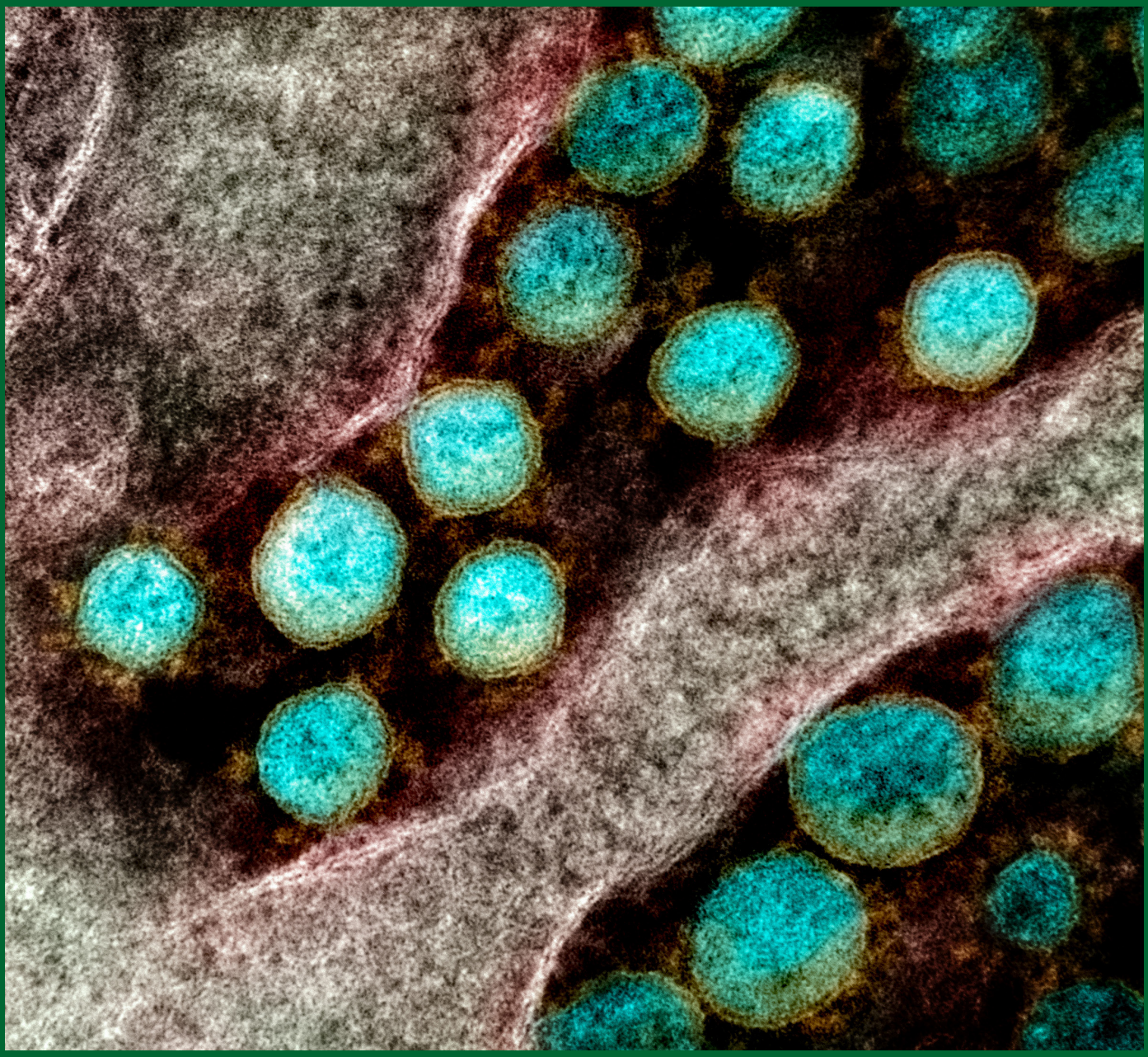
COVID-19
Rush Journal Club: Pathogenesis



NOVEL CORONAVIRUS SARS-COV-2. Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID Available at: https://www.flickr.com/photos/niaid/49597768397/in/album-72157712914621487/. Accessed April 19, 2020.

This document is a collection of efforts from students of Rush University. It provides brief reviews of research articles regarding COVID-19. We hope that this will be helpful to clinicians, students, community leaders, and the general public. This document, however, does not act as a replacement of the original source documents. Please use the DOI on each page to read more.

Is there a study you'd like us to review? Do you have questions or feedback?
Please email: Joseph_b_deBettencourt@rush.edu

Reviews are provided by students at Rush University and edited by Rush faculty. Level of evidence in each study, if applicable, was assessed using the Oxford guidelines as presented below. More information can be found at http://www.cebm.net/2016/05/ocebm-levels-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*

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Table of Contents: Pathogenesis (2/5)

Section	Manuscript	Reviewer (Date Posted)
Pathogenesis	Stumpfe FM et al. SARS-CoV-2 infection in pregnancy - A review of the current literature and possible impact on maternal and neonatal outcome. Geburtshilfe Frauenheilkd 80(4):380-390, 2020.	Kaitlyn Wehrheim (5/2)
	Kim ES et al. Clinical course and outcomes of patients with severe acute respiratory syndrome coronavirus 2 infection: A preliminary report of the first 28 patients from the Korean cohort study on COVID-19. J Korean Med Sci 35(13):e142, 2020	Kelly Harmon (5/2)
	Xu L et al. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020 [Epub ahead of print].	Bijan Zarrabi (5/2)
	Zhu H et al. Cardiovascular complications in patients with COVID-19: Consequences of viral toxicities and host immune response. Curr Cardiol Rep 22(5):32, 2020.	Kaitlyn Wehrheim (5/3)
	Diao B et al. Reduction and functional exhaustion of t cells in patients with coronavirus disease 2019 (COVID-19). medRxiv 2020.02.18.20024364, 2020.	Kaitlyn Wehrheim (5/3)
	Bansal M. Cardiovascular disease and COVID-19. Diabetes Metab Syndr 14(3):247–250, 2020. doi:10.1016/j.dsx.2020.03.013	John Bretzman (5/3)
	D'Amico, F et al. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management. Clin Gastroenterol Hepatol. 2020 Apr 8. pii: S1542-3565(20)30481-X. doi: 10.1016/j.cgh.2020.04.001. [Epub ahead of print]	Al Hornung (5/5)
	Li, B. et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol 109, 531–538 (2020). https://doi.org/10.1007/s00392-020-01626-9	Rob DeStefano (5/5)
	Cheung, KS et al. Gastrointestinal manifestation of SARS-CoV_2 infection and virus load in fecal samples from the Hong Kong cohort and systematic review and meta-analysis. Gastroenterology. 2020 Apr 3. pii: S0016-5085(20)30448-0. doi: 10.1053/j.gastro.2020.03.065. [Epub ahead of print]	Kelly Harmon (5/6)
	Yan, T et al. Angiotensin-converting enzyme 2 in severe acute respiratory syndrome coronavirus and SARS-CoV-2: A double-edged sword? FASEB J. 2020 May;34(5):6017-6026. doi: 10.1096/fj.202000782. Epub 2020 Apr 19.	Dallas Kramer (5/6)
	Tang, N et al. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020; 18: 844– 847. https://doi.org/10.1111/jth.14768	Megan Kotzin (5/6)
	Li, Guoping et al. Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19. J Autoimmun. 2020 Apr 13 : 102463. doi: 10.1016/j.jaut.2020.102463 [Epub ahead of print]	Al Hornung (5/6)

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Section	Manuscript	Reviewer (Date Posted)
Pathogenesis	Giamarellos-Bourboulis EJ et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020 [Epub ahead of print].	Al Hornung (5/6)
	Fanelli V et al. Acute kidney injury in SARS-CoV-2 infected patients. Crit Care 24(1):155, 2020.	Megan Kotzin (5/7)
	Zhang Y et al. Interferon-induced transmembrane protein-3 genetic variant rs12252-C is associated with disease severity in COVID-19. J Infect Dis 2020 [Epub ahead of print].	John Levinson (5/7)
	Spinato G et al. Alterations in Smell or Taste in Mildly Symptomatic Outpatients with SARS-CoV-2 Infection. JAMA 2020 [Epub ahead of print].	Kevin Grudzinski (5/7)
	Huang Z et al. Inhibitors of the renin–angiotensin system: The potential role in the pathogenesis of COVID-19. Cardiol J 2020 [Epub ahead of print].	Clara Ledsky (5/8)
	Toscano G et al. Guillain-Barre syndrome associated with SARS-CoV-2. N Engl J Med 2020 [Epub ahead of print].	Mira Marchioretto (5/8)
	Fogarty H et al. COVID-19 Coagulopathy in Caucasian patients. Br J Haematol 2020 [Epub ahead of print].	Al Hornung (5/8)
	Aziz M et al. Elevated interleukin-6 and severe COVID-19: A meta-analysis. J Med Virol 2020 [Epub ahead of print].	Dallas Kramer (5/11)
	Guo T et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. Published online March 27, 2020. doi:10.1001/jamacardio.2020.1017	Dallas Kramer (5/11)
	Li, Hui et al. SARS-CoV-2 and Viral Sepsis: Observations and Hypothesis. Lancet 2020. [Epub ahead of print].	Kaitlyn Wehrheim (5/11)
	Reynolds HR et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. N Engl J Med 2020 [Epub ahead of print].	Rob DeStefano (5/11)
	Qin C et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020 [Epub ahead of print].	Kaitlyn Wehrheim (5/14)
	Arentz M et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. JAMA 2020 [Epub ahead of print].	Samantha Betman (5/14)
	Mancia G et al. Renin-angiotensin-aldosterone system blockers and the risk of Covid-19. N Engl J Med 2020 [Epub ahead of print].	Dallas Kramer (5/14)
	Ong EZ et al. A dynamic immune response shapes COVID-19 progression. Cell Host Microbe 2020 [Epub ahead of print].	Al Hornung (5/14)

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PATHOGENESIS

Pathogenesis of COVID-19 from a cell biology perspective

Robert Mason

European Respiratory Journal
April 8, 2020
DOI: 10.1183/13993003.00607-2020

Purpose	To correlate the clinical stages of COVID-19 with viral activity at the cellular and molecular level.
Study design	Systematic Review
Level of evidence	Level 3
Methods	21 reference articles were reviewed, including retrospective and in-vitro studies. The author used this data to categorize 3 major stages of disease based on the clinical course of the patients and the pathogenic mechanisms taking place at the cellular/molecular level.
Findings	**Stage 1: Asymptomatic stage.** Inhaled virus enters ciliated epithelial cells in the nasal cavity. There is local spread of the virus, and very limited response by the innate immune system. **Stage 2: Upper airway response.** Viral particles infect the conducting airways, triggering a robust innate immune system response. CXCL10 (interferon responsive gene) activity has been correlated with cell response to SARS-CoV and influenza, therefore CXCL10 levels may predict prognosis COVID-19 patients. **Stage 3: Hypoxia and progression to ARDS.** The virus infects gas exchanging regions of the lung, causing apoptosis and release of viral particles, with infection of other pneumocytes and diffuse alveolar damage.
Clinical Implications	**Patients are infectious but not symptomatic during Stage 1.** RT-PCR could predict viral load and infectivity. Approximately 80% of patients will have disease limited to the upper airways - these **Stage 2 patients can predominantly be treated symptomatically at home**. Treating with epithelial growth factors such as KGF might increase ACE2 expressing cells, worsening the condition. **The Elderly are at high risk for severe, Stage 3 disease** due to decreased mucociliary clearance, diminished immune response, and limited regenerative capacity.
Limitations	The mechanisms of pathogenesis in SARS-CoV-2 are largely unknown. Due to limited data, the author is assuming that viral entry for SARS-CoV-2 is the same as SARS-CoV. The conclusions drawn in this article are based on scientific studies but are ultimately opinions of the author. Further research is needed to prove these claims.

Molecular immune pathogenesis and diagnosis of COVID-19

Xiaowei Li et al.

Journal of Pharmaceutical Analysis
March 5, 2020
DOI: https://doi.org/10.1016/j.jpha.2020.03.001

Purpose	To provide possible explanations for the immune pathogenesis of SARS-CoV-2 based on prior findings in SARS-CoV and MERS-CoV.
Study design	Systematic Review
Level of evidence	Level 5
Methods	Review of 73 published references including animal models, comparative analysis, epidemiologic and longitudinal studies examining the SARS and MERS epidemics.
Findings	SARS-CoV-2 shows 88% identity to bat-derived coronaviruses and 50% similarity to sequences of MERS-CoV. Prior research during the SARS-CoV epidemic showed that antigen detection by means of human leukocyte antigen (HLA) presentation plays a role in pathogenesis. Various HLA polymorphisms correlated to susceptibility of SARS-CoV (e.g., HLA-B*4601, HLA-B*0703) infection while other genetic variances had a relatively protective effect (e.g., HLA-A*0201). Both SARS-CoV and MERS-CoV demonstrated a critical proteolytic cleavage of its structural spike (S) protein to mediate membrane fusion and cell entry. In a longitudinal study, 14 of 23 SARS-CoV patients were found to have persistent specific T-cell memory responses to the S protein 6-years post-recovery. SARS-CoV and MERS-CoV have adapted strategies to evade immune detection, hiding pattern recognition receptors through specialized double-membrane vesicles.
Clinical Implications	Polymorphisms in HLA molecules played a role in susceptibility to SARS-CoV and MERS-CoV; **this genetic variation could possibly influence the diverse immune reaction to SARS-CoV-2. By studying SARS-CoV and MERS-CoV mechanism of entry, inhibiting S protein cleavage may serve as a possible target for therapy.**
Limitations	This review describes molecular pathogenesis for SARS-CoV and MERS-CoV and only infers molecular pathogenesis for SARS-CoV-2.

Hypothesis for potential pathogenesis of SARS-CoV-2 infection - a review of immune changes in patients with viral pneumonia.

Ling Lin et al.

Emerging Microbes and Infections
March 20, 2020
DOI: https://doi.org/10.1080/22221751.2020.1746199

Purpose	To review the immunological changes of coronaviruses like SARS, MERS and other viral pneumonia similar to SARS-CoV-2 and to infer potential pathogenesis.
Study design	Systematic review
Level of evidence	Level 5
Methods	A total of 43 published literature regarding the pathogenesis, immunological changes, and clinical observations seen in the SARS-CoV, MERS-CoV, Influenza (H1N1), and COVID-19 viral infections were reviewed.
Findings	Review of SARS-CoV, MERS-CoV and H1N1 pathogenesis suggested several common immunological changes: increased inflammatory factors (such as IL6, IL8, TNF-α) and lymphopenia. Histopathology shows diffuse alveolar damage, edematous lung lesions and pneumonia. SARS-CoV-2 virus passes through mucous membranes and enters the lungs through the respiratory tract, then the peripheral blood stream causing viremia. The virus targets organs that express angiotensin-converting enzyme 2 (ACE2) such as the lungs, heart, kidney and gastrointestinal tract. The clinical phase of SARS-CoV-2 is divided into three phases based on symptoms: Viremia phase, acute phase (pneumonia phase), and recovery period. The following scenarios are described: If the immune function is effective in the acute phase, the virus can be suppressed and enter recovery phase. Risk factors for severe or critical disease include older age, immuno-incompetence, hypertension, and diabetes.
Clinical Implications	Understanding the pathogenesis and immune related changes that take place during the COVID-19 infectious course can help build the treatment protocol for disease and improve prognosis. Clinical course can inform optimal treatment and potentially improve prognosis.
Limitations	The study was limited by the lack of immune-related research directed solely towards the immuno-pathogenesis of the SARS-CoV-2 virus. Additionally, the clinical pathogenesis and host immunity patterns of SARS-CoV, MERS-CoV, and H1N1 virus are incompletely characterized by the reviewed literature limiting the hypothesized pathogenesis of SARS-CoV-2.

Evidence for Gastrointestinal Infection of SARS-CoV-2.

Fei Xiao et al.

Gastroenterology
March 3, 2020
DOI: https://doi.org/10.1053/j.gastro.2020.02.055

Purpose	To further investigate which cells SARS-CoV-2 infects by examining the level of RNA in feces, viral RNA and nucleocapsid protein in gastrointestinal tissue.
Study design	Case series (n = 73)
Level of evidence	Level 4
Methods	Clinical specimens including serum, nasopharyngeal, and oropharyngeal swabs, urine, stool from 73 hospitalized patients infected with SARS-CoV-2 were obtained and tested for SARS-CoV-2 RNA using the China Disease Control and Prevention's standardized qPCR. Esophageal, gastric, duodenal, and rectal tissues were obtained from one patient. Histologic staining as well as viral receptor angiotensin-converting enzyme 2 (ACE2) and viral nucleocapsid staining were performed on the tissue.
Findings	In 20% of patients with SARS-CoV-2, fecal samples continued to test positive for SARS-CoV-2 despite negative respiratory samples. Additionally, immunofluorescence showed that ACE2 protein, a cell receptor for SARS-CoV-2, is abundantly expressed in the glandular cells of gastric, duodenal, and rectal epithelia, which supports the existent hypothesis of SARS-CoV-2's entry into host cells.
Clinical Implications	This study recommends rRT-PCR testing of fecal samples for SARS-CoV-2 to determine viral load and to ensure isolation precautions for hospitalized patients continue if positive. Furthermore, the authors argue that the low levels of SARS-CoV-2 nucleocapsid within the esophageal mucosa is due to their composition of squamous cells. The positive detection of viral RNA in feces implies that infectious virions are secreted from infected gastrointestinal cells. This supports the hypothesis of fecal-oral transmission as another route for viral spread and reiterates the importance of developing prevention practices addressing the fecal-oral transmission route.
Limitations	The sample size of this study was limited, particularly in regard to the tissue samples retrieved. Future research is needed to deliberate the likelihood of fecal oral transmission after viral clearance in the respiratory tract. Additionally, further histologic evidence of viral nucleocapsid in the four kinds of mucosa examined (esophageal, gastric, duodenal, and rectal epithelia) is necessary to build upon the aforementioned findings. Viral cultures were not performed on any of the specimens in this study. Some positive PCR results could represent non viable virus.

Rates of co-infection between SARS-CoV-2 and other respiratory pathogens

David Kim et al.

JAMA

April 15, 2020

DOI: 10.1001/jama.2020.6266

Purpose	To report co-infection rates between SARS-CoV-2 and other respiratory pathogens seen in Northern California.
Study design	Cross sectional study (n = 1217)
Level of evidence	Level 2
Methods	Nasopharyngeal swabs of 1217 specimens, from 1206 symptomatic patients, were collected and underwent reverse transcriptase-polymerase chain reaction (RT-PCR). Additionally, samples were tested for influenza A/B, respiratory syncytial virus, non-SARS-CoV-2 Coronaviridae, adenovirus, parainfluenza 1-4, human metapneumovirus, rhinovirus/enterovirus, Chlamydia pneumoniae, and Mycoplasma pneumoniae. Samples were then stratified based on results for SARS-CoV-2 status and non-SARS-CoV-2 pathogen status.
Findings	A total of 116 (9.5%) samples tested positive for SARS-CoV-2 and 318 (26.1%) tested positive for non-SARS-CoV-2 respiratory pathogens. Of the 116 SARS-CoV-2 positive specimens, 24 (20.7%) were also positive for 1 or more additional non-SARS-CoV-2 respiratory pathogens. Of 1101 negative samples for SARS-CoV-2, 294 (26.7%) were positive for 1 or more additional non-SARS-CoV-2 respiratory pathogens. Co-infected patients did not differ significantly in age from only SARS-CoV-2 infected patients. This study found higher rates of co-infection occurring than previously reported from China.
Clinical Implications	**Detecting the presence of a non-SARS-CoV-2 respiratory pathogen may not be sufficient to rule out that a patient does not also have SARS-CoV-2.** In this study, co-infection with influenza, RSV, Parainfluenza, Metapneumovirus, Rhinovirus/enterovirus, and other corona viruses, albeit at low frequencies, occurred.
Limitations	This study includes samples from Northern California, which regionally limits the patient population as well as the viral epidemiology. Some viruses are seasonal or sporadic in occurrence and these variations could not assessed due to the short time period of the study.

Liver injury in COVID-19: Management and challenges

Chao Zhang et al.

Lancet: Gastroenterology and Hepatology
March 4, 2020
DOI: https://doi.org/10.1016/S2468-1253(20)30057-1

Purpose	To assess how the liver is affected by COVID-19 using the available case studies and data from The Fifth Medical Center of PLS General Hospital in Beijing, China.
Study design	Case series (n = 56)
Level of evidence	Level 4
Methods	Review of 7 case studies to date reporting the clinical features of patients with COVID-19. The authors report on laboratory studies of 56 cases of COVID-19 patients who were hospitalized at their institution.
Findings	Seven large-scale case studies reported on clinical features of patients with COVID-19, indicating 2-11% of patients had liver comorbidities. During disease progression, 14-53% of patients had elevated alanine (ALT) and aspartate aminotransferase (AST). Those with severe disease, defined as necessitating care in the ICU, had higher rates of liver dysfunction. Confirmed COVID-19 cases in the subclinical phase (i.e., before symptom onset) had significantly lower AST abnormality than did patients diagnosed after symptom onset. SARS-CoV-2 RNA has been detected in stool and blood samples, and 2-10% of patients present with diarrhea, implicating the possibility of viral exposure in the liver. SARS-CoV-2 and SARS-CoV both bind to angiotensin-converting enzyme 2 (ACE2) receptors to gain cell entry. A preliminary study has suggested that cholangiocytes are rich with the ACE2 receptor, providing a direct means of liver damage. Authors reported elevated gamma-glutamyl transferase (GGT) in 30 (54%) of patients with COVID-19 during hospitalization. Additionally, they found elevated alkaline phosphatase levels in a single (1.8%) patient.
Clinical Implications	Cholangiocyte expression of ACE2 receptors may provide a means of virus inoculation. **Patients with severe disease (exhibiting massive alveolar damage and progressive respiratory failure) are more likely to have liver dysfunction.**
Limitations	While likely due to the urgency surrounding the health crisis of this novel coronavirus, this study has analyzed a small number of patients with limited follow-up. They cite preliminary studies which have yet to undergo rigorous peer-review, again due to the urgency of the present situation.

Description and proposed management of the acute COVID-19 cardiovascular syndrome.

Nicholas Hendren et al.

Circulation

April 16, 2020

DOI: https://doi.org/10.1161/CIRCULATIONAHA.120.047349

Purpose	To outline the available information about the epidemiology, pathogenesis, diagnosis, and treatment of Acute COVID-19 Cardiovascular Syndrome (ACovCS).
Study design	Systematic review
Level of evidence	Level 4
Methods	The authors evaluated data from many sources, including clinical studies, previous MERS and SARS-CoV-1 cases, and case reports from COVID-19-positive patients.
Findings	In one analysis, 15 of 52 (28.8%) critically ill COVID-19 patients in China had associated myocardial injury. Another retrospective study revealed that 32 of 54 (59.3%) COVID-19 patients who had died had myocardial injury. Only one of the 95 (1.05%) surviving patients had myocardial injury. In a small case series where three patients died from COVID-19, no SARS-CoV-2 was detected in cardiac tissue but the observed morphological changes suggested a secondary mechanism of injury, such as a cytokine storm. The contagious nature of COVID-19 is a barrier to endomyocardial biopsy. In lieu of biopsy, patients who have abnormal troponin and can be excluded from a myocardial infarction diagnosis on clinical grounds can be treated with classic management. The paper also states echocardiogram, angiography, or clinical imaging should not be done on COVID-19 patients, unless the patient is deteriorating. A cardiac ultrasound can be recommended if the physician can reduce exposure. ACE2 entry is a known mechanism of SARS-CoV-2, but its effect on cardiac cells specifically is theoretical as of now; SARS-CoV-1 was found to have affected cardiacmyocytes among other ACE-2 targets in patients who succumbed to that virus.
Clinical Implications	Treatment of ACovCS is not well understood, and therapies such as hydroxychloroquine and antivirals may increase risk for cardiac arrhythmia, further exacerbating ACovCS. IL-6 inhibitors are being studied to reduce the cytokine release thought to contribute to myocardial injury. In those with refractory shock or ventricular arrhythmias due to ACovCS, mechanical support can be used; case reports have shown rescue in these patients by using veno-arterial and veno-arterial-veno ECMO.
Limitations	Limited ability to conduct biopsies common in other cases may play a significant role in our ability to determine the effects of COVID-19 on the heart itself. Many components of this review use prior research done with SARS-CoV-1, which although in the same family, may present with a different set of symptoms and pathogenesis.

Pathological findings of COVID-19 associated with acute respiratory distress syndrome.

Zhe Xu et al.

Lancet Respiratory Medicine
February 18, 2020
DOI: https://doi.org/10.1016/S2213-2600(20)30076-X

Purpose	To investigate the clinical characteristics of a patient who died from severe acute respiratory syndrome (ARDS) secondary to a severe coronavirus (SARS-CoV-2) infection.
Study design	Case report
Level of evidence	Level 5
Methods	One participant positive with SARS-CoV-2, as confirmed by RT-PCR, was subjected to scrutiny of patient records, radiographs and histological analysis of post-mortem biopsy samples (lung, liver and heart).
Findings	Histological examination showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates. Both lungs showed evidence of hyaline membrane formation, suggestive of ARDS. Additionally, CD8+ T cells within the samples displayed high concentrations of cytotoxic granules (31.6% cells were perforin positive, 64.2% cells were granulysin positive, and 30.5% cells were both granulysin and perforin double-positive). Of note, serial bilateral radiographs indicated rapid progression of pneumonia. Liver biopsy showed moderate, microvesicular steatosis and mild lobular activity, although there was no irrefutable evidence to support SARS-CoV-2 infection as the cause.
Clinical Implications	The study results suggest that an overactivation of T cells, increased Th17 and highly cytotoxic CD8 T cells may account for the severity of injury in this patient.
Limitations	As with many studies during this time frame, the sample size was limited (n=1). Additionally, the study design itself decreases the applicability of these results. Nonetheless, the authors findings do provide a scaffolding for future studies which could clarify the pathogenesis of SARS-CoV-2-related pneumonia and also when therapeutics should be administered to in similar severe patients to reduce mortality.

Comparative pathogenesis of COVID-19, MERS, and SARS in a non-human primate model.

Barry Rockx et al.

Science
April 17, 2020
DOI: 10.1126/science.abb7314

Purpose	To identify key pathways in the pathogenesis of SARS-CoV, MERS-CoV and SARS-CoV-2 by using cynomolgus macaques as a model system, which is critical in the evaluation of therapeutic strategies against COVID-19 infection for use in humans.
Study design	Animal model study
Level of evidence	Level 5
Methods	One group of four young macaques (4-5 years) and a group of four old macaques (15-20 years) were inoculated with COVID-19. Nasal, throat, and rectal swabs were taken daily for up to 21 days and were tested for the virus by RT-qPCR and virus culture. Environmental sampling was done to determine if the surfaces where the macaques habituated were contaminated. On day 4, autopsies were completed on 4 macquaes with RT-qPCR was done on samples from their respiratory, digestive, urinary, and cardiovascular systems in addition to various lymphoid tissues. This process was repeated with 6 macaques who were inoculated with MERS-CoV. Histopathological findings of MERS-CoV and SARS-CoV-2 were compared to previous studies of SARS-CoV.
Findings	Histopathologic examination of both young and old macaques inoculated with either SARS-CoV-2 or MERS showed evidence of diffuse alveolar damage. There was syncytia and hyaline membrane formation in SARS-CoV-2 macquaes, similar to previous studies on SARS-CoV. However, there were scant findings of syncytia formation and hyaline membranes in MERS-CoV macaques. SARS-CoV-2 antigens were found in type I and II pneumocytes, similar to SARS-CoV as reported in previous studies. No MERS-CoV antigens were found in type I pneumocytes, and were only occasionally found in type II pneumocytes. SARS-CoV-2 shedding peaked early in the course of infection, similar to observations in symptomatic patients. Increased age did not affect disease outcome, but there was prolonged viral shedding in the upper respiratory tract of aged animals. Prolonged shedding was also reported in SARS-CoV and SARS-CoV-2 patients.
Clinical Implications	SARS-CoV-2's ability to infect type II pneumocytes may contribute to respiratory distress syndrome (ARDS). Authors sugest that the virus can spread early in the infection.
Limitations	The study was limited by its small sample size. Previous studies of SARS-CoV were used to compare histological findings to MERS-CoV and SARS-CoV-2. This study was done on macaques and findings may not be generalizable to humans.

Characteristics and mechanism of liver injury in 2019 coronavirus disease.

Jie Li & Jian-Gao Fan

Journal of Clinical and Translational Hepatology
March 28, 2020
DOI: 10.14218/JCTH.2020.00019

Purpose	To highlight the clinical, pathological, and laboratory characteristics of liver injury in COVID-19.
Study design	Retrospective analysis
Level of evidence	Level 4
Methods	Authors looked at studies originating from mainland China and in hospital settings, evaluating the clinical features and outcomes of SARS-CoV-2. They also evaluated prior studies of MERS and SARS-CoV to hypothesize possible pathophysiology and etiology of liver injury in COVID-19 and relied on prior understanding of secondary mechanisms of liver injury in patients suffering from infectious disease.
Findings	COVID-19-positive patients have had transient elevations in serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), and bilirubin. Some pathological changes, including microthrombi, in the liver have been observed in autopsies, but no specific features of liver failure nor bile duct injuries were noted. Prior research of SARS-CoV in mouse models has suggested upregulation of ACE2 in the liver is caused by compensatory proliferation of cholangiocyte-derived hepatocytes during acute liver injury during infection. Liver injury by SARS-CoV-2 may be through ACE-2-mediated damage to hepatocytes. Additionally, the use of acetaminophen and hepatoxic anti-viral drugs such as oseltamivir, abidol, and lopinavir/ritonavir in COVID-19 patients could be contributing to elevated liver enzymes. SARS-CoV-2 infection and related immune changes might also be regarded as a "second-hit" to existing chronic liver diseases and needs to be further investigated.
Clinical Implications	There is insufficient evidence of SARS-CoV-2 infecting hepatocytes or causing direct liver injury. However, this review argues that the liver is the second most frequently affected organ outside of the lungs in COVID-19 patients, so more research on its effects on the liver is necessary.
Limitations	Many of the proposed etiologies of liver injury in COVID-19 in this study are speculative and based on prior studies conducted on SARS-CoV. Further follow up is needed on SARS-CoV-2-specific manifestation and pathogenesis of liver injury as research on this topic continues to evolve. Liver biopsies are rarely performed unless post mortem, so future histopathological studies may be limited. Additionally, this review only looked at Chinese studies.

SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes.

Janko Nikolich-Zugich et al.

GeroScience

April 10, 2020

DOI: https://doi.org/10.1007/s11357-020-00186-0

Purpose	To compare the presentation of SARS-CoV-2 (cause of COVID-19 disease) in older adults to MERS and SARS-CoV.
Study design	Systematic Review
Level of evidence	Level 4
Methods	Reviewed 67 publications on SARS-CoV-2, MERS-CoV, and SARS-CoV-1.
Findings	SARS-CoV-2 infectivity peaks with high titers of viral load even before symptomatic infection compared to SARS-CoV-1 and MERS-CoV. Progression to ARDS after COVID-19 infection has been marked by upregulation of plasma proinflammatory mediator. Typical clinical features of COVID-19, similar to SARS-CoV-1, include fever, cough, and myalgias. **Unique to COVID-19, diarrhea and nausea may precede fever and respiratory symptoms.** Coronaviruses are recognized by TLR7, RIG-I/MDA, and cGAS/STING innate immune sensors; all result in early IFN-I responses necessary for control of infection. Neutralizing antibodies directed at the spike (S) protein binding site for the ACE2 receptor can possibly serve as protection but can be a challenge since SARS-2 S protein for ACE2 receptors have a higher affinity when compared to SARS-1.
Clinical Implications	COVID-19 patients show similar clinical symptoms to SARS-1 and although characterized as non-specific, the symptoms resemble influenza more than the common cold. Older adults are more susceptible to infections due to their immune responses being slower, less coordinated, and less efficient. Older men and men with comorbidities are at highest risk for severe disease if infected with COVID-19.
Limitations	This study was limited in sample size and diversity of presentation and based on case studies. Further research is needed to know just how disproportionately older adults are affected by SARS-CoV-2 and COVID-19.

Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases.

Cynthia Magro et al.

Translational Research

April 9, 2020

DOI: https://doi.org/10.1016/j.trsl.2020.04.007

Purpose	To define the role of complement activation and microvascular thrombosis in cases of severe COVID-19.
Study design	Case series (n = 5)
Level of evidence	Level 4
Methods	Five patients were enrolled over a two-week period based on a positive SARS-CoV-2 result (confirmed by RT-PCR on respiratory tract samples). Two patients died and were autopsied. The remaining three individuals were examined for development of an extensive skin rash. Patient records as well as tissue samples were subjected to immunohistological assessments for a variety of complement proteins.
Findings	This study found patterns of damage in both the lungs and skin consistent with complement-mediated microvascular injury in all five cases of severe COVID-19. Of note, there were depositions of C5b-9, C4d, and MASP2, which provides evidence for the authors' hypothesis surrounding an overactivation of the alternative and lectin-based pathways. The authors speculated that saturation of angiotensin converting enzyme 2 (ACE2), which normally leads to the deactivation of reactive oxygen species (ROS), may lead to amplified complement activation thus increasing the likelihood of vascular injury. Some samples had pronounced C5b-9 deposition, a key feature of many microthrombotic syndromes, indicating individuals with severe infection may benefit from the addition of anti-complement therapies.
Clinical Implications	**Labs that could indicate complement-mediated microvascular injury and thrombosis should be considered in COVID-19 positive patients**, including: d-dimer, factor VIII, fibrinogen, antiphospholipid antibodies, and circulating complement proteins.
Limitations	Case series are subject to selection bias. Additionally, this case series had a small sample size, limiting the generalizability of the findings. Further examination of the proposed hypotheses, drug recommendations and pathways as well as confirmation of the pauci-inflammatory response exhibited in this cohort is necessary.

SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor.

Markus Hoffman et al.

Cell

April 16, 2020

DOI: https://doi.org/10.1016/j.cell.2020.02.052

Purpose	1) To study the hypothesis that SARS-CoV-2 enters host cells through the binding viral spike (S) proteins to ACE2. 2) To evaluate whether S proteins undergo priming by the protease TMPRSS2, and if a protease inhibitor successfully blocks viral entry. 3) To evaluate whether neutralizing antibodies against SARS-CoV have cross reactivity with SARS-CoV-2.
Study design	In-vitro laboratory studies
Level of evidence	Not applicable
Methods	Part 1: Human cells (cell line 293T) were transfected to express SARS-2-S. A replication defective vesicular stomatitis virus (VSV) was used (one batch bearing SARS-2-S and one bearing SARS-S), infecting multiple human and animal cell lines, and genetic analysis was performed. Part 2: Authors tested whether SARS-2-S is primed by cathepsin B and L (CatB/L) by using ammonium chloride to block CatB/L activity. The serine protease inhibitor camostat mesylate (active against TMPRSS2) was used to partially block SARS-2-S. Part 3: Sera from 3 convalescent SARS patients was used to test efficacy against SARS-CoV-2.
Findings	Part 1: Western blot confirmed efficiency of human cells of this line in proteolytic processing of SARS-2-S. SARS-2-S and SARS-S-expressing viruses gained entry to an identical spectrum of cell lines, suggesting that they use similar receptors to gain entry. Genetic analysis showed similar amino acid residues between SARS-S and SARS-2-S in the receptor binding motif required for interaction with ACE2. SARS-CoV-2 infected the same cells lines as the SARS-CoV-related viruses that use ACE2 as their receptor. The amino acid sequence thought to be crucial for binding to ACE2 found in SARS-CoV-2 was not present in the SARS-CoV-related viruses that were unable to bind cells expressing ACE2. The SARS-2-S expressing virus was not able to enter cells when an antibody against ACE2 was present. Lastly, BHK-21 cells transfected to express ACE2 were easily infected, but parental cells with no ACE2 expression were not infected. Part 2: Both SARS-2-S and SARS-S viruses were inhibited by ammonium chloride, suggesting CatB/L dependence. Full inhibition was attained when camostat mesylate and E-64d (a CatB/L inhibitor) were used together. When tested in human lung cells, this caused reduced viral entry. Part 3: SARS-S expressing viruses had a concentration dependent inhibition from SARS patient sera. SARS-2-S expressing virus was also inhibited, but with lower efficiency compared to SARS-S.
Clinical Implications	SARS-CoV-2 enters cells via interaction between S protein and ACE2. Viral entry was dependent on proteolytic cleavage by TMPRSS2 as well as CatB/L. When a TMPRSS2 inhibitor was introduced, viral entry was inhibited. This may be a potential target for treatment. Antibodies against SARS-CoV from convalescent donors partially inhibited the infectivity of SARS-CoV-2. This may be a viable option for treatment/prophylaxis against the virus.
Limitations	This in vitro work requires validation in humans especially as it relates to possible drug targets for viral entry including a TMPRSS2 inhibitor.

Human leukocyte antigen susceptibility map for SARS-CoV-2

Austin Nguyen et al.

Journal of Virology
April 17, 2020
DOI: 10.1128/JVI.00510-20

Purpose	To explore the role of individual genetic variability in the immune response against SARS-CoV-2.
Study design	Observational analysis
Level of evidence	Level 5
Methods	Protein sequences of 34 representative alpha and betacoronaviruses, including all human coronaviruses were obtained. MHC class I-peptide binding affinity using 145 different HLA alleles was assessed against highly conserved sequences. These peptides were than cross-referenced with known SARS-CoV epitopes. Population allele and haplotype frequency data was aggregated by country, from which global haplotype frequency maps were generated.
Findings	**This study identified HLA-B*46:01 as the HLA allele with the fewest predicted binding peptides for SARS-CoV-2.** This was in keeping with previous clinical data associating this allele with severe disease in SARS-CoV. The top presenters of conserved peptides with high predicted binding affinities were identified as HLA-A*02:02, HLA-B*15:03, and HLA-C*12:03. 56 different HLA alleles did not demonstrate significant binding affinity suggesting lack of potential for cross-protective immunity from other human coronaviruses. There was no global correlation between conservation of SARS-CoV-2 and its predicted MHC-binding affinity was observed, suggesting lack of selective pressure to present coronavirus epitopes. Peptide presentation appears to be independent of estimated time of peptide production during the viral life cycle, with no differences in presentation of early and late peptides.
Clinical Implications	This study has the potential to inform pairing HLA typing with COVID-19 testing to rapidly develop predictors of viral severity in the population and to tailor future vaccine strategies to genotypically at-risk populations
Limitations	This in silico study does not evaluate individual-level HLA typing and clinical outcomes data for any real-world COVID-19 populations. Relative risk of HLA type versus other disease modifying risk factors was not assessed. Peptide-MHC binding affinity is used as a predictor for T-cell responses.

Virology, Epidemiology, Pathogenesis, and Control of COVID-19

Yuefei Jin et al.

Viruses

March 27, 2020

DOI: https://doi.org/10.3390/v12040372

Purpose	To provide a summary to public health authorities of COVID-19, the current state of treatment and vaccine development.
Study design	Systematic review
Level of evidence	Level 5
Methods	Review of 86 published studies on the virology, epidemiology, diagnosis, pathogenesis, potential therapeutics, and vaccine development of SARS-CoV, MERS-CoV, and SARS-CoV-2.
Findings	SARS-CoV-2 appears similar to previous SARS and MERS outbreaks with bats being a likely important reservoir. Main mode of transmission is through inhalation of respiratory droplets, indirect or direct contact. COVID-19 and SARS have similar pathogenesis, with upper respiratory tract infection leading to lower respiratory tract infection, either resulting in mild viremia, viral replication in target organs, or over-activation of T cells leading to immune dysfunction, cytokine storm and acute respiratory distress syndrome (ARDS). Antibody-dependent enhancement (ADE) can promote viral cellular uptake of infectious virus-antibody complexes resulting in enhanced invasion of target cells. The interaction of FcγR with the virus-anti-S-protein neutralizing antibodies may facilitate both inflammatory responses and persistent viral replication in the lungs of patients.
Clinical Implications	**Finding consistency in the S protein of SARS-CoV-2, which binds to human angiotensin-converting enzyme 2 (ACE2), may prove helpful for vaccination efforts.** The most urgent task is to develop more intervention to allow for effective control of infection.
Limitations	This study offered no new clinical information and was simply a review of existing literature to guide public health officials in their response. The study focused mainly on response and research performed in China and lacked global perspective.

SARS-CoV-2 Infection in Pregnancy – A Review of the Current Literature and Possible Impact on Maternal and Neonatal Outcome

Florian Stumpfe et al.

Geburtshilfe und Frauenheilkunde
March 10, 2020
DOI: https://doi.org/10.1055/a-1134-5951

Purpose	To provide an overview of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and to outline the potential risks and complications for pregnant patients.
Study design	Systematic review
Level of evidence	Level 4
Methods	Literature from cases on infection in pregnancy during the SARS and MERS epidemics as well as recent publications on cases infected with SARS-CoV-2 in pregnancy were reviewed.
Findings	Clinical symptoms of an infection of SARS-CoV-2 are identical to those cases involving non – pregnant female patients. Clinical course of COVID-19 in pregnancy can be associated with a higher mortality. Based on current literature published on SARS-CoV-2 in pregnancy, it does not appear that there is intrauterine transmission of SARS-CoV-2 onto the fetus. No pathogen has been isolated in maternal milk in the studies carried out to date, thus transmission via breastfeeding is currently regarded as improbable. Neonatal outcomes of patients born to SARS-CoV-2 infected mothers had unremarkable outcomes as compared to their gestational age and weight-matched counterparts.
Clinical Implications	No treatment regarded as appropriate for non-pregnant women should be withheld in pregnant women unless contraindicated. Empiric antibiotic treatment for secondary bacterial infections is indicated. There is no recommendation for mode of delivery. **It is assumed that transmission from mother to child in utero is unlikely and breastfeeding is possible once infection has been excluded.**
Limitations	This study was limited by the number of studies available on disease course and outcome of pregnant women infected with SARS-CoV-2. Additionally, methodology for testing vertical transmission from mother to fetus differed among studies, with several only testing throat swabs from neonates rather than including placenta, umbilical cord and amniotic fluid analysis.

Clinical Course and Outcomes of Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection: a Preliminary Report of the First 28 Patients from the Korean Cohort Study on COVID-19

Eu Suk Kim et al.

Journal of Korean Medical Science
April 6, 2020
DOI: https://doi.org/10.3346/jkms.2020.35.e142

Purpose	To investigate the clinical course and outcomes of novel coronavirus disease 2019 (COVID-19) from early cases in Republic of Korea.
Study design	Cohort study (n = 28)
Level of evidence	Level 4
Methods	The first 28 patients in the Republic of Korea were included. All cases were confirmed by real time polymerase chain reaction (RT-PCR). Clinical data were collected and analyzed for changes in clinical severity including laboratory, radiological, and virologic dynamics during the progression of illness.
Findings	Based off viral kinetics by serial RT-PCR of respiratory specimens from 9 patients from the early course of illness, viral shedding was high from the prodromal phase of the illness to the first 5 days of illness. Viral shedding decreased after day 7 of illness. Viral shedding was higher in the upper respiratory tract (URT) than the lower respiratory tract (LRT).
Clinical Implications	**Transmission of SARS-CoV-2 may begin from the prodromal phase of illness, just like common cold or influenza viruses.** The median time from symptom onset to isolation of the patients was 3 days, and that **high titers of virus shedding began from day 1 of illness with the peak around day 3–5 of illness**, early detection and isolation strategy may be relatively less effective in containing the virus in COVID-19.
Limitations	Only 28 patients were included in this study and only 9 had viral kinetics by serial RT-PCR of respiratory specimens evaluated. The proportion of elderly patients and frequency of underlying conditions were small, and therefore the first 28 patients had relatively favorable outcomes. Evaluation for coinfection of other respiratory viruses such as influenza was not conducted.

Liver injury during highly pathogenic human coronavirus infections

Ling Xu et al.

Liver International
March 14, 2020
DOI: https://doi.org/10.1111/liv.14435

Purpose	To summarize the characteristics and mechanism of liver injury caused by the highly pathogenic human coronaviruses: SARS-CoV, MERS-CoV, and the new 2019 coronavirus (SARS-CoV-2).
Study design	Systematic review
Level of evidence	Level 1
Methods	Systematic review of case series studies on SARS-CoV, MERS-CoV, and SARS-CoV-2 cases in which liver injury was measured. The number of analyzed cases for each virus was 1907, 447, and 2264, respectively.
Findings	Recent studies on COVID-19 have shown that the **incidence of liver injury ranged from 14.8% to 53.0%, mainly indicated by abnormal alanine transaminase/aspartate aminotransferase (ALT/AST) levels with slight elevations in bilirubin**. Albumin was decreased in severe cases, around 26.3-30.9 g/L. There was a larger proportion of those who developed liver injury in more severe COVID-19 cases compared to more mild cases. In those who died of COVID-19, the incidence of liver injury was between 58% and 78%. The mechanism of injury is still unclear, but since bile duct epithelial cells express angiotensin-converting enzyme (ACE2) in much higher numbers than hepatocytes, **this suggests that COVID-19 induced liver injury may be due to bile duct cell damage, rather than hepatocellular damage. However, drug-induced liver damage cannot be ruled out, given many of these patients are being treated with lopinavir/litonavir, which have hepatotoxicity as an adverse effect.**
Clinical Implications	While treating the primary disease caused by SARS-CoV-2, **clinicians should also monitor for liver injury and be mindful when applying drugs that can induce liver damage**. This paper recommends that patients with liver damage can be treated with drugs that both protect liver function and inhibit inflammatory response, such as ammonium glycyrrhizinate.
Limitations	Studies in this review were case series rather than controlled trials, so it is difficult to draw conclusions on whether the liver injury was due to COVID-19 itself or other variables such as medication adverse effects or medical comorbidities.

Cardiovascular Complications in Patients with COVID-19: Consequences of Viral Toxicities and Host Immune Response

Han Zhu et al.

Current Cardiology Reports
April 21, 2020
DOI: https://doi.org/10.1007/s11886-020-01292-3

Purpose	To review current knowledge of the biology of SARS-CoV-2 and the potential mechanisms of myocardial injury.
Study design	Systematic review
Level of evidence	Level 5
Methods	87 published studies regarding the biology, immunology, pathogenesis, and cardiovascular complications seen in the SARS-CoV-2 infection were reviewed.
Findings	SARS-CoV-2 can present with severe cardiac injury manifesting with elevated troponin and heart failure. Cardiotoxicity, pre-exiting cardio-metabolic disease, and increased frequency of adverse cardiovascular events after disease resolution is associated with increased mortality. Increased incidences of cardiac injury among those with inflammatory response syndromes and shock in the setting of SARS-CoV-2 infection suggests an important relationship between the immune response and the cardiovascular system. **The mechanism of cardiac injury is unclear but likely involves a combination of direct viral damage and immune mediated damage by inflammatory cytokines and chemokines, and cytotoxic immune cell responses.** Literature suggests that direct cell cytotoxicity through viral entry into vascular tissues via angiotensin converting enzyme 2 (ACE2) may induce endothelial shedding and dysfunction that contributes to vascular damage, local inflammation, and production of procoagulant factors predisposing to thrombosis, and myocardial infarction. Literature also suggests that there is no evidence of direct lymphocytic infiltration in the myocardium, but that the dysfunction of T cells can contribute to the cytokine storm and multiorgan damage seen in the setting of SARS-CoV-2 infection.
Clinical Implications	Understanding the pathogenesis of cardiotoxicity in the SARS-CoV-2 infection can aid in the use and development of treatments that can minimize the permanent damage to the cardiovascular system and decrease the cardiovascular – associated mortality of SARS-CoV-2.
Limitations	There are relatively few studies addressing the mechanism and pathogenesis of cardiotoxicity in the SARS-CoV-2 infection. More studies are needed on cardiovascular protection during treatment for COVID-19.

Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19)

Bo Diao et al.

medRxiv

February 20, 2020

DOI: https://doi.org/10.1101/2020.02.18.20024364

Purpose	To investigate the etiology of T-cell count reduction and activation status in COVID-19 patients.
Study design	Case control (n = 562)
Level of evidence	Level 4
Methods	Retrospective review of data from 522 patients with laboratory-confirmed COVID-19 admitted to two hospitals in Wuhan from December 2019 to January 2020, and 40 healthy controls who came to the hospitals for routine physical exam. Lab data included total T-cell count, CD4+, CD8+ T-cell subsets, and serum cytokine concentration. The expression of T cell exhaustion markers PD-1 and Tim-3 were measured by flow cytometry in the peripheral blood of 14 COVID-19 cases.
Findings	The number of total T cells, CD4 + and CD8 + T cells were dramatically reduced in COVID-19 patients, especially among elderly patients (≥60 years of age) and in patients requiring Intensive Care Unit (ICU) stay. Counts of total T cells, CD8+ T cells or CD4+ T cells lower than 800/μL, 300/μL, or 400/μL, respectively, are negatively correlated with patient survival. T cell numbers are negatively correlated to serum IL-6, IL-10 and TNF-α concentration, with patients in recovery showing reduced IL-6, IL-10 and TNF-α concentrations and restored T cell counts. T cells from COVID-19 patients have significantly higher levels of the exhausted marker PD-1 as compared to healthy controls.
Clinical Implications	**T cell counts are reduced significantly in COVID-19 patients, and the surviving T cells appear to be functionally exhausted.** Cytokines such as IL-10, IL-6 and TNF-α might directly mediate T cell reduction. Thus, new treatments focused on mitigating these findings can be further investigated for use in ICU patients. Additionally, the study suggests that treatment may even be necessary early on to preempt disease progression in higher-risk patients with low T cell counts.
Limitations	The study was limited by including only subjects admitted into two hospitals in Wuhan, China and by the limited number of healthy controls. Additionally, the co-morbidities and prior health status of the study participants were not included.

Cardiovascular disease and COVID-19.

Manish Bansal

Diabetes & Metabolic Syndrome: Clinical Research & Reviews
March 25, 2020
DOI: https://doi.org/10.1016/j.dsx.2020.03.013

Purpose	To understand the relationship between cardiovascular disease and COVID-19.
Study design	Systematic review
Level of evidence	Level 2
Methods	Search performed using PubMed and Google Scholar for original and review articles. The data from these studies were analyzed separately. The authors drew conclusions fregarding incidence of cardiac manifestations in COVID-19 and their prognostic implications.
Findings	A history of cardiovascular (CV) disease confers worse prognosis in COVID-19. **Patients with COVID-19 are also more likely to have a cardiac complication regardless of cardiac history.** A meta-analysis of 6 studies from China (n=1527) revealed the prevalence of cardiovascular disease in COVID-19 was the same as the general population, but was associated with a 3-fold greater risk of intensive care unit (ICU) admission. The Chinese Center for Disease Control and Prevention (CDC) found that out of 44,672 cases, the case fatality rate was 2.3% overall, but 10.5% in those with CV disease. Troponin I elevation is the most common CV abnormality (8-12% of patients according to multiple studies). There are multiple mechanisms of cardiac involvement in COVID-19: 1) Direct Myocardial Injury: viral myocarditis (entry via angiotensin-converting enzyme 2, ACE2). 2) Systemic Inflammation: and cytokine storm seen in some cases of COVID-19. 3) Supply/Demand mismatch: increased metabolic demand due to illness combined with decreased oxygen supply due to hypoxia injures myocardial tissue. 4) Plaque rupture and coronary thrombosis: systemic inflammation and increased stress can precipitate plaque rupture resulting in acute myocardial infarction (MI). 5) Iatrogenic: Medications used to treat COVID-19 (antivirals, chloroquine) can cause direct injury to the heart and/or prolong the QT interval, predisposing to arrhythmia. 6) Electrolyte abnormality: can occur in any critically ill patient, but hypokalemia is of particular concern in COVID-19 due to interaction of SARS-CoV-2 with renin-angiotensin-aldosterone system (RAAS).
Clinical Implications	Patients can be risk stratified based on a history of CV disease. The author suggests only performing CV testing in patients with high pre-test probability as to not overwhelm the system. The author suggests considering the use of fibrinolytics as opposed to percutaneous intervention (PCI) in patients with COVID-19 due to the unique circumstances during the pandemic.
Limitations	This article reviews observational data. Some assumptions regarding the pathogenesis of CV disease in COVID-19 are made based on the pathogenesis of SARS-CoV.

Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management

Ferdinando D'Amico et al.

Clinical Gastroenterology and Hepatology
April 2, 2020
DOI: https://doi.org/10.1016/j.cgh.2020.04.001

Purpose	To examine the epidemiology, mechanism of action, management, and prevention of COVID-19 associated diarrhea.
Study design	Systematic review
Level of evidence	Level 5
Methods	Records from PubMed, EMBASE, and Web of Science were searched, including articles up to March 2020, for studies documenting diarrhea and mechanism of intestinal inflammation in patients with confirmed diagnosis of SARS-CoV-2 infection.
Findings	This study provides multiple theoretical mechanisms of COVID-19 associated diarrhea, including alterations in intestinal permeability, modification of gut microbiome homeostasis, reduced dietary amino acid adsorption due to decreased intestinal angiotensin-converting enzyme 2 (ACE2) expression or some combination of the three. Additionally, the authors found high variability in the percentage of patients with diarrhea, ranging from 2% to 50% of cases (overall 10%). This is lower than other coronaviruses, which may indicate an underestimation of the overall burden of disease. Further evidence of SARS-CoV-2 in gastrointestinal (GI) and stool samples days after negative respiratory test result, and the persistence of other coronaviruses resistance in low temperatures (20°C and 30°C) suggests of orofecal transmission. Authors noted that supplementary studies to quantify the exact burden of diarrhea, utilizing a predetermined definition, in addition to sensitivity comparisons between fecal and nasopharyngeal tests were needed.
Clinical Implications	Diarrhea is a frequent presenting symptom in COVID-19 patients suggesting a possible oral-fecal transmission route. This highlights the importance of adhering to stringent sanitary measures to prevent fecal oral spread of COVID-19 between patients and healthcare workers.
Limitations	The search strategy was not provided in detail (i.e., the studies included have a variation of diagnostic methods with different sensitivity and specificity) and the authors failed to provide any quality criteria for selection. Both may be attributed to the relative urgency associated with the current pandemic.

Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China

Bo Li et al.

Clinical Research in Cardiology
March 11, 2020
DOI: https://doi.org/10.1007/s00392-020-01626-9

Purpose	To better understand the prevalence of cardiovascular and metabolic disease in patients with SARS-CoV-2 and the subsequent severity of COVID-19.
Study design	Meta-Analysis (n = 1,527)
Level of evidence	Level 1
Methods	Studies demonstrating the prevalence and severity of COVID-19 were identified through EMBASE and PubMed. Between December 2019 and February 2020, six studies for a total of 1527 patients were included. Key criteria included confirmation of infection, study populations greater than 10 participants, and documented comorbidities.
Findings	Analysis demonstrated the following prevalence of comorbidities among COVID-19 patients: hypertension (17.1%), cardio/cerebrovascular disease (16.4%), diabetes (9.7%). Hypertension as a comorbidity was present in 28.8% of COVID-19 ICU admissions and 14.1% of non-ICU patients. Similarly, cardio/cerebrovascular disease accounted for 16.7% and 6.2%, respectively. Patients with hypertension had a statistically significant increased risk for ICU admission (relative risk (RR) = 2.03). Those with cardio/cerebrovascular history had a RR = 3.30. Effect of diabetes on COVID-19 severity as judged by ICU admission requirement did not achieve statistical significance. There was a statistically significant increased incidence of myocardial injury (elevated Troponin I/T) among ICU patients (RR = 13.48).
Clinical Implications	The data suggests **those with hypertension or cardio/cerebrovascular disease have a 2-3x greater likelihood of requiring ICU admission**. In these cases, cardiac damage is more likely. Possible pathogenetic explanations for these results include direct viral damage to the cardiomyocytes as seen in SARS-CoV, hypoxia-induced damage, inflammation from cytokine storm, and repeated floods of catecholamines due to anxiety and medications. When compared to the general population, the prevalence of cardio/cerebrovascular disease among patients with COVID-19 was higher.
Limitations	This study's analysis of cardiac injury used only 2 of the 6 studies (n = 179). Population settings (inpatient vs outpatient) and disease criteria were vaguely defined.

Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples from the Hong Kong Cohort and Systematic Review and Meta-analysis

Ka Shing Cheung et al.

Gastroenterology

April 3, 2020

DOI: https://doi.org/10.1053/j.gastro.2020.03.065

Purpose	To summarize epidemiological characteristics of SARS-CoV-2 and the effectiveness of control measures to inform management guidelines.
Study design	Case series (n=59) and meta-analysis (n=4,243)
Level of evidence	Level 4 (case series), Level 2 (meta-analysis)
Methods	Case Series: Data were collected from a COVID-19 positive cohort of patients in Hong Kong (n=59; diagnosis from February 2 through Feb 29, 2020). Excluded patients had no virologic proof of SARS-CoV2 infection or asymptomatic SARS-CoV-2 infection. Meta-analysis: Sixty studies were included for a total of 4,243 COVID-19 patients. Fifty-three (88.3%) studies were from China.
Findings	Case series: Thirty-six (61.0%) patients did not have respiratory symptoms of cough or dyspnea on presentation. Among 15 (25.4%) patients who had gastrointestinal symptoms (vomiting: 1 [1.7%], diarrhea: 13 [22.0%], and abdominal pain/discomfort:7 [11.9%]), all had fever but 8 (53.5%) did not have cough or dyspnea. The proportion of patients with detectable stool viral RNA was higher among those with diarrhea than those without diarrhea (38.5% vs 8.7%; p=0.019). Of the 44 patients without gastrointestinal symptoms, 4 (9.1%) had positive stool viral RNA. There was a trend for higher stool viral load in patients with diarrhea (median: 5.1 [IQR: 4.8–5.6] vs 3.9 [IQR: 3.5–4.4] log10cpm; p=0.06). Meta-analysis: 68 of 138 patients (pooled prevalence: 48.1%, 95% CI: 38.3–57.9) tested positive for both respiratory and stool specimens ("R+S+") after hospitalization. Positive stool viral RNA samples persist despite negative respiratory samples. In nine studies with serial viral RNA test results of "R+S+" patients, 87 of 124 patients (pooled prevalence: 70.3%, 95% CI: 49.6–85.1) had persistent positive stool viral RNA despite negative respiratory samples ("R-S+"). Steroid use may be one factor that contributes to a longer fecal carry time, as stool viral clearance was longer in patients with steroid use compared to those without steroid use (20 vs. 11 days; p<0.001).
Clinical Implications	Fecal spread of virus may be possible even after negative respiratory test, potentially exacerbated by use of steroids. Healthcare workers should exercise caution when collecting fecal samples or performing endoscopic procedures in patients with recent history of COVID-19.
Limitations	A small number of patients were included in the case series. In the meta-analysis, the gastrointestinal symptoms may be under-reported in some of the studies, which may lead to a lower pooled prevalence rate. In addition, the majority of the studies were conducted on Chinese participants, therefore the study may not be generalizable to other ethnic groups. A positive result for RT-PCR may not indicate infectivity. Viral cultures, which were not performed in this study, are required to support active viral replication and therefore, contagion.

Angiotensin-converting enzyme 2 in severe acute respiratory syndrome coronavirus and SARS-CoV-2: A double-edged sword?

Tiantian Yan et al.

FASEB J

April 19, 2020

DOI: https://doi.org/10.1096/fj.202000782

Purpose	To evaluate the roles of angiotensin-converting enzyme 2 (ACE2) in the pathogenesis of SARS-CoV and SARS-CoV-2.
Study design	Systematic review
Level of evidence	Level 4
Methods	Literature review of in vitro and in vivo studies examining the role of ACE 2 in the pathogenesis of SARS-CoV and SARS-CoV-2 with relation to ACE2.
Findings	Expression of ACE2 in the lung is age, gender, and race-related: Asians and men express more ACE2 than other races and women of comparable age, respectively, and expression levels are negatively correlated with age. Abundant expression of ACE2 in other organ systems (heart, bile ducts, kidneys) may explain the multiorgan viral manifestations; however, it remains to be seen whether SARS-CoV-2 can replicate in these other areas after entry via ACE2. In vivo mice studies have shown SARS-CoV infected mice have reduced ACE2 expression, and that the absence of the protective role of ACE2 leads to dysfunctional renin-angiotensin system (RAS) and acute lung injury (ALI). ACE2 has been demonstrated protective in ALI/ARDS (acute respiratory distress syndrome) of patients infected by avian influenzas H5N1 and H7N9. Previous in vivo mice studies of these influenza strains demonstrated both angiotensin type 1 receptor (AT1R) blocker (ARB) and exogenous supplementation of recombinant human ACE2 (rhuACE2) significantly ameliorated ALI, improved lung function, and survival of mice. Evidence that ACEI or ARB may lead to increased ACE2 expression, and thus elevated virulence, is not fully consistent and differs by ARB and by organ.
Clinical Implications	Differential ACE2 expression may explain different symptom severity by age/sex/race. There is a paradox by which increased ACE2 expression may facilitate virus entry, but decreased ACE2 expression increases risk of ALI or ARDS. ACEI and ARB are recommended as important therapies in restoring RAS function and preventing ALI, an important consideration given the occurrence of ARDS in patients with COVID-19. Drug classes, doses, and different time courses of drug continuation are other necessary exposure parameters to consider.
Limitations	A large number of studies referenced in this review are in vivo mouse models, and thus the safety and efficacy of application of their scientific findings is uncertain.

Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia

Ning Tang et al.

Journal of Thrombosis and Haemostasis
February 19, 2020
DOI: https://doi.org/10.1111/jth.14768

Purpose	To characterize the coagulation features of patients with COVID-19 pneumonia.
Study design	Case series (n = 183)
Level of evidence	Level 4
Methods	183 consecutive patients with confirmed COVID-19 pneumonia admitted to Tongji Hospital of Huazhong University of Science and Technology in Wuhan (China) from January 1 to February 3, 2020 were enrolled in the study. Coagulation tests were collected on admission and during hospital stay. These included: prothrombin time (PT), activated partial thromboplastin time (APTT), antithrombin activity (AT), fibrinogen, fibrin degradation product (FDP), and D-dimer. Coagulation parameters were collected at three-day intervals from day 1 to day 14 and clinical outcomes were monitored until February 13, 2020.
Findings	During the course of analysis, 21 (11%) of 183 patients died. Non-survivors demonstrated significantly higher D-dimer and FDP levels and longer PT compared to survivors on admission. By late hospitalization, fibrinogen and antithrombin activity (AT) was significantly lower in non-survivors compared to survivors. Criteria for disseminated intravascular coagulation (DIC) was met by 71.4% of non-survivors (15/21) and only 0.6% of survivors (1/162). Levels of D-Dimer and FDP were elevated in all deaths.
Clinical Implications	Activation of coagulation system and abnormal coagulation parameters are associated with mortality in COVID-19 patients. These values could have prognostic value in the management of these patients. Protocols on early management to prevent progression to DIC (e.g., use of thromboprophylaxis) could be valuable to improve clinical outcomes and survival.
Limitations	This study had a relatively small sample size and was conducted at a single medical facility. 75% of patients had chronic conditions including cardiovascular and cerebrovascular disease. All patients received antiviral care after diagnosis.

Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19

Guoping Li et al.

Journal of Autoimmunity
April 13, 2020
DOI: https://doi.org/10.1016/j.jaut.2020.102463

Purpose	To determine whether patients with underlying diseases are more susceptible to SARS-CoV than the healthy population, and to examine the role and regulation of angiotensin-converting enzyme 2 (ACE2) during coronavirus infection.
Study design	Comparative analysis of ACE-2 expression in various conditions including SARS-CoV (n=623)
Level of evidence	Level 5
Methods	Gene expression data from samples of lung tissue, bronchoalveolar lavage samples, bronchial epithelial cells, small airway epithelial cells, and SARS infected cells were extracted from 6 known databases. Gene Set Enrichment Analysis (GSEA) was performed to analyze potential biological processes related to ACE2 in healthy people using the cluster Profiler package. Additionally, all proteins involved in the viral-related biological process and cytokine secretion-biological process were extracted from the gmt file and subjected to topological evaluation. The generated interaction network was screened by calculating Degree Centrality (DC) and hub proteins were determined with Cytoscape plugin CytoHubba.
Findings	This study showed that ACE2 was not substantially different between healthy populations and those with chronic airway disease, with the exception of elevated expression of ACE2 in cigarette smokers, which is divergent from current COVID-19 hypothesizes that those with certain chronic respiratory diseases may be more susceptible to the disease. Additionally, this study indicated high expression of ACE2 was related to elevated innate immune and adaptive immune responses as indicated by alterations in B cell regulation and cytokine secretion (such as IL-1, IL-10, IL-6, and IL-8). The author's posited that the immune system dysfunction involved in the high expression of ACE2 may be related to the symptoms of severe inflammatory response and potentially cytokine storm. Finally, this study suggested ADAM-17 as a potential target of treatment due to its role in decreasing the membrane bound form of ACE2 resulting in a downregulation of the immune system.
Clinical Implications	These findings provide a scaffolding for the pathogenesis of COVID-19, while at the same time indicate potential therapeutic strategies or targets for disruption of the severe inflammatory response potentially associated with SARS-CoV-2 infection.
Limitations	It is important to note that **all results in this study are based on previous data on SARS-CoV and were used as means of extrapolating SARS-CoV-2 pathogenetic characteristics.** Further examination of the proposed mechanisms and targets are necessary to determine their role in the current SARS-CoV-2 epidemic.

Complex immune dysregulation in COVID-19 patients with severe respiratory failure

Evangelos Giamarellos-Bourboulis et al.

Cell Host and Microbe

April 21, 2020

DOI: https://doi.org/10.1016/j.chom.2020.04.009

Purpose	To investigate whether a previously established classification of immune responses in critically ill, septic patients provides a pathogenetic scaffolding for patients with severe respiratory failure caused by SARS-CoV-2.
Study design	Retrospective Cohort (n=179)
Level of evidence	Level 3
Methods	Data from three patient cohorts were compared: 104 patients with sepsis caused by bacterial community-acquired pneumonia (CAP); 21 patients from the 2009 H1N1 influenza outbreak; and 54 patients with CAP caused by SARS-CoV-2. Each cohort was split into patients who developed severe respiratory failure (SRF) requiring mechanical breathing assistance and those who did not.
Findings	Three main features became evident in the comparison of sepsis caused by bacterial CAP vs SRF caused by SARS-CoV-2: 1) Lower sequential organ failure assessment (SOFA) and acute physiology and chronic health evaluation (APACHE) II in SARS-CoV-2 versus bacterial CAP; 2) Lower co-morbidities in COVID-19 patients vs. bacterial CAP (higher comorbidity index levels in COVID-19 patients with SRF than those without SRF were observed); 3) Significantly higher Glasgow Coma Scale scores of patients with COVID-19 (14.71) vs bacterial CAP (8.80), which may explain the rapid worsening following admission in COVID-19 patients. Patients with SRF displayed hyper-inflammatory responses with features of either immune dysregulation (driven by IL-6) or macrophage-activation syndrome (driven by IL-1β). Furthermore, the SRF observed with COVID-19 may be a result of immune dysregulation resulting in IL-6 induced depression of HLA-DR levels on CD14 monocytes, an inverse relationship between HLA-DR expression and IL-6, as well as restoration of HLA-DR expression with an increase in absolute lymphocyte count after Tocilizumab administration.
Clinical Implications	Immune dysregulation in severe COVID-19 is characterized by IL-6-mediated low HLA-DR expression and lymphopenia, over-production of cytokines and hyper-inflammation which may be alleviated by Tocilizumab administration.
Limitations	Despite the overall strength of this study, it lacks randomization of Tocilizimab administration. Further examination of the IL-6 inhibitor is necessary to determine not only its clinical efficacy, but overall safety in the COVID-19 patient population.

Acute kidney injury in SARS-CoV-2 infected patients

Vito Fanelli et al.

Critical Care
April 24, 2020
DOI: https://doi.org/10.1186/s13054-020-02872-z

Purpose	To discuss possible mechanisms of COVID-19 induced acute kidney injury (AKI) and strategies for risk stratification.
Study design	Systematic review
Level of evidence	Level 5
Methods	Literature review of COVID-19 patients with AKI
Findings	About 25% of patients with acute respiratory distress syndrome (ARDS) have AKI as reported by two studies in Wuhan, China and by Italian public health institution ISS (Istituto Superiore di Sanità). Age, severity of illness, presence of diabetes are risk factors for AKI development. Severity of AKI is associated with BMI and history of heart failure. ARDS patient with AKI are at high risk for severe outcomes and mortality. Possible mechanisms for AKI in COVID-19 patients include impairment of gas exchange, hemodynamic alterations, fluid overload, injury due to mechanic ventilation, secondary infection, harmful mediators released as a result of immune/inflammatory response, and ability of SARS-CoV-2 to use ACE-2 to enter kidney tubular cells. Classic measurement of AKI is using serum creatinine and urine output, but these do not catch early evidence of kidney damage. Tissue inhibitor of metalloproteinase 2 (TIMP-2) and Insulin-like growth factor binding protein (IGFBPY-7) and their product ([TIMP-2]*[IGFBP-7]) can be used as markers of acute tubular stress/damage and can show abnormalities sooner than serum creatinine and urine output.
Clinical Implications	**Early detection of AKI using novel biomarkers could lead to earlier nephrology intervention, closer monitoring of kidney function and optimization of volume and hemodynamic status**. The use of **iodine contrast and nephrotoxic drugs should be limited** in this population. Ultimately this could improve mortality in COVID-19 patients who are at high risk for developing AKI.
Limitations	Even though the exact mechanism of kidney involvement in COVID-19 infection is unclear, the level of ACE-2 expression in kidney tubules can be regarded as the risk factor for developing AKI in SARS-CoV-2 infected patients. However, authors did not cite any study reporting the expression and distribution of ACE2 in kidney cells.

Interferon-induced transmembrane protein-3 genetic variant rs12252-C is associated with disease severity in COVID-19.

Yonghong Zhang et al.

Journal of Infectious Diseases
April 29, 2020
DOI: https://doi.org/10.1093/infdis/jiaa224

Purpose	To determine if homozygosity of the C allele of rs12252 in the interferon-induced transmembrane protein 3 (IFITM3) is associated with more severe cases of COVID-19.
Study design	Case control (n= 80)
Level of evidence	Level 4
Methods	80 patients who were admitted to Beijing Youan Hospital due to COVID-19 from January to February had their genomes sequenced to see what they genotype was for IFITM3. Patients were split into two groups: mild disease (fever, respiratory symptoms, and pneumonia from imaging, n=56) and severe disease (symptoms listed previously and developed significant tachypnea, hypoxia, or respiratory, or another organ failure, n=24). Then, the cohort was genotyped by sequencing a 300bp locus spanning rs12252 to test whether the homozygous C-allele carriers associate with the severity of COVID-19.
Findings	The IFITM3 gene encodes an immune effector protein that is vital for viral restriction and inhibits membrane fusion. This variant has been associated with increased influenza severity.There was a significant difference between mild and severe cases adjusting for age on regression analysis, for homozygosity, and for C-allele (CC) with an odds ratio (OR) of 6.37 (P=0.0009). Therefore, this genotype is associated with more severe disease in an age dependent manner. Overall, 50.0% of the severe group and 28.6% of the mild group had the CC genotype. The frequency of the CC genotype in the Beijing population is 26.2%.
Clinical Implications	The study suggests a significant association between a minor IFITM3 allele (a single-nucleotide polymorphism, rs12252-C) with severe COVID-19 susceptibility. Homozygosity for the C allele of rs12252 in the IFITM3 can be identified in certain patients particularly those of Asian descent, who need early targeted intervention.
Limitations	There was a small sample size of people at one hospital. This mutation is more common in people of Asian descent so it may not be as significant for others. This was only a case-control study so further studies need to be done to confirm the genetic association with COVID-19 severity.

Alterations in Smell or Taste in Mildly Symptomatic Outpatients with SARS-CoV-2 Infection.

Giacomo Spinato et al.

JAMA

April 22, 2020

DOI: 10.1001/jama.2020.6771

Purpose	To evaluate the prevalence, intensity, and timing of anosmia in patients with SARS-CoV-2.
Study design	Cross-sectional survey (n = 202)
Level of evidence	Level 4
Methods	Adults (≥18 years) that tested positive for SARS-CoV-2 via RT-PCR and deemed suitable for home management were contacted 5-6 days after nasal swab testing. Patients underwent a phone interview utilizing the Acute Respiratory Tract Infection Questionnaire (ARTIQ) and asked whether they experienced a sudden onset of an altered sense of smell or taste within the 2 weeks preceding nasal swag testing. Symptoms were rated on the sino-nasal outcomes test 22 (SNOT-22), which grades symptom severity on a scale from 0-5 (0 represents no symptoms and 5 represents symptoms that are "as bad as it can be"). Prevalence was expressed as the percentage of total patients.
Findings	**An altered sense of taste or smell was reported in 130 of 202 patients (64.4%) that completed the telephone interview.** The median SNOT-22 score was 4, with 27 patients (13.4%) reporting 4 and 48 patients (23.8%) reporting 5. Symptom timeline presentation analysis revealed that an altered sense of smell or taste presented before other symptoms in 24 patients (11.9%); at the same time as other symptoms in 46 patients (22.8%); and after other symptoms in 54 patients (26.7%). **Gender comparison revealed that an altered sense of smell or taste was reported more frequently among the 105 women (72.4%) than among the 97 men (55.7%, P=0.02).**
Clinical Implications	This cross-sectional survey suggests that clinicians should consider isolating patients that present with new onset altered sense of taste or smell. Those are distinct symptoms of COVID-19, which do not appear in other respiratory illnesses.
Limitations	The study population was small and geographically limited to the Treviso Regional Hospital (Italy). Data was self-reported and lacked symptom evaluation on a longitudinal scale. The SNOT-22 test has been validated, but patients may have difficulty quantifying olfactory symptoms.

Inhibitors of the renin–angiotensin system: The potential role in the pathogenesis of COVID-19.

Ziyin Huang et al.

Cardiology Journal
April 14, 2020
DOI: 10.5603/CJ.a2020.0056

Purpose	To explore the role angiotensin converting enzyme 2 (ACE2) plays in the pathogenesis of COVID-19 and its implications for the use of ACE inhibitors (ACEIs) and angiotensin II (AngII) receptor blockers (ARBs) in COVID-19 patients.
Study design	Systematic review
Level of evidence	Level 5
Methods	Authors reviewed 24 research articles about the viral entry of SARS-CoV, dysregulation of ACE2 on lung injury and cardiotoxicity, and modeling of SARS-CoV2 viral entry. The authors utilized this data to propose a mechanism of cellular injury caused by SARS-CoV-2 and suggest a direction for therapeutic investigation.
Findings	ACE2 and its downstream products Ang(1-7) counter-regulate the pro-inflammatory, pro-fibrotic, pro-hyperresponsive ACE/AngII pathway. Higher ACE and AngII levels have been found to be poor prognostic factors for severe pneumonia. Experiments in ACE2 knockout (KO) mice had higher levels of lung damage than wild type (WT) mice when treated with acid. Further, injection of recombinant ACE2 rescued lung function in both ACE2 KO and controls. WT mice treated with the Spike-Fc protein from SARS-CoV were found to have diminished levels of ACE2 and higher levels of AngII. When treated with an AngII receptor type 1 (AT1R) inhibitor, severity of lung injury and pulmonary edema diminished in these mice. Models of SARS-CoV-2 indicate that it binds to ACE2 even more tightly than SARS-CoV, suggesting a similar mechanism of entry and downstream effects. ACEIs and ARBs increase ACE2 levels in chronically treated mice and rats. Those agents are well tolerated and widely used worldwide. Paradoxically, increased levels of ACE2 could provide more receptors to which SARS-CoV-2 could bind and enter cells.
Clinical Implications	**ACEIs and ARBs could help restore the balance between ACE/AngII and ACE2/Ang(1-7) and reducing the pulmonary inflammatory response in patients with COVID-19.** Prospective studies and randomized trials are needed to prove if it has beneficial clinical effects in patients with COVID-19.
Limitations	There have been minimal studies about SARS-CoV-2 and its effects on ACE2 and resultant tissue damage. Further, the studies in this review primarily used animal models, limiting the generalizability of the findings.

Guillain-Barre syndrome associated with SARS-CoV-2.

Gianpolo Toscano et al.

New England Journal of Medicine
April 17, 2020
DOI: 10.1056/NEJMc2009191

Purpose	To summarize the clinical course of five patients in northern Italy who contracted Guillain-Barre Syndrome (GBS) after the onset of COVID-19.
Study design	Case series
Level of evidence	Level 4
Methods	Five patients in northern Italy were found to have GBS symptoms after COVID-19 onset. Onset of GBS symptoms, signs and symptoms, CSF findings, antiganglioside antibodies, MRI results, treatment and outcomes at week 4 were recorded.
Findings	From February 28th to March 21st, 2020, 1000 to 1200 patients with COVID-19 were admitted to hospitals in northern Italy and five had GBS after COVID-19 onset. Four patients had positive nasopharyngeal swab at GBS onset, one had negative swab and bronchoalveolar lavage but positive serologic testing. Interval between onset of symptoms of COVID-19 and first symptom of GBS ranged from 5-10 days. Cerebrospinal fluid (CSF) in all patients was negative for SARS-CoV-2 via RT-PCR assay. All patients were given intravenous immune globulin (IVIG) and one had plasma exchange. After 4 weeks of treatment, two patients remained in the ICU, two were receiving physical therapy because of flaccid paraplegia and had minimal upper limb movement, and one was discharged and able to walk.
Clinical Implications	**Respiratory viruses penetrating the blood brain barrier is rare, but with increasing prevalence of COVID-19 cases worldwide, neurological disease is being observed in severe cases.** It is important to aware of neurological manifestations of SARS-CoV-2 infection and distinguish GBS with COVID-19 from critical illness neuropathy and myopathy which tends to occur later than GBS.
Limitations	Small sample size is the main limitation. Also, with the current setting of the study, it is not possible to determine whether severe deficits and axonal involvement are typical features of COVID-19 GBS. The authors were not able to differentiate the effect of reduced vital capacity due to neuromuscular failure from GBS. The authors did not correlate severity of COVID-19 symptoms with severity of GBS symptoms.

COVID-19 Coagulopathy in Caucasian patients.

Helen Fogarty et al.

British Journal of Haematology
April 24, 2020
DOI: https://doi.org/10.1111/bjh.16749

Purpose	To evaluate whether there is a correlation between coagulopathic features and COVID-19 disease severity in infected Caucasian patients.
Study design	Case Series (n = 83)
Level of evidence	Level 4
Methods	PCR-confirmed, COVID-19+ adult patients at St. James's Hospital (Dublin, Ireland) between March 13th and April 10th (2020) were included. Hospitalized study patients received standard of care along with weight and renally-appropriate doses of low molecular weight heparin (LMWH) thromboprophylaxis, unless contra-indicated. The hospital's electronic patient record was used to collect epidemiological, demographic, treatment and outcome data. The utility of D-dimer levels as a prognostic marker -when low molecular weight heparin (LMWH) thromboprophylaxis is utilized- was also examined.
Findings	Severe coagulopathy was positively correlated with disease severity in Caucasian individuals. Additionally, patients transferred to the ICU or those that died were more likely to have underlying co-morbidities. The progression to overt disseminated intravascular coagulation (DIC) in COVID-19 patients maintained on prophylactic dose LMWH was rare despite significantly increased D-dimers levels. The authors suggest that the COVID-19 induced diffuse bilateral pulmonary inflammation is a novel and distinct form of DIC, recently named pulmonary intravascular coagulopathy (PIC), due to its apparent pulmonary-specific nature.
Clinical Implications	Examination of individuals thrombotic risk may serve as a means of identifying those with increased mortality risk from COVID-19.
Limitations	There are several limitations associated with this study, including limited sample size and potential for selection bias. In order to fully corroborate the findings of this study, randomized controlled studies are necessary. Despite reports in the literature describing dissimilarities in thrombotic risk in individuals of different races and the authors' findings regarding the susceptibility of Caucasians to COVID-19 mortality, as it is entirely possible that the findings of this study may be explained by an alternative factor that the authors did not consider.

Elevated interleukin-6 and severe COVID-19: A meta-analysis.

Muhammad Aziz et al.

Journal of Medical Virology
April 28, 2020
DOI: https://doi.org/10.1002/jmv.25948

Purpose	To explore association between serum interleukin-6 (IL-6) levels and the severity of COVID-19 disease.
Study design	Meta-analysis (n = 1,426)
Level of evidence	Level 3
Methods	A total of 9 studies with 1426 patients were included in meta-analysis examining serum IL-6 levels in severe and non-severe COVID-19. For those studies reporting overall mortality in association with IL-6 levels (n=5), meta-regression was performed.
Findings	Mean serum IL-6 (across 7 studies reporting that data) was 56.8 pg/mL and 17.3 pg/mL for severe and non-severe COVID-19 groups, respectively (P<0.001). Subgroup analysis of studies with strict definition of respiratory distress to qualify as severe COVID-19 also demonstrated a significant elevation in IL-6 (26.5 pg/mL, P<0.001). Increasing mean IL-6 on admission was associated with increased likelihood of mortality (2.9%, P=0.03) among the 5 studies reporting that data. Based on this meta-analysis, serum IL-6 levels >55 pg/mL are considered high risk of severe COVID-19 and >80 pg/mL are at high risk of mortality. The latter cut-off value is based on one study reporting IL-6 for survivors/non-survivors.
Clinical Implications	**A vigorous IL-6 response in the circulation was detected during COVID-19 infection. Therefore, serum IL-6 levels may be used to risk stratify patients with lab confirmed infection early in the disease course.** IL-6 elevation represents a potential therapeutic target in COVID-19, and Tociluzumab (antibody against IL-6) is presently undergoing clinical trial.
Limitations	Observational study with significant heterogeneity of data (e.g., comorbidities, coinfection, follow-up, etc.). All studies included were conducted between January 1st and February 28th, 2020, meaning that availability of lab testing was variable as were lab reported normal ranges.

Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19)

Tao Guo et al.

JAMA Cardiology
March 27, 2020
DOI: 10.1001/jamacardio.2020.1017

Purpose	To evaluate association of underlying cardiovascular disease (CVD) and myocardial injury with fatal outcomes in patients with COVID-19.
Study design	Retrospective case series (n=187)
Level of evidence	Level 4
Methods	Retrospective single-institution case series in Wuhan, China, analyzing comorbidities, treatments, troponin T (TnT) levels in association with fatal outcomes. CVD included hypertension, coronary artery disease, and cardiomyopathy.
Findings	Of the 187 patients included in this study, 27.8% had myocardial injury resulting in cardiac dysfunction and arrhythmias. Mortality rate was greatest in those with underlying CVD and elevated TnT levels (69.4%) and underlying CVD with normal TnT levels (37.5%). The mortality rate in patients without underlying CVD and with elevated Tnt levels was (13.3%) and without (7.6%) TnT elevation exhibited lower mortality. TnT levels demonstrated a significant positive liner correlation with C-reactive protein ($p<0.001$) and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels ($p<0.001$). Plasma TnT ($p=0.001$) and NT-proBNP ($p<0.001$) levels increased significantly from admission in those patients who died. No significant changes were observed in those who were discharged following hospitalization. Patients with elevated TnT had a higher frequency of malignant arrythmia, and were more likely to received glucocorticoid therapy (71.2% vs. 51.1%) and mechanical ventilation (59.6% vs. 10.4%) than those with normal TnT levels. The use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)did not show a significant change in outcome.
Clinical Implications	Myocardial injury is significantly associated with fatal outcome of COVID-19, and **patients with underlying CVD +/- elevated TnT levels on admission have a poorer prognosis with COVID-19.**
Limitations	Retrospective nature with absence of echocardiogram and interleukin-6 data owing to the urgency and isolation of patients. Relatively small cohort (n=187) size. There is also limited data and follow-up to capture post-hospitalization cardiac complications and mortality. Those patients should be triage-tagged as necessary to assure more aggressive treatment strategies in an effort to increase the chance of survival.

SARS-CoV-2 and Viral Sepsis: Observations and Hypothesis

Hui Li et al.

Lancet
April 17, 2020
DOI: https://doi.org/10.1016/S0140-6736(20)30920-X

Purpose	To discuss SARS-CoV-2 pathogenesis and its relation to the development of sepsis.
Study design	Systematic review
Level of evidence	Level 5
Methods	30 studies were reviewed in order to meet the primary end point of this study: to put forward a hypothesis about the pathogenesis of SARS-CoV-2.
Findings	Based on the authors' review of published studies, including autopsy studies and basic research, the following hypothesis for pathogenesis of SARS-CoV-2 is proposed. Mild cases: Resident macrophages initiating lung inflammatory responses are able to contain the virus after SARS-CoV-2 infection; both innate and adaptive immune responses are efficiently established to curb the viral replication. Severe or critical cases: In response to the infection of SARS-CoV-2, alveolar macrophages or epithelial cells produce proinflammatory cytokines and chemokines. Monocytes and neutrophils are then chemotactic to the infection resulting in uncontrolled inflammation. There is substantial reduction and dysfunction of lymphocytes and the adaptive immune response cannot be effectively initiated. Additionally, there is a direct attack on other organs by disseminated SARS-CoV-2, immune pathogenesis caused by systemic cytokine storm, and microcirculation dysfunction that together leads to viral sepsis. Therefore, the process of viral sepsis is crucial to the disease mechanism of COVID-19.
Clinical Implications	This study investigates the viral infection immune response and pathogenesis of SARS-CoV-2 and describes the process of viral sepsis and abnormal coagulation in patients infected with SARS-CoV-2. A better understanding of the mechanism of viral sepsis in SARS-CoV-2 infection is warranted for exploring enhanced clinical care for patients infected with SARS-CoV-2.
Limitations	This study was limited by the lack of basic science research available exploring the kinetics of the cytokine storm and the immunologic response of the SARS -CoV-2 infection. Additionally, further research is needed to explore the effect of SARS-CoV-2 on coagulation, virus dissemination and its effect on the innate and adaptive immune response. The authors' hypothesize that damage to organs outside of the lungs is due to direct effects of the virus; however, as of yet, replicating virus has not been isolated from these extra-pulmonary tissues.

Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19.

Harmony Reynolds et al.

New England Journal of Medicine
May 1, 2020
DOI: 10.1056/NEJMoa2008975

Purpose	To explore the relationship between medications inhibiting the renin–angiotensin–aldosterone system (RAAS) pathway and severe COVID-19 illness.
Study design	Observational study (n=12,594)
Level of evidence	Level 4
Methods	Data on 12,594 patients with a COVID-19 test result in New York University (NYU) Langone Health system was extracted between March 1 and April 15, 2020. Positive cases were categorized as severe if resulting in ICU admission, mechanical ventilation, or death. Charted use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta-blockers, calcium-channel blockers, and thiazide diuretics were included. The primary goal was to rule out a difference (significance defined as 10%) in likelihood of positive or negative COVID-19 tests and likelihood of developing severe COVID-19 infection in the patients who took these medications.
Findings	A total of 5,894 patients were Covid-19 positive, among whom 1,002 had severe illness. There was no statistically significant difference in likelihood of testing positive among those taking a RAAS inhibiting medication compared to those unexposed. Of note, beta-blocker use was associated with a decreased likelihood of a positive test [912 (54.1%) vs 976 (57.9%) for a median difference of -3.8%], though this was not statistically relevant based on the study's criteria. Exposure to these medications did not have a statistically significant impact on severity of disease among Covid-19 infected patients. When a subgroup of patients with documented hypertension was analyzed, the use of calcium-channel blockers had an increased association with severe Covid-19 cases [253 (26.6%) vs 207 (22.3%) for a median difference of +4.4%], though this too was not statistically significant.
Clinical Implications	Given the importance of ACE2 in the mechanism of entry for SARS-CoV-2 and subsequent pathogenesis, there has been abundant speculation regarding the impact of RAAS inhibiting medications. **This study suggests these classes of medications (including ACE inhibitors and ARBs) do not play a statistically significant role in developing COVID-19 nor do they largely affect the severity of the disease.** The effect of beta-blockers and calcium-channel blockers noted may be due to ACE2 expression, dampening sympathetic effects, or residual confounding variables.
Limitations	It is important to emphasize the cut-off for statistically significant difference was defined as 10 percentage points, and thus there may be clinically relevant findings here otherwise excluded from this review. Additionally, medication adherence could not be assessed.

Dysregulation of immune response in patients with COVID-19 in Wuhan, China.

Chuan Qin et al.

Clinical Infectious Diseases
March 12, 2020
DOI: https://doi.org/10.1093/cid/ciaa248

Purpose	To analyze then compare the expression of infection-related biomarkers, inflammatory cytokines and lymphocyte subsets between confirmed cases of severe and non-severe COVID-19.
Study design	Case Control Study involving 452 patients with COVID-19 (n=286 severe and 168 non-severe)
Level of evidence	Level 4
Methods	Retrospective recruitment of 452 patients with RT-PCR confirmed COVID-19 admitted to Tongji Hospital in Wuhan, China, from January 10th to February 12th, 2020. The primary endpoint was the laboratory quantification of lymphocyte subsets, infection–related biomarkers, inflammatory cytokines, immunoglobulins and complement proteins.
Findings	Severe cases tend to have lower lymphocyte counts (0.8 vs 1.0.109; P<0.001), higher leukocyte counts (5.6 vs 4.9.109; P<0.001), and a higher neutrophil-lymphocyte ratio (5.5 vs 3.2; P<0.001). Additionally, these cases demonstrated lower percentages of monocytes (6.6 vs 8.4%; P<0.001), eosinophils (0.0 vs 0.2%; P<0.001), and basophils (0.1 vs 0.2%; P=0.015). Severe cases had elevated levels of infection-related biomarkers such as procalcitonin (0.1 vs 0.05 ng/mL; P<0.001), serum ferritin (800.4 vs 523.7 ng/mL; P<0.001), and C-reactive protein (57.9 vs 33.2 mg/L; P<0.001), and inflammatory cytokines including IL-2R (757.0 vs 663.5 U/mL; P=0.001), IL-6 (25.2 vs 13.3 pg/mL; P<0.001), IL-8 (18.4 vs 13.7 pg/mL; P<0.001), IL-10 (6.6 vs 5.0 pg/mL; P<0.001), and TNF-α (8.7 vs 8.4 pg/mL; P=0.037). Helper T cells and suppressor T cells in COVID-19 patients were below normal levels, and the decline in Th cells was more pronounced in severe cases (285.1 vs 420.5/μL; P=0.027). The percentage of naive Th cells increased (44.5 vs 35.0%; P=0.035) and memory Th cells decreased (55.5 vs 65.0%; P=0.035) in severe cases when compared with non-severe cases.
Clinical Implications	Severe COVID-19 is complicated by overwhelming immunological reactions. The virus might act on lymphocytes, especially T lymphocytes, suggesting that hyper-inflammatory responses might be responsible for lung pathology during COVID-19. Therefore, surveillance of neutrophil-lymphocyte-ratio (NLR) and lymphocyte subsets may helpful in the early screening, diagnosis. and treatment of COVID-19.
Limitations	This study was a retrospective, small-sample study of patients admitted to a single hospital, limiting its use to generally assess the temporal change of immune response after infection with COVID-19. Additionally, co-infection with bacteria or the presence of a superinfection might affect the results of the immune response in patients with COVID-19.

Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state.

Matt Arentz et al.

JAMA

March 19, 2020

DOI: 10.1001/jama.2020.4326

Purpose	To examine the clinical presentations and outcomes of patients with severe COVID-19 infections hospitalized in the ICU at Evergreen Hospital in Seattle, Washington.
Study design	Case series (n=21)
Level of evidence	Level 4
Methods	This case series included all patients hospitalized in the ICU at Evergreen Hospital who tested positive for SARS-CoV-2 via PCR of a nasopharyngeal swab between February 20, 2020 and March 5, 2020. Patient data, including age, gender, medical history, presenting symptoms, lab results, imaging, and hospital course were collected and analyzed. The primary endpoints were presenting symptoms and outcomes for each patient included in the study.
Findings	A total of 21 cases were included (mean age: 70 years, 52% male). On admission, 16 patients (76%) presented with shortness of breath, 11 patients (52%) presented with fever, and 10 patients (48%) presented with cough. An abnormal chest radiograph was observed in 20 patients (95%), while 7 patients (33%) had an elevated leukocyte count. All 15 patients (71%) requiring mechanical ventilation subsequently developed acute respiratory distress syndrome (ARDS). Cardiomyopathy developed in 7 patients (33%). By the end of the study (March 17, 2020), 14 patients (67%) lost their lives to COVID-19, 5 patients (24%) remained stable in the ICU, and 2 patients (9.5%) were discharged from the hospital.
Clinical Implications	This is the first study to examine both the initial presentation and outcomes of patients hospitalized in the ICU with COVID-19 in the United States. This study has reproduced similar results as studies in China that have detailed the severity of COVID-19 infection in hospitalized patients, including cardiomyopathy, ARDS, and death. Cardiac ultrasound can be used in the ICU to increase the effectiveness for the management of COVID-19 patients developing postviral cardiomyopathy. The high occurrence of cardiomyopathy is becoming more apparent in severely ill patients with COVID-19 infection in other studies.
Limitations	This study had a small sample size and was only conducted in one hospital in Washington, making it less applicable to patients in other geographical areas.

Renin-angiotensin-aldosterone system blockers and the risk of Covid-19.

Giuseppe Mancia et al.

New England Journal of Medicine
May 1, 2020
DOI: 10.1056/NEJMoa2006923

Purpose	To evaluate association of underlying cardiovascular disease (CVD) and myocardial injury with fatal outcomes in patients with COVID-19.
Study design	Population-based case-control study
Level of evidence	Level 4
Methods	A total of 6272 patients with confirmed SARS-CoV-2 in Italy between February 21 and March 11, 2020 were matched to 30,759 controls from the Regional Health Service according to sex, age, and region.
Findings	Use of angiotensin-converting–enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBS), other antihypertensive and non-antihypertensive drugs was more common in COVID-19 patients than controls. Among overall patients, there was no association with COVID-19 and the use of ACE inhibitors (adjusted odds ratio: 0.96) or ARBs (0.95). Among fatal case patients, there was no association with COVID-19 and the use of ACE inhibitors (adjusted odds ratio: 0.91) or ARBs (0.83). There was no association among case patients between the use of ACE inhibitors and ARBs with other variables including sex, age at diagnosis, and disease severity. Overall, the study population mean age was 68 years, and 37% were women.
Clinical Implications	**Patients with COVID-19 have a higher prevalence of cardiovascular disease as compared to controls, as evidenced by more frequent use of ACE inhibitors and ARBs. Use of ACE inhibitors and ARBs do not appear to affect the risk of COVID-19 and is unlikely to be harmful in patients with COVID-19.**
Limitations	Information on drug use and doses were limited to those captured in the National Health Service system and did not include those prescribed privately. Additionally, these results were obtained from a predominantly white population and cannot be generalized to other races.

A dynamic immune response shapes COVID-19 progression.

Eugenia Ziying Ong et al.

Cell Host and Microbe

April 30, 2020

DOI: https://doi.org/10.1016/j.chom.2020.03.021

Purpose	To evaluate the dynamic inflammatory and immune responses in the early phases of SARS-CoV-2 infection.
Study design	Case control study (n=3, COVID-19 patients; n=10, controls)
Level of evidence	Level 4
Methods	Authors collected blood samples from 3 COVID-19 patients (with different severities of disease), and 10 healthy volunteers. Case 1 samples were collected days 4-18 from illness onset; case 2 samples on days 6-19; and case 3 samples on days 9-12. Then, they profiled daily transcriptional change in immune genes (by multiplex gene expression analysis) and examined cytokine expression levels (primary outcomes). Nasal swabs were also taken at each time point in order to correlate the results with the presence of the SARS-CoV-2 by RT-PCR. Secondary outcomes were chest radiographs, disease duration and clinical features of disease course (descriptive, O2 stats, HR).
Findings	The study outlined the differences in host immune response to SARS-CoV-2 infections: Inflammatory gene expression (IL-2, IL-6, TNF, IFNα-1, and IFNα-13) were within the range of healthy controls or only peaked after the bottoming out of respiratory function. However, in one subject, IL-1 pathway genes were elevated above healthy controls prior to reaching the lowest point in respiratory function.Reduced T cell activation in the two mild cases may contribute to disease exacerbation disease or prolonged infection evident in expression of CD4, CD8A, and CD8B mRNA transcript levels comparable to the control individuals. All three patients showed the persistence of viral load for at least 3 weeks.
Clinical Implications	This study proposes that these IL-1 and related pro-inflammatory pathways may be prognostic indicators. Additionally, the T-cell activation pathway may serve as a target for COVID-19 treatment. Further investigation is necessary to corroborate these findings and proposed implications as well as to increase the understanding of the pathogenesis of COVID-19.
Limitations	The principal limitation of this study is its generalizability, evident in the number of cases (n=3). Additionally, selection bias is also a potentiality as the details of how the cases were selected, with exception of a positive test result, was not directly stated.

The pathogenesis and treatment of the `Cytokine Storm' in COVID-19.

Qing Ye et al.

Journal of Infection
April 10, 2020
DOI: https://doi.org/10.1016/j.jinf.2020.03.037

Purpose	To describe mechanisms by which human coronaviruses (HCoV) can induce cytokine storms, and potential treatments for this disease process.
Study design	Systematic review
Level of evidence	Level 5
Methods	The authors reviewed 15 studies on how the cytokine storm can affect SARS-CoV, SARS-CoV-2, and MERS-CoV.
Findings	This study first outlines how COVID-19 induces a cytokine storm in patients. At first, according to in vitro experiments, this may include delayed release of cytokines and chemokines in respiratory epithelial cells, dendritic cells (DCs), and macrophages. Later, cells released low levels of antiviral factors interferons (IFNs) and high levels of proinflammatory cytokines IL-1B, IL-6, TNF, and chemokines. Serum levels of IL-2R and IL-6 are positively correlated with the severity of COVID-19 in patients. In addition, acute respiratory distress syndrome (ARDS), the leading cause of death with patients infected with SARS-CoV, is linked with cytokine storm. The amount of cytokine increase is positively correlated with mortality rate. The pathogenesis of the cytokine storm can also explain signs of extrapulmonary organ failure.
Clinical Implications	Cytokine storm is a dangerous mechanism of how COVID-19 can increase mortality in the patients it infects, especially through routes such as ARDS. The authors believed that IFN- λ (early stages), corticosteroids, (later stages), IFN- αβ (later stages), ulinastatin, chloroquine, oxidized phospholipids (OxPL) inhibitors, sphingosine-1-phosphate receptor 1 (S1P1) agonists, mesenchymal stem cells, blood purification treatments, C-C chemokine receptor type 2 (CCR2) inhibitors, and TLR7 antagonists may help treat SARS-CoV-2. However, more studies need to be done to determine their effectiveness.
Limitations	With respect to some of the treatment options, there were only a few studies conducted on COVID-19 or similar diseases to test the efficacy of the treatment. Also, the reviewed studies were not high-quality.

Acute Hyperglycemic crises with coronavirus disease-19: Case reports.

Na-young Kim et al.

Diabetes and Metabolism Journal
April 23, 2020
DOI: https://doi.org/10.4093/dmj.2020.0091

Purpose	To describe two COVID-19 cases complicated by acute hyperglycemic events.
Study design	Case series (n = 2)
Level of evidence	Level 4
Methods	Authors described two COVID-19 patients admitted to Yeungnam University College of Medicine in Daegu, South Korea complicated by acute hyperglycemic crises - diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). Both cases were COVID-19 confirmed by RT-PCR and cross-checked by two independent physicians before inclusion in the study. Vital signs, imaging, blood chemistry, hemoglobin A1c (HbA1c), and arterial blood gas were analyzed for each of the cases. Serial chest radiographs were taken (at the day of admission and during hospitalization) to assess the severity of infection and predict the clinical outcome.
Findings	The study provides evidence of two individuals, with COVID-19 that progressed to an acute hyperglycemic event, either DKA or HHS. In both cases, diabetes was poorly controlled. This was highlighted by recent discontinuations of oral glucose management for health or monetary concerns. Chest radiographic findings included peri bronchial ground-glass opacities (GGOs) in both lungs (of the patient with DKA) and multifocal patchy consolidation at both lungs (of the patient with HHS). Both patients had adverse outcomes including dependence on ventilator support and death. This is the first case report of COVID-19 combined with DKA and HHS.
Clinical Implications	This study provides two instances of acute hyperglycemic events, DKA or HHS, in patients with poorly controlled diabetes. Their states may have been precipitated by COVID-19 suggesting that other factors (such as health or monetary concerns) could lead to diabetic crises in this patient subset.
Limitations	The principal limitation of this study is its generalizability, evident in the number of cases (n=2). Their states may have been precipitated by COVID-19 and results in catastrophic outcomes. Therefore, intensive monitoring and aggressive supportive care should be needed to inadequately controlled patients with diabetes and COVID-19 infection.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: A systematic review.

Riccardo Castagnoli et al.

JAMA Pediatrics
April 22, 2020
DOI: 10.1001/jamapediatrics.2020.1467

Purpose	To examine the presenting symptoms, potential treatment options, and prognosis of the SARS-CoV-2 infection in pediatric patients.
Study design	Systematic Review (n=1065)
Level of evidence	Level 5
Methods	Reviewed articles published between December 1, 2019 and March 3, 2020 that included participants aged 19 or younger with the SARS-CoV-2 infection. Study types included cross-sectional, case control, case series, case reports, bulletins, and national reports. Eighteen articles with a total of 1065 participants were ultimately included in this analysis. The primary endpoints included the age, presenting symptoms, diagnostic method, treatment, and prognosis of pediatric patients diagnosed with SARS-CoV-2 infection.
Findings	444 (44.5%) cases were present in children under 10 years old and 553 (55.5%) cases were present in children aged 10-19. The most common symptoms experienced by these pediatric patients were fever, cough, fatigue, nasal congestion, and rhinorrhea. Pediatric patients were found to have a good prognosis, as the majority of pediatric patients presented with mild symptoms, were treated with supportive measures, and fully recovered in 1-2 weeks. There was only one death reported in this study.
Clinical Implications	This is the first systematic review that has examined the effects of the SARS-CoV-2 virus in a pediatric population. This study demonstrates that children appear to have a better prognosis compared to adults and that these children make a full recovery with supportive measures and without the use of other medications. These case reports highlight the need for further well-designed studies focusing on the incidence of asymptomatic and symptomatic coronavirus infection in children.
Limitations	There is no indication of the proportion of symptomatic vs asymptomatic infection or the rates of infection in children. 17 (94.4%) articles included in this study came from China, except for one (5.6%) article that came from Singapore, so these results may not be generalizable to the United States pediatric population. Additionally, all 18 articles included in this study were observational studies, which makes it difficult to draw significant conclusions.

The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice

Linlin Bao et al.

Nature
February 28, 2020
DOI: https://doi.org/10.1038/s41586-020-2312-y

Purpose	To better understand the pathogenicity of SARS-CoV-2 by developing a relevant animal model of the human disease and to develop a platform to pre-clinically test potential therapeutics.
Study design	Basic science: animal experimentation
Level of evidence	N/A
Methods	Transgenic mice expressing human angiotensin-converting enzyme 2 (hACE2) were exposed to SARS-Cov-2. Results were compared to SARS-Cov-2 infected mice expressing endogenous murine ACE2 (wild type mice - WT) and mock-virus infected mice. Viral replication and pathologic changes were tracked in each group at regular intervals (1, 3, 5, and 7 days post inoculation, dpi). Viral loads were measured by qRT-PCR and autopsies were performed to study gross pathology, histopathology, and immunohistochemistry.
Findings	Only SARS-Cov-2 treated hACE2 transgenic mice showed signs of disease, including initial weight loss and a qRT-PCR detected viral load in lungs. **No SARS-CoV-2 viral mRNA was detected in other organs including myocardium, liver, spleen, kidney, cerebrum, intestine, and testis.** Of note, viral loads were detectable in the intestine at 1 dpi, which was presumed to be swallowed inoculation, as no viral particles could be isolated from the tissue. Grossly, SARS-Cov-2 infected hACE2 transgenic mice exhibited enlarged lungs with multifocal palpable pulmonary nodules by 5 dpi . **Histopathology in these mice demonstrated interstitial pneumonia with alveolar septa thickening, mild mucus production, and progressive inflammatory cell accumulation.** At day 5, a small amount of fibrous collagen development was noted in the alveolar interstitium, as well as denatured and detached bronchiolar epithelium. Perivascular inflammatory cell infiltration was observed around affected areas. Viral antigens were isolated both within affected as well as non-lesional areas of the lungs. Flourescent immunohistochemistry on mouse lung tissue provides evidence for co-localization of viral and hACE2 proteins, suggesting a similar method of cell entry for the virus.
Clinical Implications	Results from these animal models support the hypothesis that the ACE2 receptor plays an integral role for SARS-CoV-2 entry into human cells. This study illustrates that SARS-Cov-2 infection localizes to respiratory epithelium without additional organ involvement. This observation is dissimilar to SARS-CoV infection, which demonstrated extrapulmonary damage in similar studies.
Limitations	Though transgenic mice were used with appropriate controls, there may be limited translatability to humans. Tissue sampling in a more extensive time frame (greater than 7 days) would be beneficial to explore sub-acute and chronic effects of the virus.

Immune dysfunction leads to mortality and organ injury in patients with COVID-19 in China: insights from ERS-COVID-19 study

Dongze Li et al.

Signal Transduction and Targeted Therapy
May 5, 2020
DOI: https://doi.org/10.1038/s41392-020-0163-5

Purpose	To systematically report immunological characteristics and their relationship with organ injury and mortality in patients with COVID-19.
Study design	Multi-Center Retrospective Cohort Study (n=163)
Level of evidence	Level 3
Methods	Data was analyzed from the Early Risk Stratification of Novel Coronavirus Pneumonia (ERS-COVID-19) Study. A total of 163 patients were recruited between January 31st and February 18th, 2020 at West China Hospital of Sichuan University. The primary endpoint was all-cause death, and the secondary endpoint was Multi-Organ Dysfunction Syndrome (MODS) and severe pneumonia.
Findings	**Of 163 patients with COVID-19, 40.5% patients had severe pneumonia, 15.3% of patients had combined pneumonia with MODS, and 16.6% of patients died.** Of patients who died, 20.2%, 5.5%, and 3.7% of those patients developed to acute lung injury, myocardial injury, and kidney injury, respectively. Of the 163 patients, 69.3% had abnormal cellular immunity, and 35.6% had abnormal humoral immunity. Patients with abnormal cellular immunity had higher mortality, MODS, and severe pneumonia. Patients with abnormal humoral immunity only had higher mortality. Decreased lymphocyte count, increased C-reactive protein, and increased procalcitonin showed significant predictive power for in-hospital mortality, MODS, severe pneumonia, acute lung injury, myocardial injury and kidney injury in patients with COVID-19.
Clinical Implications	This study found that COVID-19 pneumonia manifests in immune dysfunction and that inflammatory markers and immunological-cellular subsets can be used to predict disease course and risk of mortality and injury. These findings can contribute to the development of immunotherapy to correct the immune changes that lead to poor prognosis in patients with COVID-19.
Limitations	This study did not include patients with chronic secondary medical conditions or simultaneous infection with other diseases for the purpose of limiting confounding. Additionally, more research is needed to clarify the immunophenotype of COVID-19 pneumonia.

D-Dimer Levels on Admission to Predict In-Hospital Mortality in Patients with Covid-19

Litao Zhang et al.

Journal of Thrombosis and Haemostasis
April 19, 2020
DOI: https://doi.org/10.1111/jth.14859

Purpose	To determine if elevated D-dimer levels on hospital admission could predict mortality in patients hospitalized with COVID-19 in Wuhan, China.
Study design	Retrospective case series (n=343)
Level of evidence	Level 4
Methods	All patients hospitalized in Wuhan Asia General Hospital who tested positive for the COVID-19 virus between January 12, 2020 and March 15, 2020 and had a D-dimer level on admission were eligible to participate. Data was collected and analyzed from the electronic medical record. The primary outcomes were the patient's D-dimer level on admission and whether the patient survived or passed away from the COVID-19 virus.
Findings	The median age of this study population was 62 years, 37.6% of patients were older than 65 years, and 50.3% of patients were female. The cutoff value for the D-dimer level to predict mortality in patients with COVID-19 was 2.0 mg/mL which resulted in a sensitivity of 92.3% and specificity of 83.3%. 276 (80.5%) patients in this study had a D-dimer level less than 2.0 mg/mL and 67 (19.5%) patients in this study had a D-dimer level greater than 2.0 mg/mL. **13 (3.8%) patients in this study died from COVID-19 and 12 (92.3%) of those patients had D-dimer levels above 2.0 mg/mL on admission.** Elevated D-dimer levels (above 2.0 mg/mL) were found to significantly predict mortality in hospitalized patients ($p<0.001$).
Clinical Implications	This study suggests that an elevated D-dimer level in patients diagnosed with COVID-19 can predict mortality in hospitalized patients, and patients with elevated D-dimer levels had higher rates of underlying disease. This gives physicians an objective lab value that is easily ordered on hospital admission and can guide medical decision making in terms of which patients may develop a more severe hospital course and are at a higher risk of death from the COVID-19 virus.
Limitations	This study was conducted at one hospital in China, making it less generalizable to patients in the United States. Additionally, this was a retrospective study that only included patients with a D-dimer level on admission, so there may have been a bias in patient selection based upon which patients had D-dimer levels initially ordered on admission. Finally, the patients in this study waited different amounts of time between the onset of COVID-19 symptoms and presenting to the hospital, which may have influenced their D-dimer levels.

Endothelial cell infection and endotheliitis in COVID-19

Zsuzsanna Varga et al.

The Lancet

April 20, 2020

DOI: https://doi.org/10.1016/S0140-6736(20)30937-5

Purpose	To present evidence of viral endothelial cell involvement in a series of patients with COVID-19.
Study design	Case Series (n=3)
Level of evidence	Level 4
Methods	SARS-CoV-2 disproportionately infects patients with underlying cardiovascular disease via pathogenic mechanisms that are incompletely understood. Three COVID-19 patients, with underlying cardiovascular comorbidities who experienced respiratory failure, underwent pathological sampling, across multiple organs, for histologic and immunohistochemical evaluation.
Findings	**Samples demonstrated evidence of direct viral infection of the endothelial cells and diffuse endothelial inflammation.** SARS-CoV-2 facilitates endotheliitis across several organs, via direct viral infection and the host inflammatory response, possibly resulting in the induction of apoptosis and pyroptosis.
Clinical Implications	This case-series study had a small sample size (n=3) that lacked explicit inclusion and exclusion criteria. There was no control group. Additionally, the study is prone to selection bias by the researchers.
Limitations	This case-series provides support for the rationale of concomitant use of therapies that promote endothelial stabilization in addition to anti-viral, anti-inflammatory, and ACE inhibitor therapies. This strategy may be of particular use for patients with underlying endothelial dysfunction. As a correspondence, this article has not been peer-reviewed.

Virological assessment of hospitalized patients with COVID-2019

Roman Wölfel et al.

Nature

April 1, 2020

DOI: https://doi.org/10.1038/s41586-020-2196-x

Purpose	To better understand replication sites, contagion, and pathogenicity of SARS-CoV-2.
Study design	Basic science: virologic analysis
Level of evidence	N/A
Methods	Virologic analysis of nine COVID-19 cases, confirmed by oro/nasopharyngeal RT-PCR specimen swabs, from a single German hospital center were performed. All oro/nasopharyngeal, sputum, urine, stool, and serum samples were analyzed using RT-PCR and virus isolation procedures by two independent laboratories. All nine patients were confirmed to be negative for confounding viral co-infections, such as other human coronavirus and influenza.
Findings	**Distinct virus populations (separate genotypes) were identified in the throat and lung of one patient, proving independent replication sites rather than passive shedding from one site to another.** While infectious virus was isolated from pharyngeal and sputum samples, no virus was detected in any blood or urine samples. Some stool samples contained subgenomic mRNA, a marker of actively infected cells; infectious virus was not isolated via culture. Viral RNA in sputum samples outlasted the end of clinical symptoms. **Two of the patients in this study who demonstrated more predominant lower respiratory symptoms had late sputum viral load peak (around day 10 or 11) compared to other patients.** Seroconversion occurred after 7 days in 50% of patients and by day 14 in all patients. Immunoanalysis demonstrated antibody cross-reactivity against four endemic human coronaviruses in several patients.
Clinical Implications	Compared to the SARS epidemic, RNA concentrations in oro/nasopharyngeal sampling peak earlier (before day 5) and were observed to be more than 1,000 times higher among COVID-19 patients. This suggests an explanation for the high transmission rate of SARS-CoV-2 and thus early testing (e.g. during the prodromal phase) may be efficacious. Gastrointestinal involvement is still unclear and viral presence can be explained as either swallowed sputum excretion or true GI site replication rendered noninfectious by the gut environment. Finally, the study suggests low concern for infectivity beyond day 10 of symptoms and when a sputum sample contains less than 100,000 viral RNA copies/mL.
Limitations	This article was made available as an unedited manuscript. The study had a small sample size of 9 patients - all mild cases and previously healthy individuals - thus limiting its generalizability.

Pulmonary embolism in COVID-19 patients: Awareness of an increased prevalence.

Julien Poissy et al.

Circulation
April 24, 2020
DOI: https://doi.org/10.1161/CIRCULATIONAHA.120.047430

Purpose	To determine if there is an increased prevalence of the development of a pulmonary embolism in patients hospitalized in the ICU with pneumonia caused by the COVID-19 virus at Lille University Hospital in France.
Study design	Case series (n=107)
Level of evidence	Level 4
Methods	All patients with confirmed COVID-19 pneumonia hospitalized in the ICU at Lille University Hospital from February 27th, 2020 through March 31st, 2020 were examined for the development of a pulmonary embolism (PE) by computed tomography pulmonary angiography (CTPA) (n=107). Additionally, chart reviews were conducted to determine the number of patients who developed a PE while hospitalized in the ICU for any indication from February 27th, 2019 through March 31st, 2019 (n=196), and the number of patients who developed a PE while hospitalized in the ICU for confirmed influenza pneumonia from January 1st, 2019 through December 31st, 2019 (n=40).
Findings	**22 patients out of 107 with COVID-19 pneumonia (20.6%) had a CTPA-confirmed diagnosis of PE** (a median of 6 days after admission) during their ICU stay between February 27th, 2020 and March 31st, 2020. 20 patients out of 22 with COVID-19 pneumonia who developed a PE (90.9%) were taking prophylactic antithrombotic treatment with either unfractionated heparin or low-molecular-weight heparin. In contrast, only 12 patients out of 196 patients (6.1%) hospitalized in ICU during the same time interval in 2019 developed a PE during their ICU stay. 3 patients out of 40 with influenza pneumonia (7.5%) developed a PE during their ICU stay between January 1st, 2019 and December 31st, 2019.
Clinical Implications	This study suggests that the development of a PE is more common in patients hospitalized in the ICU with pneumonia caused by COVID-19, as compared to patients hospitalized in the ICU with other illnesses, including pneumonia caused by influenza (20.6% vs 6.1%). This suggests that thrombotic complications could be a hallmark feature of COVID-19. Furthermore, 90.9% of the patients who developed a PE in this study were on anticoagulation, so more research is needed to determine why prophylactic anticoagulation is not sufficient in preventing the development of a PE and what is the optimal anticoagulation strategy.
Limitations	This study was conducted at one hospital in France, making it less generalizable to patients in the United States. Additionally, its small sample size warrants further investigation.

Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia

Guangchang Pei et al.

Journal of the American Society of Nephrology
April 28, 2020
DOI: https://doi.org/10.1681/ASN.2020030276

Purpose	To investigate clinical renal findings of patients with COVID-19.
Study design	Case Series (n=333)
Level of evidence	Level 4
Methods	Demographic, clinical, laboratory, radiologic and treatment information was collected via retrospective chart review of 333 patients hospitalized for COVID-19, at a single-center in China, who had a urine dipstick test the morning following admission or evidence of acute kidney injury (AKI) on admission and were serially monitored throughout their admission. Patients were screened for AKI using the Kidney Disease: Improving Global Outcomes (KDIGO) definition.
Findings	251 of the 333 (75.4%) COVID-19 patients had renal involvement on admission. 219 of 333 (65.8%) had laboratory evidence of proteinuria. 139 of 333 (41.7%) had laboratory evidence of hematuria. **A greater incidence of proteinuria and hematuria was observed in patients with more severe COVID-19 illness.** Also, COVID-19 illness severity was identified as an independent negative prognostic indicator for renal complications. The incidence of AKI in the overall cohort, utilizing the KIDGO expanded criteria, was 7.5%, which is lower compared to other critical illnesses. 16 of 35 (45.7%) achieved complete renal remission by 3 weeks, suggesting a good short-term prognosis.
Clinical Implications	The prevalence of proteinuria and hematuria in COVID-19 patients demonstrates renal involvement. However, the overall incidence of AKI is lower when compared to patients with other critical illnesses. Evidence supports that the etiology of AKI in COVID-19 patients is intrinsic in nature. Lastly, COVID-19 patients with early AKI were likely to achieve full renal recovery; however, renal complications in COVID-19 still remain to be associated with poor mortality.
Limitations	Retrospective chart review is prone to encounter missing data. The observation period was too short to evaluate and predict mortality risk and outcomes of renal damage in the long term.

Viral and host factors related to the clinical outcome of COVID-19

Xiaonon Zhang et al.

Nature

May 20, 2020

DOI: https://doi.org/10.1038/s41586-020-2355-0

Purpose	To analyze strains of COVID-19 and to identify inflammatory biomarkers and their association with disease severity.
Study design	Cohort (n=326)
Level of evidence	Level 4
Methods	The study population consists of 326 COVID-19 patients in Shanghai from January 20 to February 25, 2020. Patients were grouped based upon severity of disease: asymptomatic, mild, severe, and critical, with severe exhibiting 1 or more of the following criteria: respiratory rate ≥ 30 per minute, O2 saturation ≤ 93%, PaO2/FIO2 ≤ 300mmHg, or pulmonary imaging with lesion increase by 50%+ within 48 hours. Sequencing data from 112 patients was collected from sputum via an oropharyngeal swab and analyzed for nucleotide variation. Sequences around nucleotide number (nt) 8,782 and nt28,144 were compared with the closely related bat coronavirus Bat-SARS-CoV-RaTG13. Phylogeny analysis was also conducted.
Findings	Two major clades were identified. Clade I subclades: ORF3a: p.251G>V (subclade V), S: p.614D>G (subclade G). The 6 cases with a clear interaction with the Huanan Seafood Wholesale Market (HSWM), theorized to be the source of the COVID-19 outbreak, were in Clade I. Clades II subclades: ORF8: p.84L>S (28144T>C) and ORF1ab: p.2839S (8782C>T). 3 cases without contact history to HSWM were in Clade II. Non-HSWM sequences were identical to Bat-SARS-CoV-RaTG13 at the sequences around nt8,782 and nt28,144. **There were no significant differences in pathogenicity between the 2 clades**. COVID-19 patients, regardless of disease severity, demonstrated lymphocytopenia. Severe and critical patients exhibited progressive lymphocytopenia. CD3+ T cells were the most affected, followed by CD8+. The level of CD19+ B cells were lower in critical cases only. CD3+ T cells demonstrated gradual decline. Age, number of lymphocytes at admission, gender, and comorbidities were associated with worse disease severity, although the comorbidities group was older. Age and lymphocytopenia were independently associated with worse disease severity. IL-6 and IL-8 were increased. The critical patient group comprised a greater percentage of the highest IL-6 and IL-8 levels measured.
Clinical Implications	Lymphocytopenia and inflammatory markers may be targets for future treatment trials. Limited variation between the 2 clades suggest a stable virus, which will prove beneficial in the development of targeted treatments and vaccines.
Limitations	The study contained a limited number of participants (n=326) from Shanghai, which may limit its application to other populations, races, or ethnicities.

High Fluorescent Lymphocytes Are Increased in COVID-19 Patients

Zhao Wang et al.

British Jounral of Haemotology
May 20, 2020
DOI: https://doi.org/10.1111/bjh.16867

Purpose	To assess the association between high fluorescent lymphocytes and severity of COVID-19.
Study design	Retrospective analysis (n=111)
Level of evidence	Level 4
Methods	High fluorescent lymphocytes have been associated with activated B cells and plasma cells, indicating an immune response. This study retrospectively analyzed complete blood count results of COVID-19 cases admitted to Wuhan Union Hospital in China from January 29 to March 8, 2020. Cases were classified as mild or severe, with severe exhibiting 1 or more of the following criteria: respiratory rate ≥ 30 per minute, O2 saturation ≤ 93%, PaO2/FIO2 ≤ 300, or pulmonary imaging with lesion increase by 50%+ in 24-48 hours. Complete blood count results were performed with the Sysmex XE-5000 automated cytometry. Healthy controls were enrolled in November 2019 before the COVID-19 outbreak. The primary endpoint of the trial was between high fluorescent lymphocytes versus severity of COVID-19.
Findings	The median age was 48.6 years. Patients in the severe group were older than those in the mild group (median age: 66 years vs. 42 years, p<0.001). Of the 19 COVID-19 patients (17.1%) in the severe group, 5 died. **Lymphocytes were decreased in mild and severe COVID-19 patients versus healthy controls** (Mild: 1400 x 106/L, severe: 820 x 106/L, healthy: 2100 x 106/L; p<0.0001). Lymphocytes were more decreased in the severe COVID-19 patients versus the mild (p=0.080). High fluorescent lymphocytes (HFL) were higher in mild and severe COVID-19 patients versus healthy controls (Mild: 11.8 x 106/L, severe: 20.4 x 106/L, healthy: 0.0 x 106/L; p<0.0001). 2 patients with the highest ratio of HFL to lymphocytes died.
Clinical Implications	While young, middle aged, and older adults are affected, older patients may be at heightened risk for severe disease. As such, older individuals should more strictly adhere to social distancing guidelines. Decreased lymphocytes and increased high fluorescent lymphocytes may be a potential target in future treatment trials.
Limitations	This study comprises a small population (n=111), which may limit its broader application. This study also was conducted at 1 hospital in China, which may limit its broader application to other races and ethnicities.

Postmortem Examination of Patients With COVID-19

Tina Schaller et al.

Journal of the American Medical Association
May 21, 2020
DOI: https://doi.org/10.1001/jama.2020.8907

Purpose	To examine COVID-19 patients postmortem to determine specific factors contributing to death.
Study design	Cohort (n=10)
Level of evidence	Level 4
Methods	Postmortem examinations were conducted according to published best practice in 10 patients (3 females, 7 males; median age 79 years, range 64-90) with confirmed SARS-CoV-2 who died at the University Medical Center Augsburg in Germany between April 4 and April 19, 2020.
Findings	The median duration from hospital admission to death was 7.5 days (1-26 days). SARS-CoV-2 was detected in respiratory tracts and pleural effusions of all patients at autopsy. The patients had a median of 4 comorbidities (0-6); cardiovascular comorbidities were most frequently reported. 2 patients (20%) had preexisting structural lung damage (emphysema). Chest x-ray demonstrated 9 patients (90%) with ground glass opacities in the middle and lower lung fields. 6 patients (60%) did not receive invasive ventilation and demonstrated disseminated diffuse alveolar damage (DAD), particularly in the middle and lower lung fields. Exudative early-phase acute DAD presented with hyaline membrane, intra-alveolar edema, and thickened alveolar septa with perivascular lymphocyte-plasmocytic infiltration. Organizing DAD presented as fibroblastic proliferation, partial fibrosis, pneumocyte hyperplasia, interstitial thickening, collapsed alveoli, patchy lymphocyte infiltration, reactive osseous, and squamous metaplasia. 1 patient (10%) demonstrated full fibrosis with total destruction of pulmonary parenchyma. 5 patients (50%) demonstrated minor neutrophil infiltration, indicating secondary infection. 4 patients (40%) exhibited mild lymphocytic myocarditis and 2 patients (20%) epicarditis. Periportal lymphoplasmacellular infiltration and fibrosis was found in liver histology.
Clinical Implications	Acute and organizing diffuse DAD and viral RNA persistence represented the leading cause of death in patients with and without invasive ventilation. While there is no specific treatment for DAD, supportive measures such as low tidal volume ventilation have been used. However, the use of low tidal volume has failed to achieve adequate oxygenation in SARS-CoV-2 patients. Future trials should examine the utility of low tidal volume versus prone ventilation. In addition, future trials should examine whether cardiac inflammation represented systemic inflammation or early myocarditis
Limitations	The study contained a limited number of participants (n=10), which may limit its application to the broader SARS-CoV-2 patient population. The study comprised of a small, older (median age 79 years, range 64-90) cohort from Germany, which may limit its reproducibility in other races, ethnicities, and age groups.

Covid-19 in Critically Ill Patients in the Seattle Region — Case Series

Pavan K. Bhatraju et al.

New England Journal of Medicine
March 30, 2020
DOI: 10.1056/NEJMoa2004500

Purpose	To evaluate the outcomes of critically ill patients with confirmed COVID-19 infections in the Seattle region.
Study design	Retrospective Case Review (n=24)
Level of evidence	Level 4
Methods	The medical records of 24 critically ill patients with COVID-19 infections, from nine hospitals in Seattle, Washington, were collected between February 24 and March 9, 2020. Infections were confirmed via RT-PCR laboratory testing. Researchers analyzed patient demographics, clinical symptoms, signs of presentation, and laboratory and imaging results during ICU stays. Each patient was followed up by the hospital for 14 days. Data reported tracks each patient through March 23, 2020.
Findings	The mean (±SD) age of the patients was 64±18 years, and 63% were men. Sixteen patients (67%) were admitted from home, and 6 patients (25%) were admitted from a skilled nursing facility. Shortness of breath and cough were the most common symptoms present upon admission to the hospital, each occurring in 21 patients (88%). Documented fever was only present in 12 patients (50%) upon presentation at the hospital. The majority of the patients had chronic medical conditions including diabetes mellitus (58%), chronic kidney disease (21%), and asthma (14%). Eight patients (33%) had more than one coexisting condition. None of the patients were co-infected with other viruses. With respect to patient care, eighteen patients (75%) received invasive mechanical ventilation. By the end of the follow up on March 23, out of 24 patients, 12 (50%) died, 4 (17%) were discharged from the ICU but stayed at the hospital, 3 (13%) continued to receive mechanical ventilation in the ICU, and 5 (21%) were discharged from the hospital.
Clinical Implications	These findings indicate that patients with coexisting conditions are at a higher risk for severe disease, and face poorer outcomes following ICU admission.
Limitations	The small sample size limits the external validity of these results. Since only seven patients (29%) stayed at the hospital throughout the duration of the study period, there were limited parameters for determining the clinical outcomes of critically ill patients with COVID-19. Further studies are needed to assess the impact that COVID-19 has on medically vulnerable ICU patients who may have multiple co-morbid conditions, as optimally treating this patient population will be crucial for hospitals across America as the pandemic continues.

COVID-19: Unanswered questions on immune response and pathogenesis

Enrico Maggi et al.

The Journal of Allergy and Clinical Immunology
May 8, 2020
DOI: 10.1016/j.jaci.2020.05.001

Purpose	To discuss known and unknown variables in the immunopathogenesis of SARS-CoV-2.
Study design	Literature Review
Level of evidence	5
Methods	Reviewed literature of the immunopathogenesis in SARS-CoV-2 patients.
Findings	Immune system responses to diseases may vary greatly, but patterns emerge in patient data that may indicate future treatment targets or concerns. SARS-CoV-2 patient reports suggest that a reduced number of natural killer cells correlate with increased disease severity. The virus's escape from the immune response is relatively unknown, although it is hypothesized to relate to suppressed Type 1 interferon, early inhibition of the innate response, direct infection of T-cells, or infected antigen presenting cells. Furthermore, there are questions whether there are sufficient neutralizing antibodies (NAbs) created after infection to establish protective immunity. Antibodies that target the receptor binding domain on the S protein are considered the main target for NAbs. However, a recent study of 26 patients who recovered from SARS-CoV-2 found that only 3 patients developed antibodies to the receptor binding domain (RBD) of the S protein. Further study needs to be done to determine what antibodies lead to immunity or if they provide any protection at all.
Clinical Implications	SARS-CoV-2 infection is associated to a complex dysregulated immune response. Current patients should have their cytokines closely monitored and potentially blocked using approved therapies such as Anakira, Toculiziumab, TNF-alpha inhibitors, and JAK inhibitors. Not enough is known about antibodies to claim if they recognize SARS-CoV-2 antigenic sitesand we urgently need the related information to prevent recurrent infections of SARS-CoV-2.
Limitations	A large timeframe between infection and the onset of symptoms limits the study of immune response. The lack of information on asymptomatic individuals and regulatory mechanisms during infection limit the knowledge of disease clearance.

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review

Riccardo Castagnoli et al.

JAMA Pediatrics
April 22, 2020
DOI: 10.1001/jamapediatrics.2020.1467

Purpose	To appraise pediatric cases of SARS-CoV-2 infection for evaluation of clinical features, prognosis, effective diagnostic measures and medical management strategies.
Study design	Systematic Review
Level of evidence	Level 1
Methods	A systematic review was performed on studies published in February and March of 2020 on SARS-CoV-2 infection in patients 0-19 years of age. Retrospective studies of confirmed pediatric cases that assessed the clinical symptoms, prognosis, mechanisms of infection, diagnostic and therapeutic strategies were included. Eighteen articles met the inclusion criteria and were evaluated. Seventeen studies were conducted in China and one was conducted in Singapore. The eighteen studies included data from a total of 1065 pediatric patients.
Findings	Of the cases reviewed, 444 were cases in children under 10 years of age, and 553 were children age 10-19. The most frequent clinical manifestations of pediatric SARS-CoV-2 infection were fever, dry cough, fatigue, nasal congestion and rhinorrhea. Symptoms of nausea, vomiting and diarrhea were also noted. Only one pediatric case presented with severe disease complicated by shock and kidney failure and was successfully treated with intensive care. Radiologic findings were characterized by bronchial thickening, ground-glass opacities and inflammatory lung lesions. **Prognosis of pediatric SARS-CoV-2 infection is good, as patients recovered within 1-2 weeks of disease onset and only one death was reported in the study groups.** Despite limited therapeutic data, patients with mild disease were successfully treated with supportive therapy and, except the single case of severe pneumonia, none of the included patients required oxygen or assisted ventilation. These data indicate that unlike adults, children do not appear to be at higher risk of severe illness based on age and sex, though the role of comorbidities has yet to be evaluated.
Clinical Implications	This review indicates that pediatric patients acquire SARS-CoV-2 infection from close contacts and seem to experience less severe SARS-CoV-2 infection than their adult counterparts with mild symptoms, good prognosis and recovery within 1-2 weeks of disease onset. However, there are still knowledge gaps concerning the impact of comorbidities on disease severity and the therapeutic management of pediatric SARS-CoV-2.
Limitations	Research was conducted over a three-month period, limiting both the quantity and quality of data. Additionally, seventeen of the eighteen included studies were based in China, which may limit the external validity of the results. Third, the studies did not include data on viral burden, so correlations between viral burden and clinical symptoms could not be made. Lastly, all of the studies included were observational studies, resulting in lower quality evidence.

SARS-CoV-2 Infection in Children

Xiaoxia Lu et al.

New England Journal of Medicine
April 23, 2020
DOI: 10.1056/NEJMc2005073

Purpose	To describe the various presentations of SARS-CoV-2 infection in children.
Study design	Case Series (n=1391)
Level of evidence	Level 4
Methods	Symptomatic and asymptomatic children who had known contact with confirmed or suspected SARS-CoV-2 infected persons were tested for SARS-CoV-2 infection at the Wuhan Children's Hospital in Wuhan, China. All children were tested with established methods between January 28 and February 26, 2020, and outcomes were monitored until March 8, 2020.
Findings	A total of 1391 children were tested, and 171 (12.3%) tested positive. Ages of infected children ranged from 1 day to 15 years, with a median age of 6.7 years. Of the children who tested positive, 27 (15.8%) were asymptomatic without radiologic features of pneumonia, 12 (7.0%) were asymptomatic with radiologic features of pneumonia, 3 (1.8%) required mechanical ventilation and 1 death occurred (0.5%). All 3 children who required mechanical ventilation and the child who died had co-existing conditions. The most common symptoms were cough, affecting 83 children (48.5%), pharyngeal erythema, affecting 79 (46.2%), tachycardia, affecting 72 (42.1%), and fever, affecting 71 (41.5%). Ground-glass opacity was the most common radiologic finding, occurring in 56 children (32.7%).
Clinical Implications	**As a whole, these children had a milder disease course than that of adults during the same timeframe in Wuhan, China, but severe adverse events did occur.** Many infected children were asymptomatic, but the transmission potential in this situation is still unclear. It was not uncommon for children to be asymptomatic but have radiologic features of pneumonia, suggesting that asymptomatic carriage may have negative consequences beyond potentially infecting others.
Limitations	This is a Letter to the Editor and has not been peer-reviewed. Outcome monitoring may have been of insufficient length to detect all symptoms or adverse events, as 21 children were still hospitalized in stable condition at the conclusion of the study. Additionally, since the findings are limited to one hospital in one country, they may not be broadly applicable to children throughout the world. The large age range also makes it difficult to generalize these findings to any one age cohort.

Multisystem Inflammatory Syndrome in U.S. Children and Adolescents

Leora R. Feldstein et al.

New England Journal of Medicine
June 29, 2020
DOI: 10.1056/NEJMoa2021680

Purpose	To better understand MIS-C's (multisystem inflammatory syndrome in children) epidemiology, clinical course, and temporal association with COVID-19.
Study design	Case series (n=186) and retrospective chart review
Level of evidence	Level 4
Methods	The researchers surveilled 53 pediatric health centers throughout the U.S. from March 15 to May 20, 2020. The case definition of MIS-C contained 6 conditions: serious illness leading to hospitalization, an age of less than 21 years, report of fever for at least 24 hours, laboratory evidence of inflammation, multisystem organ involvement, and lab-confirmed SARS-CoV-2 infection (either via reverse-transcriptase polymerase chain reaction [RT-PCR], an antibody test, or a link with a Covid-19 patient in the past month).
Findings	The researchers reported on 186 MIS-C patients in 26 U.S. states over a 2-month period. The median age of these patients was 8.3 years, 62% were male, 73% had been previously healthy, and 70% were confirmed for SARS-CoV-2 via RT-PCR or antibody testing. It was found that 71% of patients had at least 4 organ systems involved. The most commonly involved organ systems were the gastrointestinal system (92%), cardiovascular (80%), hematologic (76%), mucocutaneous (74%), and respiratory (70%). The median hospitalization duration was 7 days, 80% of patients had intensive care, 20% underwent mechanical ventilation, 8% had coronary-artery aneurysms, and 4 patients (2 of whom had no diagnosed underlying conditions) died. 92% of patients had indications of inflammation in at least 4 biomarkers. Additionally, 40% of patients had clinical features mimicking Kawasaki's disease, which is an acute inflammatory syndrome, occasionally causing coronary-artery aneurysms. Both diseases involve the cardiovascular system and coronary artery aneurysms, but MIS-C had more children present with cardiovascular shock leading to vasopressor or inotropic support (50% compared to 5%). Only 8% of this study's patients had coronary artery aneurysms whereas 25% of patients with Kawasaki's disease are known to have coronary-artery aneurysms within 21 days after disease onset.
Clinical Implications	Children with COVID-19 who have associated MIS-C may develop debilitating illnesses, even without prior underlying conditions. Since MIS-C is often likened to Kawasaki's disease, healthcare providers might consider consulting Kawasaki's disease protocols for follow-ups until more is known about the long-term cardiac effects of MIS-C.
Limitations	Some limitations include: absence of a comparison group, sensitive MIS-C case definition, limited clinical testing and data, and lack of reports of MIS-C in China.

Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Ischemic Stroke

Eduard Valdes Valderrama et al.

Stroke
July 28, 2020
DOI: https://doi.org/10.1161/STROKEAHA.120.030153

Purpose	To discuss treatment, prevention, and recovery in patients with co-occurrence of COVID-19 and stroke.
Study design	Case Report
Level of evidence	Level 5
Methods	A case is presented of thrombotic stroke in a patient initially presenting with respiratory symptoms and fever. The patient tested positive for SARS-CoV-2 by RT-PCR. Additionally, authors discuss potential pathophysiology of stroke in SARS-CoV-2 infected patients.
Findings	The patient initially presented with dyspnea, cough and fever. On day 7, the patient developed right hemiparesis and aphasia. Angiography revealed a left terminal internal carotid artery thrombosis which was mechanically removed. The patient's workup showed a BNP 193pg/mL, D-dimer > 10,000 ng/mL, erythrocyte sedimentation rate 37 mm/h, fibrinogen 235 mg/DL, ferritin 588 ug/L and CRP 11mg/L. **Researchers state that the patient's stroke cause remained cryptogenic. However, elevated D-dimer suggests acquired hypercoagulability that authors speculate could be caused by SARS-CoV-2.**
Clinical Implications	SARS-CoV-2 has been shown to create a prothrombotic state with increased D-dimer levels, which increases the risk of stroke. Understanding the interaction between stroke risk factors and SARS-CoV-2 infection will be crucial for future research, as this study suggests that anticoagulation therapy may decrease stroke risk in patients with SARS-CoV-2 infections. Furthermore, affected patients could benefit from acute rehabilitation to minimize their long-term deficits.
Limitations	The study offers analysis on small sample size (n=1), making it difficult to generalize the results. The researcher notes that less than 2% of patients with stroke complications have SARS-CoV-2 co-infections. This makes it difficult to determine whether SARS-CoV-2 affects the likelihood of stroke independent of stroke risk factors. Future research is needed to determine whether or not rehabilitation therapy has a significant effect on outcomes in stroke patients with concurrent SARS-CoV-2 infections.

Incidence of thrombotic complications in critically ill ICU patients with COVID-19

F.A. Klok et al.

Thrombosis Research
April 10, 2020
DOI: https://doi.org/10.1016/j.thromres.2020.04.013

Purpose	To evaluate the incidence of the composite outcome of venous thromboembolism and arterial thrombotic complications in all COVID-19 patients admitted to the ICU of 2 Dutch university hospitals and 1 Dutch teaching hospital
Study design	Case Series
Level of evidence	Level 4
Methods	Authors studied 184 COVID-19 patients admitted to the ICU. The timeline ran from initial date of ICU admission to ICU discharge, patient's death, or April 5th 2020, whichever came first. The primary endpoint of this case series was the incidence of composite outcome consisting of acute pulmonary embolism (PE), deep vein thrombosis (DVT), ischemic stroke, myocardial infarction (MI), or systemic arterial embolism. In addition, researchers examined venous and arterial thrombotic complications separately. All patients received at least standard doses of thromboprophylaxis (nadroparin).
Findings	The cumulative incidence of composite outcome (PE, DVT, ischemic stroke, MI, and systemic arterial embolism) was 31%. Venous complications occurred in 27% of patients and arterial complications occurred in 3.7% of patients (confirmed via CTPA and/or ultrasonography). PE was the most frequent complication (n=25, 81%). Age and coagulopathy (spontaneous prolongation of prothrombin time >3s or activated PTT >5s) were independent predictors of thrombotic complications.
Clinical Implications	Although all patients in this study received systematic thrombosis prophylaxis, the 31% incidence of thrombotic complications is remarkedly high. This study confirms the need for all COVID-19 patients admitted to the ICU to receive pharmacological thrombosis prophylaxis, even suggesting that an increase towards higher dose prophylaxis may be warranted. Providers should be attentive to signs of thrombotic complications and order appropriate tests at a low threshold.
Limitations	Given timeline of the study, the incidence of composite outcomes are conservative. Most patients were still in the ICU at the end of study timeline, and the threshold for diagnostic testing was raised. Findings were not adjusted for the difference in treatment regimens between hospitals. In addition, the small sample size and geographical limitation to the Dutch area may make this study less applicable to the general population in the United States.

Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units

Lara Shekerdemian et al.

JAMA Pediatrics
May 11, 2020
DOI: 10.1001/jamapediatrics.2020.1948

Purpose	To characterize COVID-19 infection in North American PICUs via description of presentation, disease severity, clinical trajectory, impact of comorbidities and therapeutics, and clinical outcome.
Study design	Cross-sectional retrospective cohort study.
Level of evidence	Level 3
Methods	A retrospective medical record review of pediatric patients younger than 21 years with confirmed COVID-19 from North American PICUs was conducted between March 14 and April 3, 2020. Patient data included age, sex, preexisting comorbidities, disease presentation, therapies and clinical outcomes. Clinical course was described with data on survival, duration of ventilation and lengths of ICU and hospital stay. Illness severity was categorized as mild, moderate, severe or critical.
Findings	Forty-six patients were included in the study, of which 25 (52%) were male, and the median (range) age was 13 (4.2-16.6) years. 69% of participants were severely or critically ill on admission, 38% required invasive ventilation, and the overall case fatality rate was 4.2%. Of the 18 critically ill patients, 16% were ventilated at the end of the study period, 39% discontinued mechanical ventilation but remained hospitalized and 33% were discharged. Comorbidities were described in >80% of participants. 73% of patients presented with respiratory symptoms, though there were cases in which other conditions, such as vasoocclusive crisis, diabetic ketoacidosis and seizures also warranted PICU admission. Finally, the authors noted that 61% of patients were administered one or more pharmacologic therapies throughout their treatment, however, this is purely descriptive and does not imply benefit. Further studies are necessary to ascertain whether administration of these pharmaceuticals offers therapeutic benefit.
Clinical Implications	The overall ICU mortality at the end of the follow-up period was less than 5%. When the patients with mild-moderate symptoms at presentation are excluded, the adjusted mortality rate remains relatively low at 6%. This demonstrates a less severe clinical course and better outcomes in children when compared with published ICU mortalities of 50-62% in adults. It is also notable that the overall burden of COVID-19 infection in children remains relatively low when compared with seasonal influenza and, as children face a far greater risk of critical illness from influenza than COVID-19, preventative pediatric health maintenance remains vital.
Limitations	At the time of the study, there was limited effective testing for COVID-19 in North America, which may have introduced ascertainment bias.

Autopsy findings and venous thromboembolism in patients with COVID-19

Dominic Wichmann et al.

Annals of Internal Medicine
May 6, 2020
DOI: https://doi.org/10.7326/M20-2003

Purpose	To examine postmortem characteristics associated with COVID-19 by evaluating clinical findings in 12 deceased patients and using data from medical autopsy, virtual autopsy, and virologic tests.
Study design	Prospective Cohort Study
Level of evidence	Level 3
Methods	Autopsies were performed on the first 12 consecutive COVID-19 positive deaths at an academic medical center in Hamburg, Germany. Postmortem computed tomography (PMCT) and a complete autopsy, including histopathologic and virologic evaluation, were performed on all deceased patients. Clinical records and medical course were evaluated.
Findings	All patients (median age: 73 years, 75% male) had COVID-19 diagnosis confirmed by PCR Postmortem laboratory tests were remarkable for **elevated LDH** (n=10, median= 7.83 µkat/L), **D-dimer** (n=5, median= 495.24 nmol/L), and **C-reactive protein** (n=10, median =189 mg/L). PMCT (n=10) demonstrated **mixed patterns of reticular infiltrations and severe, dense consolidating infiltrates in both lungs in the absence of known preexisting patholog**y. **Autopsy revealed deep vein thrombosis in 7 of 12 patients,** with pulmonary embolism being the primary cause of death in 4 of those patients. **Lung weight was markedly elevated** (mean=1988g) compared to the standard lung weights of men (840g) and women (639g). Histopathology revealed **diffuse alveolar damage, consistent with early acute respiratory distress syndrome** in 8 cases. **SARS-CoV-2 RNA was detected in the lungs of all 12 patients and in the pharynx of 9 patients. 5 patients had viral DNA detected in other organs** (heart, liver, or kidney).
Clinical Implications	COVID-19 detection solely by PCR may cause pulmonary embolism to be overlooked by clinicians. Pulmonary embolism may contribute to a higher rate of respiratory-associated complications in COVID-19 patients than clinically thought. In COVID-19 patients with increased D-dimer levels, empiric anticoagulation may be indicated. These findings suggest that combatting coagulopathy might be a possible therapy to improve the survival rate. SARS-CoV-2 may spread via the blood stream and infect other organs.
Limitations	The prevalence of pulmonary embolism and other postmortem findings could be overexaggerated given the small sample size of the study. It is unknown how postmortem processes affect viral titers and dynamics in different tissues and body fluids. The location of a single academic medical center in Germany potentially makes this study less generalizable to the United States population.

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in COVID-19

Maximilian Ackermann et al.

New England Journal of Medicine
May 21st, 2020
DOI: 10.1056/NEJMoa2015432

Purpose	To clarify morphologic and molecular features of lungs from Covid-19 patients as compared to patients who died of pneumonia due to influenza.
Study design	Observational Analysis
Level of evidence	Level 4
Methods	The researchers analyzed seven lungs from patients who died from respiratory failure due to COVID-19 and compared them to seven lungs of patients who died from pneumonia due to influenza A virus subtype H1N1. The influenza-affected patients were picked to best match the age, sex, and disease severity of the COVID-19 patients. Ten uninfected lungs served as controls. All lungs comparisons were done using the Student's t-test set at 0.05.
Findings	**The researchers discovered 3 main distinctions in the lungs of patients with Covid-19: (1) Severe endothelial injury, disturbed endothelial membranes, disrupted intercellular junctions, a loss of contact with the basal membrane, and cell swelling, (2) More extensive vascular thrombosis and alveolar capillary occlusion, (3) Significant new vessel growth through intussusceptive angiogenesis**. The degree of intussusceptive angiogenesis was found to increase significantly with increasing length of hospitalization. An analysis also reflected that Covid-19 patients had 69 angiogenesis-related genes, influenza patients had 26 related genes, and 45 genes had shared changes in expression. Additionally, researchers found that the mean weight of lungs from influenza patients was significantly higher than lungs from Covid-19 patients, with uninfected lungs being significantly lower than both. Both set of infected lungs had higher numbers of ACE2-positive cells than uninfected lungs. Covid-19 lungs also had alveolar capillary microthrombi 9 times more than influenza lungs.
Clinical Implications	Histopathological and radiological findings suggest that, the major cause of respiratory failure and organ dysfunction in COVID-19 patients is thrombosis, inflammation and endothelial dysfunction. The researchers' unexpected discovery of enhanced intussusceptive angiogenesis in Covid-19 lungs may be linked to a greater degree of endothelialitis and thrombosis, but this relationship needs to be clarified. Additionally, greater SARS-CoV-2 presence in endothelial cells may suggest a link to perivascular inflammation or direct viral effects.
Limitations	The small sample size may have overlooked various differences between lungs. Additionally, the researchers' lack of information on timing of death may impact time-related changes or other factors that account for the differences studied.

Laboratory Findings Associated with Severe Illness and Mortality Among Hospitalized Individuals with Coronavirus Disease 2019 in Eastern Massachusetts

Victor M. Castro et al.

Journal of the American Medical Association
August 28, 2020
DOI: https://doi.org/10.1001/jamanetworkopen.2020.23934

Purpose	To assess whether laboratory values, comorbidities, and sociodemographic data can predict the severity of disease course in patients hospitalized with SARS-CoV-2 in order to determine which SARS-CoV-2 patients may be most at risk of severe illness or death.
Study design	Retrospective cohort study
Level of evidence	Level 4
Methods	Electronic health records of 2,511 patients hospitalized and diagnosed with SARS-CoV-2 in Eastern Massachusetts at 2 academic medical centers and 4 hospitals in Eastern Massachusetts between 3/1 and 6/5/2020 were examined to determine the severity of disease course in relation to laboratory values, comorbidities, and sociodemographic data. The main endpoints were severe illness requiring ICU admission, requirement of mechanical ventilation, and death. L1-penalized regression was used to create a risk prediction model that accounted for hospital course, comorbidities, and laboratory values.
Findings	Out of the 2,511 patients in the cohort, 215 of the patients (8.6%) required ICU admission, 164 (6.5%) received mechanical ventilation, and 292 (11.6%) perished. 212 of these deaths (78%) were among the highest mortality-risk quintile. **It was found that patients with severe illness often demonstrated neutrophilia, eosinopenia, lymphocytopenia, and impaired renal function. Patients who died demonstrated similar findings along with nucleated erythrocytes, atypical erythrocyte indices, elevated procalcitonin, and higher prevalence of preexisting pulmonary disease.**
Clinical Implications	Results suggest that SARS-CoV-2 patients with neutrophilia, eosinopenia, lymphocytopenia, and impaired renal function may be more at risk for serious illness requiring ICU admission while SARS-CoV-2 patients with these findings plus nucleated erythrocytes, atypical erythrocyte indices, elevated procalcitonin, and preexisting pulmonary disease may have a higher risk of mortality.
Limitations	This article has not yet been peer reviewed. Caution should be exercised in applying these findings to clinical practice. Additionally, this study included a relatively small sample size (n=2,511) that was localized to one geographic region, which means that the findings may not necessarily be generalizable to other populations. However, further studies could help to determine if similar findings are present in the larger population.