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REVIEW ARTICLE

A Comprehensive Review of Manifestations of Novel Coronaviruses in the Context of Deadly COVID-19 Global Pandemic

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ABSTRACT

Since December 2019, the global pandemic caused by the highly infectious novel coronavirus 2019-nCoV (COVID-19) has been rapidly spreading. As of April 2020, the outbreak has spread to over 210 countries, with over 2,400,000 confirmed cases and over 170,000 deaths.1 COVID-19 causes a severe pneumonia characterized by fever, cough and shortness of breath. Similar coronavirus outbreaks have occurred in the past causing severe pneumonia like COVID-19, most recently, severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV). However, over time, SARS-CoV and MERS-CoV were shown to cause extrapulmonary signs and symptoms including hepatitis, acute renal failure, encephalitis, myositis and gastroenteritis. Similarly, sporadic reports of COVID-19 related extrapulmonary manifestations emerge. Unfortunately, there is no comprehensive summary of the multiorgan manifestations of COVID-19, making it difficult for clinicians to quickly educate themselves about this highly contagious and deadly pathogen. What is more, is that SARS-CoV and MERS-CoV are the closest humanity has come to combating something similar to COVID-19, however, there exists no comparison between the manifestations of any of these novel coronaviruses. In this review, we summarize the current knowledge of the manifestations of the novel coronaviruses SARS-CoV, MERS-CoV and COVID-19, with a particular focus on the latter, and highlight their differences and similarities.

Key Indexing Terms: Severe acute respiratory syndrome coronavirus; Middle east respiratory syndrome coronavirus; COVID-19; Novel coronavirus. [Am J Med Sci 2020;360(1):5-34.]

INTRODUCTION

The current global pandemic due to the highly contagious COVID-19 infection is rapidly spreading in many countries with a high number of deaths. Many communities and countries have enforced restrictions, permitting only essential activities. Health systems around the globe are currently preparing to manage the influx of critically ill patients. During this phase, care providers, administrators and policymakers work in concert to understand and combat this deadly pandemic. The current knowledge about COVID-19 is limited but rapidly evolving. During this outbreak, the medical community used evidence gleaned from past outbreaks of SARS-CoV and MERS-CoV to predict COVID-19’s behavior, clinical presentation and treatment. In addition, coronaviruses (CoV) are known to cause signs and symptoms of multiorgan system damage, many of which are subtle and can go unnoticed by trained medical professionals. Furthermore, frontline healthcare personnel lack a comprehensive review of the numerous clinical pulmonary and extrapulmonary manifestations of deadly CoVs making self-education time consuming.

We have attempted to summarize the manifestations of COVID-19 and other CoVs in many organs with the goal of consolidating knowledge to address the current pandemic. We hope that this review will provide information that would help to manage patients, evaluate manifestations in different organs, predict complications and prognosis, allocate resources in the appropriate domains, and provide opportunities for research.

METHODS

We searched the published literature for multiple combinations of different organs, and names for
infectious conditions of those organs and novel CoVs. We only included articles written in the English language and published after 2002. We included both animal and human research studies. The search methodology resulted in nearly 2000 articles. During the further review, we limited the number of articles by eliminating articles that lacked direct relevance. We populated tables with disease manifestations in various organs (Tables 1-8).

PATHOGENS

CoVs are a large family of single-stranded RNA viruses that infect humans primarily through droplets and fomites. Before December 2019, there were 6 known human CoVs, including the alpha-CoVs, HCoV-NL63 and HCoV-229E, and the beta-CoVs, HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome-CoV (SARS-CoV) and middle east respiratory syndrome (MERS-CoV). The recently identified COVID-19 is a beta-CoV that infects both humans and animals. All 3 of these novel viruses (SARS-CoV, MERS-CoV and COVID-19) originate from zoonotic transmission. Bats may have served as the source of SARS-CoV and COVID-19 based on sequence similarity with bat CoVs. Camels are suspected to have been the zoonotic host for transmission of MERS-CoV.

The SARS-CoV outbreak spanned from 2002 to 2003 infecting 8,098, causing 774 deaths resulting in a 5-10% mortality and a 43% mortality in the elderly. The MERS-CoV outbreak was first reported in Saudi Arabia in 2012. It then spread to Europe, Asia and Africa and North America and infected 2,494 people, causing 858 death. The MERS-CoV caused severe pneumonia with an intensive care unit (ICU) admission rate of 40-50% and an inhospital ICU death rate of 75%. In December 2019, the city of Wuhan in Hubei Province, China, reported a small outbreak of a novel coronavirus, COVID-19. The fatality rate is highest in adults ≥85 years old (10-27%), followed by 65-84 years (3-11%) with 50% of ICU admission among persons ≥85 years. The World Health Organization declared COVID-19 as a pandemic on March 11, 2020.

PULMONARY MANIFESTATIONS

SARS-CoV

Patients infected with SARS-CoV initially had features of atypical pneumonia. Cough was a common presenting symptom in up to 74% of patients (Table 1). Other symptoms suggestive of an upper respiratory tract infection (e.g., rhinitis) were less frequent. Approximately 50% of patients developed hypoxia during hospitalization, and up to 26% progressed to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. The elderly and patients with multiple comorbidities had particularly high (more than 15.7%) mortality. Unilateral, focal, peripheral areas of consolidations on imaging were identified in upwards of 78% of patients. Histopathology revealed diffuse serous, fibrinous and hemorrhagic inflammation. SARS-CoV RNA has been detected in type II alveolar cells, interstitial cells and bronchial epithelial cells, suggesting infection of both proximal and distal epithelium of the lung. Most patients received antibacterial antibiotics, with or without the use of ribavirin and corticosteroids.

Angiotensin-converting enzyme 2 (ACE2) serves as a functional receptor to SARS-CoV. SARS-CoV also disrupts the urokinase pathway, which controls fibrin levels through extracellular remodeling, and is associated with pulmonary hemorrhage and fibrosis. SARS-CoV also triggers the production of high levels of proinflammatory cytokines contributing to excessive inflammation in the lungs. Hence, anticytokine and chemokine immunotherapy may be effective for minimizing collateral damage.

MERS-CoV

Common presenting symptoms of MERS include dyspnea in up to 92% and cough in 83% of patients (Table 1). In a study including 47 patients, all patients presented with an abnormal chest radiograph, 89% needed ICU admissions, and 72% required mechanical ventilation. The case fatality rate was 60%, and the rate increased with age. Most patients received antibiotics, and a small minority received corticosteroids, ribavirin and intravenous immunoglobulin. In a small case series, antiviral therapy was not beneficial. MERS-CoV also induces overexpression of inflammatory cytokines and/or chemokines.

COVID-19

A dry cough is a common symptom in COVID-19 infection, present in up to 68% of patients (Table 1). Sore throat and sputum production are uncommon (5% or less). The presence of dyspnea is predictive of ICU admission. In early descriptions of hospitalized patients in China, all patients had an abnormal chest computed tomography. Ground glass opacities are common (56%), followed by consolidation and interstitial abnormalities. In a large Chinese study, the course was complicated by ARDS in 3.4% patients, 6.1% required mechanical ventilation, and the case fatality rate was 1.4-2.1%. Other studies noted a higher incidence of ARDS among hospitalized patients (29%), and higher mortality (15%). Respiratory failure tends to have a delayed onset, occurring approximately 1 week after the onset of symptoms. Patients with critical illness were on average older (median age 66 versus [vs.] 51 noncritically patients) and had more comorbidities. Patients who received invasive mechanical ventilatory support were more likely to be male and obese. Histopathology of the lung shows diffuse alveolar damage, denuded...
Table 1. Pulmonary manifestations of SARS-CoV, MERS-CoV and COVID-19.

| Study                      | Lee et al (2003)                                      | Lang et al (2003)                                      | Liu et al (2004)                                      | Peiris et al (2003)                                      |
|----------------------------|-------------------------------------------------------|-------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|
| N                          | N = 138, confirmed cases                              | N = 3, confirmed cases                                | N = 53, confirmed cases                              | N = 75, confirmed cases                                |
| Retrospective study        | Retrospective study                                   | Clinicopathologic study                               | Retrospective study                                   | Prospective study                                       |
| Clinical features          | Preexisting chronic pulmonary disease (2.1%)           | Fever (3/3)                                            | Fever (98%)                                          | Fever (100%), recurred in 85% at mean 8.9 days         |
|                            | Fever (100%)                                          | Mildly productive cough (1/3)                          | Cough (68% on admission to isolation, 74% after hospitalization, 26% productive) |
|                            | Cough (57.3%)                                         |                                                        |                                                      | Cough (29%)                                            |
|                            | Sputum (29%)                                          |                                                        |                                                      | Spontaneous pneumomediastinum (12%) during follow-up   |
|                            | Sore throat (23.2%) Coryza (22.5%)                    |                                                        |                                                      | Sore throat (11%)                                       |
|                            | Inspiratory crackles                                  |                                                        |                                                      | Shortness of breath (4%)                               |
|                            |                                                        |                                                        |                                                      |                                                        |
| Key findings on investigations |                                             |                                                        |                                                      |                                                        |
| CXR                        | Consolidation (78.3% at fever onset, eventually 100%)  | Leukopenia (2/3)                                      | Leukopenia (2/3)                                      | Abnormal CXR (59% on admission, 98% any time)           |
|                            | 54.6% unilateral, focal                               | Lymphopenia (2/3)                                     | Lymphopenia (2/3)                                    |                                                      | Initial CXR abnormal: 71%                              |
|                            | 45.4% multifocal or bilateral                         | CXR: Bilateral interstitial infiltrates                | CXR: Bilateral interstitial infiltrates               |                                                      | One lung zone: 49%                                   |
|                            | Peripheral zone predominant                           |                                                        |                                                      |                                                      | Multizonal: 21%                                      |
|                            | CT                                                    |                                                        |                                                      |                                                      | Chest CT abnormal (55% of 33)                          |
|                            | Progression of chest CT infiltrates                   |                                                        |                                                      |                                                      | One lobe: 55%                                        |
|                            | 7-10 days after admission, resolution with treatment  |                                                        |                                                      |                                                      | Multilobar: 46%                                      |
|                            | II-defined peripheral GGO, usually subpleural         |                                                        |                                                      |                                                      | Focal ground-glass opacification: 24%                  |
| Histopathology             | Gross: Lung consolidation                             |                                                        | Gross: Diffuse hemorrhage on lung surface             | N/A                                                    | Radiologic worsening in 80% at mean 7.4 days          |
|                            | Early phase: Pulmonary edema with hyaline membrane formation |                                                        | Serous, fibrous and hemorrhagic inflammation in alveoli with desquamation of pneumocytes and hyaline-membrane formation | N/A                                                    |                                                        |
|                            | Organizing phase: Cellular fibromyxoid organizing exudates in alveoli |                                                        | Capillary engorgement and capillary microthrombosis, thromboemboli in bronchial arteries |                                                        |                                                        |
|                            | Scanty lymphocytic interstitial infiltrate            |                                                        | Hemorrhagic necrosis lymphocyte depletion in lymph nodes and spleen |                                                        |                                                        |
|                            | Vacuolated and multinucleated pneumocytes             |                                                        | Viral RNA detected in type II alveolar cells, interstitial cells and bronchiolar epithelial cells | N/A                                                    |                                                        |
|                            | Viral inclusions not detected.                        |                                                        |                                                      |                                                        |                                                        |

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Table 1. (continued)

| Study                                                                 | Year       | Study                                                                 | N     | Cases         | Type                          | Clinical features                                                                 | Key findings on investigations                                                                 | Key study findings and message                                                                 | Message                                                                 |
|-----------------------------------------------------------------------|------------|------------------------------------------------------------------------|-------|---------------|-------------------------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| SARS (only studies with large study population included)               |            |                                                                        |       |               |                               |                                                                                  |                                                                                              |                                                                            |                                                                                        |
| Key study findings and message                                         |            |                                                                        |       |               |                               |                                                                                  |                                                                                              |                                                                            |                                                                                        |
| Key findings on investigations                                         |            |                                                                        |       |               |                               |                                                                                  |                                                                                              |                                                                            |                                                                                        |
| Study                                                                 | Year       | Study                                                                 | N     | Cases         | Type                          | Clinical features                                                                 | Key findings on investigations                                                                 | Key study findings and message                                                                 | Message                                                                 |
| MERS                                                                  |            |                                                                        |       |               |                               |                                                                                  |                                                                                              |                                                                            |                                                                                        |
| Study                                                                 | Year       | Study                                                                 | N     | Cases         | Type                          | Clinical features                                                                 | Key findings on investigations                                                                 | Key study findings and message                                                                 | Message                                                                 |
| COVID-19                                                               |            |                                                                        |       |               |                               |                                                                                  |                                                                                              |                                                                            |                                                                                        |
| Study                                                                 | Year       | Study                                                                 | N     | Cases         | Type                          | Clinical features                                                                 | Key findings on investigations                                                                 | Key study findings and message                                                                 | Message                                                                 |

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Table 1. (continued)

| COVID-19 |
|------------------|---------------|------------------|
| • Hemoptysis (5%) |
| • ARDS (29%), mean 9 days after onset |
| • ↑RR >24/min (29%) |
| • Nasal congestion (4.8%) |
| • Hemoptysis (0.9%) |
| • ARDS (3.4%) |
| • 1.4% case fatality rate |
| • 4 days median incubation period |

| Key findings on investigations |
|---------------------------|
| Abnormal chest CT (100%); (98% bilateral) |
| · ↓PaO₂ |
| · ↓PaO₂:FiO₂ |
| · Abnormal CXR (59.1%) |
| · Abnormal Chest CT (86.2%) |
| · Ground glass opacity most common (56.4%) |
| · No lung imaging findings in 17.9% patients with nonsevere disease and in 2.9% with severe disease |
| CT: Patchy bilateral ground glass opacities |

| Histopathology |
|----------------|
| N/A |
| N/A |
| N/A |
| • Diffuse alveolar damage with organizing changes of fibrous plugs, with interstitial fibrosis and chronic inflammatory infiltrates |
| • Denuded alveolar lining with pneumocyte type II hyperplasia |
| • Virus detected on alveolar epithelial cells including desquamated cells, not in blood vessels |

| Key study findings and message |
|-----------------------------|
| • ICU patients had more areas of consolidation |
| • 10% mechanical ventilation rate, mean 10.5 days after onset |
| • 5% ECMO rate |
| • High-flow O2 therapy in 11.1% ICU patients, noninvasive ventilation in 41.7%, and invasive ventilation in 47.2% |
| • Older patients (P < 0.001), patients with more comorbidities, dyspnea and anorexia more likely to require ICU care |
| • Mechanical ventilation needed (6.1%) |
| • Radiographic abnormalities often absent |
| Histopathologic findings consistent with diffuse alveolar damage |

ARDS, acute respiratory distress syndrome; CXR, chest x-ray; ECMO, extracorporeal membrane oxygenation; GGO, ground glass opacities; ICU, intensive care unit; MERS-CoV, middle east respiratory syndrome coronavirus; RR, respiratory rate; SARS-COV, severe acute respiratory syndrome coronavirus; URT, upper respiratory tract.
alveolar lining cells and interstitial fibrosis. There is also evidence of a higher incidence of thromboembolism in COVID-19 patients and an association between elevated D-dimer levels and mortality. Additionally, preliminary evidence suggests that heparin use may result in lower 28-day mortality rates when compared to in COVID-19 patients not receiving this therapy.

Currently, it is speculated that respiratory compromise due to COVID-19 is driven by cytokine-mediated injury of the lung and that interventions to reduce the activity of specific inflammatory mediators may improve outcomes. COVID-19 also uses ACE2 receptor to enter into cells so therapies targeting this receptor may serve as a potential treatment option. There is no standard of care for the prevention or treatment of respiratory compromise in COVID-19 yet. Medications including glucocorticoids, IL-6 antagonists, Janus kinase inhibitors, antivirals and chloroquine and/or hydroxychloroquine are currently being studied as possible therapeutic options.

CARDIOVASCULAR MANIFESTATIONS

SARS-CoV

Patients may present with cardiac arrhythmia, failure and myocarditis (Table 1). A study on 121 hospitalized SARS-CoV patients found that tachycardia was the most frequent acute presentation followed by hypotension, bradycardia, reversible cardiomegaly and transient paroxysmal atrial fibrillation. Case reports have described acute onset myocarditis in patients with SARS-CoV; however, on autopsy, the virus was absent in the myocardium, suggesting myocardial damage may be indirectly related to the illness. Another report described several fatal cases of SARS-CoV patients with acute heart failure and, rarely, myocardial infarction in the setting of septic shock with elevated myocardial enzymes. Chronic cardiometabolic damage may also ensue in some, even 12 years after recovery with dysregulated lipid metabolism.

MERS-CoV

There are rare case reports describing acute myocarditis in MERS-CoV patients, presenting with severe chest pain and subsequent heart failure with elevated high-sensitivity TnI and probrain natriuretic peptide levels (Table 1). Few reports also note sinus tachycardia and diffuse T-wave inversion on electrocardiography and global left ventricular dysfunction on echocardiography. Rarely pericarditis may also ensue.

COVID-19

ACE2, the functional receptor of COVID-19 is expressed in the myocardium. Whether the use of the renin-angiotensin-aldosterone system inhibitors alters COVID-19 infection by upregulating ACE2 is under investigation. Similar to MERS-CoV and SARS-CoV, COVID-19 also causes acute cardiac injury in a subset of patients with corresponding elevated high-sensitivity cardiac troponin-I levels (Table 1). CK-MB and high-sensitivity cardiac troponin-I were higher in ICU patients, suggesting that myocardial injury is more likely present in patients with severe disease. As many as 7% of deaths in COVID-19 patients have been attributed to myocardial injury. Other cardiac manifestations include acute myocardial infarction, fulminant heart failure and dysrythmias. In some studies, arrhythmia with COVID-19 infection was as high as 17%. It is also important to note various drug interactions and the arrhythmogenic potential of medications often used in these patients. Additionally, patients with preexisting cardiovascular disease and hypertension have been seen to suffer from more severe disease requiring critical care.

Presenting symptoms range from mild chest pain with preserved ejection fraction to profound cardiovascular collapse requiring extracorporeal membrane oxygenation. Echocardiography may show a regional wall motion abnormality or global hypokinesis with or without pericardial effusion. Initial electrocardiogram may show low voltage QRS complexes in the limb leads, ST segment elevations in leads I, II, aVL, V2-V6 and PR elevation and ST depressions in aVR. There should be a low threshold for SARS-CoV-2 testing in patients presenting with signs of myopericarditis even in the absence of fever and respiratory symptoms.

Proposed mechanisms of cardiac injury in patients with COVID-19 include overexpression of ACE2 in patients with chronic cardiovascular disease, cytokine storm triggered by an imbalanced response by type 1 and type 2 helper cells, hypoxemia resulting in myocardial damage, plaque rupture, coronary vasospasm, or direct vascular injury. There may be a complex interplay between the accelerated immunologic dysregulation of the cytokines and T cells and the underlying cardiovascular or related metabolic conditions. Virally-induced systemic inflammation may also promote coronary plaque rupture and have a procoagulant effect necessitating the intensification of medical therapy.

HEPATOBILIARY MANIFESTATIONS

SARS-CoV

Hepatitis in SARS-CoV is a well-recognized common complication, although it is a diagnosis of exclusion. Approximately 60% of patients with SARS-CoV had a degree of liver impairment with elevated alanine aminotransferase and/or aspartate aminotransferase, hypoalbuminemia and hyperbilirubinemia (Table 2). ACE2 receptors are also found on the hepatic endothelial cells. On histopathology, SARS-CoV patients had a large number of virus particles in the hepatic parenchymal cells. Elevated levels of IL-1, IL-6 and IL-10 in patients with SARS-CoV hepatitis support coexisting...
Table 2. Cardiovascular manifestations of SARS-CoV, MERS-CoV and COVID-19.

### SARS (only studies with large study population included)

| Study | Clinical features | Key findings on investigations | Histopathology | Key study findings and message |
|-------|-------------------|------------------------------|----------------|-------------------------------|
| Booth et al (2003) | - Chest pain (10%) | - Calcium (60%) | N/A | - 20% ICU admission |
| Li et al (2003) | - No chest pain or overt CHF on admission | - Creatinine | N/A | - 6.5% Case fatality rate (21 days) |
| Pan et al (2003) | - Sudden cardiac arrest (100%) | - Troponin | N/A | - Diabetes and other comorbidities independently associated with poor prognosis |
| Ding et al (2004) | - MI and arrhythmia (33%) | - ACE2 | N/A | - Possibly reversible subclinical diastolic impairment seen in SARS patients |
| Yu et al (2006) | - Chest pain | - Myocardial edema | N/A | - Proposed causes of SCD: |

#### Clinical features
- **CHF**: Heart failure
- **ECG**: Electrocardiogram
- **BNP**: Brain natriuretic peptide
- **Creatinine**
- **Laboratory tests**
- **ECG changes**
- **CXR or CT abnormality**
- **Histopathology**: Biopsy results
- **ACE2**
- **Troponin**

#### Key findings on investigations
- **Calcium (Ca++)**: Calcium levels
- **Potassium (K+)**
- **Magnesium (Mg++)**: Magnesium levels
- **Phosphorus (P+)**
- **Creatinine**
- **LDH**: Lactic dehydrogenase
- **ALT**: Alanine aminotransferase
- **AST**: Aspartate aminotransferase
- **BUN**: Blood urea nitrogen
- **Creatinine**: Creatinine levels
- **ACE2**: Angiotensin-converting enzyme 2
- **Troponin**: Troponin levels
- **BNP**: Brain natriuretic peptide
- **Creatinine**: Creatinine levels

#### Key study findings and message
- **Proposed causes of SCD**: Hypoxemia leading to myocardial strain, Direct viral myocardial injury, Stress aggravates pre-existing disease, Sympathetic response causing electrical myocardial instability
- **ACE2 expressed in heart, but virus not detected**: ACE2 protein
- **CK likely due to myositis as cardiac enzymes normal**: CK levels
- **15% ICU admission**: ICU admission rate
- **19 (5) days mean duration of hospital stay**: Hospital stay duration
- **Tachycardia persists during follow-up**: Persistent tachycardia
- **Cardiac arrhythmia is uncommon**: Arrhythmia rates

### MERS

| Study | Clinical features | Key findings on investigations |
|-------|-------------------|------------------------------|
| Alhogbani (2016) | CHF | **↑ HR (67.7%)** |
| Almekhlafi et al (2016) | ↑ HR (67.7%) | N/A |
| Garout et al (2018) | Pericarditis | N/A |

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### MERS

- Echo: Severe global LV dysfunction
- Cardiac MRI: Myocarditis

**Key study findings and message**

| MERS-CoV may cause myocarditis and acute heart failure | Vasopressor need is a risk factor for death ($P = 0.04$) | No association of ECMO need with outcomes |

### COVID-19

| Study | Clinical features | Key findings on investigations | Key Study findings and message |
|-------|------------------|-------------------------------|------------------------------|
| Huang et al (2020) N = 41, confirmed cases | • BP 更 common in ICU patients ($P = 0.018$) | • BP 更常见在 ICU 患者 ($P = 0.018$) | • BP 更常见在 ICU 患者 ($P = 0.018$) |
| Wang et al (2020) N = 138, confirmed cases Retrospective study | • Pre-existing HTN (31.2%) (58.3% in ICU, significant) | • TnI 更高在 ICU 患者 (31.2%) (58.3% in ICU, 显著) | • TnI 更高在 ICU 患者 (31.2%) (58.3% in ICU, 显著) |
| Zheng et al (2020) Review | • Palpitations | N/A | • Diffuse ST segment elevations |
| Bhatraju et al (2020) N = 24, confirmed cases | • Chest tightness | • TnI (15%) | • Elevated cardiac enzymes |
| Fried et al (2020) N = 4, confirmed cases | • Palpitations | • TnI (48%) | • LVEF on echo |

Proposed mechanism of cardiac injury:
- ACE 2 related
- Cytokine storm
- Hypoxemia

ICU admission most commonly due to hypoxic respiratory failure, vasopressor requirement or both
- 50% mortality

Similar symptoms in heart transplant patients as nontransplant patients

BNP, B-type natriuretic peptide; BP, blood pressure; HR, heart rate; CHF, congestive heart failure; CK, creatine kinase; CKMB, creatine kinase myocardial band; CXR, chest x-ray; ECMO, extracorporeal membrane oxygenation; Hb, hemoglobin; ICU, intensive care unit; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MERS-CoV, middle east respiratory syndrome coronavirus; RBBB, right bundle branch block; SARS-COV, severe acute respiratory syndrome coronavirus; TnI, troponin-I.
acute inflammatory response. Hepatic cell damage and cell-cycle disruption was seen on hepatic biopsy with apoptosis, mitotic arrest with eosinophilic bodies and balloon-like hepatocytes. Unfortunately, hepatic damage potentially due to antivirals use complicates our understanding of the etiology of hepatitis in patients with SARS-CoV. Hepatic involvement may indicate a poor prognosis, particularly in patients with high LDH levels. Yang et al reported long-standing hyperglycemia (due to pancreatic injury) as an independent predictor for adverse outcomes in patients with SARS-CoV.

MERS-CoV

Several studies report patients with MERS-CoV and elevated liver enzymes, as well as hypoalbuminemia (Table 2). The degree of hypoalbuminemia also helps to predict disease severity. Hepatic findings may resemble SARS-CoV-related changes. However, MERS-CoV utilizes dipeptidyl peptidase-4 to infect cells, which is highly expressed in the liver. In transgenic mice, the liver injury occurred within the first week after infection resulting in hepatic necrosis and infiltration of Kupffer cells and macrophages. Similar to other coronavirus infections, high concentrations of inflammatory cytokines are noted in the acute phase, including IFN-γ, TNF-α, IL-15 and IL-17. Future investigations may clarify the role of inflammatory response in causing the liver injury.

COVID-19

The few available studies show that as many as 51% of patients with COVID-19 have abnormal liver function on admission (elevated liver enzymes, bilirubin and lactate dehydrogenase levels) (Table 2). Patients with abnormal LFTs present with a high degree of fever, and their degree of hepatic dysfunction correlates with length of hospitalization. New reports suggest that the liver dysfunction in patients with COVID-19 may be related to damage to the cholangiocytes lining the biliary epithelium, likely due to the higher expression of ACE2 receptors on those cells. Patients with preexisting metabolic fatty liver disease have been seen to have an about 6-fold higher chance of severe disease in the presence of coexisting obesity.

GASTROINTESTINAL MANIFESTATIONS

SARS-CoV

Gastrointestinal (GI) involvement in SARS-CoV was common and occurred at different stages of the disease; rarely, patients reported only GI symptoms. The most common GI presentation was loss of appetite (up to 55%) and watery diarrhea (up to 76%) (Table 3). Patients also complained of nausea, vomiting (14-22.2%) and abdominal pain (3.5-12.6%). The association between symptoms and outcomes had been mixed. Leung et al found that patients with diarrhea had a higher likelihood of requiring ICU admission and ventilatory support. Others found that GI symptoms at presentation conferred a better prognosis. Found no association between diarrhea and the development of ARDS or the requirement of ventilatory support. The mechanism of GI symptoms is unclear, but SARS-CoV particles have been detected in saliva (100%), feces (97%) and mucosal epithelial and lymphoid tissue of affected patients with associated depletion of lymphoid tissue.

A significant mode of spread in community outbreaks was fecal-oral transmission. Patients with diarrhea also had a higher rate of positive serological and nasopharyngeal secretion tests. The virus remained stable in stool up to 2-4 days, and may even be detectable as late as 4 weeks.

MERS-CoV

Patients may present with GI symptoms, pain and fever. Patients with GI symptoms have delayed MERS-CoV serological clearance. MERS-CoV RNA in stool has been detected in about 15% of patients, much lower than SARS-CoV, and may not correlate with the presence of GI symptoms. While the virus replicates in the intestinal tract, isolation of the virus from feces and fecal-oral transmission are rare.

COVID-19

There is increasing recognition of GI symptoms in COVID-19 patients (up to 50%). Loss of appetite and diarrhea have been the most commonly reported symptom (in up to 78.6% cases), and less often vomiting (up to 5%), and abdominal pain (up to 2%) (Table 3). Vomiting has been shown to be a more common presenting symptom in children. The GI features seem to worsen with overall disease severity and the presence of abdominal pain has been associated with about 4 times higher odds of severe COVID. The delayed recognition of GI symptoms and lack of awareness may lead to a delay in seeking medical care. Patients who present later during their illness were more likely to suffer from hepatic dysfunction but without a difference in mortality, ICU days or time to discharge. Patients with obesity are at significantly higher risk for severe disease requiring critical care and invasive mechanical ventilation. Compared with patients with a BMI <25 kg/m², patients with BMI >35 kg/m² have been seen to have 7 times the odds for requiring invasive mechanical ventilation.

COVID-19 virus enters enteric epithelial tissue through ACE 2 and transmembrane protease, serine 2, but the exact mechanism of GI symptoms is not known. The virus is detectable in stool in up to half of COVID-19 patients, and the feces remains positive for as much as 4 weeks. ACE 2 and viral protein have been detected in GI epithelial cells, and infectious virus particles were isolated from feces. Fecal polymerase chain reaction (PCR) testing has been shown to be as
Table 3. Hepatobiliary manifestation of SARS-CoV, MERS-CoV and COVID-19.

| Study                  | N = | Clinical Features                      | Key findings on investigations                                                                                     | Histopathology | Key study findings and message                                                                 |
|------------------------|-----|----------------------------------------|--------------------------------------------------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------------------------------|
| Duan et al (2003)      | 154 | Hepatic dysfunction                     | • ALT &/or AST (37.7%)                                                                                             | N/A            | • AST/ALT elevation rates associated with disease severity (P < 0.05)                           |
| Ding et al (2004)      | 8   | Hepatic dysfunction                     | • ALT (70.7%)                                                                                                       | N/A            | • Possibly beneficial to suppress cytokine storm in early stage                               |
| Chau et al (2004)      | 3   | Hepatic dysfunction                     | • ALT and AST normalized within 2 weeks in 75.9%                                                                    | N/A            | • Liver may also be target of infection besides lungs                                          |
| Zhao et al (2004)      | 169 | Hepatic dysfunction                     | • ALT (32.76-62.50%)                                                                                                | N/A            | • Liver damage likely by virus directly                                                      |
| Yang et al (2005)      | 168 | Hepatic dysfunction                     | • ALT (13.04-40.00%)                                                                                                | N/A            | • Total protein remained normal                                                              |
| Zhan et al (2006)      | 12  | Hepatic dysfunction                     | • ALT and AST (40.35-72.00%)                                                                                        | N/A            | • No association found between liver damage, and oxygen saturation or degree of fever or immune dysfunction |
| Yang et al (2010)      | 539 | Hepatic dysfunction                     | • Total protein remained normal within 2 weeks in 75.9%                                                            | N/A            | • Liver damage likely by virus directly                                                      |
| Clinical Features Hepatic dysfunction | N = | Hepatic dysfunction                     | • ALT and AST normalized within 2 weeks in 75.9%                                                                    | N/A            | • Hepatotoxic drugs may contribute                                                            |
|                         | 390 | Hepatic dysfunction                     | • ALT (32.76-62.50%)                                                                                                | N/A            | • Spleen damage most likely due to direct viral attack                                        |
|                         | 239 | Hepatic dysfunction                     | • ALT (13.04-40.00%)                                                                                                | N/A            | • Steroid medication may contribute                                                            |
|                         | 239 | Hepatic dysfunction                     | • Total protein remained normal within 2 weeks in 75.9%                                                            | N/A            | • Indirect viral mechanism, perhaps vascular, causing spleen injury                           |
|                         | 239 | Hepatic dysfunction                     | • No association found between liver damage, and oxygen saturation or degree of fever or immune dysfunction         | N/A            | • Higher mortality in patients with hyperglycemia. • AST (P < 0.0001)                         |
|                         | 239 | Hepatic dysfunction                     | • Liver damage likely by virus directly                                                                              | N/A            | • Mortality not higher in patients with ALT (P = 0.35)                                        |
|                         | 239 | Hepatic dysfunction                     | • Hepatotoxic drugs may contribute                                                                                  | N/A            | • SARS-CoV may cause acute insulin dependent diabetes mellitus                                |
|                         | 239 | Hepatic dysfunction                     | • Spleen damage most likely due to direct viral attack                                                              | N/A            | • 5% (2/39) still had diabetes 3 years after discharge                                        |

MERS

| Study                  | N = | Clinical Features Hepatic dysfunction | Key findings on investigations |
|------------------------|-----|----------------------------------------|------------------------------|
| Saad et al (2014)      | 70  | Hepatic dysfunction (31.4%)             | • ALT, AST, T.bil             |
| Al-Hameed et al (2016) | 6   | Hepatic dysfunction later during ICU stay (62.5%) | • ALT, AST, T.bil             |
| Alsaad et al (2017)    | 1   | Hepatic dysfunction                     | • ALT, AST, T.bil             |
| Clinical Features Hepatic dysfunction | N = | Hepatic dysfunction                     | • ALT, AST, T.bil             |
|                         | 8   | Hepatic dysfunction                     | • ALT, AST, T.bil             |
| Histopathology         | N/A | N/A                                    | Liver                        |

(continued on next page)
### Table 3. (continued)

| MERS | COVID-19 |
|------|----------|
| **Key study findings and message** | **Study** | **Clinical features** | **Key findings on investigations** | **Histopathology** | **Key study findings and message** |
| Albumin <35 g/L at diagnosis predictor of severe infection (**P** = 0.026) | Fan et al (2020) | Hepatic dysfunction at admission (50.7%) | ▼ CD4+ and CD8+ T cells in patients with hepatic dysfunction | N/A | Patients with hepatic dysfunction more likely to have moderate-high fever, more in males (**P** = 0.035, 0.005) |
| | Chai et al (2020) | | | | • Hepatic dysfunction more likely due to cholangiocyte damage by virus, not hepatocyte |
| | Huang et al (2020) | Preexisting chronic liver disease (2%) | | N/A | • Drug induced damage, SIRS may also play a role |
| | Wang et al (2020) | Pre-existing chronic liver disease (2.9%) | | | **ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; MERS-CoV, middle east respiratory syndrome coronavirus; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-COV, severe acute respiratory syndrome coronavirus; T. Bili, total bilirubin.** |

- Mild portal inflammation, chronic, with CD4+ and CD8+ T lymphocytes. Necroinflammatory foci in hepatic lobules
- Reactive parenchyma with mild hydropic degeneration, more in perivenular area
- Rare multinucleated hepatocytes
- Mild disarray of the hepatic plates
- Minimal macrovesicular perivenular steatotic change, sinusoidal congestion, hemorrhage and focal perivenular hepatocytes loss

- 41% developed multiorgan failure

- Portal and lobular hepatitis, viral particles not identified in liver on EM

- Albumin <35 g/L at diagnosis predictor of severe infection (**P** = 0.026)

- Retrospective study

- Confirmed cases

- **N** = 148, confirmed cases

- **N** = 4 (healthy)

- **N** = 41, confirmed cases

- **N** = 138, confirmed cases

- Clinicopathologic

- **P** = 0.02

- **P** < 0.001

- **P** = 0.007

- **P** < 0.001

- **P** = 0.007

- **P** < 0.001
accurate as PCR detection from a sputum sample, and in some cases, fecal PCR is positive before sputum PCR. It remains unclear if the fecal-oral route is a significant mode of transmission.

RENAral MANIFESTATIONS

SARS-CoV
Renal impairment in SARS-CoV seems multifactorial and could include secondary sepsis, comorbidities, rhabdomyolysis, treatment-related interstitial nephritis, and altered immune response (Table 4). In most SARS-CoV patients, acute renal damage was not common at presentation. However, acute renal failure was noted in 5-15% of patients and more often developed subsequently 7-20 days after presentation. Choi et al reported a 6% incidence of acute renal failure in a study of 267 patients, more commonly in elderly diabetics. A large study with 536 patients stated that patients with ARF had hyponatremia and hypoalbuminemia at the time of admission. Patients with renal dysfunction had mortality rates around 90%. Patients with hypouricemia and chronic renal replacement therapy also had poor outcomes.

On microscopy, acute tubular necrosis has been observed in these patients. Viral detection in the urine at the onset was rare but gradually increased with the disease progression and remained detectable up to 30 days after symptom onset. Xu et al reported that 6 patients who died of SARS-CoV had testicular damage, which was also likely secondary to the immune response.

MERS-CoV
MERS-CoV uses the exopeptidase dipeptidyl peptidase 4 or CD 26 as its cellular receptor, which is highly expressed in kidneys. Renal involvement is as high as 41% and required dialysis more than SARS-CoV patients. Cha et al reported (n = 30 patients), 60% and 73% of patients with proteinuria and hematuria, respectively, approximately 27% of them developed acute kidney injury within 18 days. Patients with acute kidney injury were older and had elevated levels of albumin to creatinine ratios. Patients requiring renal replacement therapy had a higher mortality. Preexisting chronic kidney disease is also a predictor of poor outcomes. The virus has been detected in urine and renal tissue and causes apoptosis, suggesting direct viral pathogenicity complements the other mechanisms of renal injury.

COVID-19
Acute renal dysfunction in COVID-19 at the time of presentation is not uncommon. The incidence of acute kidney injury either at presentation or later is as high as 15% with a high mortality rate of 60-90%. Other researchers report albuminuria or proteinurias on admission in 44-63% patients, hematuria in 27%, elevated urea and creatinine in 13-27% and 14-19%, respectively, and low eGFR in 13%. There may also be imaging evidence of active renal edema and inflammation. Since renal dysfunction is early, an immunopathology response or direct viral injury may be contributing along with other systemic factors. Similar to other novel CoVs, renal involvement, acute or chronic, tends to associate with an adverse prognosis. The COVID-19 virus has been detected in renal tissue and in the urine. Due to the presence of ACE2 receptors in the Leydig cells and seminiferous tubules, it is also reasonable to speculate that testicular injury may be a consequence of COVID-19 infection.

NEUROLOGIC MANIFESTATIONS

SARS-CoV
Patients with SARS-CoV presented with ischemic stroke, likely due to the hypercoagulable state and vasculitis induced during the illness (Table 5). Case reports mentioned the detection of SARS-CoV in the cerebral spinal fluid (CSF) of patients who subsequently developed seizures. Tsai et al studied 4 patients with SARS-CoV who developed neuropathy and myopathy. Since they did not find CSF evidence of viral invasion, they attributed these findings to critical illness polyneuropathy and myopathy.

Ocular manifestations have not been widely reported in patients with SARS-CoV infection. However, in 1 case report, tears from a female patient were analyzed by PCR and shown to be positive for SARS-CoV when other testing methods were negative. Still, risk of SARS-CoV transmission through tears remains low.

MERS-CoV
MERS-CoV causes both central and peripheral neurological abnormalities. Neurological symptoms occur later in the course of the illness as weakness and neuropathy and less frequently hypersomnia and ataxia (Table 5). In a study of 4 patients with neurological symptoms conducted by Kim et al, MERS-CoV was not detected in the CSF, however, patients developed Guillain-Barre’ syndrome, Bickerstaff’s encephalitis, critical illness myopathy, viral myopathy or toxin associated myopathy and neuropathy. Algahtani et al also report a case of cerebrovascular accident attributable to disseminated intravascular coagulation (DIC) and viral-induced autoimmune response. The authors are not aware of evidence describing the ocular manifestations of MERS-CoV or the ability to isolate the virus in tear samples.

COVID-19
Increasingly recognized sensory symptoms of COVID-19 infection include the sudden onset of anosmia, and, to a lesser extent, dysgeusia (Table 6).
### Table 4. Gastrointestinal manifestations of SARS-CoV, MERS-CoV and COVID-19.

#### SARS (only studies with large study population included)

| Study                        | N     | Clinical Features                                                                 | Key findings on investigations                                                                 | Histopathology                                      | Key study findings and GI symptoms were less common |
|------------------------------|-------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|----------------------------------------------------|-----------------------------------------------------|
| Lee et al (2003)             | 138   | • Diarrhea (19.6%)                                                               | • Diarrhea (19.6%)                                                                               | N/A                                                | N/A                                                 |
| Donnelly et al (2003)        | 1425  | • Loss of appetite (54.6%)                                                       | • Loss of appetite (54.6%)                                                                       | N/A                                                | N/A                                                 |
| Peiris et al (2003)          | 75    | • Abdominal pain (13%)                                                           | • Nausea and vomiting (19.6%)                                                                   | N/A                                                | N/A                                                 |
| Leung et al (2003)           | 138   | • Watery diarrhea (73%)                                                           | • Watery diarrhea (19.6% on admission, increased to 53% after hospitalization, median 3 days after) | N/A                                                | N/A                                                 |
| Choi et al (2003)            | 267   | • Vomiting (14%)                                                                 | • Average duration: 3.7 ± 2.7 5.8% only GI symptoms on presentation                             | N/A                                                | N/A                                                 |
| Shi et al (2005)             | 14    | • Upper GI hemorrhage (2/7)                                                      | • Peak 3-20/day                                                                                  | N/A                                                | N/A                                                 |
| Kwan et al (2005)            | 240   | • Hematochezia (1/7)                                                             | • Watery diarrhea (38.4 % within first week, 20.3% on presentation)                              | N/A                                                | N/A                                                 |

#### Clinical Features

- Diarrhea (19.6%)
- Nausea and vomiting (19.6%)
- Loss of appetite (54.6%)
- Abdominal pain (13%)
- Vomiting (14%)
- Watery diarrhea (38.4% within first week, 20.3% on presentation)
- Average duration: 3.7 ± 2.7 5.8% only GI symptoms on presentation
- Peak 3-20/day

#### Key findings on investigations

- Diarrhea (19.6%)
- Nausea and vomiting (19.6%)
- Loss of appetite (54.6%)
- Abdominal pain (13%)
- Vomiting (14%)
- Watery diarrhea (38.4 % within first week, 20.3% on presentation)
- Average duration: 3.7 ± 2.7 5.8% only GI symptoms on presentation
- Peak 3-20/day

#### Histopathology

- N/A
- N/A
- N/A

#### Key study findings and GI symptoms were less common

- GI symptoms less common at presentation
- 21% concomitant fever, diarrhea, and radiological worsening
- Patients with GI symptoms had higher ICU admission ($P < 0.001$)

#### Key findings on investigations

- Viral RNA in stool (97%) (14.4 ± 2.2 days from onset)
- N/A
- N/A
- N/A
- Pseudomembranous plaques, shallow ulcers in TI, scattered hemorrhagic spots in gastric mucosa
- Patients with bleeding: coffee ground liquid in GIT
- Lymphoid tissue depletion in all
- SARS-CoV particles detected in epithelial cells in diarrheal patient only
- GI symptoms may be due to: Acute immune damage
- GI symptoms may be due to: Acute immune damage
- GI symptoms more common in:
  - F>M (6:1) ($P < 0.001$)
  - Geographical
  - Patients with GI symptoms had lower mortality and ventilator requirement ($P < 0.005$)

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### Table 4. (continued)

| Study | Assiri et al (2013) | Corman et al (2015) | Alenazi et al (2017) | Zhou et al (2017) | Al-Abdley et al (2019) |
|-------|---------------------|---------------------|---------------------|-----------------|----------------------|
|       | N = 47, confirmed cases | N = 37, confirmed cases | N = 130, confirmed cases | Human intestinal epithelial cell culture, hDDP4 transgenic mice | N = 33, confirmed cases |
|       | Retrospective study | Clinicopathologic study | Clinicopathologic study | Clinicopathologic study | Clinicopathologic study |

#### MERS

**Clinical features**
- Diarrhea (26%)
- Nausea (21%)
- Vomiting (21%)
- Abdominal pain (17%) (at presentation)

**Key findings on investigations**
- 14.6% stool yielded viral RNA

**Key study findings and message**
- GI symptoms in community acquired infection: 46.2%
- Healthcare associated infection: 46.6%
- HAI in healthcare workers: 16%

- RNA positive stool (57%) did not correlate with presence of GI symptoms

- GI symptoms among the commonest extrapulmonary symptoms
- Intestinal epithelial cells could support viral replication
- Primary gastric infection can lead to respiratory symptoms via hematogenous or lymphatic spread
- Diarrhea may be associated with prolonged viral detection (p 0.069)

#### COVID-19

| Study | Wang et al (2020) | Guan et al (2020) | To et al (2020) | Xie et al (2020) | Pan et al (2020) | Wu et al (2020) |
|-------|-------------------|-------------------|----------------|-----------------|-----------------|---------------|
|       | N = 138, confirmed cases | N = 1099, confirmed cases | N = 12, suspected cases | N = 19 suspected cases | N = 204, confirmed cases | N = 74, confirmed cases |
|       | Clinicopathologic study | Retrospective study | Clinicopathologic study | (9 confirmed cases) Clinicopathologic study | Retrospective study | Clinicopathologic study |

- CXR scores at peak of diarrhea did not correlate with frequency

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Table 4. (continued)

| COVID-19 |    |    |    |    |    |
|----------|----|----|----|----|----|
| Clinical features | • Anorexia (39.9) | • Diarrhea (3.8%) | • Any GI symptom: 50.5% | • Any GI symptom: 50.5% |
| | • Diarrhea (10.1) | • Nausea or vomiting (5%) | • Only GI symptoms: 0.03% | • Only GI symptoms: 0.03% |
| | • Nausea (10.1%) | | • Loss of appetite (39.7% of total, 78.6% of all GI symptoms) | • Loss of appetite (39.7% of total, 78.6% of all GI symptoms) |
| | • Vomiting (3.6%) | • Abdominal pain (2.2%) | • Diarrhea (17.1%, 34%, usually 3/day) | • Diarrhea (17.1%, 34%, usually 3/day) |
| | • Abdominal pain (2.2%) | | • Vomiting (0.02%, 3.9%) | • Vomiting (0.02%, 3.9%) |

Key findings on investigations

| N/A | N/A | 2019-nCoV detected in 91.7% saliva samples | RNA positive stool samples: 88.9% of confirmed (overall 42%) |

Key study findings and message

| ICU patients more likely to have anorexia and abdominal pain | GI symptoms less common | Presence of GI symptoms not associated with stool RNA positivity | Fecal transmission possible |
|----------------------------------------------------------------|------------------------|----------------------------------------------------------------|---------------------------|
| (P < 0.001, P = 0.02) | GI symptoms had longer interval from symptom onset to admission (P = 0.013) | GI symptoms worsened with severity of disease | Patients with GI symptoms more likely to get antibiotics (P = 0.018) |
| | Patients with GI symptoms not associated with stool positivity | | No association presence of GI symptoms with total hospital stay, ICU days or mortality |
| | Prolonged fecal viral shedding up to 5 weeks | | Presence of GI symptoms not associated with prolonged fecal viral shedding |
| | Disease severity not associated with prolonged fecal viral shedding | | Fecal transmission possible |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CXR, chest x-ray; EM, electron microscopy; F, female; GIT, gastrointestinal tract; HAI, healthcare associated infection; HAI, healthcare associated infection; MERS-CoV, middle east respiratory syndrome coronavirus; SARS-COV, severe acute respiratory syndrome coronavirus; TI, terminal ileum.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CXR, chest x-ray; EM, electron microscopy; F, female; GIT, gastrointestinal tract; HAI, healthcare associated infection; HAI, healthcare associated infection; MERS-CoV, middle east respiratory syndrome coronavirus; SARS-COV, severe acute respiratory syndrome coronavirus; TI, terminal ileum.
Table 5. Renal manifestations of SARS-CoV, MERS-CoV and COVID-19.

### SARS (only studies with large study population included)

| Study                  | N, confirmed cases | Clinical features | Key findings on investigations | Key study findings and message | Histopathology | Key study findings and message |
|------------------------|--------------------|-------------------|--------------------------------|--------------------------------|----------------|--------------------------------|
| Booth et al (2003)     | 144                | Renal dysfunction| ARF (6%) during course          |                               | N/A            |                               |
|                        |                    |                   | of hospitalization              |                               | N/A            |                               |
| Zou et al (2004)       | 165                | Renal dysfunction| N/A                            |                               | N/A            |                               |
| Chan et al (2004)      | 669                | ARF (17%)         | 7.2 ± 4.3 days after admission  |                               | N/A            |                               |
| Huang et al (2004)     | 78                 | N/A               | Cr normal at presentation, then |                               | N/A            |                               |
| Ding et al (2004)      | 8                  | ARF (6.7%)        | within 5-48 days of onset       |                               | N/A            |                               |
| Chu et al (2005)       | 536                | N/A               |                               |                               | N/A            |                               |

### MERS

| Study                  | N, confirmed cases | Clinical feature | Histopathology |
|------------------------|--------------------|------------------|----------------|
| Assiri et al (2013)    | 47                 | Coexisting renal | N/A            |
| Arabi et al (2014)     | 12                 | disease (49%)    | N/A            |
| Saad et al (2014)      | 70                 | Coexisting renal | N/A            |
| Cha et al (2015)       | 30                 | disease (42%)    | N/A            |
| Yeung et al (2016)     | 1                  | ARF (42.9%)      | N/A            |
| Alsaad et al (2017)    | 1                  | Coexisting renal | N/A            |

### ACE2 expressed and virus detected in kidneys

- ARF significant risk factor for mortality (P < 0.001)
- ARF more likely in older age group, patients with ARDS, and requiring inotropes (P < 0.001)
- Albumin, ALT at presentation, peak CPK after admission associated with development of ARF (P < 0.001, P < 0.04, P < 0.001)
- Renal features likely multiorgan failure related, no direct viral pathology

### Tubular epithelial cell degenerative and regenerative changes

- Mild glomerular ischemic changes

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### MERS

| Key study findings and message | Chronic renal disease was a common comorbidity | Renal features may be due to: | Acute kidney injury is a common complication | MERS-CoV induced apoptosis via upregulation of Smad7 and FGF2 expression | Tissue tropism in kidneys |
|---|---|---|---|---|---|
| | | • Cytokine dysregulation | • AKI more likely in older patients ($P = 0.016$) | | |
| | | • Direct viral invasion | • Preexisting CKD not associated with later development of AKI | | |
| | | • Autoimmune | • AKI, RRT risk factors for mortality (univariate) | | |

### COVID-19

| Study | Wang et al (2020)  
N = 138, confirmed cases  
Retrospective study | Cheng et al (2020)  
N = 701, confirmed cases  
Retrospective study | Wang et al (2020)  
N = 205, confirmed cases  
Clinicopathologic | Li et al (2020)  
N = 193, confirmed cases  
Retrospective study | Zhou et al (2020)  
N = 191, confirmed cases  
Retrospective study |
|---|---|---|---|---|---|
| Clinical Features | • Coexisting chronic renal disease (2.9%)  
AKI (3.6%) | • Coexisting chronic renal disease (2%)  
AKI (3.2%) | N/A | AKI (28%) | AKI (15%) (Av 15 days after symptom onset) |
| Key findings on investigations | † Cr | † Urea (13.1%)  
eGFR < 60 (13.1%)  
Proteinuria (43.9%)  
Hematuria (26.7%) | No viral detection in urine (72 samples) | • † Cr (10%)  
† Urea (14%)  
Proteinuria (59%)  
Hematuria (44%) | † Cr |
| Key study findings and message | ICU patients more likely to have † Cr ($P = 0.04$)  
† BUN (0.001)  
Cr and urea increased with disease progression | † Cr at admission more common in males, older patients, more severe disease ($P < 0.001$, $P < 0.001$, $P = 0.026$)  
AKI, in hospital death, mechanical ventilation more common in patients with baseline † Cr ($P < 0.001$, $P < 0.001$, $P = 0.012$)  
Higher in hospital death rate with proteinuria, hematuria, baseline † Cr, Urea, AKI Stage 2 or 3 ($P < 0.001$; $P = 0.003$ for AKI stage 1)  
Renal features may be due to direct viral effect, immune mediated, virus induced cytokines and mediators. | No viral shedding in urine | AKI associated with severe outcome ($P < 0.001$) | † Cr associated with in-hospital death ($P = 0.045$)  
Higher incidence of AKI in nonsurvivors ($P < 0.001$) |

ACE2, Angiotensin-converting enzyme 2; AKI, acute kidney injury; ARF, acute renal failure; BUN, blood urea nitrogen; CKD, chronic kidney disease; CPK, creatine phosphokinase; Cr, creatinine; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; MERS-CoV, middle east respiratory syndrome coronavirus; SARS-COV, severe acute respiratory syndrome coronavirus; RRT, rapid response team.
### Table 6. Neurological manifestations of SARS-CoV, MERS-CoV and COVID-19.

| Study | Neurological manifestations of SARS-CoV, MERS-CoV and COVID-19. |
|-------|---------------------------------------------------------------|
| **SARS (only studies with large study population included)** | |
| **Clinical features** | |
| Study | Hung et al (2003) | Lau et al (2004) | Tsai et al (2004) | Tsai et al (2005) |
| Cases | $N = 1$, confirmed cases | $N = 1$, confirmed cases | $N = 4$, confirmed cases | $N = 664$, probable |
| | Case report | Case report | Case reports | Case report |
| Seizures (4 limb twitching) starting day 5, lasting up to 30 min | Seizures (GTCS) started on day 22 | Neurological disturbances - 3 weeks after symptom onset | Axonopathic polyneuropathy (2) 3-4 weeks after onset |
| | | Motor predominant peripheral neuropathy (50%) | Myopathy (2) |
| | | Myopathy (25%) | Rhabdomyolysis (3) |
| | | Myopathy and Neuropathy (25%) | Large vessel ischemic stroke (5) |
| | | Mild hyporeflexia (75%) | |
| | | Hypesthesia in legs (75%) | |
| | | Axonopathic polyneuropathy (2) | |
| | | Myopathy (2) | |
| | | Rhabdomyolysis (3) | |
| | | Large vessel ischemic stroke (5) | |
| **Key findings on investigations** | |
| Study | Case report, review | Case report | Case report | Retrospective study |
| CSF: | SARS-CoV RNA detected | Normal cell counts, glucose, opening pressure | Virus not detected in CSF | Virus not detected in CSF |
| | 1 glucose | | 1 CK | 1 Myoglobin |
| | SARS-CoV RNA detected | Nerve conduction studies: amplitudes of compound muscle action potential (50%) | Nerve conduction studies: amplitudes of compound muscle action potential (50%) | Nerve conduction studies: amplitudes of compound muscle action potential (50%) |
| | | | | |
| **Key study findings and message** | |
| Study | Case report, review | Case report | Case report | Retrospective study |
| Symptoms may be due to direct viral pathogenicity | Symptoms likely due to critical illness polyneuropathy and/or myopathy | Symptoms likely due to critical illness polyneuropathy and/or myopathy | Symptoms likely due to critical illness polyneuropathy and/or myopathy, cannot exclude direct viral attack |
| | | | | |
| **MERS** | |
| Study | Algahtani et al (2016) | Kim et al (2017) | | |
| Cases | $N = 2$, confirmed cases | $N = 23$, confirmed cases | | |
| | Case report, review | Retrospective study | | |
| **Clinical features** | |
| | Neuropathy | Neurological disturbances – 2-3 weeks after respiratory symptoms | | |
| | Myopathy | Myalgia | | |
| | Confusion | Headache | | |
| | Ataxia, dizziness | Confusion | | |
| | Intracranial hemorrhage | Hypersomnolence | | |
| | | Weakness | | |
| | | Paresthesia | | |
| | | Hyporeflexia | | |
| | | CSF and nerve conduction studies normal | | |
| **Key findings on investigations** | |
| Study | | | | |
| **Key study findings and message** | |
| Study | | | | |
| Symptoms may be due to critical illness polyneuropathy and/or myopathy | Symptoms may be due to critical illness polyneuropathy and/or myopathy or toxin or viral induced | | |
| Hemorrhage secondary to DIC, platelet dysfunction | | | |
| **COVID-19** | |
| Study | Mao et al (2020) | Filatov et al (2020) | Bagheri et al (2020) | Poyiadji et al (2020) | Helms et al (2020) |
| Cases | $N = 214$, confirmed cases | $N = 1$, suspected | $N = 10069$, with olfactory | $N = 1$, confirmed cases | $N = 58$, confirmed cases |
| | Retrospective study | Case report | Case report | Case report | Retrospective study |
| **Clinical features** | |
| | | | | |
| | | | | |
| | | | | |
| **Key findings on investigations** | |
| Study | | | | |
| **Key study findings and message** | |
| Study | | | | |
| Symptoms may be due to critical illness polyneuropathy and/or myopathy | Symptoms may be due to critical illness polyneuropathy and/or myopathy or toxin or viral induced | | |
| | | | |
(continued on next page)
### Table 6. (continued)

| Clinical features | Altered mental status | Acute necrotizing encephalopathy | Key findings on investigations |
|-------------------|-----------------------|---------------------------------|------------------------------|
| Neurological symptoms: 36.4% | Anosmia/hyposmia (48.23%) | Agitation (69%) |
| CNS symptoms: 24.8%, most common dizziness (16.8%), headache (13.1%) | Sudden onset in 76.24% | Corticospinal tract signs (67%) |
| PNS symptoms: 8.9%, most common hypogeusia (5.6%) and hyposmia (5.1%) | Associated hyposmia in 83.38% | Confusion (65%) |
| Skeletal muscle symptoms: 10.7% | Duration: 0-30 days | Dysexecutive syndrome (56%) |

#### Key study findings and message

- Acute CVA (5.7%), impaired consciousness (14.8%), skeletal muscle injury (19.3%) more likely in severe disease ($P < 0.05$, $P < 0.001$)
- Patients with CNS symptoms more likely to have lower lymphocyte and platelet counts and higher BUN ($P < 0.05$, $P < 0.01$, $P < 0.05$)
- Patients with muscle injury more likely to have higher neutrophils, CRP, D-dimer and lower lymphocyte count ($P < 0.05$, $P < 0.001$, $P < 0.05$, $P < 0.01$)
- Neurologic symptoms may be due to direct viral pathogenicity via hematogenous or retrograde neuronal spread, immuno-suppression, or coagulation disorders
- High correlation between reported olfactory symptoms and regional reporting of COVID-19
- Olfactory symptoms may be due to neuroepithelia injury and damage to olfactory roots.
- Cytokine storm (known in influenza, other viral infections, more common in pediatrics)
- Mechanism unknown, may be due to critical illness-related encephalopathy, cytokines, medication-induced or direct viral pathogenicity.

- *ARDS, acute respiratory distress syndrome; CK, creatine kinase; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; CVA, cerebrovascular accident; EEG, electroencephalogram; GTCS, generalized tonic clonic seizures; MERS-CoV, middle east respiratory syndrome coronavirus; MRI, magnetic resonance imaging; NCCT, noncontrast computed tomography; PNS, peripheral nervous system; SARS-CoV, severe acute respiratory syndrome coronavirus.*
Patients with pre-existing neurological diseases may also have a higher risk for encephalopathy and altered mental status. As many as 36.4% patients have neurological symptoms, and these are seen more commonly in patients with severe disease. Acute cerebrovascular accidents, altered mental status, and myopathy occurred in approximately one-third of patients. In an observational series of 58 COVID-19 positive patients, Helms et al documented confusion and agitation as the most common neurologic symptoms. Corticospinal tract signs were also evident in nearly two-thirds of patients including increased deep tendon reflexes, ankle clonus and bilateral extensor plantar reflexes. One recent case report described acute hemorrhagic necrotizing encephalopathy in a patient with COVID-19 infection. Guillain-Barré syndrome has been observed after the onset of COVID-19 in a few patients presenting with lower-limb weakness and paresthesia as well as facial diplegia and ataxia. Neurological involvement is present in more severely affected patients, and patients with central neurologic symptoms also had severe lymphopenia, thrombocytopenia and uremia. Patients with myopathy have a higher inflammatory response and a higher association with hepatic and renal disease.

Patients who underwent magnetic resonance imaging showed leptomeningeal enhancement with bilateral frontotemporal hypoperfusion. Electroencephalography showed mostly nonspecific changes with findings consistent with encephalopathy. CSF analysis may show oligoclonal bands or elevated IgG levels, however, the significance of these findings is uncertain.

Ocular manifestations of COVID-19 are garnering increasing attention. Animal studies show ACE2 and transmembrane serine protease 2, both established receptors for this virus, are expressed in the conjunctiva, although to a lesser extent than in the kidneys and lungs, and lesser in females. A study reported conjunctivitis in as many as 31.6% patients, and more commonly in patients with severe disease. It has also been reported as the sole initial presentation. SARS-CoV-2 has been isolated from conjunctival swabs in patients with ocular symptoms and reportedly detected for as many as 27 days after symptom onset. Interestingly, an animal model has also shown that the conjunctival route may lead to systemic infection as well, but viral replication in the conjunctiva and chances of virus release into the bloodstream are very low.

MUSCULOCUTANEOUS MANIFESTATIONS

SARS-CoV

As many as 60% of patients with SARS-CoV had myalgia with up to 30% presenting with muscle weakness and increased creatinine phosphokinase (Table 6). However, there was no statistically significant difference in creatinine phosphokinase levels between SARS-CoV patients with ARDS vs. patients without ARDS. Muscle weakness was typically symmetric and involves truncal and weakness of the proximal limbs and neck muscles with sparing of the facial and small hand muscles. Muscle atrophy may also be the result of steroid myopathy or critical illness myopathy. A variable degree of focal myofibril necrosis noted postmortem without evidence of viral particles suggests that muscle damage is likely the result of immune-mediated damage. Cutaneous manifestations of SARS-CoV hasn’t yet been reported in the literature to the authors’ knowledge.

MERS-CoV

Myositis and muscle atrophy are less prevalent than SARS-CoV. Muscle weakness was common in patients with MERS-CoV (Table 6). Pathologic specimens mimic SARS-CoV specimens with myopathy and inflammatory cells in the areas of myofibril atrophy. Similar to SARS-CoV, cutaneous manifestation of MERS-CoV infection is rare and has not been widely reported.

COVID-19

Myalgia is also a common presenting symptom of COVID-19 infection, and 36% of patients develop muscle pain during their illness (Table 6). High creatinine kinase (CK) levels present in 14% to 33% of patients. Patients with suspected COVID-19 and muscle aches were more likely to have abnormal lung imaging findings. Higher CK levels noted in ICU-level patients in a study compared to non-ICU patients, although it was not a statistically significant finding. Rhabdomyolysis has been reported in patients with COVID-19 with MYO levels >12,000 ug/L and CK levels >11,000 U/L.

The cutaneous manifestations of COVID-19 are not widely known beyond the dermatology community. From a series of 88 patients 20% developed cutaneous manifestations including erythematous rash, widespread urticaria, and chickenpox like vesicles. The most common region involved was the trunk and pruritis was uncommon. Several recent case series have reported a viral exanthem similar to chilblains disease in patients with COVID-19. To date, there has been no correlation between cutaneous manifestations of COVID-19 and disease severity.

HEMATOLOGY MANIFESTATIONS

SARS-CoVa

Reactive lymphocytosis and severe lymphopenia (<500 cells/mm3) are uncommon in patients with SARS (Table 7). Patients with SARS-CoV infection often presented with a normal total leukocyte counts. There was no correlation between the degree of leukopenia and disease severity. However, patients with a high initial neutrophil count had worse outcomes. Cough et al reported mild to moderate (<1000 cells/mm3) lymphopenia as a common finding in SARS-CoV (70-98% of patients), especially during the first 10 days of illness. Initial hemoglobin levels were often normal but gradually decrease later. Thrombocytopenia was present in up to half of the patients, although platelet count levels...
### Table 7. Musculoskeletal Manifestation of SARS-CoV, MERS-CoV and COVID-19.

#### SARS (only studies with large study population included)

| Study         | Lee et al (2003) | Donnelly et al (2003) | Choi et al (2003) | Chen et al (2005) | Leung et al (2005) | Yu et al (2006) |
|---------------|------------------|-----------------------|-------------------|-------------------|-------------------|-----------------|
| N             | 138, confirmed cases | 1425, confirmed cases | 267 (227 confirmed cases) | 67, confirmed cases | 8, probable clinicopathologic study | 121, confirmed cases |
| Features      | Myalgia: 60.9% | Myalgia: 50.8% | Myalgia: 50% | Myalgia/arthralgia: 13.4% | N/A | Myalgia: 71% |
| Key findings  | CK (32.1%) | N/A | N/A | N/A | CK (20.9%) | CK (26%) |
| Histopathology| N/A | N/A | N/A | N/A | N/A | N/A |
| Key study findings | High peak CK predictive of ICU admission and death (univariate, \( P = 0.04 \)) | Myalgia commonly reported | No significant difference in CK levels in probable and confirmed patients | No difference in reporting of myalgia/arthralgia in patients with ARDS vs. without | • Higher CK associated with more myofiber necrosis | • CK likely due to myositis as cardiac enzymes normal |
| Clinical features | • Myalgia commonly reported | • Myalgia or arthralgia: 20% | • Myalgia or arthralgia: 26.9% | • Neuromuscular complications during MERS treatment may be underdiagnosed | • Muscle atrophy and inflammation | • Viral particles in muscle |

#### MERS

| Study         | Omrani et al (2013) | Saad et al (2014) | Kim et al (2017) | Alsaad et al (2017) |
|---------------|---------------------|------------------|------------------|---------------------|
| N             | 3, confirmed cases | 70, confirmed cases | 23, confirmed cases | 1, confirmed cases |
| Signs and symptoms | Myalgia or arthralgia: 20% | Myalgia or arthralgia: 26.9% | N/A | N/A |
| Labs          | Electromyogram in 1 normal | N/A | N/A | N/A |
| Histopathology| N/A | N/A | N/A | N/A |
| Key study findings | Mild/asymptomatic cases may contribute to spread more than recognised | Myalgia/arthralgia common nonrespiratory symptom | Neuromuscular complications during MERS treatment may be underdiagnosed | • Atrophic and myopathic changes | • • Muscle atrophy and inflammation |
| Clinical features | • Focal myofiber coagulative necrosis | • Myofiber atrophy in patients who received steroids | • No virus detected or cultured | • Viral particles detected in macrophages infiltrating muscles | • Viral particles in muscle |

#### COVID-19

| Study         | Huang et al (2020) | Chen et al (2020) | Wang et al (2020) | Guan et al (2020) | Li et al (2020) | Zhang et al (2020) |
|---------------|---------------------|-------------------|-------------------|------------------|----------------|-------------------|
| N             | 41, confirmed cases | 99, confirmed cases | 138, confirmed cases | 1099, confirmed cases | 1994, confirmed cases | 645, confirmed cases |
| Features      | N/A | N/A | N/A | N/A | N/A | N/A |
| Key study findings | N/A | N/A | N/A | N/A | N/A | N/A |
| Clinical features | N/A | N/A | N/A | N/A | N/A | N/A |
10,000 cells/mm³ are rare, and they usually normalized later. Prolonged activated partial thromboplastin time and elevated D-dimer levels were also common abnormalities (63% and 45%, respectively).

The pathogenesis of lymphopenia and thrombocytopenia in SARS has been controversial. In addition to traditional theories, vascular adhesion molecule-1, ligand and severe cytokine storm may play a vital role. Thrombocytopenia could be due to the result of interplay between autoantibodies, immune complexes, increased consumption, and decreased production of platelets.

MERS-CoV

Most patients present with a normal total leukocyte count. One-third of the patients may present with lymphopenia of <1,500 cells/mm³ and severely low levels during the early stage of the illness 600 cells/mm³ or less. Hemoglobin levels are usually normal in patients with MERS-CoV. Mild thrombocytopenia was frequently present in critically ill patients with MERS-CoV and indicates poor prognosis. Patients with a fatal form had developed DIC. However, there is a paucity of studies explaining the pathogenesis.

COVID-19

Data regarding the hematologic manifestations of COVID-19 infection are emerging. Patients with severe disease may have higher total white cell counts (median 6100 cells/mm³). Otherwise, similar to the other novel coronavirus infections, lymphopenia is a frequent finding, is present in a third of patients. Hence, lymphopenia may help as a reference index. However, there may not be any differences in lymphocyte counts between mild and severe forms of COVID-19. Neutrophilia may help to predict ICU admissions. Hemoglobin seems to be mostly unaffected by COVID-19 infection. DIC is a rare complication. In general, mild thrombocytopenia is present in one-third of patients. Patients requiring ICU admissions are seen to have higher levels of D-dimer. A meta-analysis of 9 studies showed significantly higher PT and D-dimer levels in patients with more severe disease, indicating the likelihood of DIC or a highly inflammatory state. The incidence of thromboembolic events in these patients is garnering a lot of attention. A study conducted by Litiós et al found a 69% incidence of thromboembolic events, with a 56% incidence even in patients treated with therapeutic anticoagulation. Increased levels of circulating cytokines, ferritin, C-reactive protein, and procalcitonin also seem to correlate with the severity of the disease.

OBSTETRICS MANIFESTATIONS

SARS-CoV

Although the data are limited for SARS-CoV in pregnancy, evidence suggests poorer clinical outcomes for pregnant women. Reports are available for 12 pregnant women in Hong Kong and 2 in the United States (Table 8). Among
### Table 8. Hematological manifestations of SARS-CoV, MERS-CoV and COVID-19.

| **SARS (only studies with large study population included)** | **Key findings on investigations** | **Clinical features** | **Key findings on investigations** | **Clinical features** | **Key study findings and message** | **Key study findings and message** |
|-------------------------------------------------------------|-----------------------------------|-----------------------|-----------------------------------|-----------------------|-----------------------------------|-----------------------------------|
| **Study**                                                   | **Lee et al (2003)**              | **Wong et al (2003)**  | **Chng et al (2005)**             | **Yang et al (2013)**  | **Histopathology**                | **Histopathology**                |
| **N**                                                       | 138, confirmed cases             | 157, confirmed cases  | Retrospective study               | Review                | N/A                               | N/A                               |
| **N**                                                      | 185, confirmed cases             |                       | Retrospective study               |                       | N/A                               | N/A                               |
| **Key findings on investigations**                         | Moderate lymphopenia (69.6%), continued to drop | Thrombocytopenia on admission (44.8%) | 1D-Dimer (45%) | Prolonged aPTT(42.8%) | Reactive lymphocytes in peripheral blood (15.2%) | Reactive lymphocytes in ICU group, no recovery by Day 12 |
| **Key study findings and message**                         | Moderate lymphopenia (88%)      | Neutrophilia (62%)    | Prolonged aPTT (83%)              | Lymphopenia (86%)     | Neutrophilia associated with ICU care or death (P = 0.02) | Lymphopenia commonly seen |
|                                                            | Lymphopenia (98%)                | Thrombocytopenia (81.5%) | Hb by >20g/L (61%) | Thrombocytopenia (95%) | Lymphopenia in lymphoid organs on postmortem, including splenic white pulp | Lymphopenia in lymphoid organs on postmortem, including splenic white pulp |
|                                                            | Thrombocytopenia on admission (33.9%) | Leukopenia on admission (33.9%) | DIC (2.5%) | L. CD4+, CD8+ cells | Lymphopenia (98%) | Lymphopenia (98%) |
|                                                            | Reactive lymphocytes in peripheral blood (15.2%) | Reactive lymphocytes in peripheral blood (15.2%) | | | | |
| **Histopathology**                                         | N/A                               |                       | N/A                               |                       | N/A                               | N/A                               |
| **Key findings on investigations**                         | Lymphopenia in lymphoid organs on postmortem, including splenic white pulp | Thrombocytopenia (36%) | Lymphopenia (34%) | Lymphocytosis (11%) | White count and ANC associated with ICU admission (univariate) (P = 0.030, 0.021) | White count and ANC associated with ICU admission (univariate) (P = 0.030, 0.021) |
| **Key study findings and message**                         | Neutrophilia associated with ICU care or death (P = 0.02) | Lymphocytopenia on admission (83.2%) | | | Mechanism of thrombocytopenia: | Mechanism of thrombocytopenia: |
|                                                            |                                   | Leukopenia (29.4%)    | | | • Direct viral attack on hematopoietic stem cells and megakaryocytes | • Direct viral attack on hematopoietic stem cells and megakaryocytes |
|                                                            |                                   | D-dimer               | | | • Immune mediated | • Immune mediated |
|                                                            |                                   |                      | | | • Secondary to lung damage | • Secondary to lung damage |
| **MERS**                                                   | Asari et al (2013)                | Arabi et al (2014)    | Asari et al (2014)                |                         | Preexisting malignancy (2%) | Preexisting malignancy (2%) |
| **N**                                                      | 47, confirmed cases              | 11, confirmed cases  | N = 12, (11 confirmed cases, 1 suspected) | Case series            | Thrombocytopenia (36%) | Thrombocytopenia (36%) |
| **Clinical features**                                      | Preexisting malignancy (2%)      | Preexisting malignancy (2%) | Lymphopenia (75%, 92% on presentation, in ICU) | Lympocytopenia (95%) | Lymphopenia (75%, 92% on presentation, in ICU) | Lymphopenia (75%, 92% on presentation, in ICU) |
| **Key findings on investigations**                         | Thrombocytopenia (36%) | Lymphopenia (34%) | Lymphocytosis (11%) | Thrombocytopenia (16.6%, 58% on presentation, in ICU) | | |
| **Key study findings and message**                         | Hematological manifestations common, lymphopenia most common | Lymphocytopenia (64.5%) | | | Lymphopenia commonly seen | Lymphopenia commonly seen |
| **COVID-19**                                               | Chen et al (2020)                | Wang et al (2020)     | Guan et al (2020)                 | Li et al (2020)        | Tang et al (2020)                | Zhou et al (2020)                |
| **N**                                                      | 99, confirmed cases              | 138, confirmed cases  | 1099, confirmed cases            | 1994, confirmed cases  | 449, confirmed cases             | 191, confirmed cases             |
| **Clinical features**                                      | Preexisting malignancy (7.2%)    | Preexisting malignancy (7.2%) | Lymphopenia (70.3%), | Lymphopenia (64.5%) | Lymphopenia (64.5%) | Lymphopenia (40%) |
| **Key findings on investigations**                         | Hb (51%)                         | D-dimer               | Lymphocytopenia on admission (83.2%) | Leukocytopenia (29.4%) | D-dimer | Lymphopenia (40%) |
|                                                            | Neutrophilia (38%)               |                      | | | | |

(continued on next page)
Table 8 (continued)

![Table 8](https://example.com/table8.png)

**COVID-19**

The twelve women in Hong Kong, pregnancy did not appear to impact the initial clinical presentation of SARS. Four of the 7 women presenting in the first trimester miscarried, though this finding is confounded by treatment with the purported teratogen Ribavirin in 6 patients. When compared to matched controls ($n=10$), the rate of ICU admission was significantly higher in the pregnant group (60% vs. 17.5%, $P=0.012$). Three pregnant women died, whereas no women died in the matched nonpregnant group ($P=0.01$). Of the 5 women presenting in the second or third trimester of pregnancy, 4 delivered preterm, 1 spontaneously due to preterm labor and 3 iatrogenic due to worsening maternal status.

There was no evidence of transplacental or intrapartum vertical transmission of SARS-CoV (Table 8). However, there may be hypoxia-induced placental blood flow alterations, consequent increased placental fibrin deposition, and thrombotic vasculopathy, resulting in intrauterine growth restriction in women who deliver after convalescence.

**MERS-CoV**

Pregnant women with symptomatic MERS-CoV infection may be at a higher risk of adverse events. There are 9 reported cases of symptomatic MERS-CoV in pregnant women, and 7 of them required ICU admission, 5 required mechanical ventilation, and 3 died (Table 8).

One case report of a term delivery in a recovered patient and another report of a patient delivered preterm while in the active phase of infection showed negative viral testing in the infant. There are 2 reported cases of asymptomatic MERS-CoV infection in pregnant women, both identified via contact tracing. One was identified at 6 weeks gestation, and the other at 24 weeks. Both had healthy term deliveries. Based on available epidemiologic data, it is unclear whether pregnant women with MERS-CoV have worse outcomes, though 3 deaths among eleven reported cases are concerning compared to an 8.9% death rate reported in a nonpregnant female population.

**COVID-19**

Unlike SARS-CoV and MERS-CoV, the risk of severe COVID-19 disease in the pregnant population compares favorably to the general population. Recently, a World Health Organization mission group studied 147 pregnant women with COVID-19, 65 confirmed and 82 presumed, of whom 8% had severe disease, and 1% were critical with multiorgan failure (Table 8). As the rate of adverse events seemed less compared to the general population (13.8% severe and 6.1% critical), the mission concluded that pregnant women might not be at increased risk. However, this determination may evolve with more data (Table 9).

There are a few case reports and mini case series discussing the late trimester pregnancy and COVID-19. A study on 38 third trimester pregnant women did not show any severe pneumonia requiring mechanical
### Table 9. Obstetrics and gynecology manifestations of SARS-CoV, MERS-CoV and COVID-19.

| Study | N | Clinical features | Key findings on investigations | Histopathology | Key study findings and message |
|-------|---|-------------------|-------------------------------|----------------|--------------------------------|
| **SARS** (only studies with large study population included) |
| Study | N=1, confirmed cases (19 weeks) Case report | N=10, pregnant, 40 nonpregnant confirmed cases Case-control study | N=1, confirmed case (7 weeks) Case report | N=1, confirmed case (32 weeks) Case report | N=1, confirmed case (32 weeks) Case report |
| **Clinical features** | Healthy infant at term via C-section (due to placenta previa) | Spontaneous miscarriage (57%) in first trimester pregnancies (confounded by treatment with Ribavirin) | ICU admission 60% (pregnant) vs. 18% nonpregnant (P=0.01) | Renal failure: 30% vs. 0 (P=0.01) | Spontaneous PRDM, Healthy infant via C-section (due to fetal distress) |
| | ICU admission (60%) (pregnant) vs. 18% (nonpregnant) (P=0.01) | Sepsis: 20% vs. 0 (P=0.04) | Death: 30% vs. 0 (P=0.01) (2/3 in second and third trimesters) | | Renal failure: 30% vs. 0 (P=0.01) |
| | Spontaneous delivery (60%) (pregnant) vs. 18% (nonpregnant) (P=0.01) | Preterm delivery (50%) in >24 weeks gestation | IUGR (16.6%) | | | |
| **Key findings on investigations** | N/A | Newborns tested negative for SARS | 1LDH in pregnant patients (P=0.04, <0.0001) | Cord blood, placenta, breast milk negative for antibodies | N/A |
| **Histopathology** | N/A | N/A | N/A | Convalescent, infection in third trimester: Extensive fetal thrombotic vasculopathy (FTV), sharply demarcated areas of necrotic villi |
| **Key study findings and message** | Healthy mother and infant, no vertical transmission | No perinatal SARS infection | Physiologic pregnancy related changes in immune system and respiratory mechanics | No vertical transmission | FTV possibly due to pro-thrombotic state, induced directly by virus, or hypoxia |

### MERS

| Study | N=2, confirmed cases (6 weeks and 24 weeks) Case report review | N=1, confirmed case (32 weeks) Case report review | N=1, confirmed case (32 weeks) Case report review | N=2, confirmed cases (6 weeks and 24 weeks) Case report review |
|-------|-------------------------------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| **Clinical features** | Healthy infant at 32 weeks via C-section | All required ICU | Asymptomatic patient | Asymptomatic patients |
| | | 1 stillbirth, 1 neonatal death | Healthy infant at 37 weeks via C-section due to placental abruption | ICU admission (54%) |
| | | 2 patients died | | Death (27%) (1 infected in second trimester, 2 in third) |
| **Key findings on investigations** | Infant negative for MERS-CoV | None | Neonatal IgG | N/A |
| **Key study findings and message** | Younger age, infection in later gestational period and immune response may contribute to successful outcome | Infection may be associated with maternal and perinatal death and disease | Healthy mother and infant, benign course | Case fatality similar to nonpregnant cases |

### COVID-19

| Study | N=118, confirmed or suspected Retrosp | WHO-China Joint Mission (2020) N=147 pregnant (84 confirmed cases, 82 suspected, 1 asymptomatic) | WHO-China Joint Mission (2020) N=147 pregnant (84 confirmed cases, 82 suspected, 1 asymptomatic) | WHO-China Joint Mission (2020) N=147 pregnant (84 confirmed cases, 82 suspected, 1 asymptomatic) |
|-------|-------------------------------------|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| **Clinical features** | 8% severe disease (general: 13.8%) | Mothers: No maternal deaths Outcomes: Live births: 70/7 | Mothers: No maternal deaths Outcomes: Live births: 70/7 | Mothers: No maternal deaths Outcomes: Live births: 70/7 |

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ventilation or maternal deaths, despite co-morbid conditions. There were also no fetal or neonatal deaths.143 Another study (13 women in the second and third trimesters) reported 1 ARDS and septic shock case with a stillbirth at 34 weeks of gestation.144 Other reports on women with gestational ages of 25-39 weeks raise concern for an increased risk of preterm rupture of membranes and preterm delivery.144-146 However, in contrast, a retrospective study of 16 pregnant women infected with COVID-19 compared with 45 noninfected pregnant women showed no differences in preterm labor or preterm delivery, though the youngest gestational age included was only 35 weeks. Also, there was no difference in birth weight between the 2 groups.143 Pathophysiology in obstetric patients could be due to naturally suppressed cell-mediated immunity and physiologic respiratory changes.133 A noteworthy observation by Abbas et al has been an increasing incidence of hydriatomata moles with the onset of the pandemic. The majority of these cases were primigravidae without other risk factors. They suggest an immune mediated mechanism triggered by the virus and recommend COVID testing in all women with hydatiform moles.147

Currently, there is no evidence of vertical transmission of COVID-19, as confirmed by negative viral PCR in 30 neonates.143 One study of 6 women showed no detectable virus in amniotic fluid, cord blood and breastmilk, nor on a neonatal throat swab.146 There is a paucity of data regarding COVID-19 infection in the first and second trimesters.

A study investigating the possibility of sexual transmission of COVID-19 found no virus in the vaginal discharge of 35 COVID-19-infected nonpregnant patients, possibly due to the lack of ACE2 expression in the vagina.147

CONCLUSIONS

The current COVID-19 pandemic is the third major global illness due to a novel coronavirus. Understanding COVID-19 along with the other known novel CoVs places the newest coronavirus in context. We presented the similarities and differences in pathogenesis, manifestations and outcomes with respect to a spectrum of extrapulmonary organ systems. Increasing knowledge about COVID-19 literature will aid in earlier recognition and more effective therapy.

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