The Daily COVID-19 Literature Surveillance Summary

August 4, 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:

- An article by Talha Burki in The Lancet argues that the COVID-19 pandemic has had a more negative impact on women compared to men across the globe. She suggests this is in large part due to the indirect effects of the pandemic on women's health, such as an increase in economic, social, and political disparities between men and women, increased domestic violence against women, and decreased access to care for pregnant women. In short, despite COVID-19 causing a disproportionately higher number of deaths in men, there is mounting evidence that the indirect effects the pandemic has on women may even be worse.
- In the article titled, "Should Pediatric Patients Be Prioritized When Rationing Life-Saving Treatments During the COVID-19 Pandemic", ethicists discuss whether age should guide rationing of scarce life-saving resources after a pediatric hospital sought to establish guidelines for the use of extracorporeal membrane oxygenation (ECMO) devices based on age. The authors recommend a multi-pronged approach in allocating resources by prioritizing the "worst off" and maximizing benefits based off of prognosis, saving the most lives, extending life-years, an individual's instrumental value in society, and treating people equally with dignity.

MANAGEMENT:

- Physicians in Seattle, WA describe characteristics and basic outcomes of a retrospective cohort of 83 adults hospitalized with COVID-19 between March 16, 2020 and April 17, 2020, 42 of whom received the IL-6 antagonist tocilizumab with 41 matched controls. They found overall mortality was similar in both groups, but patients with severe illness treated with tocilizumab had lower mortality by day 7 compared to controls (14.2% vs. 28.6%) and critically ill patients (14.2% vs 28.5%). The authors imply tocilizumab may improve outcomes for select patients and suggest randomized controlled trials are warranted to better understand its potential benefits.

ADJUSTING PRACTICE DURING THE COVID-19 PANDEMIC:

- A review by the American Heart Association discusses several ways healthcare workers can provide critical care for COVID-19 patients that have sustained concurrent cardiopulmonary complications including ARDS, MI, and pulmonary circulatory disease. The article additionally outlines proper use of PPE, limiting exposure to COVID-19, and following pre-planned procedures to deal with these diseases as means to help promote safety for the patients and the providers.

R&D DIAGNOSIS AND TREATMENT:

- Researchers in Madrid, Spain analyzed samples from 53 hospitalized COVID-19 patients and discovered a unique immunofluorescence (IF) pattern involving staining of the gastric mucosa and hepatocytes for autoantibodies. This IF pattern was found in 12 of the 53 patients and was associated with increased incidence of neurologic and thrombotic complications. This implicates cross-reactive autoantibodies in the thrombotic and neurologic complications of COVID-19, and may be a potential therapeutic target for immunomodulatory treatments. Because of the continued demonstration of an autoimmune component to COVID-19 this also brings up concerns for molecular mimicry and proceeding towards mandatory vaccinations for all with caution.

TRAUMA OF MAJOR SURGERY: A GLOBAL PROBLEM THAT IS NOT GOING AWAY

Dobson GP.. Int J Surg. 2020 Jul 29:S1743-9191(20)30552-5. doi: 10.1016/j.ijsu.2020.07.017. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

A 2020 review study conducted in Queensland, Australia by the James Cook University College of Medicine and Dentistry discussed that annually, major surgery is responsible for the deaths of 8 million people globally (Table 1) and that interventions to preserve CNS-cardiovascular coupling, endothelial glycocalyx health, and mitochondrial integrity could be utilized to reduce surgery morbidity and mortality. This review suggests that future studies must focus on finding a therapy which could be utilized and that Mg, adenosine, ALM and lidocaine are currently being reviewed.

SUMMARY

Additional findings of the study include:
-The brain is still physiologically awake under anesthesia, which results in reacting to the stresses of surgery (pain, incision, and manipulation) causing hyperinflamation, immune dysfunction, and coagulopathy, cardiac dysfunction, and hypoperfusion (Figure 2)
-Surgery results in the activation of the hypothalamic-pituitary-adrenal axis whereby IL-1, IL-6 and TNF-α trigger the release of cortisol and catecholamines
-The ideal time to administer an intervention is after the patient is under anesthesia, but before incisions are started
-Major surgery can result in a wide variety of injuries including cognitive dysfunction, acute kidney injury, and myocardial infarction (Figure 1)

ABSTRACT

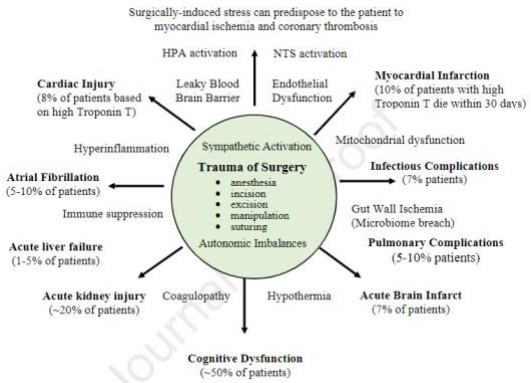
Globally, a staggering 310 million major surgeries are performed each year; around 40 to 50 million in USA and 20 million in Europe. It is estimated that 1 to 4% of these patients will die, up to 15% will have serious postoperative morbidity, and 5 to 15% will be readmitted within 30 days. An annual global mortality of around 8 million patients places major surgery comparable with the leading causes of death from cardiovascular disease and stroke, cancer and injury. If surgical complications were classified as a pandemic, like HIV/AIDS or coronavirus (COVID-19), developed countries would work together and devise an immediate action plan and allocate resources to address it. Seeking to reduce preventable deaths and post-surgical complications would save billions of dollars in healthcare costs. Part of the global problem resides in differences in institutional practice patterns in high- and low-income countries, and part from a lack of effective perioperative drug therapies to protect the patient from surgical stress. We briefly review the history of surgical stress and provide a path forward from a systems-based approach. Key to progress is recognizing that the anesthetized brain is still physiologically 'awake' and responsive to the sterile stressors of surgery. New intravenous drug therapies are urgently required after anesthesia and before the first incision to prevent the brain from switching to sympathetic overdrive and activating secondary injury progression such as hyperinflammation, coagulopathy, immune activation and metabolic dysfunction. A systems-based approach targeting central nervous system-mitochondrial coupling may help drive research to improve outcomes following major surgery in civilian and military medicine.

FIGURES

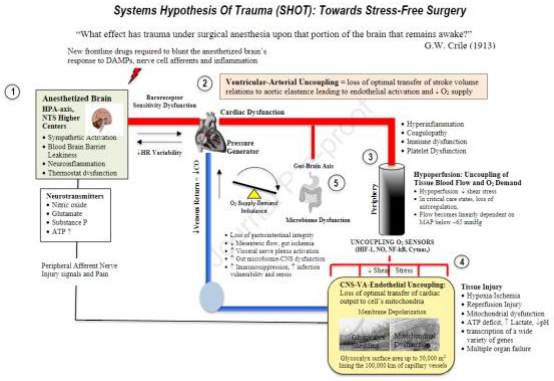
Table 1. Estimated Annual Global Mortality from Major Surgery compared to Cardiovascular Disease and Stroke, Cancer and Injury

	Deaths per year (million)	Year	Percent Total Deaths	Reference
Total All-Aged Deaths	56.9	2017		10
Cardiovascular and Stroke	17.9	2016	31%	WHO
Cancer	9.6	2018	17%	WHO
Injury	5.8	2014	10%	WHO
Major Surgery (1 to 4% of 310M)	~8.0*	See Text	14%	See Text

*Average mortality. World Health Organization (WHO) data from website



'Figure 1': Perioperative Complications after Non-Cardiac Major Surgery Major surgery and anesthesia are associated with stress-induced activation of the sympathetic nervous system, hemodynamic compromise, hyperinflammation, coagulopathy, immune dysfunction, metabolic imbalances and hypothermia. Large population studies indicate that ~8% of adult patients will suffer heart ischemia/injury, and 10% of these will die within 30 days (118, 119). Surgical stress also leads to perioperative complications involving brain (120, 121), kidney (122), lung (123), liver (124), and possibly the gut microbiome (97). Atrial fibrillation (125) and infections (126) are also significant complications following major surgery. It is estimated that around 50% of these complications are potentially preventable (13-15).



'Figure 1': Perioperative Complications after Non-Cardiac Major Surgery Major surgery and anesthesia are associated with stress-induced activation of the sympathetic nervous system, hemodynamic compromise, hyperinflammation, coagulopathy, immune dysfunction, metabolic imbalances and hypothermia. Large population studies indicate that ~8% of adult patients will suffer heart ischemia/injury, and 10% of these will die within 30 days (118, 119). Surgical stress also leads to perioperative complications involving brain (120, 121), kidney (122), lung (123), liver (124), and possibly the gut microbiome (97). Atrial fibrillation (125) and infections (126) are also significant complications following major surgery. It is estimated that around 50% of these complications are potentially preventable (13-15).

DISPARITIES

THE INDIRECT IMPACT OF COVID-19 ON WOMEN

Burki T.. Lancet Infect Dis. 2020 Aug;20(8):904-905. doi: 10.1016/S1473-3099(20)30568-5.
Level of Evidence: Other - Opinion

BLUF

An article by Talha Burki in The Lancet argues that the COVID-19 pandemic has had a more negative impact on women compared to men across the globe. She suggests this is in large part due to the indirect effects of the pandemic on women's health, such as an increase in economic, social, and political disparities between men and women, increased domestic violence against women, and decreased access to care for pregnant women. In short, despite COVID-19 causing a disproportionately higher number of deaths in men, there is mounting evidence that the indirect effects the pandemic has on women may even be worse.

SHOULD PEDIATRIC PATIENTS BE PRIORITIZED WHEN RATIONING LIFE-SAVING TREATMENTS DURING THE COVID-19 PANDEMIC?

Antiel RM, Curlin FA, Persad G, White DB, Zhang C, Glickman A, Emanuel EJ, Lantos JD.. Pediatrics. 2020 Jul 9:e2020012542. doi: 10.1542/peds.2020-012542. Online ahead of print.
Level of Evidence: Other - Opinion

BLUF

Ethicists discuss whether age should guide rationing scarce life-saving resources after a pediatric hospital sought to establish guidelines for the use of extracorporeal membrane oxygenation (ECMO) devices based on age. The authors recommend a multi-pronged approach in allocating resources by prioritizing the "worst off" and maximizing benefits based off of prognosis, saving the most lives, extending life-years, an individual's instrumental value in society, and treating people equally with dignity.

SUMMARY

Multiple options have been proposed for the allocation of scarce resources: considering patient prognosis first, the social worth of the patient, using a simple lottery to ensure avoidance of bias, and considering age.

The ethical justification for prioritizing younger patients is based on reducing disparities and offering children the equal opportunity of living a longer, complete life compared to older patients. The legal permissibility of using age is based on the Age Discrimination Act that permits giving children special priority unless this opportunity excludes others from consideration. When determining how to allocate life-saving treatment, some states have adopted using age as a 'tie-breaker' or factor for consideration with some portion of resources (such as ventilators) held in reserve for pediatric patients. The authors emphasize the importance of non-discrimination and suggest that prioritizing younger patients is based on fairness when allocating scarce resources.

MANAGEMENT

ACUTE CARE

CRITICAL CARE

USE OF THE IL-6R ANTAGONIST TOCILIZUMAB IN HOSPITALIZED COVID-19 PATIENTS

Patel K, Gooley TA, Bailey N, Bailey M, Hegerova L, Batchelder A, Holdread H, Dunleavy V, Downey T, Frisvold J, Megrath S, Pagarigan K, Szeto J, Rueda J, Islam A, Maree C, Nyatsatsang S, Bork SE, Lipke A, O'Mahony DS, Wagner T, Pulido J, Mignone J, Youssef S, Hartman M, Goldman JD, Pagel JM.. J Intern Med. 2020 Aug 3. doi: 10.1111/joim.13163. Online ahead of print.

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

BLUF

Physicians in Seattle, WA describe characteristics and basic outcomes (Summary, Figure 1) of a retrospective cohort of 83 adults hospitalized with COVID-19 between March 16, 2020 and April 17, 2020, 42 of whom received the IL-6 antagonist tocilizumab with 41 matched controls (Summary). They found overall mortality was similar in both groups but patients with severe illness treated with tocilizumab had lower mortality by day 7 compared to controls (14.2% vs. 28.6%, p-values not calculated) and critically ill patients (14.2% vs 28.5%). The authors imply tocilizumab may improve outcomes for select patients and suggest randomized controlled trials are warranted to better understand its potential benefits.

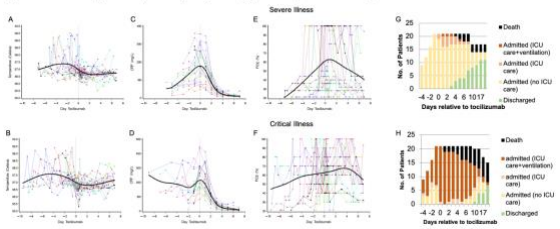
SUMMARY

Demographics and clinical characteristics of 42 patients with COVID-19 treated with tocilizumab were collected and informally compared to 41 controls matched by the World Health Organization (WHO) score on admission and hospital day on which therapy was initiated (details of score were not included in article and could not be identified by contributing author). Patients were followed for 7 days, until discharge, or until death, whichever was shortest. Hypothesis testing was not performed. Findings were as follows:

- Median timing of tocilizumab was hospital day 4, with 50% (n=21) of patients severely ill and 50% (n=21) critically ill (definition of these severity descriptors not provided)
- Half (n=21) of patients receiving tocilizumab also received antiviral therapy
- All patients treated with tocilizumab exhibited sustained improvement in CRP (mean baseline of 180mg/L decreased to mean of 11mg/L) and oxygen requirements (Figure 1)
- Among all tocilizumab patients, 7 (16.7%) were discharged and 9 (21.4%) died by day 7. A lower proportion of severely ill patients died than critically ill patients (14.2% vs 28.5%) and control patients (14.2% vs 28.6%).

FIGURES

Figure 1: Serial Change in Temperature, CRP, and Oxygenation by Illness Severity in Tocilizumab-treated Patients



CARDIOLOGY

PERSPECTIVES ON CARDIOPULMONARY CRITICAL CARE FOR PATIENTS WITH COVID-19: FROM MEMBERS OF THE AMERICAN HEART ASSOCIATION COUNCIL ON CARDIOPULMONARY, CRITICAL CARE, PERIOPERATIVE AND RESUSCITATION

Maron BA, Gladwin MT, Bonnet S, De Jesus Perez V, Perman SM, Yu PB, Ichinose F.. J Am Heart Assoc. 2020 Jul 21;9(14):e017111. doi: 10.1161/JAHA.120.017111. Epub 2020 Jun 18.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

A review by the American Heart Association discusses several ways healthcare workers can provide critical care for COVID-19 patients that have sustained concurrent cardiopulmonary complications including ARDS, MI, and pulmonary circulatory disease (see below). The article additionally outlines proper use of PPE, limiting exposure to COVID-19, and following pre-planned procedures to deal with these diseases as means to help promote safety for the patients and the providers.

SUMMARY

-ARDS: "(1) titrate FiO2 to a goal oxyhemoglobin saturation of 92% to 96%, (2) low tidal volume ventilation (4–6 mL/kg of predicted body weight) with positive end-expiratory pressure (PEEP) >10 cm H2O while maintaining plateau pressure <30 cm H2O, and (3) conservative fluid management if vasopressors are not required."
-MI: Let hypotension dictate the use of ACE inhibitors.
-Pulmonary circulatory disease: "thrombolytic agents should not be considered for routine management of patients with COVID-19 outside of clinical trials."

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), marks a global event that will permanently reshape implementation of intensive care medicine. As of June 4, 2020, there are 6,606,455 reported cases of COVID-19 including 388,556 fatalities spanning 215 countries and territories, although epidemiological data remain incomplete. Early autopsy reports emphasize proximal airway and distal airspace involvement, including alveolar epithelial inflammation and capillary thickening.

IMMUNOSEROLOGIC DETECTION AND DIAGNOSTIC RELEVANCE OF CROSS-REACTIVE AUTO-ANTIBODIES IN COVID-19 PATIENTS

Schiaffino MT, Di Natale M, García-Martínez E, Navarro J, Muñoz-Blanco JL, Demelo-Rodríguez P, Sánchez-Mateos P.. J Infect Dis. 2020 Aug 1:jiaa485. doi: 10.1093/infdis/jiaa485. Online ahead of print.
Level of Evidence: 4 - Case-control studies, or "poor or non-independent reference standard

BLUF

A laboratory study conducted in Madrid, Spain from March-April 2020 analyzed samples from 53 hospitalized COVID-19 patients and discovered a unique immunofluorescence (IF) pattern involving staining of the gastric mucosa and hepatocytes for autoantibodies. This IF pattern was found in 12 of the 53 patients (Figure 1), and was associated with increased incidence of neurologic and thrombotic complications among this population in comparison to the IF-negative patients (Table 1). This suggested association of cross-reactive autoantibodies with thrombotic and neurologic complications in COVID-19 infection may be key in providing a potential therapeutic target for immunomodulatory treatments. Because of the continued demonstration of an autoimmune component to COVID-19 this also brings up concerns for molecular mimicry and proceeding towards mandatory vaccinations for all with caution.

ABSTRACT

During the COVID-19 pandemic, we detected a new immunofluorescence (IF) pattern in serum autoantibody (autoAb) screening of laboratory-confirmed COVID-19 patients. The IF pattern was composed of liver and gastric mucosa staining on rat kidney/liver/stomach sections. We describe 12 patients positive for the cross-reactive Ab, compared to a negative group of 43 hospitalized COVID-19 patients, finding association with either neurologic or thrombotic complications. In sequential pre- and post-COVID-19 serum samples, we confirmed autoAb seroconversion. Our data indicate that autoAb screening in COVID-19 patients may be easily performed by IF and alert for auto-reactive mediated complications such as thrombotic or neurologic events.

FIGURES

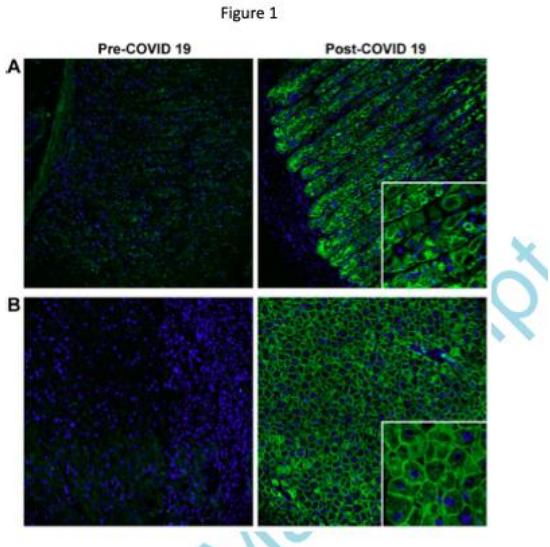


Figure 1. New IF pattern detected after COVID-19 infection. Sequential serum samples from the same patient, before and after COVID-19, were incubated on rat triple tissue sections. Auto-reactive Ab were revealed with goat anti-human IgG/A/M conjugated with FITC (green). Cell nuclei were stained with DAPI (blue). Double fluorescent (green and blue) images of stomach (A), showing the bases of gastric glands, rich in chief cell, or liver (B). No specific green fluorescence, indicative of auto-reactive Ab absence, was detected with pre-COVID-19 serum sample (images on the left, as indicated). After the disease

(right images), a new autoAb was detected bound to the plasma membrane of gastric mucosa cells and hepatocytes (higher magnification in right panel inserts).

	POSITIVE COVID-IF PATTERN (N=12)	NEGATIVE COVID-IF PATTERN (N=41)	TOTAL (N=53)
Demographics characteristics			
Age (y)**	73 (53-91)	61 (24-87)	64 (24-91)
Gender (F/M)	3/9	19/22	22/31
COVID-19 signs and symptoms			
Bilateral pneumonia	10/12 (83.3%)	35/41 (85.4%)	45/53 (84.9%)
Fever	8/12 (66.7%)	34/41 (82.9%)	42/53 (72.9%)
Cough	8/12 (66.7%)	32/41 (78%)	40/53 (75.5%)
Dyspnoea	5/12 (41.7 %)	22/41 (53.7%)	27/53 (50.9%)
Diarrhoea	3/12 (25%)	7/41 (17.1%)	10/53 (18.9%)
PE/DVT*	8/12 (66.7%)	14/41 (34.1%)	22/53 (41.5%)
Neurological symptoms*	4/12 (33.3%)	4/41 (9.8%)	8/53 (15,1%)
Confusion	1/12 (8.3%)	0/41 (0)	1/53 (1,9%)
Anosmia	1/12 (8.3%)	2/41 (4.9%)	3/53 (5.7%)
Peripheric neuropathies	2/12 (16.7%)	2/41 (4.9%)	4/53 (7.5%)
Previous clinical history of autoimmunity	0/12 (0)	5/41 (12,2%)	5/53 (9.4%)
AST/ALT/GGT alterations	8/12 (66.7%)	32/41 (78%)	40/53 (75.5%)
AST > 37 U/L	5/12 (41.7%)	20/41 (48.8%)	25/53 (47.2%)
ALT > 41 U/L	6/12 (50%)	28/41 (68.3%)	34/53 (64.2%)
GGT > 60 U/L	7/12 (58.3%)	26/41 (63.4%)	33/53 (62.3%)
C reactive protein (CRP, mg/dl)	7.3 (± 8.0)	9.7 (± 10.2)	9.2 (± 9.8)
Ferritin (µg/L)*	654.7 (± 384.0)	1503.2 (± 1875.7)	1310.4 (± 1691.2)
Leukocytes count (cells/µl)	7650 (± 3089)	6407 (± 3420)	6689 (± 3361)
Lymphocyte count (cells/µl)	1158 (± 533)	1068 (± 579)	1089 (± 565)
Lymphocyte/µl <600	1/12 (8.3%)	6/41 (14.6%)	7/53 (13.2%)
Antiphospholipid antibodies:	0/12 (0)	5/41 (12.2%)	5/53 (9.4%)
Anti-cardiolipin IgG	0/12 (0)	1/41 (2.4%)	1/53 (1.9%)
Anti-cardiolipin IgM	0/12 (0)	5/41 (12.2%)	5/53 (9.4%)
Anti-β2 glicoprotein IgG	0/12 (0)	1/41 (2.4%)	1/53 (1.9%)
Anti-β2 glicoprotein IgM	0/12 (0)	3/41 (7.3%)	3/53 (5.7%)
Antinuclear antibodies (ANA)	0/12	2/41 (4.9%)	2/53 (3.8%)
Days post symptom onset at collection	21.2	19.6	19.9

Table 1. Clinical characteristics of the patients with or without COVID-IF pattern. Data are median (SD) or n/N (%). F: female; M: male; y: years; PE: pulmonary embolism; DVT: deep vein thrombosis; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyl transferase. *p<0.05; **p<0.01.

DEVELOPMENTS IN TREATMENTS

ANTI-SARS-COV-2 ACTIVITIES IN VITRO OF SHUANGHUANGLIAN PREPARATIONS AND BIOACTIVE INGREDIENTS

Su HX, Yao S, Zhao WF, Li MJ, Liu J, Shang WJ, Xie H, Ke CQ, Hu HC, Gao MN, Yu KQ, Liu H, Shen JS, Tang W, Zhang LK, Xiao GF, Ni L, Wang DW, Zuo JP, Jiang HL, Bai F, Wu Y, Ye Y, Xu YC.. Acta Pharmacol Sin. 2020 Jul 31. doi: 10.1038/s41401-020-0483-6. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Chinese biologists investigated the in vitro activity of Shuanghuanglian preparation, a traditional Chinese herbal remedy, against SARS-CoV-2 proteolytic enzymes 3CLpro and PLpro. They found Shuanghuanglian preparations inhibited both enzymes (Table 3) and SARS-CoV-2 replication in Vero E6 cells (Figure 5), with the bioactive component baicalein strongly

shielding both catalytic residues within the substrate binding pocket (Figure 3). The authors suggest their results warrant in vivo study of these compounds as potential COVID-19 treatments.

ABSTRACT

Human infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) and there is no cure currently. The 3CL protease (3CLpro) is a highly conserved protease which is indispensable for CoVs replication, and is a promising target for development of broad-spectrum antiviral drugs. In this study we investigated the anti-SARS-CoV-2 potential of Shuanghuanglian preparation, a Chinese traditional patent medicine with a long history for treating respiratory tract infection in China. We showed that either the oral liquid of Shuanghuanglian, the lyophilized powder of Shuanghuanglian for injection or their bioactive components dose-dependently inhibited SARS-CoV-2 3CLpro as well as the replication of SARS-CoV-2 in Vero E6 cells. Baicalin and baicalein, two ingredients of Shuanghuanglian, were characterized as the first noncovalent, nonpeptidomimetic inhibitors of SARS-CoV-2 3CLpro and exhibited potent antiviral activities in a cell-based system. Remarkably, the binding mode of baicalein with SARS-CoV-2 3CLpro determined by X-ray protein crystallography was distinctly different from those of known 3CLpro inhibitors. Baicalein was productively ensconced in the core of the substrate-binding pocket by interacting with two catalytic residues, the crucial S1/S2 subsites and the oxyanion loop, acting as a "shield" in front of the catalytic dyad to effectively prevent substrate access to the catalytic dyad within the active site. Overall, this study provides an example for exploring the in vitro potency of Chinese traditional patent medicines and effectively identifying bioactive ingredients toward a specific target, and gains evidence supporting the in vivo studies of Shuanghuanglian oral liquid as well as two natural products for COVID-19 treatment.

FIGURES

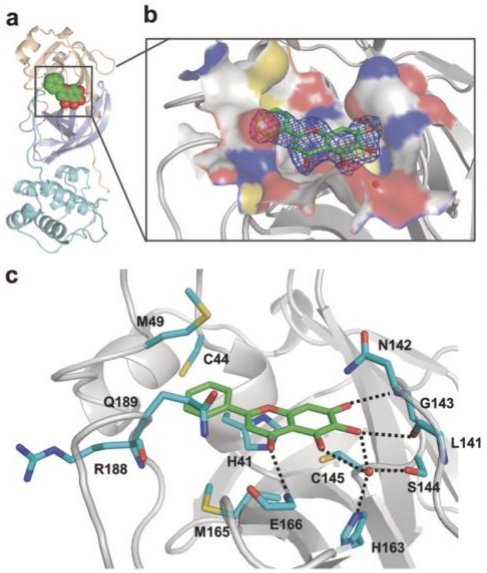


Fig. 3 Crystal structure of SARS-CoV-2 3CLpro in complex with baicalein. a Overview of the structure of baicalein-bound SARS-CoV-2 3CLpro (PDB code 6M2N). Protein is shown in cartoon representation and three domains are shown by different colors. Baicalein is shown as spheres with carbons in green. **b** 2*Fo-Fc* density map contoured at 1.0 σ is shown for baicalein in complex with SARS-CoV-2 3CLpro. The protein is colored gray. The substrate-binding pocket is represented by an intermolecular surface. The inhibitor, baicalein, is shown as green sticks and a buried water molecule is displayed as a red ball. **c** Interactions formed between baicalein (green) and surrounding residues (cyan). Residues as well as the ligand are shown as sticks and hydrogen bonds are represented by black-dashed lines.

Table 3. Inhibition of SARS-CoV-2 3CLpro and PLpro by 28 compounds included in Shuanghuanglian oral liquids.

	Chemical name	Plant resource	3CLpro			PLpro	
			Inhibition (%) (μM)		IC_{50} (μM)	Inhibition (%) (μM)	
			100	10		50	12.5
1	Chlorogenic acid	*L. japonica*	76.4	20.2	39.48 ± 5.51	12.5	/
2	Neochlorogenic acid		49.2	10.4	/	6.2	/
3	Cryptochlorogenic acid		39.7	/	/	14.0	/
4	Isochlorogenic acid A		77.0	18.9	/	18.7	/
5	Isochlorogenic acid B		52.4	26.3	/	24.2	/
6	Isochlorogenic acid C		78.2	18.4	/	11.0	/
7	1,3-Dicaffeoylquinic acid		87.3	27.8	/	14.4	/
8	Loganin		10.6	/	/	−1.7	/
9	Secoxyloganin		4.6	/	/	−13.0	/
10	Luteoloside		65.4	14.8	/	21.5	/
11	Baicalin	*S. baicalensis*	97.6	68.9	6.41 ± 0.95	15.9	/
12	Baicalein		99.4	87.0	0.94 ± 0.20	45.1	12.4
13	Wogonoside		20.4	/	/	14.4	/
14	Wogonin		3.6	/	/	52.0	35.9
15	Scutellarin		76.8	18.9	/	41.8	12.7
16	Scutellarein		101.6	90.7	3.02 ± 0.11	65.7	14.4
17	Oroxylin A-7-*O*-β-D-glucuronide		33.0	/	/	7.4	/
18	Chrysin-7-*O*-β-D-glucoronide		50.6	24.2	/	16.3	/
19	Phillyrin	*F. suspensa*	−18.1	−2.8	/	−1.2	/
20	Phillygenin		11.4	/	/	8.5	/
21	Forsythoside A		95.3	70.5	3.18 ± 0.12	7.1	/
22	Forsythoside B		101.4	80.9	2.88 ± 0.13	12.7	/
23	Forsythoside E		96.6	41.9	6.68 ± 0.22	−7.0	/
24	Forsythoside H		99.3	61.7	10.17 ± 0.39	2.5	/
25	Forsythoside I		95.9	46.3	5.47 ± 0.31	1.7	/
26	Isoforsythiaside		94.4	46.8	5.85 ± 0.06	61.4	25.1
27	Acteoside		97.0	34.6	/	15.6	/
28	(+)-Pinoresinol-4-*O*-β-D-glucopyraside		13.3	/	/	8.0	/

/ not detected.

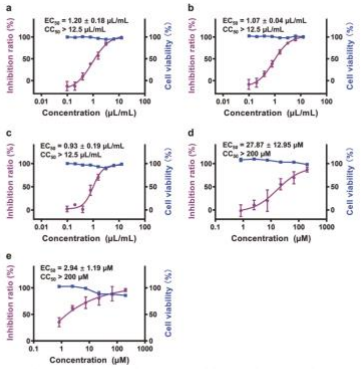


Fig. 5 Antiviral activities and cytotoxicities of Shuanghuanglian oral liquids, baicalin and baicalein. a–c Antiviral activities and cytotoxicities of the three Shuanghuanglian oral liquids, (**d**) baicalin, and (**e**) baicalein against SARS-CoV-2 in Vero E6 cells. Cells were infected with SARS-CoV-2 at a multiplicity of infection (MOI) of 0.01 in the presence of different concentrations of oral liquids, baicalin or baicalein for 48 h. Viral yield in the cell supernatant was then quantified by qRT-PCR. All data are shown as mean ± SD.

ACKNOWLEDGEMENTS

CONTRIBUTORS

Akshara Malla
Ben Showalter
Dax Cvancara
Julia Ghering
Maresa Woodfield
Renate Meckl

EDITORS

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