

Journal Pre-proof

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

Aishwarya Gulati M.D. , Corbin Pomeranz M.D. ,
Zahra Qamar M.D. , Stephanie Thomas M.D. , Daniel Frisch M.D. ,
Gautam George M.D. , Ross Summer M.D. ,
Joeseeph DeSimone M.D. , Baskaran Sundaram M.D.

PII: S0002-9629(20)30179-8
DOI: <https://doi.org/10.1016/j.amjms.2020.05.006>
Reference: AMJMS 1068



To appear in: *The American Journal of the Medical Sciences*

Received date: 1 May 2020

Accepted date: 1 May 2020

Please cite this article as: Aishwarya Gulati M.D. , Corbin Pomeranz M.D. , Zahra Qamar M.D. , Stephanie Thomas M.D. , Daniel Frisch M.D. , Gautam George M.D. , Ross Summer M.D. , Joeseeph DeSimone M.D. , Baskaran Sundaram M.D. , A Comprehensive Review of Manifestations of Novel Coronaviruses in the Context of Deadly COVID-19 Global Pandemic, *The American Journal of the Medical Sciences* (2020), doi: <https://doi.org/10.1016/j.amjms.2020.05.006>

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Global Pandemic

Authors:

¹Aishwarya Gulati, M.D.

¹Corbin Pomeranz, M.D.

²Zahra Qamar, M.D.

³Stephanie Thomas, M.D.

²Daniel Frisch, M.D.

^{2,4}Gautam George, M.D.

^{2,4}Ross Summer, M.D.

²Joeseph DeSimone, M.D.

¹Baskaran Sundaram, M.D.

Departments of ¹Radiology, ²Medicine and ³Obstetrics and Gynecology

⁴Jane and Leonard Korman Respiratory Institute

Address for correspondence:

Baskaran Sundaram, M.D.

Professor & Director of Cardiothoracic Imaging

Department of Radiology, Thomas Jefferson University

132 S 10th St; Suite 861, Main Bldg.

Philadelphia, PA 19107

T: (215) 955-4214, F: (215) 955-8549

E-mail: Baskaran.sundaram@jefferson.edu

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 extra-pulmonary 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 multi-organ manifestations of COVID-19, making it difficult for clinicians to quickly educate themselves about this highly contagious and deadly pathogen. What's 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.

Keywords: SARS-CoV, MERS-CoV, COVID-19, Novel coronavirus

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 surge of 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 are known to cause signs and symptoms of multi-organ 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 extra-pulmonary manifestations of deadly coronaviruses making self-education time consuming.

We have attempted to summarize the manifestations of COVID-19 and other coronaviruses 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 coronaviruses. 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

Coronaviruses (CoVs) are a large family of single-stranded RNA viruses that infect humans primarily through droplets and fomites. Before December 2019, there were six known human coronaviruses, 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)[2]. The recently identified COVID-19 is a beta-CoV that infects both humans and animals. All three 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 coronaviruses. Camels are suspected to have been the zoonotic host for transmission of MERS-CoV.

The SARS-CoV outbreak spanned from 2002 to 2003 infecting 8098, causing 774 deaths resulting in a 5-10% mortality and a 43% mortality in the elderly [3, 4]. The MERS-CoV outbreak was first reported in Saudi Arabia in 2012 [4]. It then spread to Europe, Asia, Africa, and North America and infected 2494 people, causing 858 death [5]. The MERS-CoV caused severe pneumonia with an ICU admission rate of 40-50% and an in-hospital ICU death rate of 75% [6, 7]. 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 ≥ 65 years. The World Health Organization (WHO) 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 [8-10] (Table 1). Other symptoms suggestive of an upper respiratory tract infection (e.g. rhinitis) were less frequent [11]. Approximately 50% of patients developed hypoxia during hospitalization, and up to 26% progressed to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation [8, 12]. The elderly and patients with multiple comorbidities had particularly high (more than 15.7%) mortality [12, 13]. Unilateral, focal, peripheral areas of consolidations on imaging were identified in upwards of 78% of patients [10]. 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 [13]. Most patients received antibacterial antibiotics, with or without the use of ribavirin and corticosteroids [9-11].

Angiotensin-converting enzyme 2 (ACE2) serves as a functional receptor to SARS-CoV [13, 14]. SARS-CoV also disrupts the urokinase pathway, which controls fibrin levels through extracellular remodeling, and is associated with pulmonary hemorrhage and fibrosis [15]. SARS-CoV also triggers the production of high levels of proinflammatory cytokines contributing to excessive inflammation in the lungs. Hence, anti-cytokine and chemokine immunotherapy may be effective for minimizing collateral damage [12].

MERS-CoV

Common presenting symptoms of MERS include dyspnea in up to 92% and cough in 83% of patients [16, 17] (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 [16]. Most patients received antibiotics, and a small minority

received corticosteroids, ribavirin, and intravenous immunoglobulin (IVIG)[17]. In a small case series, antiviral therapy was not beneficial [18]. MERS-CoV also induces overexpression of inflammatory cytokines/chemokines [19].

COVID-19

A dry cough is a common symptom in COVID-19 infection, present in up to 68% of patients [20] (Table 1). Sore throat and sputum production are uncommon (5% or less) [21]. The presence of dyspnea is predictive of ICU admission [21]. In early descriptions of hospitalized patients in China, all patients had an abnormal chest computed tomography [20, 22]. Ground glass opacities are common (56%), followed by consolidation and interstitial abnormalities [21]. 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%[21]. Other studies noted a higher incidence of ARDS among hospitalized patients (29%), and higher mortality (15%) [20, 22]. Respiratory failure tends to have a delayed onset, occurring approximately one week after the onset of symptoms. Patients with critical illness were on average older (median age 66 vs 51 non-critically patients) and had more comorbidities [20]. Patients who received invasive mechanical ventilatory support were more likely to be male and obese [23]. Histopathology of the lung shows diffuse alveolar damage, denuded alveolar lining cells, and interstitial fibrosis [24]. There is also evidence of a higher incidence of thromboembolism in COVID-19 patients and an association between elevated D-dimer levels and mortality [25]. 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 [26].

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 [27, 28]. COVID-19 also uses angiotensin-converting enzyme 2 (ACE2) receptor to enter into cells so therapies targeting this receptor may serve as a potential treatment

option [29-32]. 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/hydroxychloroquine are currently being studied as possible therapeutic options[33].

CARDIOVASCULAR MANIFESTATIONS

SARS-CoV

Patients may present with cardiac arrhythmia, failure, and myocarditis[34-37] (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 [34]. 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 [38, 39]. 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 [40] [41]. Chronic cardiometabolic damage may also ensue in some, even 12 years after recovery with dysregulated lipid metabolism [42].

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 pro-brain natriuretic peptide levels (pro-BNP) [22, 43] (Table 1). Few reports also note sinus tachycardia and diffuse T-wave inversion on electrocardiography and global left ventricular dysfunction on echocardiography [43]. Rarely pericarditis may also ensue [6].

COVID-19

ACE2, the functional receptor of COVID-19 is expressed in the myocardium. Whether the use of the renin-angiotensin-aldosterone system (RAAS) 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 (hs-cTnI) levels [22, 44] (Table 1). CK-MB and hs-cTnI were higher in ICU patients, suggesting that myocardial injury is more likely present in patients with severe disease [45, 46]. As many as 7% of deaths in COVID-19 patients have been attributed to myocardial injury [47]. Other cardiac manifestations include acute MI, fulminant heart failure, and dysrhythmias [48]. In some studies, arrhythmia with COVID-19 infection was as high as 17% [20, 45]. 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 [48].

Presenting symptoms range from mild chest pain with preserved ejection fraction (EF) to profound cardiovascular collapse requiring extra-corporeal membrane oxygenation (ECMO). Echocardiography may show a regional wall motion abnormality or global hypokinesis with or without pericardial effusion [49, 50]. 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 [49, 50]. 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 [22, 45, 51]. 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 pro-coagulant effect necessitating the intensification of medical therapy[52].

HEPATOBIILIARY 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 ALT and or AST, hypoalbuminemia, and hyperbilirubinemia [53] (Table 2). ACE2 receptors are also found on the hepatic endothelial cells [54]. On histopathology, SARS-CoV patients had a large number of virus particles in the hepatic parenchymal cells [38, 39, 55]. Elevated levels of IL-1, IL-6, and IL-10 in patients with SARS-CoV hepatitis support coexisting acute inflammatory response [56]. Hepatic cell damage and cell-cycle disruption was seen on hepatic biopsy with apoptosis, mitotic arrest with eosinophilic bodies, and balloon-like hepatocytes [22]. Unfortunately, hepatic damage potentially due to antivirals use complicates our understanding of the etiology of hepatitis in patients with SARS-CoV [57]. Hepatic involvement may indicate a poor prognosis, particularly in patients with high LDH levels [58]. Yang et al. reported long-standing hyperglycemia (due to pancreatic injury) as an independent predictor for adverse outcomes in patients with SARS-CoV [58].

MERS-CoV

Several studies report patients with MERS-CoV and elevated liver enzymes, as well as hypoalbuminemia [59, 60] (Table 2). The degree of hypoalbuminemia also helps to predict disease severity [60]. Hepatic findings may resemble SARS-CoV-related changes [61]. However, MERS-CoV utilizes dipeptidyl peptidase-4 to infect cells (DPP-4), which is highly expressed in the liver [62, 63]. In transgenic mice, the liver injury occurred within the first week after infection resulting in hepatic necrosis and infiltration of Kupffer cells and macrophages [64]. Similar to other coronavirus infections, high

concentrations of inflammatory cytokines are noted in the acute phase, including IFN-g, TNF-a, IL-15, and IL-17 [65]. 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 LDH levels) [66] (Table 2). Patients with abnormal LFTs present with a high degree of fever, and their degree of hepatic dysfunction correlates with length of hospitalization [66]. 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 [67]. 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 [21].

GASTROINTESTINAL MANIFESTATIONS

SARS-CoV

Gastrointestinal involvement in SARS-CoV was common and occurred at different stages of the disease; rarely, patients reported only GI symptoms [68-70]. The most common gastrointestinal presentation was loss of appetite (up to 55%) and watery diarrhea (up to 76%) [69, 71] (Table 3). Patients also complained of nausea, vomiting (14-22.2%) and abdominal pain (3.5-12.6%) [72]. 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 [68]. Others found that GI symptoms at presentation conferred a better prognosis [69]. Others found no association between diarrhea and the development of ARDS or the requirement of ventilatory support [70]. 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 [72].

A significant mode of spread in community outbreaks was fecal-oral transmission [70, 73, 74]. Patients with diarrhea also had a higher rate of positive serological and nasopharyngeal secretion tests [75]. The virus remained stable in stool up to 2 to 4 days, and may even be detectable as late as four weeks [73] [70, 76].

MERS-CoV

Patients may present with GI symptoms, pain, and fever [16, 77, 78] (Table 3). Patients with gastrointestinal symptoms have delayed MERS-CoV serological clearance [60, 79]. 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 gastrointestinal symptoms [79, 80]. While the virus replicates in the intestinal tract, isolation of the virus from feces and fecal-oral transmission are rare [81-83].

COVID-19

There is increasing recognition of gastrointestinal symptoms in COVID-19 patients (up to 50%) [84]. Patients may present only with gastrointestinal symptoms [20, 84]. 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) [20-22, 84]. Vomiting has been shown to be a more common presenting symptoms 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 [22, 24]. The delayed recognition of GI symptoms and lack of awareness may lead to a delay in seeking medical care [22]. 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 [22]. Patients with obesity are at significantly higher risk for severe disease requiring critical care and invasive mechanical

ventilation. Compared with patients with a BMI $<25 \text{ kg/m}^2$, patients with BMI $>35 \text{ kg/m}^2$ have been seen to have 7 times the odds for requiring invasive mechanical ventilation [25, 26].

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 [85]. The virus is detectable in stool in up to half of COVID-19 patients [86, 87], and the feces remains positive for as much as four weeks [87]. ACE 2 and viral protein have been detected in gastrointestinal epithelial cells, and infectious virus particles were isolated from feces [88]. Fecal PCR testing has been shown to be as accurate as PCR detection from a sputum sample, and in some cases, fecal PCR is positive before sputum PCR [88]. It remains unclear if the fecal-oral route is a significant mode of transmission.

RENAL 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 [89]. However, acute renal failure was noted in 5-15% of patients and more often developed subsequently 7-20 days after presentation [89-92]. 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 [75, 91]. Patients with renal dysfunction had mortality rates around 90% [75, 90, 91, 93, 94]. Patients with hypouricemia and chronic renal replacement therapy also had poor outcomes [95-97].

On microscopy, acute tubular necrosis has been observed in these patients [91]. 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 [76, 98]. Xu et al. reported that six patients who died of SARS-CoV had testicular damage, which was also likely secondary to the immune response [99].

MERS-CoV

MERS-CoV uses the exopeptidase dipeptidyl peptidase 4 (DPP4) or CD 26 as its cellular receptor, which is highly expressed in kidneys [100]. Renal involvement is as high as 41% and required dialysis more than SARS-CoV patients [4, 17, 60] (Table 4). 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 [16, 101, 102]. The virus has been detected in urine and renal tissue and causes apoptosis, suggesting direct viral pathogenicity complements the other mechanisms of renal injury [17, 61, 103].

COVID-19

Acute renal dysfunction in COVID-19 at the time of presentation is not uncommon [92, 104, 105]. The incidence of acute kidney injury either at presentation or later is as high as 15% with a high mortality rate of 60-90% [106, 107] (Table 4). Other researchers report albuminuria or proteinuria 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% [104, 105]. There may also be imaging evidence of active renal edema and inflammation [104]. Since renal dysfunction is early, an immunopathology response or direct viral injury may be contributing along with other systemic factors [20, 92]. Similar to other novel coronaviruses, renal involvement, acute or chronic, tends to associate with an adverse prognosis [22, 105, 107]. The COVID-19 virus has been detected in renal tissue and in the urine [39, 70, 108]. 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[109].

NEUROLOGIC MANIFESTATIONS

SARS-CoV

Patients with SARS-CoV presented with ischemic stroke, likely due to the hypercoagulable state and vasculitis induced during the illness [110] (Table 5). Case reports mentioned the detection of SARS-CoV in the cerebral spinal fluid (CSF) of patients who subsequently developed seizures [111, 112]. Tsai et al. studied four 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 [113].

Ocular manifestations have not been widely reported in patients with SARS-CoV infection. However, in one 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 hypersomnolence and ataxia (Table 5) [114, 115]. 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, CIM, viral myopathy or toxin associated myopathy and neuropathy [114]. Algahtani et al. also report a case of cerebrovascular accident (CVA) attributable to disseminated intravascular coagulation and viral-induced autoimmune response [115]. 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) [40]. Patients with pre-existing neurological diseases may also have a higher risk for encephalopathy and altered mental status [41]. As many as 36.4% patients

have neurological symptoms, and these are seen more commonly in patients with severe disease [42]. 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 [43]. One recent case report described acute hemorrhagic necrotizing encephalopathy in a patient with COVID-19 infection [44]. 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 [45]. Neurological involvement is present in more severely affected patients, and patients with central neurologic symptoms also had severe lymphopenia, thrombocytopenia, and uremia [42]. Patients with myopathy have a higher inflammatory response and a higher association with hepatic and renal disease [42].

Patients who underwent magnetic resonance imaging (MRI) showed leptomeningeal enhancement with bilateral frontotemporal hypoperfusion[43]. Electroencephalography showed mostly nonspecific changes with findings consistent with encephalopathy [43]. 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 TMPRSS2 (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 [46]. A study reported conjunctivitis in as many as 31.6% patients, and more commonly in patients with severe disease [47]. It has also been reported as the sole initial presentation [48]. 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 [49]. 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 [50].

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 (CPK) (Table 6) [10, 34, 126-128]. However, there was no statistically significant difference in CPK levels between SARS-CoV patients with ARDS versus patients without ARDS[126]. 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[128]. Muscle atrophy may also be the result of steroid myopathy or critical illness myopathy (CIM) [128]. 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 [128]. 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 [61, 129]. Muscle weakness was common in patients with MERS-CoV (Table 6) [114]. Pathologic specimens mimic SARS-CoV specimens with myopathy and inflammatory cells in the areas of myofibril atrophy [61]. Similar to SARS-CoV, cutaneous manifestation of MERS-CoV infection is rare and hasn't 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) [130]. High creatinine kinase (CK) levels present in 14% to 33% of patients [22, 41, 106, 131]. Patients with suspected COVID-19 and muscle aches were more likely to have abnormal lung imaging findings [131]. 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[132].

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[133]. The most common region involved was the trunk and pruritis was uncommon. Several recent case series have reported a viral exanthum similar to chilblains disease in patients with COVID-19[134]. 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) [10, 135]. Patients with SARS-CoV infection often presented with a normal total leukocyte counts [135, 136]. There was no correlation between the degree of leukopenia and disease severity. However, patients with a high initial neutrophil count had worse outcomes [1]. Chng 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 ten days of illness. Initial hemoglobin levels were often normal but gradually decrease later [10]. Thrombocytopenia was present in up to half of the patients, although platelet count levels $<100,000$ cells/mm³ are rare, and they usually normalized later [137]. Prolonged activated partial thromboplastin time (aPTT) and elevated D-dimer levels were also common abnormalities (63% and 45%, respectively)[10].

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 [138, 139]. Thrombocytopenia could be due to the result of interplay between autoantibodies, immune complexes, increased consumption and decreased production of platelets [137].

MERS-CoV

Most patients present with a normal total leukocyte count [17]. One-third of the patients may present with lymphopenia of <1500 cells/mm³ and severely low levels during the early stage of the illness 600 cells/mm³ or less (Table 7) [16, 17]. Hemoglobin levels are usually normal in patients with MERS-CoV [140]. Mild thrombocytopenia was frequently present in critically ill patients with MERS-CoV and indicates poor prognosis [17, 140]. Patients with a fatal form had developed disseminated intravascular coagulation (DIC) [17, 141]. 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 (Table 7) (median 6100 cells/mm³) [20, 21]. Otherwise, similar to the other novel coronavirus infections, lymphopenia is a frequent finding, is present in a third of patients [21, 130]. Hence, lymphopenia may help as a reference index [130]. However, there may not be any differences in lymphocyte counts between mild and severe forms of COVID-19. Neutrophilia may help to predict intensive care unit (ICU) admissions. Hemoglobin seems to be mostly unaffected by COVID-19 infection. DIC is a rare complication [21]. In general, mild thrombocytopenia is present in one-third of patients [21]. Patients requiring ICU admissions are seen to have higher levels of D-dimer [14]. A meta-analysis of 9 studies showed significantly higher PT and d-dimer levels in patients with more severe disease, indicating the likelihood of disseminated intravascular coagulation (DIC) or a highly inflammatory state [56]. The incidence of thromboembolic events in these patients is garnering a lot of attention. A study conducted by Llitjos et al found a 69% incidence of thromboembolic events, with a 56% incidence even in patients treated with therapeutic anticoagulation [57]. Increased levels of circulatory cytokines, ferritin, C-reactive protein and procalcitonin also seem to correlate with the severity of the disease [34, 58].

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 twelve pregnant women in Hong Kong and two in the United States (Table 8) [142]. Among the twelve women in Hong Kong, pregnancy did not appear to impact the initial clinical presentation of SARS. Four of the seven women presenting in the first trimester miscarried, though this finding is confounded by treatment with the purported teratogen Ribavirin in six 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 non-pregnant group ($P = 0.01$) [132]. Of the five women presenting in the second or third trimester of pregnancy, four delivered preterm, one spontaneously due to preterm labor and three iatrogenic due to worsening maternal status [133].

There was no evidence of transplacental or intrapartum vertical transmission of SARS-CoV (Table 8) [143-145]. 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 [143, 146].

MERS-CoV

Pregnant women with symptomatic MERS-CoV infection may be at a higher risk of adverse events. There are nine reported cases of symptomatic MERS-CoV in pregnant women, and seven of them required ICU admission, five required mechanical ventilation, and three died (Table 8) [147]. 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 [147, 148]. There are two reported cases of asymptomatic MERS-CoV infection in pregnant women, both identified via contact tracing. One was identified at six weeks gestation, and the other at 24 weeks. Both had healthy term deliveries [149]. Based on available epidemiologic data, it is unclear whether pregnant women with MERS-CoV have worse outcomes, though three deaths among eleven reported cases are concerning compared to an 8.9% death rate reported in a non-pregnant female population [150].

COVID-19

Unlike SARS-CoV and MER-CoV, the risk of severe COVID-19 disease in the pregnant population compares favorably to the general population[120]. Recently, a WHO 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 multi-organ 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 [151]. However, this determination may evolve with more data.

There are a few case reports and mini case series discussing the late trimester pregnancy and COVID-19. A study on thirty-eight third trimester pregnant women did not show any severe pneumonia requiring mechanical ventilation or maternal deaths, despite co-morbid conditions. There were also no fetal or neonatal deaths [152]. Another study (thirteen women in the second and third trimesters) reported one ARDS and septic shock case with a stillbirth at 34 weeks of gestation [153]. Other reports on women with gestational ages of 25 to 39 weeks raise concern for an increased risk of preterm rupture of membranes and preterm delivery [153-155]. However, in contrast, a retrospective study of sixteen pregnant women infected with COVID-19 compared with 45 non-infected 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 two groups [152]. Pathophysiology in obstetric patients could be due to naturally suppressed cell-mediated immunity and physiologic respiratory changes [142]. A noteworthy observation by Abbas et al has been an increasing incidence of hydatiform 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 [65].

Currently, there is no evidence of vertical transmission of COVID-19, as confirmed by negative viral PCR in thirty neonates [152]. One study of six women showed no detectable virus in amniotic fluid, cord blood, and breastmilk, nor on a neonatal throat swab [155]. 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 non-pregnant patients, possibly due to the lack of ACE2 expression in the vagina [156].

CONCLUSION:

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 coronaviruses places the newest coronavirus in context. We presented the similarities and differences in pathogenesis, manifestations, and outcomes with respect to a spectrum of extra-pulmonary organ systems. Increasing knowledge about COVID-19 literature will aid in earlier recognition and more effective therapy.

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Table 1. Pulmonary Manifestations of SARS-CoV, MERS-CoV, and COVID-19. *Legend* CXR, chest x-ray; GGO, ground glass opacities; ARDS, acute respiratory distress syndrome; URT, upper respiratory tract; RR, respiratory rate; ECMO, extracorporeal membrane oxygenation.

Journal Pre-proof

ARS (only studies with large study population included)

Study	Lee et al (2003)	Lang et al (2003)	Liu et al (2004)	Peiris et al (2003)
	N=138, confirmed cases Retrospective study	N=3, confirmed cases Clinicopathologic study	N=53, confirmed cases Retrospective study	N=75, confirmed cases Prospective study
Clinical Features	<ul style="list-style-type: none"> Preexisting chronic pulmonary disease (2.1%) Fever (100%) Cough (57.3%) Sputum (29%) Sore throat (23.2%) Coryza (22.5%) Inspiratory crackles 	<ul style="list-style-type: none"> Fever (3/3) Dyspnea (3/3) Mildly productive cough (1/3) Death within 9-15 days of illness 	<ul style="list-style-type: none"> Fever (98%) Cough (68% on admission to isolation, 74% after hospitalization, 26% productive) 4.5 ± 1.9 days after fever onset Dyspnea (40% on admission to isolation) O₂ saturation < 90% on room air (51% on hospitalization, 11% on admission to isolation) 	<ul style="list-style-type: none"> Fever (100%), recurred in 85% at mean 8.9 days Cough (29%) Spontaneous pneumomediastinum (12%) during follow-up Sore throat (11%) Shortness of breath (4%) O₂ saturation < 90% on room air (44% mean 9.1 days after symptom onset)
Key findings on investigations	<p>CXR</p> <ul style="list-style-type: none"> Consolidation (78.3% at fever onset, eventually 100%) 54.6% unilateral, focal 45.4% multifocal or bilateral Peripheral zone predominant <p>CT</p> <ul style="list-style-type: none"> Progression of chest CT infiltrates 7-10 days after admission, resolution with treatment Ill-defined peripheral GGO, usually subpleural 	<ul style="list-style-type: none"> Leukopenia (2/3) Lymphopenia (2/3) CXR: Bilateral interstitial infiltrates 	<ul style="list-style-type: none"> Abnormal CXR (59% on admission, 98% anytime) 63% patients – first unifocal infiltrates at 4.5 ± 2.1 days 37% patients - started as multifocal infiltrates at 5.8 ± 1.3 days after fever onset 	<p>Initial CXR abnormal: 71%</p> <ul style="list-style-type: none"> One lung zone: 49% Multizonal: 21% <p>Chest CT abnormal (55% of 33)</p> <ul style="list-style-type: none"> One lobe: 55% Multilobar: 46% Focal ground-glass opacification: 24% Consolidation: 36% Both: 39% <p>Radiologic worsening in 80% at mean 7.4 days</p>
Histopathology	<ul style="list-style-type: none"> Gross: Lung consolidation Early phase: Pulmonary edema with hyaline membrane formation Organizing phase: Cellular fibromyxoid organizing exudates in alveoli Scanty lymphocytic interstitial infiltrate 	<ul style="list-style-type: none"> Gross: Diffuse hemorrhage on lung surface Serous, fibrinous and hemorrhagic inflammation in alveoli with desquamation of pneumocytes and hyaline-membrane formation Capillary engorgement and 	N/A	N/A

	<ul style="list-style-type: none"> Vacuolated and multinucleated pneumocytes Viral inclusions not detected. 	<p>capillary microthrombosis, thromboemboli in bronchial arterioles</p> <ul style="list-style-type: none"> Hemorrhagic necrosis lymphocyte depletion in lymph nodes and spleen Viral RNA detected in type II alveolar cells, interstitial cells and bronchiolar epithelial cells 		
Key Study Findings and Message	<ul style="list-style-type: none"> 23.2% ICU admission, at day 6 (mean) 13.8% mechanical ventilation rate 3.6% crude mortality rate ICU patients more likely to be of older age (p=0.009) 	Severe immunological damage to lung tissue causes clinical features	<ul style="list-style-type: none"> Fever most common and earliest symptom 23% mechanical ventilation rate 	<ul style="list-style-type: none"> 83.33% of patients with GGO developed ARDS 20% mechanical ventilation 17% ICU admission Recurrence of fever (univariate) and age (multivariate) risk factors for ARDS and ICU admission
MERS				
Study	Assiri et al (2013) N=47, confirmed cases Retrospective study	Arabi et al (2014) N=12, (11 confirmed cases, 1 probable) Case series	Al-Abdley et al (2019) N=33, confirmed cases Retrospective study	Almekhlafi et al (2016) N=31, confirmed cases Retrospective study
Clinical Features	<ul style="list-style-type: none"> Preexisting chronic lung disease (26%) Smokers (23%) Fever (98%) Cough (83%) <ul style="list-style-type: none"> Dry (47%) Productive (36%) Dyspnea (72%) Sore throat (21%) Rhinorrhea (4%) 	<ul style="list-style-type: none"> Preexisting chronic lung disease (8%) Dyspnea (92%) Cough (83%) Fever (67%) Wheezing (17%) Productive cough (17%) Rhinorrhea (8%) Hemoptysis (8%) Sore throat (8%) 	<ul style="list-style-type: none"> Preexisting chronic lung disease (12%) Fever (75.7%) Cough (72%) Dyspnea (59%) Sore throat (12%) Rhinorrhea (9%) 	<ul style="list-style-type: none"> Cough (100%) Tachypnea (100%) Fever (87.1%) Sore throat (25.8%) Crackles (93.5 %) Rhonchi (32.3 %)
Key findings on investigations	CXR abnormality (100%) – ARDS pattern	CXR, CT: lobular to bilateral extensive ARDS pattern	N/A	CXR abnormality (96.4%)
Key Study Findings and Message	<ul style="list-style-type: none"> 89% ICU admission 72% mechanical ventilation 60% case fatality rate 	100% invasive mechanical ventilation, mean duration 100 days	<ul style="list-style-type: none"> Dyspnea before admission was associated with a more severe outcome (p<0.001) 	<ul style="list-style-type: none"> 87.1 % invasive mechanical ventilation (87.1%) 74.2% overall ICU mortality rate

			Prolonged MERS-CoV detection in URT in diabetics (p=0.049)	• Mortality in ICU associated with older age, severe disease and organ failure.
COVID-19				
Study	Huang et al (2020) N=41, confirmed cases Retrospective study	Wang et al (2020) N=138, confirmed cases Retrospective study	Guan et al (2020) N=1099, confirmed cases Retrospective study	Zhang et al (2020) N=1, confirmed cases Clinicopathologic study
Clinical Features	<ul style="list-style-type: none"> • Smoker (7%) • Preexisting COPD (2%) • Fever 98% • Dry cough (76%) • Dyspnea (55%), mean 8 days after onset • Sputum (28%) • Hemoptysis (5%) • ARDS (29%), mean 9 days after onset • \uparrowRR >24/min (29%) 	<ul style="list-style-type: none"> • Preexisting COPD (2.9%) • Fever 98.6% • Dry cough (59.4) • Sputum (26.8%) • Dyspnea, mean 5 days after onset <ul style="list-style-type: none"> • ARDS (19.6%), mean 8 days after onset 	<ul style="list-style-type: none"> • Preexisting chronic pulmonary disease (1.1%) • Fever (43.8% on admission, 88.7% during hospitalization) • Cough (67.8%) • Sputum (33.7%) • Sore throat (13.9%) • Nasal congestion (4.8%) • Hemoptysis (0.9%) • ARDS (3.4%) • 1.4% case fatality rate • 4 days median incubation period 	<ul style="list-style-type: none"> • Fever • Cough • ARDS requiring mechanical ventilation within 1 week
Key findings on investigations	Abnormal chest CT (100%); (98% bilateral)	<ul style="list-style-type: none"> • \downarrowPaO₂ • \downarrowPaO₂:FIO₂ 	<ul style="list-style-type: none"> • 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 non-severe disease and in 2.9% with severe disease 	CT: Patchy bilateral ground glass opacities
Histopathology	N/A	N/A	N/A	<ul style="list-style-type: none"> • 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	• ICU patients had more areas of consolidation	• High-flow O ₂ therapy in 11.1% ICU patients, non-invasive ventilation	<ul style="list-style-type: none"> • Mechanical ventilation needed (6.1%) • Radiographic abnormalities often 	Histopathologic findings consistent with diffuse

nd Message	<ul style="list-style-type: none">• 10% mechanical ventilation rate, mean 10.5 days after onset• 5% ECMO rate	<ul style="list-style-type: none">• 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• Mortality: 4.3%	absent	alveolar damage
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Table 2. Cardiovascular Manifestations of SARS-CoV, MERS-CoV, and COVID-19. *Legend* HR, heart rate; CHF, congestive heart failure; MI, myocardial infarction; BP, blood pressure; LDH, lactate dehydrogenase; CK, creatine kinase; Hb, hemoglobin; RBBB, right bundle branch block; LVEF, left ventricular ejection fraction; TnI, troponin-I; CKMB, creatine kinase myocardial band; CXR; chest x-ray; BNP, B-type natriuretic peptide; ECMO, extracorporeal membrane oxygenation.

SARS (only studies with large study population included)					
Study	Booth et al (2003)	Li et al (2003)	Pan et al (2003)	Ding et al (2004)	Yu et al (2006)
	N=144, confirmed cases Retrospective study	N=46, confirmed cases Prospective study	N=15, confirmed cases Retrospective study	N=8 (4 confirmed cases, 4 control) Clinicopathologic study	N=121, confirmed cases Retrospective study
Clinical Features	<ul style="list-style-type: none"> • Chest pain (10%) • ↑HR (46%) 	<ul style="list-style-type: none"> • No chest pain or overt CHF on admission • ↓HR (non-ICU) ↑HR (ICU) • CHF exacerbation 	<ul style="list-style-type: none"> • Sudden cardiac arrest (100%) • MI and arrhythmia (33%) 	<ul style="list-style-type: none"> • Chest pain 	<ul style="list-style-type: none"> • ↑HR (71.9%) (62.8%, 45.4%, 35.5%) • ↓BP (50.4%) (28.1%, 21.5%, 14.8% during the 1st, 2nd, 3rd week) ↓HR, transient (14.9%) • Reversible cardiomegaly (10.7%), no clinical heart failure • Chest discomfort (7%) • Palpitations (4%)
Key findings on investigations	<ul style="list-style-type: none"> • ↓Ca⁺⁺ (60%) • ↓K⁺ (26%) • ↓Mg⁺⁺ (18%) • ↓P⁺ (27%) • ↑LDH (87%) 	<ul style="list-style-type: none"> • ↑CK • ↑LDH • ↓Hb • EKG: RBBB • Echo: ↓LVEF 	<ul style="list-style-type: none"> • Abnormal cardiac enzymes (66%) 	N/A	<ul style="list-style-type: none"> • ↑CK • ↑CK (26%) without TnI or CKMB • ↑LDH • CXR or CT abnormality: 100%
Histopathology	N/A	N/A	N/A	<ul style="list-style-type: none"> • Myocardial stromal edema • Infiltration of vessels by lymphocytes • Focal hyaline degeneration • Muscle fiber lysis 	N/A

Key Study Findings and Message	<ul style="list-style-type: none"> • 20% ICU admission • 6.5% Case fatality rate (21 days) • Diabetes and other comorbidities independently associated with poor prognosis 	Possibly reversible subclinical diastolic impairment seen in SARS patients	Proposed causes of SCD: <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • ↑CK likely due to myositis as cardiac enzymes normal • 15% ICU admission • 18 (5) days mean duration of hospital stay • Tachycardia persists during follow up • Cardiac arrhythmia is uncommon
MERS					
Study	Alhogbani (2016) N=1 confirmed case Case report	Almekhlafi et al (2016) N=31, confirmed cases Retrospective study	Garout et al (2018) N=52, confirmed cases Retrospective study		
Clinical Features	CHF	↑HR (67.7%)	Pericarditis		
Key findings on investigations	<ul style="list-style-type: none"> • ↑ Tnl • ↑ BNP • ↑ Creatinine • Echo: Severe global LV dysfunction • Cardiac MRI: Myocarditis 	N/A	N/A		
Key Study Findings and Message	MERS-CoV may cause myocarditis and acute heart failure	<ul style="list-style-type: none"> • Vasopressor need is a risk factor for death (p=0.04) • 80.6% vasopressor support rate 	No association of ECMO need with outcomes		

COVID-19					
Study	Huang et al (2020) N=41, confirmed cases Retrospective study	Wang et al (2020) N=138, confirmed cases Retrospective study	Zheng et al (2020) Review	Bhatraju et al (2020) N=24, confirmed cases Retrospective study	Fried et al (2020) N=4, confirmed cases Case reports
Clinical Features	<ul style="list-style-type: none"> • ↑BP • Acute cardiac injury (12% more in ICU patients than non-ICU patients (31% vs. 4%)) 	<ul style="list-style-type: none"> • Pre-existing HTN (31.2%) (58.3% in ICU, significant) • Pre-existing CVD (14.5%) (25% in ICU, significant) • Acute cardiac injury (7.2%) (22.2% in ICU, significant) • Arrhythmia (16.7%) (44.4% in ICU patients) 	<ul style="list-style-type: none"> • Palpitations • Chest tightness 	<ul style="list-style-type: none"> • ↑HR (48%) • Vasopressor need (71%) 	<ul style="list-style-type: none"> • Myopericarditis • Decompensated heart failure • Cardiogenic Shock
Key findings on investigations	<ul style="list-style-type: none"> • ↑ TnI (12%) (31% in ICU patients, 4% in non-ICU patients) 	<ul style="list-style-type: none"> • ↑ TnI • ↑ CK-MB 	N/A	<ul style="list-style-type: none"> • ↑ TnI (15%) 	<ul style="list-style-type: none"> • Diffuse ST segment elevations • Elevated cardiac enzymes • LVEF on echo
Key Study Findings and Message	↑BP more common in ICU patients (p=0.018)	ICU patients more likely to have pre-existing hypertension, develop arrhythmias, acute cardiac injury (p<0.001)	Proposed mechanism of cardiac injury: <ul style="list-style-type: none"> • ACE 2 related • Cytokine storm • Hypoxemia 	<ul style="list-style-type: none"> • ICU admission most commonly due to hypoxemic respiratory failure, vasopressor requirement or both • 50% mortality 	<ul style="list-style-type: none"> • Similar symptoms in heart transplant patients as non-transplant patients

Table 3. Hepatobiliary Manifestation of SARS-CoV, MERS-CoV, and COVID-19. *Legend* ALT, alanine aminotransferase; AST, aspartate aminotransferase; T. Bili; total bilirubin; RT-PCR, reverse transcriptase polymerase chain reaction; LDH, lactate dehydrogenase.

SARS (only studies with large study population included)							
Study	Duan et al (2003) N=154, confirmed cases Retrospective study	Ding et al (2004) N=8 (4 confirmed cases, 4 control) Clinicopathologic study	Chau et al (2004) N=3, confirmed Case report	Zhao et al (2004) N=169, confirmed cases Retrospective study	Yang et al (2005) N=168, confirmed cases Retrospective study	Zhan et al (2006) N=12 (6 confirmed cases, 6 controls) Clinicopathologic study	Yang et al (2010) N=539 (520 confirmed cases) Prospective study
Clinical Features	Hepatic dysfunction	Hepatic dysfunction	Hepatic dysfunction	Hepatic dysfunction	Hepatic dysfunction		Diabetes: • 35.9% within 3 days • 51.3% within 2 weeks
Key findings on investigations	<ul style="list-style-type: none"> • ↑ALT &/or AST (37.7%) • ↑ALT (70.7%) • ↑ALT and AST (22.4%) • ALT and AST normalized within 2 weeks in 75.9% • ↑T. bili (8.4%) • ↑Albumin 		<ul style="list-style-type: none"> • ↑ ALT • + viral RT-PCR in liver, not sera 	<ul style="list-style-type: none"> • ↑ ALT (32.76%-62.50%) • ↑ AST (13.04%-40.00%) • ↓ Albumin (40.35%-72.00%) • Total protein remained normal 	<ul style="list-style-type: none"> • ↑ ALT: • Peak: 111.32+/- 160.24 U/L • At admission: 52.5% • First week: 71.8% • Second week: 85.7% • Third week: 85.2% • ↓ Albumin 		<ul style="list-style-type: none"> • ↑ blood glucose

	(24%) • ↓ Prealbumin (28.6%)						
Histopathology	N/A	<ul style="list-style-type: none"> • Virus detected in liver, pancreas • Virus not detected in spleen. 	<ul style="list-style-type: none"> • Apoptosis (3/3) • Accumulated cells in mitosis (2/3) • Ballooning hepatocytes • Mild to moderate lobular lymphocytic infiltration • Ki-67 + nuclei (0.5% -11.4%) • Virus detected in liver by RT-PCR, but not by EM 	N/A	Nonspecific inflammation	<p>Spleen:</p> <ul style="list-style-type: none"> • Severe white pulp damage • Altered cell distribution • Markedly reduced or absent CD3+, CD4+, and CD8+ cells • CD68+ macrophages most numerous 	ACE2 receptors found in pancreatic islet cells
Key Study Findings and Message	<ul style="list-style-type: none"> • AST/ALT elevation rates associated with disease severity ($p < 0.05$) • Possibly beneficial to suppress cytokine 	Liver may also be target of infection besides lungs	Liver damage likely by virus directly	Total protein remained normal despite albuminemia	<ul style="list-style-type: none"> • No association found between liver damage, and oxygen saturation or degree of fever or immune dysfunction • Liver 	<ul style="list-style-type: none"> • Spleen damage most likely due to direct viral attack • Steroid medication may contribute • Indirect viral mechanism, perhaps vascular, causing spleen injury 	<ul style="list-style-type: none"> • Higher mortality in patients with hyperglycemia, \uparrow AST ($p < 0.0001$) • Mortality not higher in patients with \uparrow ALT ($p = 0.35$) • SARS-CoV may cause acute insulin dependent diabetes mellitus • 5% (2/39) still had diabetes 3 years after

	storm in early stage			damage likely by virus directly • Hepatotoxic drugs may contribute		discharge
MERS						
Study	Saad et al (2014) N=70, confirmed cases Retrospective	Al-Hameed et al (2016) N=8, confirmed cases Prospective study	Alsaad et al (2017) N= 1, confirmed cases Clinicopathologic			
Clinical Features	Hepatic dysfunction (31.4%)	Hepatic dysfunction later during ICU stay (62.5%)	N/A			
Key findings on investigations	<ul style="list-style-type: none"> • ↓ Albumin • ↑ AST • ↑ T.bil 	<ul style="list-style-type: none"> • ↑ AST, ALT • ↑ T.bil 	N/A			
Histopathology	N/A	N/A	Liver: <ul style="list-style-type: none"> • 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 			
Key Study Findings and Message	Albumin <35 g/L at diagnosis predictor of severe infection (p=0.026)	41% developed multiorgan failure	Portal and lobular hepatitis, viral particles not identified in liver on EM			

COVID-19				
Study	Fan et al (2020) n=148, confirmed cases Retrospective study	Chai et al (2020) N=4 (healthy) Clinicopathologic	Huang et al (2020) N=41, confirmed cases Retrospective study	Wang et al (2020) N= 138, confirmed cases Retrospective study
Clinical Features	Hepatic dysfunction at admission (50.7%)		Preexisting chronic liver disease (2%)	Preexisting chronic liver disease (2.9%)
Key findings on investigations	↓ CD4+ and CD8+ T cells in patients with hepatic dysfunction	N/A	↑ AST (37%)(62% ICU, 25% non-ICU)	↑ LDH
Histopathology	N/A	ACE2 expression in cholangiocytes (59.7%) and hepatocytes (2.6%)	N/A	N/A
Key Study Findings and Message	<ul style="list-style-type: none"> Patients with hepatic dysfunction more likely to have moderate-high fever, more in males (p=0.035, 0.005) Abnormal liver function after admission associated with prolonged stay (p=0.02) 	<ul style="list-style-type: none"> Hepatic dysfunction more likely due to cholangiocyte damage by virus, not hepatocyte Drug induced damage, SIRS may also play a role 	Cytokine storm possible associated with disease severity	AST, ALT, T.bil, LDH higher in ICU patients (p<0.001, p=0.007, p=0.02, p<0.001)

Table 4. Gastrointestinal manifestations of SARS-CoV, MERS-CoV, and COVID-19. *Legend* TI, terminal ileum; GIT, gastrointestinal tract; EM, electron microscopy; CXR, chest x-ray; F, female; M, male; HAI, healthcare associated infection; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time.

SARS (only studies with large study population included)							
Study	Lee et al (2003) N=138, suspected Retrospective study	Donnelly et al (2003) N=1425, confirmed cases Retrospective study	Peiris et al (2003) N=75, confirmed cases Prospective study	Leung et al (2003) N=138, confirmed cases Retrospective study	Choi et al (2003) N=267 (227 confirmed cases) Retrospective study	Shi et al (2005) N=14, (7 confirmed cases, 7 suspected) Clinicopathologic study	Kwan et al (2005) N=240, confirmed cases Retrospective Study
Clinical Features	<ul style="list-style-type: none"> • Diarrhea (19.6%) • Nausea and vomiting (19.6%) 	<ul style="list-style-type: none"> • Loss of appetite (54.6%) • Diarrhea (27%) • Vomiting (14%) • Abdominal pain (13%) 	<ul style="list-style-type: none"> • Watery diarrhea (73%) (1% on admission) • 7.5 +/- 2.3 days of symptom onset • frequency 6.3 +/- 3.5/day • Peak 8.7 +/- 2.3 days, improved in all by day 13 	<ul style="list-style-type: none"> • Watery diarrhea (38.4% within 1st week, 20.3% on presentation) • Average duration: 3.7 +/- 2.7 • 5.8% only GI symptoms on presentation 	<ul style="list-style-type: none"> • Loss of appetite (23%) • Watery diarrhea (15% on admission, increased to 53% after hospitalization, median 3 days after) (frequency 3-20/day) • Vomiting (7%) 	<ul style="list-style-type: none"> • Diarrhea (1/7) • Upper GI hemorrhage (2/7) • Hematochezia (1/7) 	<ul style="list-style-type: none"> • Watery diarrhea (20.4%) • 7.5 +/- 2.8 days after fever onset • (Peak day 12) • OR: 3 for patients with diarrhea to have continued diarrhea on follow up

Key findings on investigations	<ul style="list-style-type: none"> • ↑ baseline albumin • ↓ K⁺ 	N/A	Viral RNA in stool (97%) (14.4 +/- 2.2 days from onset)	<ul style="list-style-type: none"> • ↓ K⁺ • Viral RNA in stool (16%) • No viral isolation from stool • Colonoscopy (1) grossly within normal limits 	↓ K ⁺ (41%)	N/A	K ⁺ nadir lower in diarrheal patients than non-diarrheal (p<0.05)
Histopathology	N/A	N/A	N/A	<ul style="list-style-type: none"> • On EM, viral particles detected in epithelial cells of bowel within ER, and in surface microvilli, active viral replication in intestines • Able to isolate virus by culture from small intestine 	N/A	<ul style="list-style-type: none"> • Diarrheal patient: 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 	N/A
Key Study Findings and Message	GI symptoms were less common	GI symptoms less common at presentation	21%: concomitant fever, diarrhea, and radiological worsening	<ul style="list-style-type: none"> • Patients with GI symptoms had higher ICU admission (p<0.001, higher 	<ul style="list-style-type: none"> • Diarrheal patients had non-statistically significant higher rates of positive serological 	GI symptoms may be due to: <ul style="list-style-type: none"> • Acute immune damage • Via infected lymphocytes • Opportunistic 	GI symptoms more common in: <ul style="list-style-type: none"> • F>M (6:1) (p<0.001) • Geographical (Amoy Gardens Estate residents)

			requirement of ventilatory support (p=0.004) <ul style="list-style-type: none"> GI symptoms may be due to proteins or toxins produced during viral replication 	and nasopharyngeal secretion testing <ul style="list-style-type: none"> GI symptoms may be due to direct enteric infection by virus or antibiotic treatment 	infections	(p=0.01) <ul style="list-style-type: none"> Patients with GI symptoms had lower mortality and ventilator requirement (p<0.005) CXR scores at peak of diarrhea did not correlate with frequency
MERS						
Study	Assiri et al (2013) N=47, confirmed cases Retrospective study	Corman et al (2015) N= 37, confirmed cases Clinicopathologic study	Alenazi et al (2017) N= 130, confirmed cases Clinicopathologic study	Zhou et al (2017) Human intestinal epithelial cell culture, hDDP4 transgenic mice Clinicopathologic	Al-Abdley et al (2019) N=33, confirmed cases Clinicopathologic study	
Clinical Features	<ul style="list-style-type: none"> Diarrhea (26%) Nausea (21%) Vomiting (21%) Abdominal pain (17%) (at presentation)	N/A	GI symptoms in <ul style="list-style-type: none"> Community acquired infection: 46.2% Healthcare associated infection: 46.6% HAI in healthcare workers: 16% 	N/A	<ul style="list-style-type: none"> Vomiting (31%) Diarrhea (15%) 	

Key findings on investigations	N/A	<ul style="list-style-type: none"> 14.6% stool yielded viral RNA 	N/A	N/A	RNA positive stool (57%) did not correlate with presence of GI symptoms	
Key Study Findings and Message	GI symptoms are frequent at presentation	<ul style="list-style-type: none"> Viral load in stool is significantly lower than in lower respiratory tract Virus not cultivable from stool 	MERS-CoV high in healthcare environment	<ul style="list-style-type: none"> 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)
Total Cases	N=138, confirmed cases Clinicopathologic study	N=1099, confirmed cases Retrospective study	N=12, suspected cases Clinicopathologic study	N= 19 suspected (9 confirmed cases) Clinicopathologic	N=204, confirmed cases Retrospective study	N=74, confirmed cases Clinicopathologic study

				study		
Clinical Features	<ul style="list-style-type: none"> Anorexia (39.9) Diarrhea (10.1) Nausea (10.1%) Vomiting (3.6%) Abdominal pain (2.2%) 	<ul style="list-style-type: none"> Diarrhea (3.8%) Nausea or vomiting (5%) 		Diarrhea (11.1% of confirmed)	<ul style="list-style-type: none"> Any GI symptom: 50.5% Only GI symptoms: 0.03% Loss of appetite (39.7% of total, 78.6% of all GI symptoms) Diarrhea (17.1%, 34%, usually 3/day) Vomiting (0.02%, 3.9%) Abdominal pain (0.01%, 1.9%) 	Diarrhea/Vomit/Stomachache (44.6%)
Key findings on investigations	N/A	N/A	<ul style="list-style-type: none"> 2019-nCoV detected in 91.7% saliva samples Virus cultured from 3/12 saliva samples 	RNA positive stool samples: 88.9% of confirmed (overall 42%)	↑ALT, AST ↑PT ↓monocyte count	<ul style="list-style-type: none"> RNA positive stool samples: 55%
Key Study Findings and Message	ICU patients more likely to have anorexia and abdominal pain (p<0.001, p=0.02)	GI symptoms less common		<ul style="list-style-type: none"> Presence of GI symptoms not associated with stool RNA positivity Fecal transmission possible 	<ul style="list-style-type: none"> Patients with GI symptoms had longer interval from symptom onset to admission (p=0.013) GI symptoms worsened with 	<ul style="list-style-type: none"> Presence of GI symptoms not associated with stool positivity Prolonged fecal viral shedding up to 5 weeks Disease severity not associated with prolonged fecal viral shedding Fecal transmission

					<p>severity of disease</p> <ul style="list-style-type: none">• Patients with GI symptoms more likely to get antibiotics (p=0.018)• No association presence of GI symptoms with total hospital stay, ICU days or mortality	<p>possible</p>
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Table 5. Renal Manifestations of SARS-CoV, MERS-CoV, and COVID-19. *Legend* ARF, acute renal failure; LDH, lactate dehydrogenase; Cr, creatinine; CPK, creatine phosphokinase; RRT, rapid response team; AKI, acute kidney injury; CKD, chronic kidney disease; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

ARS (only studies with large study population included)							
Study	Booth et al (2003) N=144, confirmed cases Retrospective study	Choi et al (2003) N=267 (227 confirmed cases) Retrospective study	Zou et al (2004) N=165, confirmed cases Retrospective study	Chan et al (2004) N=669, (323 tested positive) Clinicopathologic study	Huang et al (2004) N=78, probable Retrospective study	Ding et al (2004) N=8 (4 confirmed cases, 4 control) Clinicopathologic study	Chu et al (2005) N=536, confirmed cases Retrospective study
Clinical Features	Renal dysfunction	ARF (6%) during course of hospitalization	Renal dysfunction	N/A	ARF (17%). 7.2 +/- 4.3 days after admission	N/A	ARF (6.7%) within 5-48 days of onset (median 20)
Key findings on investigations	<ul style="list-style-type: none"> • ↑ Cr • ↑ Urea • ↓Ca⁺⁺ (60%) • ↓K⁺ (26%) • ↓Mg⁺⁺ (18%) • ↓P⁺ (27%) • ↑ LDH (87%) 	↑ Cr	↑ Cr ↑ Urea	<ul style="list-style-type: none"> • Virus first detected in urine on day 7, started to decline after day 16 	↑ Cr	N/A	Cr normal at presentation, then ↑
Histopathology	N/A	N/A	N/A	N/A	N/A	Virus detected in distal convoluted renal tubule	Acute tubular necrosis, no evidence of glomerular pathology
Key Study Findings and Message	↑ Urea > ↑ Cr associated with mortality (p=0.003,	↑ Cr associated with mortality	↑ Cr, ↑ Urea associated with poor prognosis (p=0.001, p=0.003)	Virus can persist >30 days after symptom onset	<ul style="list-style-type: none"> • ARF more common in older age, 	ACE2 expressed and virus detected in	<ul style="list-style-type: none"> • ARF significant risk factor for mortality (p<0.001) (uni and multivariate)

	p=0.02)	(p<0.001, univariate)		in urine	<p>males (p<0.05), diabetics (p<0.01), patients with heart failure (p<0.001)</p> <ul style="list-style-type: none"> Renal features may be due to pre-renal factors, hypotension, rhabdomyolysis, comorbidities including diabetes, age 	kidneys	<ul style="list-style-type: none"> 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=0.004, p<0.001) Renal features likely multiorgan failure related, no direct viral pathology
STUDIES							
Study	Assiri et al (2013) N=47, confirmed cases Retrospective study	Arabi et al (2014) N=12 (11 confirmed cases, 1 probable) Case series	Saad et al (2014) N=70, confirmed cases Retrospective study	Cha et al (2015) N=30, confirmed cases Retrospective study	Yeung et al (2016) Ex-vivo organ culture Non-human primate model Clinicopathologic	Alsaad et al (2017) N=1, confirmed cases Clinicopathologic study	
Clinical Features	Coexisting chronic renal disease (49%)	<ul style="list-style-type: none"> Coexisting chronic renal disease (42%) ARF requiring RRT (58%) 	ARF (42.9%)	<ul style="list-style-type: none"> Coexisting chronic renal disease 	N/A		

				(10%) • ARF (26.7%)		
histopathology	N/A	N/A	N/A	N/A	Smad7 and FGF2 expression elevated in kidneys of infected animals	<ul style="list-style-type: none"> • Tubular epithelial cell degenerative and regenerative changes • Mild glomerular ischemic changes • Viral particles detected in proximal tubular epithelial cells
Key Study Findings and Message	Chronic renal disease was a common comorbidity	Renal features may be due to: <ul style="list-style-type: none"> • Cytokine dysregulation • Direct viral invasion • Autoimmune 	Acute kidney injury is a common complication	<ul style="list-style-type: none"> • AKI more likely in older patients (p=0.016) • Preexisting CKD not associated with later development of AKI • AKI, RRT risk factors for mortality (univariate) 	MERS-CoV induced apoptosis via upregulation of Smad7 and FGF2 expression	Tissue trophism in kidneys

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
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Clinical Features	<ul style="list-style-type: none"> Coexisting chronic renal disease (2.9%) AKI (3.6%) 	<ul style="list-style-type: none"> Coexisting chronic renal disease (2%) AKI (3.2%) 	N/A	<ul style="list-style-type: none"> AKI (28%) 	<ul style="list-style-type: none"> AKI (15%) (Av 15 days after symptom onset)
Key findings on investigations	↑ Cr	<ul style="list-style-type: none"> ↑ Cr (14.4%) ↑ Urea (13.1%) eGFR<60 (13.1%) Proteinuria (43.9%) Hematuria (26.7%) 	No viral detection in urine (72 samples)	<ul style="list-style-type: none"> ↑ Cr (10%) ↑ Urea (14.%) Proteinuria (59%) Hematuria (44%) 	↑ Cr
Key Study Findings and Message	<ul style="list-style-type: none"> ICU patients more likely to have ↑ Cr (p=0.04), ↑ BUN (0.001) Cr and urea increased with disease progression 	<ul style="list-style-type: none"> ↑ 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)	<ul style="list-style-type: none"> ↑ Cr associated with in-hospital death (p=0.045) Higher incidence of AKI in non-survivors (p<0.001)

Table 6. Neurological Manifestations of SARS-CoV, MERS-CoV, and COVID-19. *Legend* GTCS, generalized tonic clonic seizures; CSF, cerebrospinal fluid; CK, creatine kinase; CNS, central nervous system; PNS, peripheral nervous system; EEG, electroencephalogram; NCCT, non-contrast computed tomography; MRI, magnetic resonance imaging; CVA, cerebrovascular accident; CRP, C-reactive protein.

Journal Pre-proof

SARS (only studies with large study population included)				
Study	Hung et al (2003) N=1, confirmed cases Case report	Lau et al (2004) N=1, confirmed cases Case report	Tsai et al (2004) N=4, confirmed cases Case reports	Tsai et al (2005) N=664, probable Retrospective study
Clinical Features	Seizures (four limb twitching) starting day 5, lasting up to 30 min	Seizures (GTCS) started on day 22	<ul style="list-style-type: none"> Neurological disturbances - 3 weeks after symptom onset Motor predominant peripheral neuropathy (50%) Myopathy (25%) Myopathy and Neuropathy (25%) Mild hyporeflexia (75%) Hypesthesia in legs (75%) 	<ul style="list-style-type: none"> Axonopathic polyneuropathy (2) 3-4 weeks after onset Myopathy (2) Rhabdomyolysis (3) Large vessel ischemic stroke (5)
Key findings on investigations	CSF: <ul style="list-style-type: none"> ↑ glucose SARS-CoV RNA detected 	CSF: <ul style="list-style-type: none"> SARS-CoV RNA detected Normal cell counts, glucose, opening pressure 	<ul style="list-style-type: none"> Virus not detected in CSF ↑ CK ↑ Myoglobin Nerve conduction studies: ↓ amplitudes of compound muscle action potential (50%) 	
Key Study Findings and Message	Symptoms may be due to direct viral pathogenicity		Symptoms likely due to critical illness polyneuropathy and/or	<ul style="list-style-type: none"> Symptoms likely due to critical illness polyneuropathy and/or myopathy, cannot exclude direct viral attack Strokes due to hypercoagulable state due to virus, medication related, vasculitis, shock

			myopathy		
MERS					
Study	Algahtani et al (2016) N=2, confirmed cases Case report, review		Kim et al (2017) N=23, confirmed cases Retrospective study		
Clinical Features	<ul style="list-style-type: none"> • Neuropathy • Myopathy • Confusion • Ataxia, dizziness • Intracranial hemorrhage 		<ul style="list-style-type: none"> • Neurological disturbances – 2- 3 weeks after respiratory symptoms • Myalgia • Headache • Confusion • Hypersomnolence • Weakness • Paresthesia • Hyporeflexia 		
Key findings on investigations			CSF and nerve conduction studies normal		
Key Study Findings and Message	<ul style="list-style-type: none"> • Symptoms may be due to critical illness polyneuropathy and/or myopathy • Hemorrhage secondary to DIC, platelet dysfunction 		<ul style="list-style-type: none"> • Symptoms may be due to critical illness polyneuropathy and/or myopathy or toxin or viral induced 		
COVID-19					
Study	Mao et al (2020) N=214, confirmed cases Retrospective study	Filatov et al (2020) N=1, suspected Case report	Bagheri et al (2020) N=10069, with olfactory dysfunction Cross-sectional	Poyiadji et al (2020) N=1, confirmed cases Case report	Helms et al (2020) N=58, confirmed cases Retrospective study

Clinical Features	<ul style="list-style-type: none"> Neurological symptoms: 36.4% CNS symptoms: 24.8%, most common dizziness (16.8%), headache (13.1%) PNS symptoms: 8.9%, most common hypogeusia (5.6%) and hyposmia (5.1%). Skeletal muscle symptoms: 10.7% 	Altered mental status	<ul style="list-style-type: none"> Anosmia/hyposmia (48.23%) Sudden onset in 76.24% Associated hypogeusia in 83.38% Duration: 0-30 days 	Acute necrotizing encephalopathy	<ul style="list-style-type: none"> Agitation (69%) Corticospinal tract signs (67%) Confusion (65%) Dysexecutive syndrome (36%)
Key findings on investigations	N/A	<ul style="list-style-type: none"> CT Head: no acute changes EEG: bilateral slowing and focal slowing in the left temporal region with sharply countered waves, possible subclinical seizures CSF studies: normal 	N/A	<ul style="list-style-type: none"> CSF unremarkable (not tested for COVID) NCCT Head: symmetric hypoattenuation within the bilateral medial thalami CT angiogram, venogram: normal MRI Brain: hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions 	<p>Brain MRI:</p> <ul style="list-style-type: none"> Perfusion abnormalities (100% of 11) Leptomeningeal enhancement (62% of 13) Ischemic stroke (23% of 13) <p>CSF (N=7):</p> <ul style="list-style-type: none"> Oligoclonal bands (29%) Elevated IgG and protein (14%) Low albumin (57%) Negative RT-PCR in CSF (100%) <p>EEG (N=8): Non-specific</p>
Key Study Findings and Message	<ul style="list-style-type: none"> 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 	Can present with encephalopathy acutely or during hospitalization	<ul style="list-style-type: none"> High correlation between reported olfactory symptoms and regional reporting of COVID-19 Olfactory symptoms 	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.

<p>more likely to have lower lymphocyte and platelet counts and higher BUN ($p < 0.05$, $p < 0.01$, $p < 0.05$)</p> <ul style="list-style-type: none">• 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, immunosuppression, or coagulation disorders		<p>may be due to neuroepithelia injury and damage to olfactory roots.</p>		
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Table 7. Musculoskeletal Manifestation of SARS-CoV, MERS-CoV, and COVID-19. *Legend* CK, Creatine kinase; ARDS, acute respiratory distress syndrome.

SARS (only studies with large study population included)						
Study	Lee et al (2003) N=138, confirmed cases Retrospective study	Donnelly et al (2003) N=1425, confirmed cases Retrospective study	Choi et al (2003) N=267 (227 confirmed cases) Retrospective study	Chen et al (2005) N=67, confirmed cases Retrospective study	Leung et al (2005) N=8, probable Clinicopathologic study	Yu et al (2006) N=121, confirmed cases Retrospective study
Clinical Features	Myalgia: 60.9%	Myalgia: 50.8%	Myalgia: 50%	Myalgia/arthritis: 13.4%	N/A	Myalgia: 71%
Key findings on investigations	↑ CK (32.1%)	N/A	N/A	↑ CK (20.9%)	↑ CK	↑CK (26%)
Histopathology	N/A	N/A	N/A	N/A	<ul style="list-style-type: none"> Focal myofiber coagulative necrosis Myofiber atrophy in patients who received steroids No virus detected or cultured 	N/A
Key Study Findings and Message	High peak CK predictive of ICU admission and death (univariate, $p=0.04$) (Association with CK on admission had $p=0.06$)	Myalgia commonly reported	No significant difference in CK levels in probable and confirmed patients	No difference in reporting of myalgia/arthritis in patients with ARDS vs. without	<ul style="list-style-type: none"> Higher CK associated with more myofiber necrosis Myopathy possibly immune mediated, possible component of steroid and critical illness myopathy 	↑CK likely due to myositis as cardiac enzymes normal
MERS						
Study	Omrani et al (2013)	Saad et al (2014)	Kim et al (2017)	Alsaad et al (2017)		

	N=3, confirmed cases Retrospective study	N=70, confirmed cases Retrospective study	N=23, confirmed cases Retrospective study	N=1, Clinicopathologic
Signs and Symptoms		Myalgia or arthralgia: 20%	Myalgia or arthralgia: 26.9%	N/A
Labs	↑ CK	N/A	Electromyogram in 1 normal	N/A
Histopathology	N/A	N/A	N/A	<ul style="list-style-type: none"> • Atrophic and myopathic changes • Inflammatory changes in perimysium and endomysium, more in areas of atrophy • Viral particles detected in macrophages infiltrating muscles
Key Study Findings and Message	Mild/asymptomatic cases may contribute to spread more than recognised	Myalgia/arthralgia common non-respiratory symptom	Neuromuscular complications during MERS treatment may be underdiagnosed	<ul style="list-style-type: none"> • Muscle atrophy and inflammation • Viral particles in muscle

COVID-19

Study	Huang et al (2020) N=41, confirmed cases Retrospective study	Chen et al (2020) N=99, confirmed cases Retrospective	Wang et al (2020) N= 138, confirmed cases, Retrospective study	Guan et al (2020) N=1099, confirmed cases Retrospective study	Li et al (2020) N=1994, confirmed cases Meta-analysis, 10 studies	Zhang et al (2020) N=645, confirmed cases Retrospective study
Clinical Features	Myalgia or fatigue: 44%	Myalgia: 11%	Myalgia: 34.8%	Myalgia or arthralgia: 14.9%	Myalgia or fatigue: 35.8% (11 – 50%)	Myalgia:11%
Key findings on investigations	↑ CK (33%)	↑ CK (13%) (associated with ↑ myocardial enzymes)	↑CK	↑ CK>= 200 U/mL: 13.7%	↑ CK: 13-33%	↑ CK

Key Study Findings and Message	No difference in level of CK in ICU and non-ICU patients	Muscle ache less commonly reported	Higher CK in ICU patients ($p=0.08$)	Muscle ache less commonly reported	<ul style="list-style-type: none">• Myalgia or fatigue more commonly reported• 5% case fatality rate overall	<ul style="list-style-type: none">• Muscle ache at admission associated with more severe/critical disease ($p=0.002$)• Higher CK in patients with abnormal imaging ($p<0.05$)
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Table 8. Hematological Manifestations of SARS-CoV, MERS-CoV, and COVID-19. *Legend* aPTT, activated partial thromboplastin time; Hb, hemoglobin; DIC, disseminated intravascular coagulation; WBC, white blood cell count; ANC, absolute neutrophil count; TPO, thyroperoxidase; PT, prothrombin time.

SARS (only studies with large study population included)				
Study	Lee et al (2003)	Wong et al (2003)	Chng et al (2005)	Yang et al (2013)
	N=138, confirmed cases Retrospective study	N=157, confirmed cases Retrospective	N=185, confirmed cases Retrospective study	Review
Key findings on investigations	<ul style="list-style-type: none"> Moderate lymphopenia (69.6%), continued to drop Thrombocytopenia on admission (44.8%) ↑D-Dimer (45%) Prolonged aPTT(42.8%) Leukopenia on admission (33.9%) Reactive lymphocytes in peripheral blood (15.2%) 	<ul style="list-style-type: none"> Lymphopenia (98%) Neutrophilia (82%) Prolonged aPTT (63%) Hb↓ by >20g/L (61%) Thrombocytopenia (55%) Thrombocytosis (49%), DIC (2.5%) ↓ CD4⁺, CD8⁺ cells 	<ul style="list-style-type: none"> Moderate lymphopenia (61.5%, 80.6% at days 5,10) Leukopenia (19.7%, 50%) Severe lymphopenia (9.8, 18.9%) Severe leukopenia (3.3%, after day 5) Thrombocytopenia (2.5%, 6.6% at days 5, 10) Severe neutropenia (1.6%, 5%) Reactive lymphocytes absent <p>V shaped trend of cell lines:</p> <ul style="list-style-type: none"> Hb nadir: Day 12 WBC (ANC) nadir: Day 7 or 8 Platelet nadir: Day 6 or 7 <ul style="list-style-type: none"> Prolonged ↓ lymphocytes in ICU group, no recovery by Day 12 	<ul style="list-style-type: none"> Lymphopenia (68-100%) Thrombocytopenia (20-55%) Leukopenia (19.4-64%) Thrombocytosis in recovery with elevated TPO
Histopathology	N/A	Lymphopenia in lymphoid organs on postmortem, including splenic white pulp	N/A	N/A
Key Study Findings and Message	Neutrophilia associated with ICU care or death (p=0.02)	↓ CD4 ⁺ , CD8 ⁺ cells at presentation associated with ICU care or death	White count and ANC associated with ICU admission (univariate)(p=0.034,	Mechanism of thrombocytopenia: <ul style="list-style-type: none"> Direct viral attack on

		(p=0.029, 0.006)		0.021)		hematopoietic stem cells and megakaryocytes • Immune mediated • Secondary to lung damage
MERS						
Study	Assiri et al (2013) N=47, confirmed cases Retrospective study		Arabi et al (2014) N=12, (11 confirmed cases, 1 suspected) Case series			
Clinical Features	Preexisting malignancy (2%)					
Key findings on investigations	<ul style="list-style-type: none"> • Thrombocytopenia (36%) • Lymphopenia (34%) • Lymphocytosis (11%) 		<ul style="list-style-type: none"> • Lymphopenia (75%, 92% on presentation, in ICU) • Thrombocytopenia (16.6%, 58% on presentation, in ICU) 			
Key Study Findings and Message	Hematological manifestations common, lymphopenia most common		Lymphopenia commonly seen			
COVID-19						
Study	Chen et al (2020) N=99, confirmed cases Retrospective study	Wang et al (2020) N= 138, confirmed cases Retrospective study	Guan et al (2020) N=1099, confirmed cases Retrospective study	Li et al (2020) N=1994, confirmed cases Meta-analysis, 10 studies	Tang et al (2020) N=449, confirmed cases Prospective study	Zhou et al (2020) N=191, confirmed cases Retrospective study
Clinical Features	N/A	Preexisting malignancy (7.2%)	Preexisting malignancy (0.9%)	N/A	N/A	Preexisting malignancy (1%)
Key findings on investigations	<ul style="list-style-type: none"> • ↓Hb (51%) • Neutrophilia (38%) • ↑D-dimer (36%) 	<ul style="list-style-type: none"> • Lymphopenia (70.3%), • ↑PT (58%) 	<ul style="list-style-type: none"> • Lymphocytopenia on admission (83.2%) • ↑D-dimer (46.4%) • Thrombocytopenia 	<ul style="list-style-type: none"> • Lymphocytopenia (64.5%) • Leukocytopenia (29.4%) 	↑D-dimer	<ul style="list-style-type: none"> • Lymphopenia (40%) • ↑D-dimer (42%)

	<ul style="list-style-type: none"> • Lymphopenia (35%) • ↓PT (30%) • Leukocytosis (24%) • ↓aPTT (16%) • Thrombocytopenia (12%) • Leukopenia (9%) • Thrombocytosis (4%) • ↑aPTT (6%) • ↑PT (5%) 		<p>(36.2%)</p> <ul style="list-style-type: none"> • Leukopenia (33.7%) • DIC (0.1%) 			
Key Study Findings and Message	Various hematological abnormalities commonly seen	<ul style="list-style-type: none"> • Leukocytosis, neutrophilia, lymphopenia, ↑D-dimer more common in ICU patients ($p=0.003$, $p<0.001$, $p=0.03$, $p<0.001$) • Lymphopenia worsened with disease severity 	More severe derangements in more severe disease	<ul style="list-style-type: none"> • Lymphocytopenia and leukocytopenia more common lab abnormalities • Lymphocytopenia may be used as reference index for coronavirus diagnosis 	<ul style="list-style-type: none"> • 28-day mortality of heparin users and non-users similar ($p=0.910$) • 28-day mortality of heparin users less than non-users in patients with SIC score ≥ 4 ($p=0.29$), or with D-dimer $>6x$ normal (0.017) 	<ul style="list-style-type: none"> • Leukocytosis, ↑D-dimer, ↑PT associated with in-hospital death ($p<0.0001$) • ↓D-dimer not solely due to sepsis, but possible underlying thromboembolic event, patients should be managed as such. <p>(Comment by Oudkerk et al)</p>

Table 9. Obstetrics and Gynecology manifestations of SARS-CoV, MERS-CoV, and COVID-19. *Legend* IUGR, intrauterine growth restriction; DIC, disseminated intravascular coagulation; PROM, premature rupture of membranes; SGA, small for gestational age; LGA, large for gestational age; Hb, hemoglobin; LDH, lactate dehydrogenase; FT, full term; HR, heart rate.

SARS (only studies with large study population included)					
Study	Robertson et al (2004) N=1, confirmed cases (19 weeks) Case report	Wong et al (2004) N=12, confirmed cases Retrospective study	Lam et al (2004) N=10 pregnant, 40 non-pregnant confirmed cases Case-control study	Stockman et al (2004) N=1, confirmed case (7 weeks) Case report	Ng et al (2009) 7 placentas Clinicopathologic study
Clinical Features	Healthy infant at term via C-section (due to placenta previa)	<ul style="list-style-type: none"> Spontaneous miscarriage (57%) in first trimester pregnancies (confounded by treatment with Ribavirin) Preterm delivery (80%) in >24 weeks gestation IUGR (16.6%) 	<ul style="list-style-type: none"> ICU admission: 60% (pregnant) vs. 18% (non-pregnant) (p= 0.01) Renal failure: 30% vs. 0 (p= 0.01) Sepsis: 20% vs 0 (p=0.04) DIC: 20% vs 0 (p=0.04) Death: 30% vs 0 (p=0.01) (2/3 in 2nd and 3rd trimesters) Hospital stay longer in pregnant patients (p= 0.01) 	<ul style="list-style-type: none"> Spontaneous PROM Healthy infant via C-section (due to fetal distress) 	<ul style="list-style-type: none"> Preterm birth (delivery in acute infection) IUGR, oligohydramnios, SGA (convalescent after third trimester infection)
Key findings on investigations	N/A	Newborns tested negative for SARS	↑LDH 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	N/A	Convalescent, infection in third trimester: Extensive fetal thrombotic vasculopathy (FTV), sharply demarcated areas of necrotic villi
Key Study Findings	Healthy mother and infant,	No perinatal SARS infection	Physiologic pregnancy related changes in immune system and	<ul style="list-style-type: none"> No vertical transmission Antibody formation may 	FTV possibly due to pro-thrombotic state, induced

and Message	no vertical transmission		respiratory mechanics	be influenced by gestation at infection	directly by virus, or hypoxia	
MERS						
Study	Alserehi et al (2016)	Assiri et al (2016)	Jeong et al (2017)	Alfaraj et al (2019)		
Type	N=1, confirmed case (32 weeks) Case report	N=5, confirmed cases (all \geq 22 weeks) Case series, retrospective	N=1, confirmed case 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	<ul style="list-style-type: none"> All required ICU 1 stillbirth, 1 neonatal death 2 patients died 	<ul style="list-style-type: none"> Asymptomatic patient Healthy infant at 37 weeks via C-section due to placental abruption 	<ul style="list-style-type: none"> Asymptomatic patients ICU care (54%) Death (27%) (one infected in 2nd trimester, 2 in 3rd) Infant death rate: 27% Case fatality rate: 35% (similar to non-pregnant, $p=0.75$) 		
Key findings on investigations	Infant negative for MERS-CoV	N/A	No 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 non-pregnant cases		
COVID-19						
Study	Chen et al (2020)	WHO-China Joint Mission (2020)	Zhu et al (2020)	Liu et al (2020)	Schwartz (2020)	Chen et al (2020)
	N=9, confirmed cases Retrospective study	N=147 pregnant (64 confirmed cases, 82 suspected, 1 asymptomatic)	N= 10 neonates, 9 mothers (1 twin) Retrospective study	N= 13 confirmed cases (2<28weeks) Retrospective study	N=38, confirmed cases Review	N=118, confirmed or suspected Retrospective study

Clinical Features	<ul style="list-style-type: none"> • Similar to other COVID-19 patients, no severe pneumonia or death • Fetal distress in 2 • All live births, no complications 	<ul style="list-style-type: none"> • 8% severe disease (general: 13.8%) • 1% critical (general: 1%) 	<p>Mothers: Similar to other COVID-19 patients</p> <p>Neonates:</p> <ul style="list-style-type: none"> • Intrauterine distress, PROM • 4 FT, 6 premature • 2 SGA, 1 LGA • Shortness of breath (6) • Fever • Vomiting • Pneumothorax • ↑HR 	<p>Mothers:</p> <ul style="list-style-type: none"> • Similar to other COVID-19 patients, 1 asymptomatic • 7.6% required ICU care (general 5%) <p>Neonates:</p> <ul style="list-style-type: none"> • Preterm labor (46%) • C-section (77%) • Fetal distress 3/10 • PROM 1/10 • Stillbirth 1/10 	No maternal deaths	<p>Outcomes:</p> <ul style="list-style-type: none"> • Live births: 70/7 • Preterm: 14/68 (iatrogenic 8/14) • Spontaneous abortion: 9 (8%) • C-section due to COVID concerns: 38/62 <p>Neonates:</p> <ul style="list-style-type: none"> • Deaths: 0 • Asphyxia: 0 • Median APGAR score: 8-9
Key findings on investigations	Amniotic fluid, cord blood, breastmilk, neonate negative for virus	N/A	<p>Neonates:</p> <p>Thrombocytopenia with abnormal liver function</p>	N/A	N/A	N/A
Message	No vertical transmission in patients with COVID-19 in late pregnancy	Pregnant women do not appear to be at higher risk	No vertical transmission detected	Infection may increase risk to mothers and neonates	No maternal-fetal transmission (30-40 weeks of gestation)	<ul style="list-style-type: none"> • No increased risk of severe disease in pregnant women. • Exacerbation of respiratory symptoms in postpartum period likely related to pathophysiological changes.