about potential exposures. Diagnosing COVID-19 was hampered by inadequate supplies of reagents and kits, which was compounded by clinical and radiographic features that overlap with numerous seasonal viral respiratory infections.

FIGURES

Lab handling (heat inactivation)
Limit of detection (RNA particle detection)
Mutations in the probe target
Sampling procedure (training, fidelity, patient cooperation)
Selective virus replication (patient variability, disease severity variability)
Specimen sampled (NP, OP, saliva, sputum, BAL, stool)
Test kit quality
Timing of sampling in course of disease

Table 1. Common Causes of False Negative rRT-PCR

Expert consensus months after acute illness, including

- Exposure history
- Symptoms
- Laboratory tests
- rRT-PCR
- Imaging
- Serology
- Viral cultures

Table 2. Proposed COVID-19 Gold Standard

LINKING STATISTICS WITH TESTING POLICY TO MANAGE COVID-19 IN THE COMMUNITY

Hilborne LH, Wagner Z, Cabreros I, Brook RH.. Am J Clin Pathol. 2020 Jun 10:aqaa099. doi: 10.1093/ajcp/aqaa099. Online ahead of print.
Level of Evidence: Other - Modeling

BLUF

A multidisciplinary group from the United States emphasized the benefit of statistical sampling principles to determine testing capacities needed to improve policies and calculations during the COVID-19 pandemic (Supplement 1). They proposed a method to estimate the sample sizes necessary for various testing and populations (see summary for descriptions). The authors believe that in order to perform appropriate health surveillance and decision-making, the number of individuals that need to be tested is in the thousands (not millions).

SUMMARY

The authors discuss statistical sampling principles that can help determine testing capacities necessary to answer important questions regarding the COVID-19 pandemic such as:
1. "What is the current seroprevalence and acute infection prevalence?"
2. "How do infection rates vary by age, sex, ethnicity, population density, and comorbidities?"
3. "How is seroprevalence changing over time?"
4. "How do active infection rates change after a change in policy?"
See Figure 1, Table 3, and Table 4 for estimates of sample sizes necessary for populations and various testings.

ABSTRACT

OBJECTIVES: To determine the public health surveillance severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing volume needed, both for acute infection and seroprevalence.
METHODS: Required testing volumes were developed using standard statistical methods based on test analytical performance, disease prevalence, desired precision, and population size.
RESULTS: Widespread testing for individual health management cannot address surveillance needs. The number of people who must be sampled for public health surveillance and decision making, although not trivial, is potentially in the thousands for any given population or subpopulation, not millions.
CONCLUSIONS: While the contributions of diagnostic testing for SARS-CoV-2 have received considerable attention, concerns abound regarding the availability of sufficient testing capacity to meet demand. Different testing goals require different numbers of tests and different testing strategies; testing strategies for national or local disease surveillance, including monitoring of prevalence, receive less attention. Our clinical laboratory and diagnostic infrastructure are capable of incorporating required volumes for many local, regional, and national public health surveillance studies into their current and projected testing capacity. However, testing for surveillance requires careful design and randomization to provide meaningful insights.

FIGURES

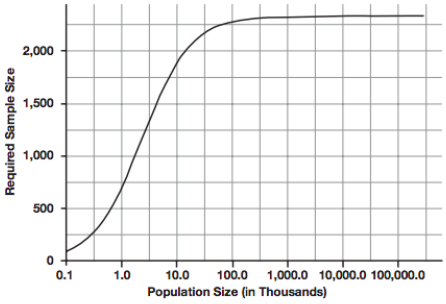


Figure 1 Required sample size as a function of population size (at sensitivity 95%, specificity 99%, true prevalence 5%, and precision 1% [ie, 4%-6%]).

Figure 1: Changes in required sample size as a function of population size.

Table 3

Sample Sizes Required for Molecular Testing

Prevalence	Precision (95% Confidence Interval)	No. of Random Sample Tests Required
0.2%	0.1%-0.3%	21,615
0.5%	0.3%-0.7%	8,980
1%	0.6%-1.4%	3,726
5%	4.0%-6.0%	2,422

Table 4

Sample Sizes Required for Serology Testing

Prevalence	Precision (95% Confidence Interval)	No. of Random Sample Tests Required
1%	0.6%-1.4%	5,170
5%	4.0%-6.0%	2,337
10%	8.0%-12.0%	1,013
20%	16%-24%	432
40%	35%-45%	413

Table 3 and 4: Sample sizes required for molecular testing and serology testing, respectively.

DEVELOPMENTS IN DIAGNOSTICS

ULTRA-SENSITIVE AND HIGH-THROUGHPUT CRISPR-P OWERED COVID-19 DIAGNOSIS

32553350. Ultra-sensitive and high-throughput CRISPR-p owered COVID-19 diagnosis
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

Researchers from Tulane University School of Medicine and Nanchang University, China developed a CRISPR-based Fluorescent Diagnosis System (COVID-19 CRISPR-FDS) to detect SARS-CoV-2 positive samples in ~50 minutes (Figure 1). The researchers tested 29 nasal swab specimens from individuals with suspected COVID-19 between April 1 and April 10, 2020, and found that the COVID-19 CRISPR-FDS method allowed similarly sensitive detection of SARS-CoV-2 positive samples compared to a state testing lab using CDC-approved RT-qPCR assays; 19/29 SARS-CoV-2 positive, 100% sensitivity (Figure 3). Specificity was measured at 71.6% based on positive results with CRISPR-FDS in three samples "judged negative by the state testing laboratory". The authors note these may not truly represent false positives but rather may be true cases that were incorrectly diagnosed by the RT-qPCR assay. These findings suggest COVID-19 CRISPR-FDS has the potential to provide reliable COVID-19 diagnosis at remote testing sites. However, further efforts are needed to improve point-of-care settings in clinics with limited resources.

ABSTRACT

Recent research suggests that SARS-CoV-2-infected individuals can be highly infectious while asymptomatic or pre-symptomatic, and that an infected person may infect 5.6 other individuals on average. This situation highlights the need for rapid, sensitive SARS-CoV-2 diagnostic assays capable of high-throughput operation that can preferably utilize existing equipment to facilitate broad, large-scale screening efforts. We have developed a CRISPR-based assay that can meet all these criteria. This assay utilizes a custom CRISPR Cas12a/gRNA complex and a fluorescent probe to detect target amplicons produced by standard RT-PCR or isothermal recombinase polymerase amplification (RPA), to allow sensitive detection at sites not equipped with real-time PCR systems required for qPCR diagnostics. We found this approach allowed sensitive and robust detection of SARS-CoV-2 positive samples, with a sample-to-answer time of ~50 min, and a limit of detection of 2 copies per sample. CRISPR assay diagnostic results obtained nasal swab samples of individuals with suspected COVID-19 cases were comparable to paired results from a CDC-approved quantitative RT-PCR (RT-qPCR) assay performed in a state testing lab, and superior to those produced by same assay in a clinical lab, where the RT-qPCR assay exhibited multiple invalid or inconclusive results. Our assay also demonstrated greater analytical sensitivity and more robust diagnostic performance than other recently reported CRISPR-based assays. Based on these findings, we believe that a CRISPR-based fluorescent application has potential to improve current COVID-19 screening efforts.

FIGURES

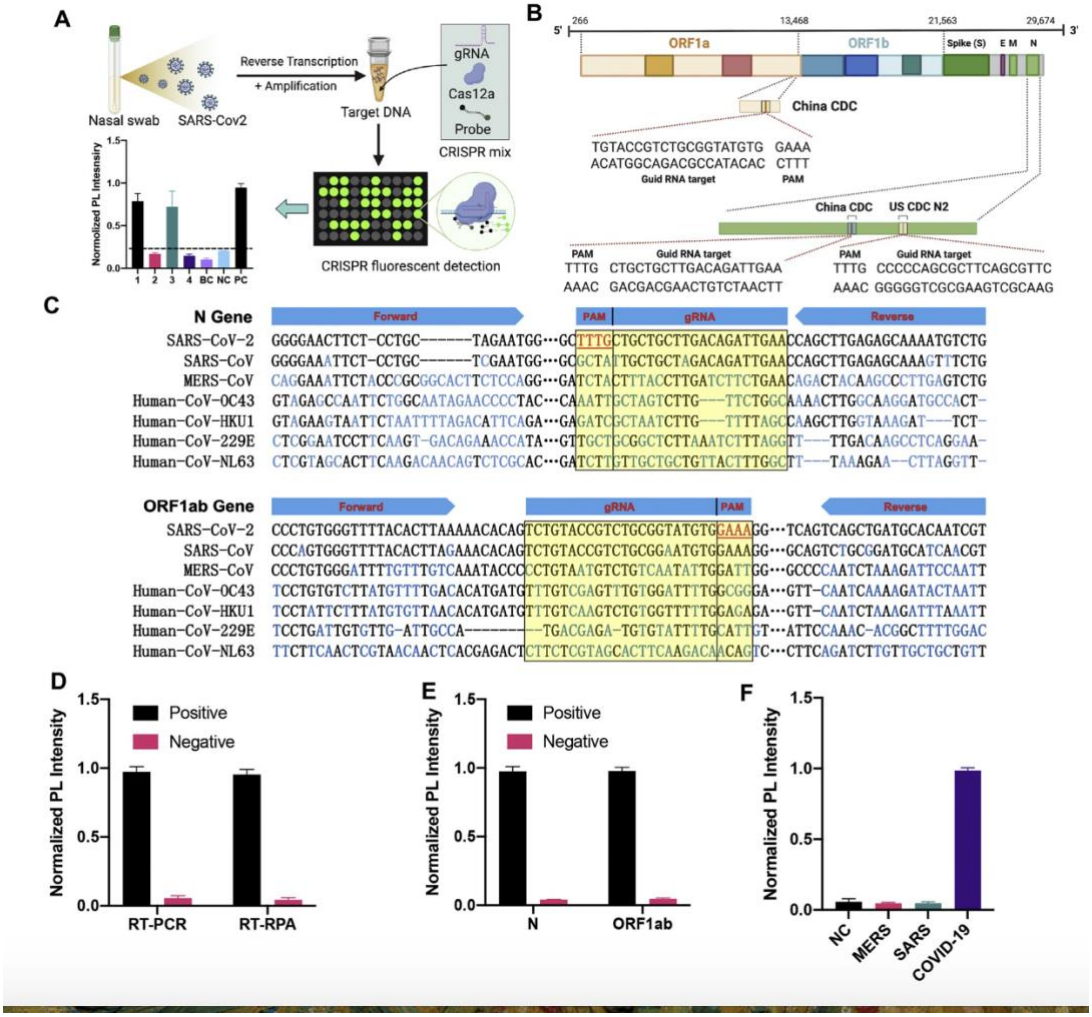


Figure 1. A CRISPR-based Fluorescent Diagnosis System for COVID-19 (COVID-19 CRISPR-FDS). (A) Schematic illustration of a CRISPR-FDS assay for detection of SARS-CoV-2 RNA in clinical samples. (B) SARS-CoV-2 genome map of COVID-19 CRISPR-FDS target sequences, and (C) sites in ORF1ab gene and the N protein gene that are detected COVID-19 CRISPR-FDS. Normalized CRISPR-FDS photoluminescent (PL) signal from SARS-CoV-2 RNA positive (109 copies/sample) and negative control (polyA carrier RNA) samples following (D) target amplification by RT-PCR or RPA, (E) by RT-PCR for each assay target, and (F) by RT-PCR for related beta coronavirus species (109 copies/sample). Bar graph data represents the mean +/- SD, of three experimental replicates.

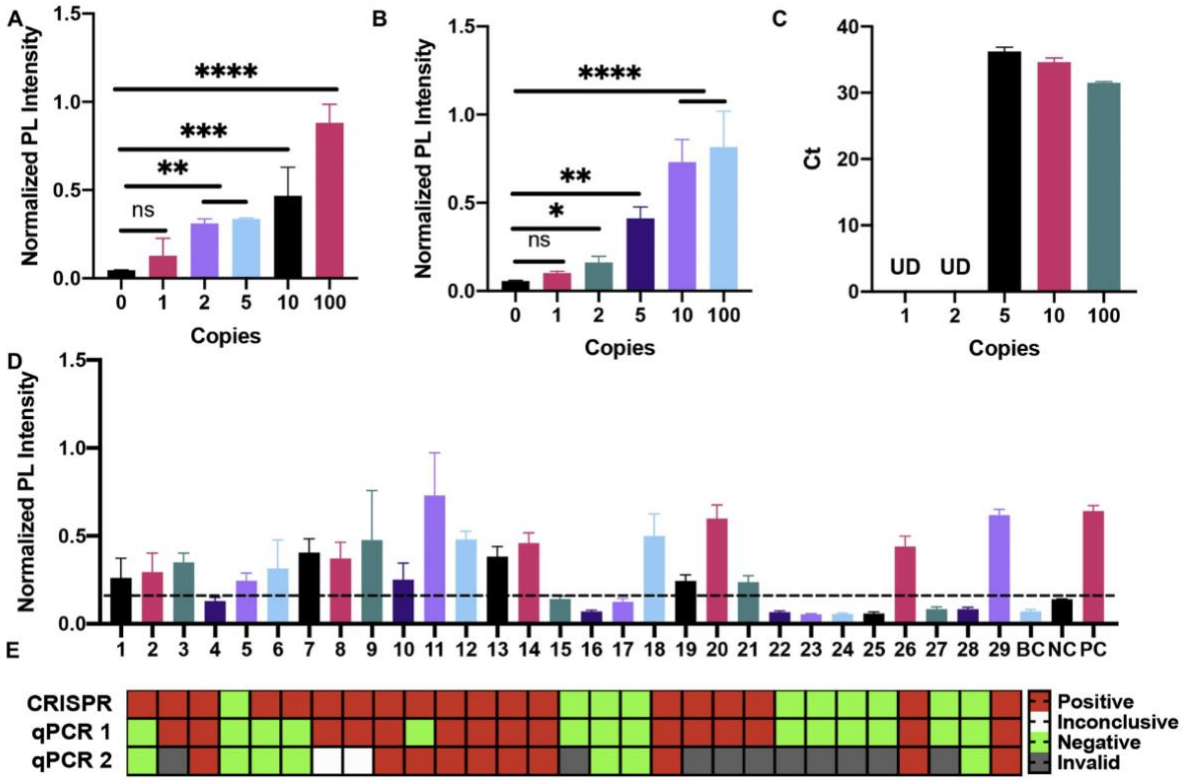


Figure 3. COVID-19 CRISPR-FDS analytical and diagnostic performance. Limit of detection (LOD) samples containing the indicated number of viral genomes afteamplification by (A) RT-PCR and (B) RT-RPA for COVID-19 CRISPR-FDS analysis or by (C) RT-qPCR, indicated significant differences and undetermined (UD) results. (D) RT-PCR COVID-19 CRISPR-FDS results for a cohort of 29 individuals with suspected COVID-19 cases, run in parallel with blank (BC; nuclease free water), negative (NC; carrier RNA) and positive (PC; 109 target amplicon copies) control samples, where the dashed line indicates the threshold for a positive result. Results depict the mean ±SD of three experimental replicates. (E) Comparison of SARS-CoV-2 test results for matching patient samples analyzed by CRISPR-FDS, or by RT- qPCR by a state (qPCR 1) and a clinical testing laboratory (qPCR 2). (ns, P less than 0.05; P less than 0.05; P less than 0.01;P less than 0.001; P less than 0.0001).

DEVELOPMENTS IN TREATMENTS

OUTCOMES IN PATIENTS WITH SEVERE COVID-19 DISEASE TREATED WITH TOCILIZUMAB - A CASE- CONTROLLED STUDY

Rojas-Marte GR, Khalid M, Mukhtar O, Hashmi AT, Waheed MA, Ehrlich S, Aslam A, Siddiqui S, Agarwal C, Malyshev Y, Henriquez-Felipe C, Sharma D, Sharma S, Chukwuka N, Rodriguez DC, Alliu S, Le J, Shani J.. QJM. 2020 Jun 22:hcaa206. doi: 10.1093/qjmed/hcaa206. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

This retrospective case-control study conducted at Maimonides Medical Center, New York evaluates mortality differences in severe and critical COVID-19 patients treated with tocilizumab, an interleukin-6 inhibitor. While there was no significant difference in mortality between the tocilizumab-treated cohort (n=96) and the control patients (n=97; 52% vs. 62.1% P= 0.09), exclusion of intubated patients revealed a significantly decreased mortality rate in the treated cohort (6% vs. 27% P= 0.024; Table 3). Given limitations in exact matching of the cohorts, the authors urge for randomized control trials to evaluate tocilizumab's role in controlling the cytokine storm linked to high mortality in COVID-19 patients.

ABSTRACT

BACKGROUND: COVID-19 is an ongoing threat to society. Patients who develop the most severe forms of the disease have high mortality. The interleukin-6 inhibitor tocilizumab has the potential to improve outcomes in these patients by preventing the development of cytokine release storm.
METHODS: We conducted a retrospective, case-control, single-center study in patients with severe to critical COVID-19 disease treated with tocilizumab. Disease severity was defined based on the amount of oxygen supplementation required. The primary endpoint was the overall mortality. Secondary endpoints were mortality in non-intubated patients, and mortality in intubated patients.
RESULTS: A total of 193 patients were included in the study. 96 patients received tocilizumab, while 97 served as control group. The mean age was 60 years. Patients over 65 years represented 43% of the population. More patients in the tocilizumab group reported fever, cough, and shortness of breath (83%, 80%, and 96% versus 73%, 69%, and 71%, respectively). There was a non-statistically significant lower mortality in the treatment group (52% versus 62.1% P = 0.09). When excluding intubated patients, there was statistically significant lower mortality in patients treated with tocilizumab (6 vs. 27% P = 0.024). Bacteremia was more common in the control group (24% vs 13% P = 0.43), while fungemia was the similar for both (3% vs 4% P = 0.72).
CONCLUSION: Our study showed a non-statistically significant lower mortality in patients with severe to critical COVID-19 disease who received tocilizumab. When intubated patients were excluded, the use of tocilizumab was associated with lower mortality.

FIGURES

Table 3. Outcomes

	Total	Tocilizumab group	Control group	P- value
Outcome - No. (%)	(N=193)	(N= 96)	(N=97)	
Overall mortality	98 (50.8)	43 (44.8)	55 (56.7)	0.09
Mortality in non-intubated patients (excluding patients still hospitalized)	11 (16.4)	2 (6.1)	9 (26.5)	0.024
Mortality in intubated patients (excluding patients still hospitalized)	86 (71)	41 (67.2)	45 (75)	0.34
Length of stay, excluding patients still hospitalized- (days ± SD)	15.3± 9.9	14.5± 8.8	16.5± 10.8	0.329
Bacteremia	35 (18.1)	12 (12.5)	23 (23.7)	0.04
Fungemia	7 (3.6)	4 (4.2)	3 (3.1)	0.72
Renal replacement therapy	35 (18.1)	22 (22.9)	13 (13.4)	0.08
Need for ECMO	1(0.5)	1 (1)	0	0.49
Need for vasopressors	113 (58.5)	59 (61.5)	54 (55.7)	0.41

IGY - TURNING THE PAGE TOWARD PASSIVE IMMUNIZATION IN COVID-19 INFECTION (REVIEW)

Constantin C, Neagu M, Diana Supeanu T, Chiurciu V, A Spandidos D.. Exp Ther Med. 2020 Jul;20(1):151-158. doi: 10.3892/etm.2020.8704. Epub 2020 Apr 30.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Authors in Romania and Greece present a review article on the potential role of passive immunization of IgY (immunoglobulin in egg yolk) against respiratory infections by SARS-CoV-2. They explain that IgY is functionally equivalent to human IgG and has therapeutic and diagnostic applications for Salmonella species, Pseudomonas, Influenza viruses, SARS coronavirus, and Vibrio cholera infections. Since it does not react with mammalian Fc receptors, it can be safely administered to egg-allergic patients as well as pregnant and immunodeficient individuals. Furthermore, IgY can be extracted in considerable quantities from egg yolks at low cost and may be purified by ammonium sulfate, PEG, and chromatographic techniques. Thus, the authors suggest the IgY may serve a novel role against SARS-CoV-2 in the COVID-19 pandemic.

ABSTRACT

The world is facing one of the major outbreaks of viral infection of the modern history, however, as vaccine development workflow is still tedious and can not control the infection spreading, researchers are turning to passive immunization as a

good and quick alternative to treat and contain the spreading. Within passive immunization domain, raising specific immunoglobulin (Ig)Y against acute respiratory tract infection has been developing for more than 20 years. Far from being an obsolete chapter we will revise the IgY-technology as a new frontier for research and clinic. A wide range of IgY applications has been effectively confirmed in both human and animal health. The molecular particularities of IgY give them functional advantages recommending them as good candidates in this endeavor. Obtaining specific IgY is sustained by reliable and nature friendly methodology as an alternative for mammalian antibodies. The aria of application is continuously enlarging from bacterial and viral infections to tumor biology. Specific anti-viral IgY were previously tested in several designs, thus its worth pointing out that in the actual COVID-19 pandemic context, respiratory infections need an enlarged arsenal of therapeutic approaches and clearly the roles of IgY should be exploited in depth.

IVERMECTIN: A SYSTEMATIC REVIEW FROM ANTIVIRAL EFFECTS TO COVID-19 COMPLEMENTARY REGIMEN

Heidary F, Gharebaghi R.. J Antibiot (Tokyo). 2020 Jun 12. doi: 10.1038/s41429-020-0336-z. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Iranian authors performed a review of in vivo and in vitro studies from the last 50 years to document Ivermectin's antiviral activities against a wide variety of DNA and RNA viruses, including SARS-CoV-2 (Table 1). Although an in vitro study has shown Ivermectin's antiviral activity against COVID-19, the authors warn against immediately using Ivermectin as a therapy, which is consistent with Food and Drug Administration (FDA) recommendations as well; the lack of in vivo studies available support the need for more clinical trials and safer formulations of Ivermectin prior to its establishment as a treatment for COVID-19.

ABSTRACT

Ivermectin proposes many potentials effects to treat a range of diseases, with its antimicrobial, antiviral, and anti-cancer properties as a wonder drug. It is highly effective against many microorganisms including some viruses. In this comprehensive systematic review, antiviral effects of ivermectin are summarized including in vitro and in vivo studies over the past 50 years. Several studies reported antiviral effects of ivermectin on RNA viruses such as Zika, dengue, yellow fever, West Nile, Hendra, Newcastle, Venezuelan equine encephalitis, chikungunya, Semliki Forest, Sindbis, Avian influenza A, Porcine Reproductive and Respiratory Syndrome, Human immunodeficiency virus type 1, and severe acute respiratory syndrome coronavirus 2. Furthermore, there are some studies showing antiviral effects of ivermectin against DNA viruses such as Equine herpes type 1, BK polyomavirus, pseudorabies, porcine circovirus 2, and bovine herpesvirus 1. Ivermectin plays a role in several biological mechanisms, therefore it could serve as a potential candidate in the treatment of a wide range of viruses including COVID-19 as well as other types of positive-sense single-stranded RNA viruses. In vivo studies of animal models revealed a broad range of antiviral effects of ivermectin, however, clinical trials are necessary to appraise the potential efficacy of ivermectin in clinical setting.

FIGURES

	Viral characteristic	Genus	Family	References
RNA viruses				
[a]SARS-CoV-2 or COVID-19	An enveloped, positive-sense, single-stranded	*Betacoronavirus*	Coronaviridae	[15]
[a]Zika virus	An enveloped, positive-sense, single-stranded	*Flavivirus*	Flaviviridae	[16, 17, 19, 22, 23]
[a]Dengue virus	An enveloped, positive-sense, single-stranded	*Flavivirus*	Flaviviridae	[20, 21, 23, 25,26,27]
[a]Yellow fever virus	An enveloped, positive-sense, single-stranded	*Flavivirus*	Flaviviridae	[25]
[a]West Nile virus	An enveloped, positive-sense, single-stranded	*Flavivirus*	Flaviviridae	[25]
Hendra virus	An enveloped, negative-sense, single-stranded	*Henipavirus*	Paramyxoviridae	[28]
Newcastle virus	An enveloped, negative-sense, single-stranded		Paramyxoviridae	[29]
[a]Venezuelan equine encephalitis virus	An enveloped, positive-sense, single-stranded	*Alphavirus*	Togaviridae	[30, 31]
[a]Chikungunya virus	An enveloped, positive-sense, single-stranded	*Alphavirus*	Togaviridae	[32]
[a]Semliki Forest virus	An enveloped, positive-sense, single-stranded	*Alphavirus*	Togaviridae	[32]
[a]Sindbis virus	An enveloped, positive-sense, single-stranded	*Alphavirus*	Togaviridae	[32]
Avian influenza A virus	An enveloped, negative-sense, single-stranded	*Alphainfluenzavirus*	Orthomyxoviridae	[33]
[a]Porcine Reproductive and Respiratory Syndrome virus	An enveloped, positive-sense, single-stranded	*Arterivirus*	Arteriviridae	[34]
[a]Human immunodeficiency virus type 1	An enveloped, positive-sense, single-stranded	*Lentivirus*	Retroviridae	[21, 35]
DNA viruses				
Equine herpesvirus type 1	An enveloped, double-stranded	*Varicellovirus*	Herpesviridae	[36]
Pseudorabies virus	An enveloped, double-stranded	*Varicellovirus*	Herpesviridae	[37]
BK polyomavirus	A non-enveloped, double-stranded	*Polyomavirus*	Polyomaviridae	[40]
Porcine circovirus 2	A non-enveloped, single-stranded	*Circovirus*	Circoviridae	[41]

[a]Ivermectin is effective on a number of enveloped, positive-sense, single-stranded RNA viruses including SARS-CoV-2

Table 1. Various studies of Ivermectin's antiviral activity against various DNA and RNA viruses

STATIN THERAPY IN COVID-19 INFECTION: MUCH MORE THAN A SINGLE PATHWAY

Bifulco M, Gazzerro P.. Eur Heart J Cardiovasc Pharmacother. 2020 Jun 12:pvaa055. doi: 10.1093/ehjcvp/pvaa055. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

A group of international researchers examine the role of statin therapy in the treatment of COVID-19. They explore evidence detailing the potential benefits of statin therapy, and argue that the antithrombotic and anti-inflammatory properties of statins may prevent thrombotic complications of COVID-19 and the progression of acute respiratory distress syndrome (ARDS) in patients infected with SARS-CoV-2.

COVID-19, STRESS, TRAUMA, AND PEER SUPPORT-OBSERVATIONS FROM THE FIELD

Fisher EB, Miller SM, Evans M, Luu SL, Tang PY, Dreyer Valovcin D, Castellano C.. Transl Behav Med. 2020 Jun 22:ibaa056. doi: 10.1093/tbm/ibaa056. Online ahead of print.
Level of Evidence: Other - Expert Opinion

BLUF

Authors from the United States conducted a qualitative review on April 2020 in order to determine the effects of COVID-19 on both the callers and operators of three peer support services: Mom2Mom (mothers of children with special needs), Worker2Worker (child protective services), and Cop2Cop (police services). Overall, operators in each service note that their callers have reported increased stressors directly related to COVID-19, the authors suggest that these ancillary support services have an important role in managing social and psychological stress during the pandemic.

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