The Daily COVID-19 Literature Surveillance Summary

July 16, 2020

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

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

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

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

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EXECUTIVE SUMMARY

Climate

- A review of health-related workplace absenteeism in the United States during the pandemic found that workplace absenteeism during the pandemic had only increased in certain occupational subgroups: personal care service, healthcare support, and food processing. The authors postulate that this is due to the close interpersonal contact experienced in these occupations which creates a higher risk of COVID-19 transmission.

Epidemiology

- A case report describes an 11-year-old boy who presented with symptoms of Guillain-Barre Syndrome three weeks after COVID-19 infection. The authors discuss that Guillain-Barre is a rare but documented phenomenon in adult COVID-19 patients but believe this to be one of the first descriptions of the condition in a pediatric patient.

Understanding the Pathology

- A study of lab values in COVID-19 positive patients admitted to the ICU at Tongji hospital, Wuhan observed 12 thrombotic events in 9 patients with coagulation abnormalities which included lower natural anticoagulants, elevated Factor VIII, and presence of anti-phospholipid antibodies. In near-terminal patients, Factors V and VII were lower and prothrombin time was prolonged. These results suggest elevated Factor VIII and presence of anti-phospholipid antibodies may be involved in the etiopathology of COVID-19 hypercoagulable status, while lower Factor V and VII and prolonged PT may indicate advancing illness.

Management

- A systematic review and meta-analysis of 22 observational cohort studies on renal complications in COVID-19 found that acute kidney injury was the most widely reported renal complication followed by need for renal replacement therapy, electrolyte disturbances, and acidosis. Meta-regression found a significant association between preexisting chronic kidney disease and COVID-19 associated acute kidney injury suggesting increased risk in these patients.

R&D: Diagnosis and Treatments

- American pathologists developed and evaluated immunohistochemical and in situ hybridization assays for tissue identification of SARS-CoV-2. They validated their methods through staining of COVID-19 autopsy samples including 8 lungs, 1 placenta, and 10 kidneys finding their protocols to be sensitive and specific for the virus. They provide protocols and reagent lists so that other pathology labs could easily replicate these techniques to study SARS-CoV-2 distribution across tissue types, allowing for a better understanding of tissue-specific pathogenesis.

TABLE OF CONTENTS

CLIMATE

INCREASES IN HEALTH-RELATED WORKPLACE ABSENTEEISM AMONG WORKERS IN ESSENTIAL CRITICAL INFRASTRUCTURE OCCUPATIONS DURING THE COVID-19 PANDEMIC - UNITED STATES, MARCH-APRIL 2020

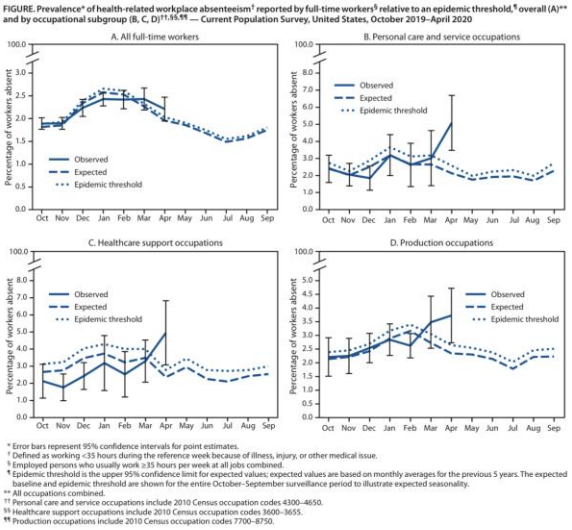
Groenewold MR, Burrer SL, Ahmed F, Uzicanin A, Free H, Luckhaupt SE.. MMWR Morb Mortal Wkly Rep. 2020 Jul 10;69(27):853-858. doi: 10.15585/mmwr.mm6927a1.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

This article reviews compiled data from the Current Population Survey (CPS) between October 2019 and April 2020 to determine how workplace absenteeism was affected by the COVID-19 pandemic. The results indicate that during April 2020 workplace absenteeism was significantly greater than the previous five-year average only in certain occupational subgroups - personal care service, healthcare support, and food processing (Figure, Table) - possibly because the close interpersonal contact experienced in these occupations creates a higher risk of COVID-19 transmission. Overall, this data sheds light on how the current COVID-19 pandemic is affecting particular industries, highlights the importance of employers following guidelines for prevention of COVID-19 transmission in these industries, and reveals a need for additional surveillance methods to enable an improved understanding of workplace-specific morbidity and mortality.

ABSTRACT

During a pandemic, syndromic methods for monitoring illness outside of health care settings, such as tracking absenteeism trends in schools and workplaces, can be useful adjuncts to conventional disease reporting (1,2). Each month, CDC's National Institute for Occupational Safety and Health (NIOSH) monitors the prevalence of health-related workplace absenteeism among currently employed full-time workers in the United States, overall and by demographic and occupational subgroups, using data from the Current Population Survey (CPS).* This report describes trends in absenteeism during October 2019-April 2020, including March and April 2020, the period of rapidly accelerating transmission of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19). Overall, the prevalence of health-related workplace absenteeism in March and April 2020 were similar to their 5-year baselines. However, compared with occupation-specific baselines, absenteeism among workers in several occupational groups that define or contain essential critical infrastructure workforce categories was significantly higher than expected in April. Significant increases in absenteeism were observed in personal care and service (includes child care workers and personal care aides); healthcare support ; and production** (includes meat, poultry, and fish processing workers). Although health-related workplace absenteeism remained relatively unchanged or decreased in other groups, the increase in absenteeism among workers in occupational groups less able to avoid exposure to SARS-CoV-2 (3) highlights the potential impact of COVID-19 on the essential critical infrastructure workforce because of the risks and concerns of occupational transmission of SARS-CoV-2. More widespread and complete collection of occupational data in COVID-19 surveillance is required to fully understand workers' occupational risks and inform intervention strategies. Employers should follow available recommendations to protect workers' health.



* Error bars represent 95% confidence intervals for point estimates.
† Defined as working <35 hours during the reference week because of illness, injury, or other medical issue.
§ Employed persons who usually work ≥35 hours per week at all jobs combined.
¶ Epidemic threshold is the upper 95% confidence limit for expected values; expected values are based on monthly averages for the previous 5 years. The expected baseline and epidemic threshold are shown for the entire October–September surveillance period to illustrate expected seasonality.
** All occupations combined.
†† Personal care and service occupations include 2010 Census occupation codes 4300–4650.
§§ Healthcare support occupations include 2010 Census occupation codes 3600–3655.
¶¶ Production occupations include 2010 Census occupation codes 7700–8750.

Figure. Prevalence* of health-related workplace absenteeism† reported by full-time workers§ relative to an epidemic threshold,¶ overall (A)** and by occupational subgroup (B, C, D)††,§§,¶¶ — Current Population Survey, United States, October 2019–April 2020

TABLE. Monthly prevalence of health-related workplace absenteeism* among full-time workers,† by occupational group — Current Population Survey, United States, October 2019–April 2020

	Weighted % (95% CI)						
	Oct–Dec 2019			Jan–Apr 2020			
Occupational group	Oct	Nov	Dec	Jan	Feb	Mar	Apr
Total	**1.9 (1.8–2.0)§**	**1.9 (1.8–2.0)**	**2.2 (2.0–2.4)**	**2.4 (2.3–2.6)**	**2.4 (2.2–2.6)**	**2.4 (2.2–2.7)§**	**2.2 (1.9–2.5)§**
Personal care and service	2.4 (1.6–3.2)	2.1 (1.4–2.7)	1.9 (1.1–2.6)	3.2 (2.0–4.4)	2.6 (1.4–3.9)	3.0 (1.4–4.6)	5.1 (3.5–6.7)¶
Healthcare support	2.1 (1.1–3.1)	1.8 (1.0–2.5)	2.4 (1.6–3.2)	3.2 (1.6–4.8)	2.5 (1.2–3.9)	3.3 (2.1–4.5)	5.0 (3.1–6.8)¶
Production	2.2 (1.5–2.9)	2.2 (1.6–2.9)	2.5 (2.0–3.1)	2.8 (2.3–3.4)	2.6 (2.2–3.1)	3.5 (2.5–4.4)§	3.7 (2.7–4.7)¶
Transportation and material moving	2.9 (2.1–3.6)§	2.2 (1.4–3.0)	2.9 (2.4–3.5)	2.8 (1.8–3.8)	3.1 (2.4–3.8)	3.1 (2.3–3.9)	3.6 (2.6–4.6)**
Building and grounds cleaning and maintenance	1.9 (1.0–2.8)	1.9 (0.9–2.9)	2.9 (2.1–3.8)	2.9 (1.7–4.2)	3.4 (2.4–4.4)	3.2 (1.9–4.5)	3.3 (2.1–4.5)
Food preparation and serving related	2.1 (1.3–2.9)	2.2 (1.3–3.1)	2.7 (1.7–3.6)	2.7 (1.5–3.9)	3.0 (1.9–4.0)	2.8 (1.7–3.8)	3.1 (1.1–5.1)
Construction and extraction	1.4 (0.9–2.0)	1.6 (1.0–2.2)	2.2 (1.7–2.7)	3.1 (2.0–4.1)§	2.5 (1.7–3.2)	2.3 (1.4–3.1)	2.9 (1.8–4.1)§
Healthcare practitioner and technical	2.3 (1.8–2.8)	2.0 (1.5–2.5)	2.3 (1.7–2.9)	2.4 (1.6–3.2)	2.5 (1.9–3.0)	2.1 (1.5–2.7)	2.8 (2.0–3.6)**
Farming, fishing, and forestry	1.1 (0.0–2.4)	1.4 (0.0–3.5)	1.6 (0.1–3.2)	4.2 (2.1–6.2)§	3.7 (0.9–6.5)	2.6 (0.0–5.4)§	2.6 (0.0–6.5)
Office and administrative support	2.6 (2.1–3.1)§	2.4 (2.1–2.7)	2.7 (2.3–3.1)	3.0 (2.2–3.7)	2.5 (2.1–2.9)	3.0 (2.5–3.5)	2.5 (1.8–3.1)
Legal occupations	2.0 (0.7–3.3)	1.0 (0.1–1.9)	1.5 (0.6–2.5)	2.9 (1.5–4.3)§	2.7 (1.0–4.3)	0.9 (0.1–1.8)	2.3 (0.7–3.8)
Sales and related	1.7 (1.3–2.1)§	2.1 (1.6–2.7)**	2.0 (1.5–2.6)	2.0 (1.6–2.5)	2.3 (1.5–3.1)§	2.1 (1.7–2.6)	2.1 (1.6–2.6)
Protective service	2.7 (1.4–3.9)§	2.4 (1.3–3.5)§	2.9 (1.6–4.1)	3.3 (2.2–4.3)§	2.6 (1.8–3.3)§	2.3 (1.6–3.1)	2.1 (1.3–3.0)
Installation, maintenance and repair	2.4 (1.6–3.1)	2.4 (1.6–3.2)	1.9 (1.2–2.6)	1.8 (1.0–2.7)	2.8 (2.1–3.5)	3.5 (2.3–4.7)§	2.0 (1.2–2.9)
Education, training, and library	1.5 (1.1–2.0)	2.3 (1.7–2.8)**	2.7 (1.9–3.4)§	2.7 (2.1–3.2)§	2.5 (1.9–3.0)	2.2 (1.5–2.9)	1.5 (0.8–2.3)
Architecture and engineering	0.8 (0.0–1.7)	1.3 (0.4–2.2)	1.4 (0.6–2.2)	2.5 (1.3–3.6)	1.5 (0.7–2.4)	2.4 (1.3–3.4)§	1.4 (0.6–2.1)
Arts, design, entertainment, sports, and media	2.1 (0.7–3.5)	2.1 (0.9–3.3)	2.3 (0.7–3.9)	2.0 (0.7–3.3)	1.6 (0.9–2.4)	2.5 (0.6–4.4)	1.4 (0.3–2.5)
Business and financial operations	1.5 (1.1–2.0)	1.3 (0.7–1.9)	2.1 (1.5–2.6)	2.5 (1.8–3.1)	2.4 (1.9–2.8)§	1.6 (0.9–2.2)	1.2 (0.7–1.8)
Computer and mathematical science	1.4 (0.8–2.0)	0.8 (0.3–1.2)	1.6 (0.9–2.2)	1.6 (1.0–2.3)	2.2 (1.3–3.1)	2.0 (1.2–2.8)§	1.1 (0.5–1.8)
Community and social service	1.9 (0.7–3.1)	2.5 (1.4–3.6)	1.8 (1.0–2.5)	1.6 (0.8–2.4)	2.3 (1.1–3.4)	3.1 (1.9–4.2)	1.0 (0.0–2.2)
Management	1.1 (0.8–1.4)	1.3 (0.9–1.6)	1.7 (1.4–1.9)	1.3 (1.0–1.6)	1.6 (1.3–1.9)	1.6 (1.3–2.0)	0.9 (0.6–1.2)
Life, physical, and social science	1.9 (0.5–3.4)	2.8 (1.0–4.5)	2.4 (0.8–4.0)	2.9 (1.4–4.4)	2.5 (1.0–3.9)	1.2 (0.3–2.1)	0.5 (0.0–1.2)

Abbreviation: CI = confidence interval.
* Defined as working <35 hours during the reference week because of illness, injury or other medical issue.
† Defined as employed persons who usually work ≥35 hours per week at all jobs combined.
§ Point estimate, but not its lower 95% confidence limit, exceeded an epidemic threshold defined as the upper 95% confidence limit of the expected value, based on monthly average for the previous 5 years, and p-value for post hoc observed versus expected comparison using Z-test for independent proportion ≥0.05.
¶ Significantly exceeded the epidemic threshold (i.e., lower 95% confidence limit of the point estimate exceeded the epidemic threshold).
** Point estimate, but not its lower 95% confidence limit, exceeded the epidemic threshold and p-value for post hoc observed versus expected comparison using Z-test for independent proportion <0.05.

Table. Monthly prevalence of health-related workplace absenteeism* among full-time workers,† by occupational group — Current Population Survey, United States, October 2019–April 2020

PEDIATRICS

GUILLAIN-BARRE SYNDROME ASSOCIATED WITH SARS-COV-2 DETECTION AND A COVID-19 INFECTION IN A CHILD

Khalifa M, Zakaria F, Ragab Y, Saad A, Bamaga A, Emad Y, Rasker JJ.. J Pediatric Infect Dis Soc. 2020 Jul 11:piaa086. doi: 10.1093/jpids/piaa086. Online ahead of print.
Level of Evidence: Other - Case Report

BLUF

A case report conducted at the Dr. Erfan and Bagedo General Hospital in Saudi Arabia discusses an 11-year-old boy who presented with symptoms of Guillain-Barre Syndrome (GBS) three weeks after a respiratory infection (Figure 1) later diagnosed as COVID-19. Per the authors, GBS is a rare but documented phenomenon in adult patients (7 case reports known to the authors). However, this case report is one of the first to describe GBS in a pediatric COVID-19 patients and the authors believe there may be an association between SARS-CoV-2 and GBS in the pediatric population as well as in adults.

SUMMARY

11 year-old male patient presented on April 10th, 2020 to the emergency room with complaints of inability to walk, unsteady gait, and tingling sensation in both legs and feet. Of note, the patient had a mild upper respiratory infection with fever three weeks prior, which was treated with paracetamol and azithromycin, reduced to a dry cough. Physical exam was positive for hypotonia and decreased muscle strength in the lower extremities bilaterally. Vital signs were normal. An MRI and nerve conduction studies were performed on April 10th, which revealed enhancement of the cauda equina nerve roots and decreased conduction velocity bilaterally in the lower extremities, respectively. These imaging results supported a diagnosis of GBS. A plain chest XR and chest CT were also performed, which showed bilateral opacities and atelectasis of the lingula (Figure 1). Multiplex PCR for GBS agents performed on April 11th were all negative, however, a follow-up RT-PCR for SARS-CoV-2 was positive. On April 15th, the patient developed a morbilliform rash over the palmar aspect of both hands. Treatment was initiated with a combination of paracetamol, hydroxychloroquine, and enoxaparin. The patient's neurological symptoms slowly began to improve over the next few days. Negative SARS-CoV-2 PCR tests were performed on April 20th and April 22nd, and the patient was discharged on April 25th with improvement in both neurological and respiratory symptoms.

ABSTRACT

Coronavirus disease (COVID-19) is caused by SARS-CoV-2. Physicians in China reported what is believed to be the first adult case of a SARS-CoV-2 infection associated with acute Guillain-Barre syndrome (GBS), followed by five adult Italian patients and another case in the United States of America. In the current report we present one of the first descriptions of an association of GBS and SARS-CoV-2 infection within a child. In our facility, and eleven year old boy presented with typical features of GBS and after five days a morbilliform skin rash over the palms of both hands. Three weeks before the start of the neurological symptoms, the boy had experienced an episode of mild febrile illness with mild respiratory manifestations and a persisting cough. The diagnosis of the SARS-CoV-2 infection was confirmed by oropharyngeal swab on reverse transcription polymerase chain reaction assay. The disease course of our patient strongly suggests a possible relationship between the development of GBS and SARS-CoV-2 infection. The case is discussed in view of the previous case reports with the association of GBS and Covid-19.

FIGURES

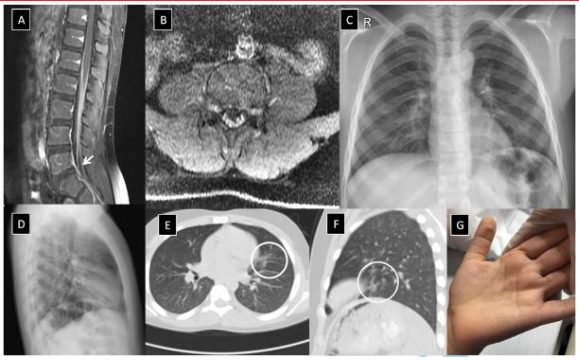


Figure.1: (a,b): Sagittal and axial T1 Fat saturation post contrast magnetic resonance imaging showing cauda equina nerve roots enhancement (white arrow) impressive of GBS; (c,d): X-ray chest PA and left lateral views showing bilateral paracardiac and basal veiling: (e,f): Computed tomography (CT) of the chest showing small patchy subsegmental faint opacity with atelectasis band in the lingula on week after admission (white circles); (g) Morbilliform skin rash over the palmar aspect of the left hand.

PROFILE OF NATURAL ANTICOAGULANT, COAGULANT FACTOR AND ANTI-PHOSPHOLIPID ANTIBODY IN CRITICALLY ILL COVID-19 PATIENTS

Zhang Y, Cao W, Jiang W, Xiao M, Li Y, Tang N, Liu Z, Yan X, Zhao Y, Li T, Zhu T.. J Thromb Thrombolysis. 2020 Jul 9. doi: 10.1007/s11239-020-02182-9. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A cross-sectional study of 19 COVID-19 positive patients (confirmed via reverse transcription polymerase chain reaction [RT-PCR]) admitted to the ICU at Tongji hospital, Wuhan between 23 February to 3 March 2020 (Table 1) observed 12 thrombotic events in 9 patients with coagulation abnormalities including lower natural anticoagulants (protein C, Protein S, antithrombin), elevated Factor VIII, and presence of anti-phospholipid antibodies (aPLs) (Tables 2, 3). In near-terminal patients, Factors V and VII were lower and prothrombin time (PT) was prolonged. These results suggest elevated Factor VIII and presence of aPLs may be involved in the etiopathology of COVID-19 hypercoagulable status, while lower Factor V and VII and prolonged PT may indicate advancing illness (see summary).

SUMMARY

Summary of study findings:

Patients were divided into 2 groups:
- Terminal stage group (n=5) - patients who died within 24 hours of coagulation sampling
- Non-terminal stage group (n=14) - patients who survived more than 3 days since coagulation sampling.

Authors observed a total of 12 thrombotic events in 9 patients including 4 cerebral infarctions, 7 acro-ischemia, and 1 IJV thrombosis. Coagulation abnormalities from routine tests (Tables 2,3):
- Lower Protein C levels in both groups with no significant difference (p=0.559).
- Elevated Factor VIII in both groups with no significant difference (p=0.893).
- Factor V and VII were lower in terminal-stage than non-terminal stage group (p=0.005 and p=0.014, respectively)
- D-dimer and FDP were elevated and comparable in both groups.
- Prolonged PT in both groups, moreso in terminal stage group (p=0.044)
- aPLs were elevated in 10 patients (7 of which had multiple aPL isotypes), while no thrombotic events occurred in 9 aPL negative patients.

ABSTRACT

The outbreak of novel coronavirus disease 2019 (COVID-19) has now become a global pandemic. Coagulopathy has been reported widely in critically ill COVID-19 patients and was related to high mortality. However, the comprehensive coagulation profiles have not been examined and the underlying mechanism of the coagulopathy in COVID-19 patients is unclear. To study the coagulation profiles of routine hemostasis tests, natural anticoagulants, coagulant factors and antiphospholipid antibodies in critically ill COVID-19 patients. This single-center and cross-section study included 19 patients with COVID-19, who were admitted to intensive care unit (ICU) at Tongji hospital in Wuhan, China, from Feb 23 to Mar 3, 2020. Demographic data, laboratory parameters, treatments and clinical outcomes of the patients were collected and analyzed. The final date of follow-up was Mar 31, 2020. In this study, 12 thrombotic events occurred in 9 patients, including 4 cerebral infarctions, 7 acro-ischemia and 1 internal jugular vein thrombosis. The common abnormalities of routine coagulation tests included evelated D-Dimer level (100%), prolonged prothrombin time (73.7%) and hyperfibrinogenemia (73.7%). The median activities of natural anticoagulants including protein C, protein S and antithrombin were all below the normal range. Factor VIII activities were significantly above normal range (median value 307%, IQR 198-441) in all patients. Factor V and factor VII activities were significantly lower in near-terminal stage patients. Anti-phospholipid antibodies were present in 10 patients. Strikingly, 4 cerebral infarction events were in patients had anti-phospholipid antibodies of multiple isotypes. Sustained hypercoagulable status and thrombotic events were common in critically ill patients with COVID-19. The low activities of natural anticoagulants, elevated factor VIII level and the presence of antiphospholipid antibodies, together, may contribute to the etiopathology of coagulopathy in COVID-19 patients.

FIGURES

	Terminal stage (N = 5)	Non-terminal (N = 14)	Total (N = 19)
Age (median)	71 (63–72)	65 (59–68)	65 (60–70)
Male (n, %)	3 (60%)	7 (50%)	10 (52.6%)
Comorbidity (n, %)	4 (80%)	8 (57.2%)	12 (63.2%)
The interval from Onset to sampling (days, IQR)	29 (23–30)	30 (20–33.5)	30 (29–32)
Survival time (days, IQR)	30 (24–31)	50 (39.25–64.75)	40 (32–62)
SIC scores at sampling (IQR)	5 (4–6)	2.5 (2–4)	3 (2–5)
SOFA scores at sampling (IQR)	13 (11.5–15.5)	7.5 (5.5–10.25)	9 (6–13)
Overt-DIC scores at sampling (IQR)	4 (3–4)	2 (2–3)	3 (2–3.5)
Thrombotic events	0	12	12
Arterial thrombosis	0	4	4
Venous thrombosis	0	1	1
Micro-thrombi (acro-ischemia)	0	7	7
Bleeding events	1[a]	0	1[a]

DIC disseminated intravascular coagulation, *SOFA* sequential organ failure assessment, *SIC* sepsis-induced coagulopathy
[a]only 1 gastrointestinal bleeding event occurred after anticoagulation

Table 1: Clinical characters of critically ill patients with COVID-19.

	Terminal stage (N = 5)	Non-termina (N = 14)	Total (N = 19)	P value
PLT (100–300 × 10^9/l)	88 (27.5–275)	214 (160.25–251.5)	202 (88–249)	0.156
PT (11.5–14.5 s)	17.7 (16.35–19.6)	15.2 (14.125–16.4)	15.8 (14.5–17.7)	0.044
FIB (2.00–4.00 g/l)	3.6 (2.85–5.965)	4.8 (4.12–5.30)	4.42 (3.6–5.22)	0.298
APTT (29.0–42.0 s)	71.9 (40.35–75.4)	46.75 (40.625–54.175)	47.5 (40.9–56.1)	0.257
D-Dimer (<0.5 μg/ml FEU)	3.61 (0.81–6.835)	2.72 (1.995–4.105)	2.72 (1.55–4.93)	0.754
FDP (< 5.0 μg/ml)	20.7 (13.7–20.7)	11.75 (7.525–17.75)	14.5 (7.975–20.65)	0.533
AT, (80–120%)	59 (59–85)	73 (67–89.5)	72.5 (60.75–82.75)	1.000
PC (70–142%)	66 (26–88.5)	62 (56–106.5)	63 (50–99)	0.559
PS (77–143%)	81 (13–121)	67.5 (39.25–83.5)	70 (31–88)	0.893
FVIII (60–150%)	316 (184.5–488.5)	300 (216.5–414)	307 (198–441)	0.893
FIX (60–150%)	137 (76–169.5)	143 (115.75–182.75)	137 (119–176)	0.500
FXI (60–150%)	54 (29.5–164.5)	98.5 (32.5–97.25)	92 (43–138)	0.500
FXII (50–150%)	45 (33–85)	56.5 (32.5–97.25)	56 (43–87)	0.687
FII (70–120%)	60 (26.5–69)	64 (52.5–72.25)	62 (45–72)	0.391
FV (70–120%)	68 (50–106.5)	160 (100–193.25)	129 (73–190)	0.005
FVII (55–170%)	58 (31–72.5)	98.5 (77.25–107.25)	93 (58–106)	0.014
FX (70–120%)	51 (29–84.5)	74 (47–89.25)	73 (47–85)	0.257

All the parameters in this table were displayed by the form: median value, 25% to 75% IQR
aCL anti-cardiolipin, *aβ2GP1* anti-β2-glycoprotein 1, *APTT* activated partial thromboplastin time, *AT* antithrombin, *FIB* fibrinogen, *FDP* fibrinogen degradation products, *LA* lupus anticoagulant, *PC* protein C, *PLT* platelet, *PT* prothrombin time, *PS* protein S

Table 2: Coagulation parameter profile in critically ill patients with COVID-19.

	aCL			aβ2GP1			LA
	IgA	IgG	IgM	IgA	IgG	IgM	
Positive	6	2	1	7	6	0	1

aCL anti-cardiolipin, *aβ2GP1* anti-β2-glycoprotein 1, *LA* lupus anticoagulant

Table 2: Coagulation parameter profile in critically ill patients with COVID-19.

TWIRLS, A KNOWLEDGE-MINING TECHNOLOGY, SUGGESTS A POSSIBLE MECHANISM FOR THE PATHOLOGICAL CHANGES IN THE HUMAN HOST AFTER CORONAVIRUS INFECTION VIA ACE2

Ji X, Tan W, Zhang C, Zhai Y, Hsueh Y, Zhang Z, Zhang C, Lu Y, Duan B, Tan G, Na R, Deng G, Niu G.. Drug Dev Res. 2020 Jul 13. doi: 10.1002/ddr.21717. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

Chinese researchers analyzed an automated technology-based literature mining system (see summary). Their analysis found SARS-CoV-2 binding angiotensin-converting enzyme 2 (ACE2) causes imbalance of the renin-angiotensin system (RAS) pathway (Figure 7) leading to cytokine storm via overexpression of IL-6 and IP-10. Additionally, COVID-19 patients on angiotensin receptor blockers (ARBs) for hypertension had lower risk of severe illness, suggesting ARBs may be beneficial for acute lung injury in COVID-19 (Table 5).

SUMMARY

Topic-wise inference engine of massive biomedical literature (TWIRLS) was used as a literature mining system to collect and analyze ~15,000 articles. Findings of analysis as follows:
- Articles (gathered from PubMed) identified coronavirus study-specific human genes (CSHG) and coronavirus study-specific entities (CSSE) and the relative position of any CSHG to a specific CSSE (Table 1).
- Authors found coronavirus binding to ACE2 alters homeostasis of RAS pathway due to functional changes in ACE2/angiotensin II type 2 (AT2) receptor, leading to increased action of angiotensin II on angiotensin II type 1 (AT1) receptor and increased expression of IL-6 and IP-10 thereby triggering cytokine storm and causing acute lung injury (Figure 7).
- Z scores for numerical blood indices including functional markers of the liver, kidney, and heart were analyzed in 6 groups (ARB, non-ARB, patients without medical history, mild illness, severe illness, and critical illness), which showed a relationship between the non-ARB group and severe illness (Table 5).

- Out of 31 hypertensive patients analyzed, the ARB group (n=8) developed less severe illness compared to the non-ARB group.

Although the data is limited by the small n, the authors suggest ARBs may reduce COVID-19 severity and benefit COVID-19 patients with acute lung injury.

ABSTRACT

Faced with the current large-scale public health emergency, collecting, sorting, and analyzing biomedical information related to the "SARS-CoV-2" should be done as quickly as possible to gain a global perspective, which is a basic requirement for strengthening epidemic control capacity. However, for human researchers studying viruses and hosts, the vast amount of information available cannot be processed effectively and in a timely manner, particularly if our scientific understanding is also limited, which further lowers the information processing efficiency. We present TWIRLS (Topic-wise inference engine of massive biomedical literatures), a method that can deal with various scientific problems, such as liver cancer, acute myeloid leukemia, and so forth, which can automatically acquire, organize, and classify information. Additionally, this information can be combined with independent functional data sources to build an inference system via a machine-based approach, which can provide relevant knowledge to help human researchers quickly establish subject cognition and to make more effective decisions. Using TWIRLS, we automatically analyzed more than three million words in more than 14,000 literature articles in only 4 hr. We found that an important regulatory factor angiotensin-converting enzyme 2 (ACE2) may be involved in host pathological changes on binding to the coronavirus after infection. On triggering functional changes in ACE2/AT2R, the cytokine homeostasis regulation axis becomes imbalanced via the Renin-Angiotensin System and IP-10, leading to a cytokine storm. Through a preliminary analysis of blood indices of COVID-19 patients with a history of hypertension, we found that non-ARB (Angiotensin II receptor blockers) users had more symptoms of severe illness than ARB users. This suggests ARBs could potentially be used to treat acute lung injury caused by coronavirus infection.

FIGURES

Category	HR label
C0	MISC
C1	Canine coronavirus
C2	Porcine epidemic diarrhea (PED)
C3	Neurotropic coronavirus correlated with immune-mediated demyelination
C4	Coronavirus that infects humans
C5	Coronavirus spike protein
C6	Protease enhances SARS-CoV infection
C7	Monoclonal antibody to the coronavirus nucleocapsid protein
C8	SARS-CoV genome
C9	Avian infectious bronchitis coronavirus
C10	Coronavirus and interferon
C11	Feline infectious peritonitis (FIP)
C12	Vectors of novel coronaviruses
C13	Mouse hepatitis virus
C14	Interaction between coronaviruses and receptors
C15	Coronavirus-related vaccines
C16	Identification of MHC class I restricted T-cell epitopes
C17	Transmissible gastroenteritis coronavirus
C18	SARS coronavirus inhibitors and diagnostic methods
C19	Coronavirus fusion with host cells and virus replication
C20	Gene therapy-inhibition of coronavirus by antisense RNA, sense RNA and protein
C21	Imaging
C22	Cytotoxic T-lymphocyte escape
C23	SARS coronavirus compound inhibitors
C24	Coronavirus studies using biophysical methods
C25	Detection of viral pathogenicity and distribution (RT-PCR, immunohistochemistry and in situ hybridization)
C26	Coronavirus immunization
C27	Gastroenteritis virus and coronavirus
C28	Effects of coronavirus infection on the body
C29	Coronavirus detection evidence and methods
C30	Human respiratory coronavirus NL63
C31	The antibodies against SARS-CoV

Table 1. Coronavirus-entity category labels and genes associated with each category. MISC indicates the label cannot be summarized.

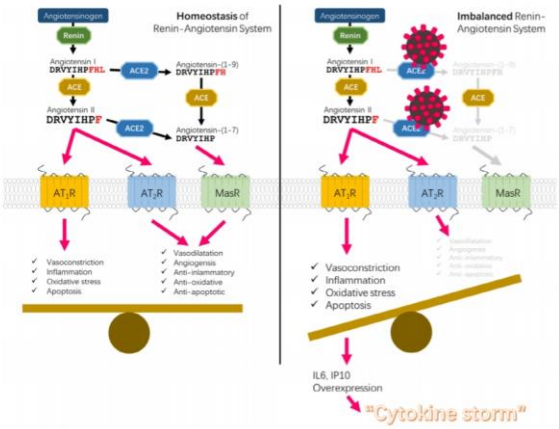


Figure 7. Disequilibrium of RAS-cytokine signaling homeostasis causing cytokine storms triggered by ACE2- mediated coronaviral infection.

Clinical characteristics		ARB	Non-ARB	With other medical history	Severe illness	Critical illness	Mild illness
Routine blood tests	White blood cells(WBC)count	1.35	1.06	0.90	1.93	−0.58	−0.32
	Neutrophil count(Neu)	1.42	1.47	1.23	2.77	0.03	−0.58
	Lymphocyte count(lymph)	−0.26	−1.37	−0.93	−2.78	−1.75	0.82
	Monocyte count(mono)	1.20	−0.21	−0.03	1.02	−1.63	0.02
	Neu%	1.18	2.51	1.43	3.49	1.52	−0.94
	Lymph%	−1.25	−2.58	−1.44	−3.66	−1.25	0.94
	Mono%	−0.27	−1.57	−0.76	−0.61	−0.85	0.24
	Red blood cell (RBC) count	0.76	−2.24	−1.05	−1.77	−0.48	0.43
	Hemoglobin(Hb)	0.55	−0.09	0.99	1.38	−0.04	−0.26
	Platelet(PLT)	0.41	0.97	0.72	0.97	−1.91	0.07
Liver function	Alanine aminotransferase (ALT)	−0.41	−0.73	−0.07	1.61	0.52	−0.40
	Aspartate aminotransferase (AST)	−0.68	0.39	0.58	0.22	2.99	−0.47
	Total bilirubin (TBIL)	1.01	0.92	0.11	0.34	0.20	−0.11
	Direct bilirubin (DBIL)	−0.04	−0.51	−0.13	−0.32	2.96	−0.37
	Indirect bilirubin (IBIL)	1.26	0.67	0.03	0.49	0.00	−0.11
	Gamma-glutamyl transferase (GGT)	0.18	0.34	0.64	3.83	1.39	−0.97
	Alkaline phosphatase (ALP)	0.11	−0.01	−0.41	−0.30	−0.50	0.13
	Lactic dehydrogenase (LDH)	−0.54	0.32	0.74	2.70	3.55	−1.07
	Total protein (TP)	3.10	−0.73	−1.24	−1.11	−1.35	0.42
	Albumin (Alb)	1.97	−1.72	−2.22	−3.65	−1.52	0.99
	Globulin (Glb)	2.77	0.54	0.28	2.10	−0.47	−0.38
	ALB/GLB (A/G)	−1.20	−1.64	−1.54	−3.71	−0.49	0.86
Renal function	Na+	0.31	0.81	0.44	0.63	−3.49	0.37
	K+	1.31	−1.97	−0.47	−3.13	−1.36	0.83
	Fasting blood glucose (FBG)	0.03	1.94	0.05	0.41	−0.34	−0.05
	Uric acid(UA)	3.07	−1.99	−0.74	−0.84	−1.14	0.34
	Urea nitrogen(UN)	0.40	−0.55	−0.28	−0.21	−0.33	0.10
	Creatinine(Cr)	2.33	−1.57	−0.76	−0.51	−0.47	0.17
	Glomerular filtration rate(CDK-EPI)	−2.83	−1.89	−0.43	−0.48	−1.34	0.29
Cardiac enzymes	Creatine kinase(CK)	−0.44	1.14	0.56	−0.26	2.79	−0.32
	Creatine kinase-MB (CK-MB)	−0.67	0.74	1.76	0.37	0.71	−0.18

Figure 7. Disequilibrium of RAS-cytokine signaling homeostasis causing cytokine storms triggered by ACE2- mediated coronaviral infection.

ENDOCRINE SIGNIFICANCE OF SARS-COV-2'S RELIANCE ON ACE2

Lazartigues E, Qadir MMF, Mauvais-Jarvis F.. Endocrinology. 2020 Jul 11:bqaa108. doi: 10.1210/endocr/bqaa108. Online ahead of print.
Level of Evidence: Other - Mechanism-based reasoning

BLUF

A literature review on Angiotensin Converting Enzyme type 2 (ACE2), the main receptor for SARS-CoV-2 and TMPRSS2, a direct androgen receptor target gene. Evidence suggests reducing renin-angiotensin system (RAS) overactivity may protect against new metabolic abnormalities secondary to COVID-19 infection (discussed further below). The authors urge further study of endocrine pathogenicity in SARS-CoV-2 (ie., pancreatic islet, testicular, pituitary, and thyroid dysfunction) and whether risk of metabolic comorbidities is associated with increased or decreased ACE2 or TMPRSS2 expression (Figure 1A).

SUMMARY

The authors recognize the role of ACE2 within the RAS axis in maintaining endocrine and metabolic function as it relates to SARS-CoV-2. In particular, SARS-CoV-2 infections are associated with the following comorbidities: new onset hyperglycemia, pancreatic injury, Leydig cell failure and sterility, transient hypothalamic-pituitary-adrenal axis dysfunction, and thyroid dysfunction.

In addition to recognizing the clinical differences of COVID-19 infections in endocrinology, the authors also discuss possible sex differences. Current studies have mixed results on ACE2 regulation between males versus females. Some studies suggest that since ACE2 is located on the X chromosome, the ACE2 enzyme may be regulated differently in men (XY) than in women (XX). Other studies have shown no difference in ACE2 overall gene expression, suggesting that the regulation is similar between the sexes. In response to this dissonance, the authors instead discuss TMPRSS2, a direct androgen receptor target gene expressed in both males and females, as a possible contributor affecting SARS-CoV-2 cell entry and its pathogenicity along with ACE2. However, more data is needed is study how gene expression levels are associated with the comorbidities related to the SARS-CoV-2 infection.

ABSTRACT

The current COVID-19 pandemic is the most disruptive event in the last 50 years with global impact on healthcare and world economies. It is caused by SARS-CoV-2, a coronavirus that uses angiotensin converting enzyme 2 (ACE2), as an entry point to the cells. ACE2 is a transmembrane carboxypeptidase and member of the renin-angiotensin system. This mini-review, summarizes the main findings regarding ACE2 expression and function in endocrine tissues. We discuss rapidly evolving knowledge on the potential role of ACE2 and SARS coronaviruses in endocrinology and the development of diabetes mellitus, hypogonadism, pituitary and thyroid diseases.

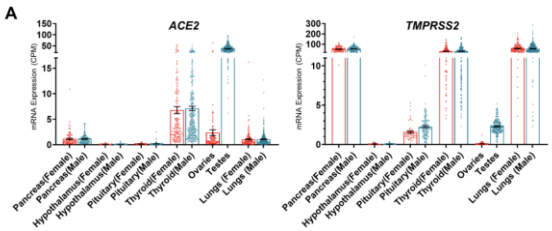


Figure 1: Patterns of gene expression for ACE2 and TMPRSS2 across select human tissues and pancreatic islet cells. (A) Scatter plots showing mRNA expression in various human male and female tissues. Left panel: ACE2 expression levels; right panel: TMPRSS2 expression levels. Data shown are derived from the human protein atlas and genotype tissue expression project (62-64).

NEPHROLOGY

RENAL COMPLICATIONS IN COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

Kunutsor SK, Laukkanen JA.. Ann Med. 2020 Jul 10:1-9. doi: 10.1080/07853890.2020.1790643. Online ahead of print.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

Researchers in the UK and Finland conducted a systematic review and meta-analysis of 22 observational cohort studies on renal complications in COVID-19 (n=17,391) through June 13, 2020. The review's goals included defining these complications, their incidence, and determining if pre-existing chronic kidney disease affects risk. Acute kidney injury (AKI) was the most widely reported renal complication followed by need for renal replacement therapy (RRT), electrolyte disturbance, and acidosis (Figure 3). Meta-regression found a significant association between preexisting CKD and COVID-19 associated AKI. This suggest increased risk in this patients and the authors urge close monitoring and management of renal function for favorable outcomes. Of note, the heterogeneity was high (i^2 97-98%) somewhat limiting these conclusions.

SUMMARY

- The authors searched MEDLINE, Embase, and The Cochrane Library from 2019 [specific date not given] to June 13, 2020 for studies related to renal complications from COVID-19.
- 22 observational cohort studies were ultimately included. Sixteen based in China, six in the US, 17,391 patients in total.
- Average age was between 46 and 71 years depending on the study, with a weighted average of 60 years. Hospital stays were between 2 and 28 days, with weighted average of 7 days.
- Across the 20 studies that reported prevalence of pre-existing chronic kidney disease, prevalence was found to be 5.2% (Figure 1) based on pooled random effects (range = 0.7% to 47.6%; i^2 = 98%, 95% CI: 2.8-8.1%, p for heterogeneity < 0.01).
- Acute kidney injury (AKI) was the most widely reported outcome (reported in all 22 studies). Pooled incidence was 11.0% (i^2 = 97%, 95% CI: 7.4-15.1%, p for heterogeneity < 0.01).
- Other complications included electrolyte disturbance (incidence 12.5%, n=2), need for renal replacement therapy (incidence 6.8%, n=3), and acidosis (incidence 5.0%, n=2).
- Stratified analysis and meta-regression found a significant association between pre-existing chronic kidney disease and AKI resulting from COVID-19.

ABSTRACT

Purpose: Emerging data suggests coronavirus disease 2019 (COVID-19) has extrapulmonary manifestations but its renal manifestations are not clearly defined. We aimed to evaluate renal complications of COVID-19 and their incidence using a systematic meta-analysis.
Design: Observational studies reporting renal complications in COVID-19 patients were sought from MEDLINE, Embase and the Cochrane Library from 2019 to June 2020. The nine-star Newcastle-Ottawa Scale was used to evaluate methodological quality. Incidence with 95% confidence intervals (CIs) were pooled using random-effects models.
Results: We included 22observational cohort studies comprising of 17,391COVID-19 patients. Quality scores of studies ranged from 4-6.The pooled prevalence of pre-existing chronic kidney disease (CKD) and end-stage kidney disease was 5.2% (2.8-8.1)and 2.3% (1.8-2.8) respectively. The pooled incidence over follow-up of 2-28 days was 12.5% (10.1-15.0) for electrolyte disturbance (eg, hyperkalaemia), 11.0% (7.4-15.1) for acute kidney injury (AKI) and 6.8% (1.0-17.0) for renal replacement therapy (RRT). In subgroup analyses, there was a higher incidence of AKI in US populations and groups with higher prevalence of pre-existing CKD.
Conclusions: Frequent renal complications reported among hospitalised COVID-19 patients are electrolyte disturbance, AKI and RRT. Aggressive monitoring and management of these renal complications may help in the prediction of favourable outcomes.
Systematic review registration: PROSPERO 2020: CRD42020186873
Key messages: COVID-19 affects multiple organs apart from the respiratory system; however, its renal manifestations are not clearly defined. In this systematic meta-analysis of 22 observational cohort studies, the prevalence of pre-existing chronic

kidney disease (CKD) in COVID-19 patients was 5.2%.The most frequent renal complication was electrolyte disturbance (particularly hyperkalaemia) with an incidence of 12.5% followed by acute kidney injury (AKI)with an incidence of 11.0%;US populations and groups with higher prevalence of CKD had higher incidence of AKI.

FIGURES

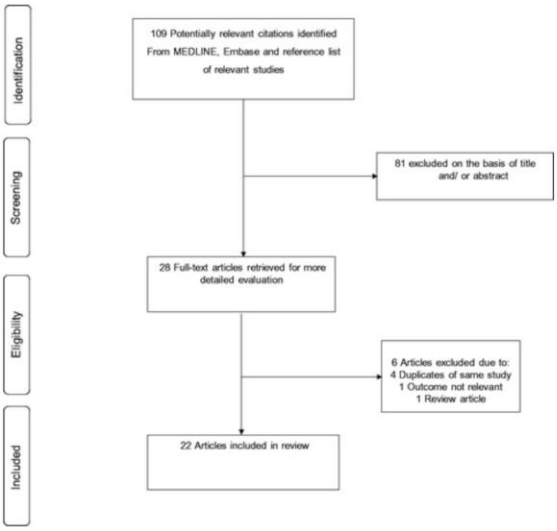


Figure 1. Chart displaying selection process for articles included in the meta-analysis.

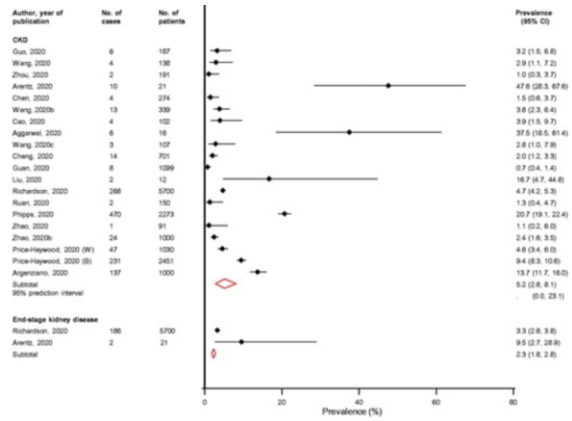


Figure 2. Prevalence of pre-existing renal conditions in COVID-19 patients. B: black; CI: confidence interval (bars); CKD: chronickidney disease; W: white.

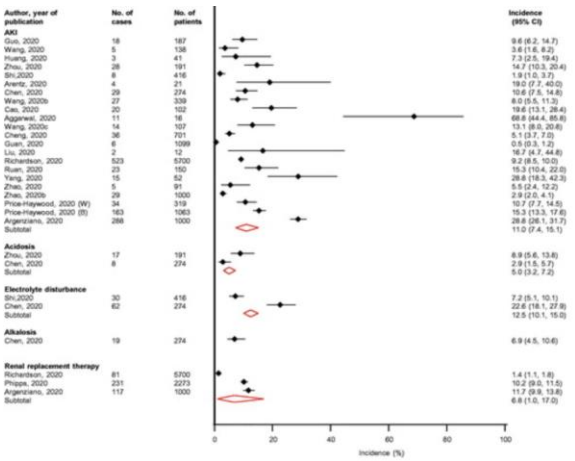


Figure 2. Prevalence of pre-existing renal conditions in COVID-19 patients. B: black; CI: confidence interval (bars); CKD: chronickidney disease; W: white.

DETECTION OF SARS-COV-2 IN FORMALIN-FIXED PARAFFIN-EMBEDDED TISSUE SECTIONS USING COMMERCIALLY AVAILABLE REAGENTS

Best Rocha A, Stroberg E, Barton LM, Duval EJ, Mukhopadhyay S, Yarid N, Caza T, Wilson JD, Kenan DJ, Kuperman M, Sharma SG, Larsen CP.. Lab Invest. 2020 Jul 9. doi: 10.1038/s41374-020-0464-x. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

American pathologists developed and evaluated immunohistochemical and in situ hybridization assays for tissue identification of SARS-CoV-2 in order to characterize COVID-19's pathophysiology and distribution within different organ systems. They found that their assays stained positive in lung and placenta but not kidney samples from COVID-19 patients (Figures 1 and 2, Table 2) while none of the control samples were positive. They suggest that other pathology labs could easily replicate these techniques to study SARS-CoV-2 distribution across tissue types, allowing for a better understanding of tissue-specific pathogenesis.

ABSTRACT

Coronavirus Disease-19 (COVID-19), caused by the coronavirus SARS-CoV-2, was initially recognized in Wuhan, China and subsequently spread to all continents. The disease primarily affects the lower respiratory system, but may involve other organs and systems. Histopathologic evaluation of tissue from affected patients is crucial for diagnostic purposes, but also for advancing our understanding of the disease. For that reason, we developed immunohistochemical (IHC) and in situ hybridization (ISH) assays for detection of the. virus. A total of eight autopsy lungs, one placenta, and ten kidney biopsies from COVID-19 patients were stained with a panel of commercially available antibodies for IHC and commercially available RNA probes for ISH. Similarly, autopsy lungs, placentas and renal biopsies from non-COVID-19 patients were stained with the same antibodies and probes. All eight lungs and the placenta from COVID-19 patients stained positive by IHC and ISH, while the kidney biopsies stained negative by both methodologies. As expected, all specimens from non-COVID-19 patients were IHC and ISH negative. These two assays represent a sensitive and specific method for detecting the virus in tissue samples. We provide the protocols and the list of commercially available antibodies and probes for these assays, so they can be readily implemented in pathology laboratories and medical examiner offices for diagnostic and research purposes.

FIGURES

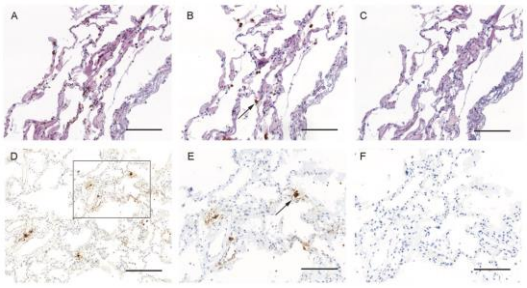


Fig. 1 SARS-CoV-2 IHC and ISH in lung. SARS-CoV-2 ISH (**a**–**c**) and IHC (**d**–**f**) in lung parenchyma from the autopsy of a patient who died secondary to COVID-19. Positive reaction for the (**a**) control probes to the housekeeping gene peptidylprolyl isomerase B (*PPIB*) by in situ hybridization confirms the presence of intact nucleic acid. **b** There is a positive reaction for the probes directed against SARS-CoV-2 (arrow) and **c** a negative reaction for the negative control probes (bacterial gene dapB) in a serial section (Periodic acid-Schiff counterstain; original magnifications ×200; bar = 50 µm). **d**–**f** Immunohistochemical analysis for SARS-CoV-2 is positive (arrow) in the tissue (**d** with higher power of outlined region in **e**) with negative staining in the **f** negative control (hematoxylin counterstain; original magnifications ×100 in D and ×200 in **e** and **f**; bar = 100 µm in **d** and bar = 50 µm in **e** and **f**).

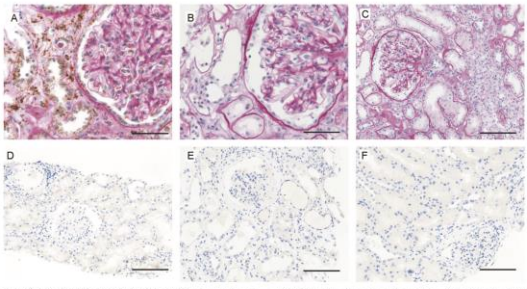


Fig. 2 SARS-CoV-2 IHC and ISH in kidney. ISH in a renal biopsy tissue from a patient with active COVID-19 at the time of biopsy shows (**a**) reactivity for the positive control probe to the housekeeping gene peptidylprolyl isomerase B (*PPIB*) (original magnification ×400; bar = 25 µm) and **b**, **c** negativity for the presence of SARS-CoV-2 RNA (Periodic acid-Schiff counterstain; original magnifications ×400 and ×200; bar = 25 µm for B and bar = 50 µm for c). **d**–**f** IHC staining of renal biopsy tissue from three different patients with active COVID-19 at the time of biopsy shows negative staining in the parenchyma (hematoxylin counterstain; original magnification ×200; bars = 50 µm).

Table 2 Tissue samples from patients with COVID-19 stained by IHC and ISH.

Organ (number of samples)	# Positive by IHC	# Positive by ISH
Lung from decedents with COVID-19 (8)	8	8
Placenta from patient with active COVID-19 (1)	1	1
Kidney from patient with active COVID-19 (10)	0	0

LABORATORY-DEVELOPED TEST REGULATION AND THE IMMUNOCOMPROMISED PATIENT: UNCERTAINTY AHEAD

Clark AE, Levy J, Lee FM.. Curr Opin Infect Dis. 2020 Aug;33(4):304-311. doi: 10.1097/QCO.0000000000000659.
Level of Evidence: Other - Expert Opinion

BLUF

This article describes how legislative changes such as the Verifying Accurate and Leading-Edge In-Vitro Clinical Tests Development (VALID) Act (introduced to the US Congress on March 5, 2020) may change laboratory-developed tests (LDTs) by changing FDA regulations to improve patient safety and "reduce the impact of harmful or unnecessary testing." Alternately, the authors argue that a balance must be maintained so that the benefits of traditional LDTs such as the development of evidence-based practice guidelines, reduced cost, encouraged innovation, and provision of quick data, may be upheld during the COVID-19 pandemic, as the authors express concern that overregulation could negatively impact labs, physicians, and patients through the remainder of the pandemic.

ABSTRACT

PURPOSE OF THE REVIEW: Laboratory-developed tests (LDTs) are essential for the clinical care of immunocompromised individuals. These patients often require specialized testing not available from commercial manufacturers and are therefore dependent on the laboratory to create, validate, and perform these assays. Recent paradigm-shifting legislation could alter the way that LDTs are operationalized and regulated.
RECENT FINDINGS: On March 5th, 2020 the Verifying Accurate and Leading-Edge In-Vitro Clinical Tests Development Act (VALID) was introduced in the US Congress. This statute would overhaul existing regulatory framework by unifying the oversight of LDTs and commercial in-vitro diagnostic tests (IVDs) through the FDA. If enacted, LDTs would be subject to regulatory requirements like those found in commercial submissions for market review. Stakeholders continue to discuss the details and scope of the proposed legislation in the setting of the Severe Acute Respiratory Syndrome Coronavirus 2 pandemic, where LDTs are integral to the national COVID-19 response.
SUMMARY: Congressional lawmakers have introduced legislation to alter the regulatory framework governing LDTs. Moving forward, a balance must be struck to ensure the availability of safe and accurate testing without delays or overregulation that could be harmful to patients. The downstream implications of how VALID and other legislation will impact laboratories, clinicians, and patients warrant close examination.

THE POTENTIAL OF VARIOUS NANOTECHNOLOGIES FOR CORONAVIRUS DIAGNOSIS/TREATMENT HIGHLIGHTED THROUGH A LITERATURE ANALYSIS

Alphandéry E.. Bioconjug Chem. 2020 Jul 8. doi: 10.1021/acs.bioconjchem.0c00287. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

An author affiliated with nanotechnology company for cancer treatment (Nanobacterie) in France discusses nanotechnology-based techniques available for the detection of coronaviruses (Figure 1) and potential uses of nanotechnology in development of coronavirus vaccines and therapeutics (Figure 2), highlighting advantages of nanotherapeutics including increased sensitivity, improved safety and solubility, enhanced viral inhibition, and efficient host immune response against coronaviruses. The author advocates for nanotherapeutics as viable options for COVID-19 vaccines and antivirals but acknowledges further research on nanotherapeutic-cell interactions and within animal models is needed.

SUMMARY

Summary of nanotechnologies:
- COVID-19 prevention: dual fabric (i.e. cotton and silk/flannel) and nanostructured graphene masks useful for enhanced viral filtering, sterilizing and reuse.
- Coronavirus diagnosis: nanotechnology CoV detection methods (Figure 1) are highly sensitive and specific thereby useful in avoiding false positive/negative results as seen in standard detection methods (i.e. PCR).
- Nanoformulated anticoronavirus vaccines (Figure 2): often resulted in greater efficacy than non-nanoformulated counterparts but more research is needed to confirm suspicions (Table 1).
- Antiviral nanomaterial drugs (Figure 2): hypothesized to be beneficial via blocking CoV replication, inhibiting viral RNA synthesis, enhancing immune response, and reducing CoV-induced apoptotic cell death.
- Indirect treatment/detection: nanomaterials may be used for detection of a disturbed host microbiome to indirectly reveal a COVID-19 infection, or aid in local delivery of drugs to the gut to fight COVID-19 by restoring healthy microbiome.

Despite promising findings, authors recognize the need for further research on nanotechnologies via parallel benefit/risk ratio studies on nanomaterial-based treatments in COVID-19, as well as suitable animal models to examine drug efficacy in humans (including dose and administration route).

ABSTRACT

With the current COVID-19 outbreak, it has become essential to develop efficient methods for the treatment and detection of this virus. Among the new approaches that could be tested, that relying on nanotechnology finds one of its main grounds in the similarity between nanoparticle (NP) and coronavirus (COV) sizes, which promotes NP-COV interactions. Since COVID-19 is very recent, most studies in this field have focused on other types of coronavirus than COVID-19, such as those involved in MERS or SARS diseases. Although their number is limited, they have led to promising results on various COV using a wide range of different types of nanosystems, e.g., nanoparticles, quantum dos, or nanoassemblies of polymers/proteins. Additional efforts deserve to be spent in this field to consolidate these findings. Here, I first summarize the different nanotechnology-based methods used for COV detection, i.e., optical, electrical, or PCR ones, whose sensitivity was improved by the presence of nanoparticles. Furthermore, I present vaccination methods, which comprise nanoparticles used either as adjuvants or as active principles. They often yield a better-controlled immune response, possibly due to an improved antigen presentation/processing than in non-nanoformulated vaccines. Certain antiviral approaches also took advantage of nanoparticle uses, leading to specific mechanisms such as the blocking of virus replication at the cellular level or the reduction of a COV induced apoptotic cellular death.

Nanomaterial backbone	Size (nm) Shape ZP[a]	VACCINE Active substance	COV type	Admin route[b]	In vivo data	refs
Gold	16 nm sphere	Antigen of gastroenteritis COV	SARS	Subcutaneous	Mice immunized with Gold-COV:antigen: ↑ activation of antigen presenting cells, ↑ IFN, IL-1β, IL-6, macrophages, B cells	47
PLGA	100–600 nm sphere	Killed vaccine antigen (KVA)	PEDV	Intranasal	Pregnant sows inoculated with PLGA-Kag → passively immunized suckling piglets ↑ lymphocytes, IFN-γ, humoral immune response, IgA, IgG ↓ Mortality of suckling piglets	48
chitosan	286 nm sphere 20 mV	Inactivated infectious bronchitis virus (IBV)	IBV	Oculo-nasal	Chicken immunized with chitosan-IBV: ↑ Humoral and cellular immune response against IBV ↓ Viral load in trachea and kidney	49
chitosan	210 nm 10 mV	DNA expressing COV protein (DNA-COV)	SARS	Intranasal Intramuscular	Mice immunized with chitosan DNA-COV: → DC targeting + both humoral and cellular immune responses	50
PEI	195 nm	pci-S: SARS DNA Vaccine	SARS	Intranasal	Mice immunized with PEI-pci-S: ↑ IgG1/IgA antibodies	51
chitosan	122 nm sphere 53 mV	Antigen of infectious bronchitis virus (A-IBV)	IBV	Intranasal	Chicken immunized with chitosan—A-IBV: ↑ IgG/IgA antibodies, lymphocyte proliferation, IL-2, IL-4, IFN-γ ↑ Humoral + cellular immune response	52
Nanoassembly of COV spike proteins (Nano-COV-P)	25 nm 160–180 kDa	Spike proteins of COV	MERS SARS	Intramuscular	Nano-COV-P inoculated into Balb/C mice: → Production of neutralizing antibodies	53, 54
Nanoassembly of COV spike proteins (Nano-COV-P)	80 nm 140 kDa	Spike proteins of COV	MERS	Intranasal	Mice immunized three times with (Nano-COV-P): → induces both Th1 and Th2 immune responses against COV	55
Ferritin (FR): scaffold of nanoassembly SSG: linker between FR and RBD	28–30 nm sphere 1080 kDa	Receptor binding domain (RBD) of COV	MERS	Intramuscular	Mice immunized 2 times with RBD-[SSG]-FR: ↑ RBD-specific antibody responses	56
Self-Assembling Protein Nanoparticle with flagellin adjuvant (COV-Flagellin-SAPN)	23 nm 38 kDa	Epitope of COV spike proteins	IBV	Intranasal	Chickens immunized with IBV-Flagellin-SAPN: → Antibody response (less tracheal lesion)	57
Spike protein nanoparticle vaccine (SPNV)	NA	COV spike protein	MERS	Intranasal	Bovine/mice immunized 1/3 times with SPNV → immunoglobulin IgG antibodies	58
Self-assembled polypeptide nanoparticle with epitome of spike COV protein (COV-SAPN)	25 nm sphere 1.4 MDa	COV spike protein	SARS	Interperitoneally	Mice immunized with COV-SAPN: → anti-SARS antibodies were obtained without adjuvant	59
Incorporation of SARS peptide in synthetic NP (SARSP-N)	Sphere	COV peptide	SARS	Interperitoneally	Mice injected with SARSP-N → Targets T cell receptor → Suppresses Collagen-Induced Arthritis	60
Protein cage nanoparticle (PCN)	12 nm hollow sphere	PCN (no antigen)	SARS	Intranasal	Mice inoculated with PCN:	61

Table 1: Vaccines against COV Based on Various Nanotechnologies.

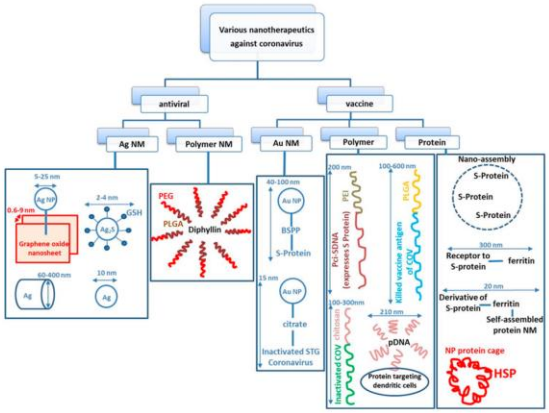


Figure 2: Schematic diagram presenting various types of nanotherapies used against COV, which are categorized as vaccines or antiviral drugs, and comprise various types of Ag nanomaterials, i.e., free NP/NW or NP attached to graphene nanosheets, diphyllin inserted within PEG–PLGA vesicles, various nanomaterials, i.e., Au NP, polymers such as PEI, PLGA, or chitosan, bound to COV antigens, nanoassemblies comprising COV antigens, as well as an interesting nanocage used as vaccine despite its lack of COV antigen.

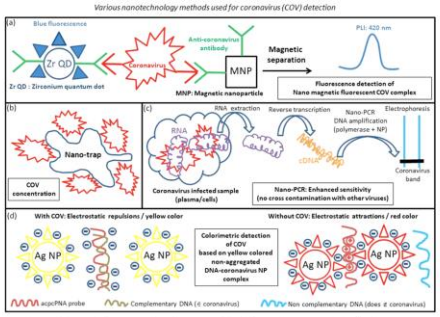


Figure 1. Schematic diagrams showing different examples of nanomaterial-based COV detection methods. (a) Fluorescent Zr QDs and magnetic nanoparticles are conjugated with antibodies that specifically bind to COV. In the presence of COV, a magnetic fluorescent complex is formed, which is isolated magnetically and detected by fluorescence measurements. (b) Nanotraps are used to concentrate COV and improve their stability, hence facilitating their detection. (c) Reverse transcription PCR is carried out in the presence nanoparticles, improving the efficacy of the polymerase chain reaction, and resulting in a better detection sensitivity of this method. (d) COV detection method, which is based on the interactions between complementary DNA originating from COV and acpnPNA probe at the surface of Ag NP, which results in a separation between Ag NPs, and a yellow color associated with the luminescence of well dispersed Ag NPs, further revealing COV presence.

Figure 2: Schematic diagram presenting various types of nanotherapies used against COV, which are categorized as vaccines or antiviral drugs, and comprise various types of Ag nanomaterials, i.e., free NP/NW or NP attached to graphene nanosheets, diphyllin inserted within PEG–PLGA vesicles, various nanomaterials, i.e., Au NP, polymers such as PEI, PLGA, or chitosan, bound to COV antigens, nanoassemblies comprising COV antigens, as well as an interesting nanocage used as vaccine despite its lack of COV antigen.

PHARMACOLOGICAL AGENTS UNDER INVESTIGATION IN THE TREATMENT OF CORONAVIRUS DISEASE 2019 AND THE IMPORTANCE OF MELATONIN

Parlakpinar H, Polat S, Acet HA.. Fundam Clin Pharmacol. 2020 Jul 13. doi: 10.1111/fcp.12589. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A literature review conducted by the Department of Medical Pharmacology at Inonu University in Turkey discusses the current pharmacological treatments being used for COVID-19 and their mechanisms of action (Figure 1); it also provides mechanism-based reasoning for melatonin's potential as an additional treatment option. Citing prior studies, the authors suggest that due to its role as a RAAS modulator (Table 1), anti-oxidant, anti-inflammatory, free radical scavenger, antiviral, and immunomodulator, melatonin may help prevent multiple organ injury and disease progression in patients with COVID-19.

ABSTRACT

Coronavirus disease 2019 (COVID-19) is a life-threatening infectious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 pandemic causing morbidities and even deaths worldwide revealed that there is urgent need to find pharmacological agents or vaccines. Although there are a lot of agents under investigation, there is no approved agent for the prevention or treatment of the COVID-19 yet. Treatment of patients remains mainly supportive as well as compassionate use of the agents under investigation. It is well established that excessive inflammatory and immune response as well as oxidative injury play a critical role in the pathogenesis of COVID-19. In this review, we aimed to update knowledge about pathogenesis, clinical features and pharmacological treatment of COVID-19 and review the potential beneficial effects of ancient antioxidant, anti-inflammatory and immunomodulatory molecule melatonin for prevention and treatment of COVID-19.

FIGURES

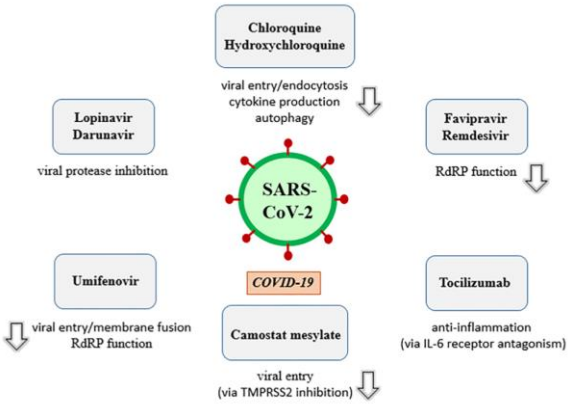


Figure 1. Important pharmacological agents under investigation against COVID-19 and their mechanism of action. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2. TMPRSS2: Transmembrane serine protease 2. COVID-19: Coronavirus disease 2019. RdRP: RNA-dependent RNA polymerase. IL-6: Interleukin 6.

Table I. Effects of melatonin on RAS components in *in vivo* experiments

Investigators	Disease model	Animals	Dosing	Effects
Tain, Y. L. *et al* (105)	Programmed hypertension (PH) induced by prenatal dexamethasone (DEX) administration	Female 12-16 weeks old Sprague-Dawley (SD) rats	0.01% melatonin in drinking water during pregnancy and lactation	Increase in ACE2 and AT2R expression as well as MAS receptor protein levels in the kidney of male offspring
Wu, T. H. *et al* (106)	PH induced by neonatal DEX administration	Male neonate offspring of female 12-16 weeks old SD rats	0.01% melatonin in drinking water during the lactation period	Increase in ACE2 expression in the kidney and heart of male offspring
Tain, Y. L. *et al* (107)	PH induced by maternal caloric restriction	Female 12-16 weeks old SD rats	0.01% melatonin in drinking water during pregnancy	Increase in ACE2 expression and protein levels in the kidney of the male offspring
Tain, Y. L. *et al* (108)	PH induced by maternal exposure to continuous light	Female 12-16 weeks old SD rats	50 mg/day ip agomelatine during pregnancy and lactation 0.01% melatonin in drinking water during pregnancy and lactation	*Agomelalatine* Decrease in expression of ACE and ACE2 Increase in expression of AT2 receptor and MAS receptor in kidney. *Melatonin* Decrease in renal ACE expression.
Tain, Y. L. *et al* (109)	PH induced by prenatal DEX and postnatal high-fat diet	Female 12-16 weeks old SD rats	0.01% melatonin in drinking water during pregnancy and lactation	Increase in renal expression of AT2 receptor and MAS receptor in male offspring

ACKNOWLEDGEMENTS

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