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Non-respiratory presentations of COVID-19, a clinical review

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ABSTRACT

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19) is a highly infectious viral syndrome currently threatening millions of people worldwide. It is widely recognized as a disease of the pulmonary system, presenting with fever, cough, and shortness of breath. However, a number of extrapulmonary manifestations have been described in the literature.

Objective: In this review, we seek to provide a comprehensive summary of the hematologic, gastroenterological, renal, dermatologic, neurologic, and psychiatric manifestations of COVID-19.

Discussion: Hematological presentations of COVID-19 include laboratory abnormalities such as decreased total lymphocyte count, prolonged prothrombin time (PT), elevated d-dimer, and increased lactate dehydrogenase (LDH). Several of these findings are associated with increased mortality among infected patients. The most common gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal pain. Furthermore, presence of viral RNA in patient stool suggests the possibility of additional testing modalities for COVID-19. Nephrological findings such as proteinuria, hematuria, and elevated BUN and creatinine levels have been observed. Additionally, several studies demonstrated that patients with COVID-19 who developed acute kidney injury (AKI) had a greater risk of mortality. The virus can also present with cutaneous symptoms such as erythematous rashes, urticaria, and chicken pox-like lesions. Neuropsychiatric symptoms have been described in the literature, and patients can exhibit findings consistent with viral encephalitis, cerebral vascular disease, peripheral nerve disorders, and psychosis.

Conclusion: Although COVID-19 does usually present primarily with respiratory symptoms, the extra-pulmonary manifestations of the virus are unpredictable and varied. Better understanding and awareness of these symptoms can lead to more efficient diagnosis, rapid treatment, isolation, and decreased spread of the disease.

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1. Introduction

On December 31st, 2019, the city of Wuhan, China first reported cases of a novel virus that was causing severe pulmonary symptoms and deaths [1]. From December to February, SARS-CoV-2 quickly spread to other provinces in China and Europe. This virus was taxonomically related to the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), and it similarly originated in a non-human host (most likely bat) [2]. To date, the SARS-CoV-2 virus has had devastating effects on human life, healthcare systems, and economies.

SARS-CoV-2 is a beta-coronavirus that has, as of June 2020, infected over 7 million people and resulted in more than 400,000 deaths worldwide. COVID-19 typically presents with pulmonary symptoms such as cough and sore throat and can progress to pneumonia, bronchitis, and acute respiratory distress syndrome (ARDS). While the respiratory

spread of COVID-19 has been well documented in the literature, further case reports have shown that the virus is not confined to just the lung. SARS-CoV-2 utilizes a spike protein to attach to the host ACE2 receptor, which is found in several organ systems [2]. Upon entering the cell, the virus initiates an immune cascade, which stimulates immune cells, leading to a cytokine storm and eventual destruction of tissues [3]. Its primary mode of transmission is through inhalation, though studies have suggested potential alternative means of spread.

Much has been documented in the literature regarding the respiratory presentations of the virus, but the extrapulmonary manifestations need further investigation. In this article, we review research on the hematological, gastrointestinal, renal, dermatologic, neurologic, and psychiatric complications of COVID-19.

2. Methods

The authors searched PubMed, Google Scholar, medRxiv, and SCOPUS for articles using a combination of the keywords "COVID-19," "SARS-CoV-2," and "hematology," "Neurology," "gastrointestinal," "psychiatry," "dermatology," "renal". This narrative review summarizes the

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extrapulmonary manifestations of COVID-19 and addresses key points regarding multiorgan involvement. All types of studies were evaluated including systematic reviews, case reports, case-studies, retrospective and prospective studies, letters, perspective, commentaries, and clinical guidelines. The references of all included studies were also reviewed to identify additional sources. Only studies in English (including translated studies) were reviewed. The initial literature search identified 1653 articles, of which 151 articles were deemed relevant to our research question. Data from these articles is summarized and reported by organ system.

3. Results

3.1. Hematological symptoms

Several studies have shown that patients infected with COVID-19 share similar laboratory abnormalities including decreased total lymphocyte count, prolonged prothrombin time, elevated d-dimer levels and increased lactate dehydrogenase (LDH) [2-8]. A recent meta-analysis of the laboratory derangements in COVID-19 demonstrated that lymphopenia (35–75% of cases), increased LDH (27–92% of cases), elevated and d-dimer (36–43% of cases) were among the most frequent findings [9].

3.1.1. Lab abnormalities and severity of disease

Patients with significant lab derangements had more severe disease and a greater need for critical care [2,3,5,6,9-12]. Lymphopenia is often more pronounced in those requiring ICU level care [11-15]. In Singapore, Fan et al. noted that 28% of patients infected with COVID-19 had lymphopenia, with critical care patients demonstrating significantly decreased lymphocytes compared with those not requiring ICU treatment [14]. Furthermore, 4 of the 9 ICU patients also exhibited increased levels of LDH (median value of 1684 U/L) compared to the non-ICU patients where only 5 of 26 had moderately elevated LDH [14]. Huang et al. demonstrated that in addition to marked lymphopenia, patients needing intensive care had higher levels of d-dimer (level 2.4 mg/L [0.6–14.4]) on admission than those who did not require it (0.5 mg/L [0.3–0.8], $p = 0.0042$) and also higher prothrombin times 12.2 s [IQR 11.2–13.4] when compared with non-ICU patients (10.7 s [9.8–12.1], $p = 0.012$) [3]. In a study of 140 COVID-19 positive patients by Zhang et al., 58 patients who were considered to have “severe disease” demonstrated a 2-fold increase in d-dimer compared to those with mild disease [16]. Guan et al. also determined that a significant elevation in d-dimer was more pronounced in severe cases (59.6% vs. 43.2% in non-severe) [5].

A meta-analysis examining the role of laboratory abnormalities in patients with severe COVID-19 vs. those with milder disease determined that the most predictive parameters of critical infection were lymphopenia (96.1% vs. 80.4%), thrombocytopenia (57.7% vs. 31.6%), increased LDH (58.1% vs. 37.2%) and elevated d-dimer (59.6% vs. 43.2%) [9]. Specifically, in Wu et al.'s retrospective analysis of the risk factors for disease progression to ARDS, they observed a statistically significant association between lymphopenia and the development of ARDS ($P < 0.001$) [8]. Several studies also established that higher CRP levels correlated with worse outcomes in COVID-19 such as ARDS, myocardial injury, and death [8,15,17]. As such, tracking hematologic parameters is crucial in determining prognosis and management, particularly with regard to level of care and monitoring.

3.1.2. Lab abnormalities and mortality

In addition to indicating the potential for more severe disease, laboratory abnormalities are also a predictor of mortality in infected patients [2,13]. In a case series of 138 patients with COVID-19, the mortality rate was about 4.3% (6 patients). Of those 6, 5 patients had persistent lab derangements including increased d-dimer and decreased lymphocyte counts [2]. Another retrospective cohort showed that elevated

d-dimer was associated with a higher rate of in-hospital death with 81% of terminal cases exhibiting d-dimer $> 1 \mu\text{g}$ [13]. Tang et al. analyzed abnormal coagulation parameters in patients with SARS-CoV-2 pneumonia and determined that non-survivors had significantly higher d-dimer, fibrin degradation products (FDP), and prothrombin time on admission compared to survivors ($P < 0.05$) [18]. This study was further supported by Han et al. who also demonstrated that d-dimer and FDP were especially predictive of disease progression [19]. A recent report investigating the factors affecting 28-day mortality of patients with severe illness showed that elevated d-dimer, increased age, and prolonged PT were associated with a higher mortality [20]. Early recognition of these abnormal results will play a critical role in predicting disease severity and improving outcomes with earlier intervention and supportive therapy.

3.1.3. COVID-19 and coagulopathy

Coagulation parameters are often cited as indicators for worse prognosis in patients infected with COVID-19 [17,19,21]. Compared to a healthy control, d-dimer, FDP, and fibrinogen levels are all increased in COVID-19 patients, while antithrombin (AT) levels are significantly reduced [19]. Emerging data suggests that deregulated thrombin generation and abnormal activation of the coagulation cascade can lead to the development of disseminated intravascular coagulation (DIC) and is associated with worsening pneumonia and mortality [7,22-24]. DIC was a significantly more common finding in non-survivors (71.4%) vs. survivors (0.6%) [18]. Other manifestations of coagulopathy such as the development of antiphospholipid antibodies and subsequent thrombotic events were reported in 3 ICU patients infected with SARS-CoV-2 in Wuhan, China [25]. Due to coagulation abnormalities, COVID-19 patients are at a higher risk of VTE, especially those with pre-existing comorbidities [23]. Early monitoring of these parameters can help guide medical management such as the use of VTE prophylaxis and escalation of care.

A study of COVID-19 patients from the First Affiliated Hospital of Zhengzhou University, Henan, China demonstrated that infected patients have an overall pro-thrombotic state due to platelet hyperactivity [26]. When SARS-CoV-2 and its spike protein bind directly to the platelet and ACE2 receptor, there is increased platelet activation and thrombus formation due to activation of the MAPK pathway. This facilitates the release of coagulation and inflammatory factors, leading to an overall pro-thrombotic and pro-inflammatory state [26]. The authors also suggest that the addition of ACE2 protein and anti-Spike neutralizing antibodies may be a therapeutic approach to avoid thrombotic events in these patients.

3.2. Cardiovascular symptoms

Patients with critical COVID-19 infection can also present with various cardiovascular symptoms. Animal models and cardiac autopsies suggest that COVID-19 can infect the cardiac tissue by binding to the angiotensin-converting enzyme (ACE) receptors, which can result in myocardial inflammation and damage [27]. Among the reported cardiac manifestations of COVID-19 are myocardial injury, myocarditis, arrhythmias, cardiomyopathy, and heart failure. These symptoms are summarized in Table 1.

3.2.1. Myocardial injury and myocarditis

Myocardial injury is defined as an elevation in biomarkers such as cardiac troponin I. Acute myocardial injury was reported in some of the earliest cases of COVID-19 in Wuhan, China. An early 2019 study among 41 admitted hospital patients in Wuhan reported acute cardiac injury in 12% of the patients [3]. Furthermore, another study of 138 hospitalized patients in Wuhan reported that as high as 22% of those who required ICU care experienced acute myocardial injury [2]. Another retrospective, observational study of 52 critically ill patients in Wuhan, China reported cardiac injury in 23% of the patients [28]. The increased

Table 1
Studies with COVID-19 patients presenting with cardiac symptoms.

Authors	Publication year	Type of study	Number of patients	Cardiac symptoms (%)
Yang et al. [28]	2020	Retrospective	52	Chest pain (2%), cardiac injury (23%)
Lippi et al. [29]	2020	Meta-analysis	341	Cardiac injury
Huang et al. [3]	2020	Retrospective	41	Cardiac injury (12%)
Ruan et al. [34]	2020	Retrospective	150	Myocardial damage (7%)
Liu, et al. [40]	2020	Retrospective	137	Heart palpitation (7.3%),
Wang, et al. [2]	2020	Retrospective	138	Acute cardiac injury (7.2%), Arrythmia (16.7%)
Bhatla, et al. [41]	2020	Retrospective	700	Cardiac arrest (1.3%), Atrial fibrillation (3.6%), Bradycardia (1.3%), Non-sustained ventricular tachycardia (1.4%)
Amaratunga, et al. [42]	2020	Retrospective case series	4	Bradycardia (75%), Prolonged QTc (25%)
Zhou, et al. [13]	2020	Retrospective	191	Coronary heart disease (8%), Heart failure (23%), Acute cardiac injury (17%)

prevalence of cardiac injury among patients with COVID-19 could be explained by the significantly higher levels of cardiac troponin I in severely ill patients [29].

A recent multi-hospital retrospective cohort of nearly 3000 patients demonstrated that myocardial injury was common among hospitalized COVID-19 patients ($n = 985$, 36%), and that those with a history of cardiovascular disease (CVD) were more likely to experience myocardial injury than those without [30]. Similarly, A study of 44,672 patients with COVID-19 demonstrated that a history of CVD was associated with a five-fold increase in case fatality rate compared to those without CVD (10.5% VS. 2.3%) [31,32].

A study by Lala, et al., showed that mild myocardial injury as evidenced by small increases in troponin was significantly associated with death (adjusted hazard ratio: 1.75; 95% CI: 1.37 to 2.24; $p < 0.001$), and that greater elevations correlated with a higher risk of mortality (adjusted HR: 3.03; 95% CI: 2.42 to 3.80; $p < 0.001$) [30]. Similarly, a single center retrospective study of 50 COVID-19 ICU patients in Turkey demonstrated that cardiac biomarkers including troponin I and NT-proBNP were higher in non-survivors compared to survivors [33].

Myocarditis has also contributed to mortality associated with COVID-19. In a case series of 150 patients, researchers determined that 7% died from myocarditis with circulatory failure [34]. Clinically, diagnosing myocarditis can be challenging, especially when differentiating it from acute coronary syndrome. For this reason, echocardiogram evaluation is recommended, and myocarditis associated with COVID-19 will appear as global wall motion dysfunction without focal wall motion defects [31,35,36]. Additionally, ECG abnormalities may occur as a result of myocardial inflammation, such as T wave inversion, PR and ST segment deviations [31]. Autopsy reports of COVID-19 patients have reported high viral loads, mononuclear cells, and lymphocytic infiltration as key players in mediating acute myocarditis [37-39].

3.2.2. Arrhythmias

A wide variety of arrhythmias have been observed in patients with COVID-19. In a study of 137 patients in Hubei Province, 7.3% of patients reported heart palpitations [40]. In another report of 138 hospitalized patients, cardiac arrythmia was noted in 16.7%, and these arrhythmias were more common in ICU patients [2]. In a much larger study of 700 patients, 9 cardiac arrests, 25 atrial fibrillation events, 9 clinically significant bradyarrhythmias, and 10 non-sustained ventricular tachycardias were reported [41]. Additionally, this study noted that ICU admissions were associated with incidents of atrial fibrillation among COVID-19 patients, indicating that these arrhythmias can contribute to severity of illness [41]. Lastly, a retrospective case series published in *Cureus* discussed COVID-19 related prolonged QTc and transient bradycardia as manifestations of the illness [42].

Many etiologies have been proposed to explain the occurrence of arrhythmias among COVID-19 patients. Hypoxia, inflammatory damage, abnormal metabolism, neurohormonal stress, and response to medications are some of the likely etiologies [31,35,42]. Furthermore, the effect of pro-inflammatory cytokines on the sinoatrial node could lead to the development of bradycardia in patients with COVID-19 [42].

3.2.3. Cardiomyopathy and heart failure

In a retrospective cohort study of COVID-19 patients in Wuhan, China, Zhou et al. reported heart failure in 23% of admitted patients [13]. This number was as high as 52% in those who did not survive the infection [13]. Another retrospective study demonstrated that heart failure and acute cardiac injury were more common in deceased patients, regardless of their cardiovascular history [43]. Specifically, this study reported heart failure in 24% of deceased patients, nearly half of whom did not have any history of cardiovascular disease or hypertension [43]. It is unclear whether the heart failure was due to a new cardiomyopathy or an exacerbation of existing undiagnosed left ventricular dysfunction, and the etiology is still being investigated [31,35]. Additionally, right heart failure can occur in patients with severe lung injury and ARDS [31,35]. As such, physicians should be cautious of underlying cardiac dysfunction when administering IV fluids [31,35].

Several recent case reports have also highlighted the development of Takotsubo Syndrome (TTS) in those infected with COVID-19 [44-47]. One report detailed the case of a patient who developed cardiogenic shock 16 days after infection despite normal initial troponin levels and LVEF [44]. Her bedside echo demonstrated the apical ballooning typical of TTS. Similarly, another case report discussed the case of a previously healthy 50 years old male who developed chest pain and signs of cardiogenic shock 8 days after the onset of symptoms. His echocardiogram showed akinesia of all of his basal segments, and he was ultimately diagnosed with inverted Takotsubo cardiomyopathy [45].

3.3. Gastrointestinal symptoms

While the most fatal complications of COVID-19 include ARDS, heart failure, renal failure, liver injury, and multiple organ dysfunction syndrome (MODS), GI symptoms can contribute significantly to morbidity in infected patients [48]. With regard to the gastrointestinal system, SARS-CoV-2 can present with nausea, vomiting, diarrhea, and/or abdominal discomfort [3,49-53]. A cross-sectional analysis of 204 Chinese patients with COVID-19 demonstrated that over half (103 patients, 50.5%) reported experiencing at least one of the GI symptoms. Among those, 78.6% expressed loss of appetite, 34% complained of diarrhea, 3.9% reported vomiting, and 1.9% indicated they had abdominal pain [54]. Similar clinical studies among COVID-19 patients have observed diarrhea in 3% to 61% of patients, nausea in 10% to 58%, and vomiting in 2% to 5%. Other gastrointestinal symptoms included epigastric pain, belching, and anorexia [16,55-58] (summarized in Table 2).

Healthcare workers can easily be overwhelmed by the complex symptomology and acuity of cases. While focusing primarily on the most critical respiratory symptoms, gastrointestinal manifestations can be overlooked. Though GI symptoms are not prominent in most cases and are unlikely life-threatening on their own, clinicians should endeavor to identify these early symptoms in order to prevent the potential spread of COVID-19.

3.3.1. GI symptoms and disease severity

Some studies have shown that GI symptoms can manifest before the onset of typical respiratory symptoms [2,59]. The first confirmed case of COVID-19 in the US presented with a two-day history of nausea without respiratory complaint. Days into the illness, the patient also complained of abdominal discomfort and loose stools [60]. Similarly, a recent report described a COVID-19 patient presenting with diarrhea, borborygmus, anorexia, and nausea in the absence of any respiratory symptoms [61]. Early research has suggested a correlation between GI symptoms and severity of illness. Henry et al. performed a pooled analysis of 10 different studies with a total sample of 1989 COVID-19 patients, 598 of whom (30.1%) were deemed as having "severe disease." This study examined whether patients presenting with GI symptoms could be at an increased risk of critical illness and poor prognosis. The research highlighted a significant association between abdominal pain and illness severity. Furthermore, nausea and vomiting correlated with a marginally increased risk of severe COVID-19, while diarrhea was not reported to be associated with worse disease [62]. Another retrospective case-controlled study of 278 COVID-19 positive patients and 238 COVID-19 negative patients suggested that patients presenting with GI symptoms at time of testing were more likely to test positive for the virus [63]. In comparison, patients without GI symptoms were equally likely to test positive or negative for COVID-19 [63]. Lastly, in the past few months, two cases of paralytic ileus were reported among COVID-19 patients [64]. Histopathology of resected bowel specimen in these cases suggests a role for COVID-19-induced micro-thrombosis leading to GI perforation [64].

3.3.2. Fecal shedding of COVID-19

In addition to research showing the potential correlation between GI symptoms and disease severity, several studies have determined that infected patients can shed viral particles in their stool [65-67]. One study of 42 COVID-19 positive patients demonstrated that about 67% of the patients had viral RNA present in their stool even in the absence of diarrhea or other GI symptoms. Interestingly, among this group, 64% of the patients continued to shed viral particles in fecal specimens even after the nasopharyngeal swabs turned negative [65]. This has been documented in both adult and pediatric patients. Xu et al. conducted an epidemiological and clinical study of 10 children with COVID-19 and found that 8 persistently tested positive in stool despite their nasopharyngeal swabs being negative [68].

Fecal specimen testing is just as accurate in detecting COVID-19 as nasopharyngeal swabs [66,69]. Physiologically, the presence of viral particles in feces is plausible as there is a high level of viral receptor angiotensin converting enzyme 2 (ACE2) in the gastrointestinal tract [70]. While the current research is not definitive, studies have indicated that asymptomatic patients may shed COVID-19 viral particles in their stool [66,71-74]. Whether these particles are infectious and support the argument for possible the fecal-oral transmission of SARS-CoV-2 remains unclear.

Table 2

Studies with COVID-19 patients presenting with GI symptoms.

Authors	Publication year	Type of study	Number of patients	GI symptoms (%)
Azwar et al. [52]	2020	Case report	1	Epigastric pain, vomiting
Xu et al. [53]	2020	Retrospective case series	62	Diarrhea (8%)
Huang et al. [3]	2020	Prospective	41	Diarrhea (3%)
Pan et al. [54]	2020	Cross-sectional	204	Diarrhea (17%), vomiting (2%), abdominal pain (1%)
Jin et al. [58]	2020	Retrospective	651	Diarrhea (8.14%), nausea, vomiting
Zhang et al. [16]	2020	Retrospective	140	Nausea (17.3%), Diarrhea (12.9%), Anorexia (12.2%), Abdominal pain (5.8%), Belching (5%), Emesis (5%)
Wang et al. [2]	2020	Retrospective case series	138	Diarrhea (10.1%), Nausea (10.1%), Vomiting (3.6%), Abdominal pain (2.2%)
Nobel et al. [63]	2020	Case-control	278	Diarrhea (61%), Nausea (58%)

3.3.3. Endoscopies

Several studies have examined whether GI procedures such as endoscopies can safely be performed on COVID-19 positive patients. A study conducted in northern Italy identified 23 COVID-19 patients presenting with signs of upper GI bleeding, therefore necessitating urgent endoscopy [75]. The virus has been detected in biopsies of the esophagus, stomach, duodenum, and rectum [76]. Since endoscopes are in contact with mucus membrane and body fluids, it is possible that these instruments can be implicated in transmission the virus [77]. As such, most guidelines recommend the use of personal protective equipment (PPE) during endoscopic examination in order to prevent nosocomial outbreaks of COVID-19 [78-81]. When the virus is highly suspected or confirmed, double gloves and N95 or FFP2/3 masks are indicated and the operative team should be properly trained to wear and remove PPE safely [79].

3.4. Renal symptoms

SARS-CoV-2 can have a profound impact on the renal system. Early research has determined that COVID-19 can directly infect kidney tubules and cause acute tubular damage and subsequent renal failure [82,83]. An analysis of kidney findings at autopsy of 26 COVID-19 positive patients in Wuhan showed tubular injury and direct viral infiltration of the tubular epithelium [84,85]. Data also suggests that renal dysfunction may be multifactorial due to cytokine storm, hemodynamic changes, direct viral toxicity, or thrombotic microangiopathy [86]. Renal deterioration has been associated with a 5.3-fold increased mortality in COVID-19 patients. Often these patients demonstrate radiographic evidence of kidney dysfunction, such as renal interstitial inflammation and edema on CT [87]. A recent published report detailed the case of an African American male patient who presented with acute kidney injury due to collapsing glomerulopathy in the context of a COVID-19 infection without any signs of respiratory disease, indicating that renal manifestations of COVID-19 are possible even in patients with otherwise mild symptoms [85].

3.4.1. Renal laboratory abnormalities & disease severity

While research suggests that advanced age, organ failure, and elevated d-dimer levels are indicators of poor prognosis in COVID-19 patients, a recent study highlights kidney dysfunction as a potential risk factor for mortality, as well [13,87]. A multi-center retrospective study of 193 COVID-19 patients (128 with non-severe disease, 65 severe) investigated the presence of kidney dysfunction and demonstrated that, on admission, 59% of patients had proteinuria, 44% had hematuria, 14% had elevated BUN, and 10% had elevated creatinine levels [87]. These lab derangements were found to be significantly worse in those with critical illness (including non-survivors), and 66% of the patients who developed an AKI (43/65) were considered to have severe disease [87]. Per Pei et al., 75.4% of patients with COVID-19 had an abnormal urine dipstick at initial presentation [88]. These findings have been reproduced by several other studies which have shown that development of an AKI is a common lab finding in COVID-19 and a feature of

those with severe disease [5,10,43,89–91]. Patients with elevated creatinine at admission were more likely to be admitted to the ICU [4,91–93]. Patients who survive COVID-19-related AKI have been shown to be at an increased risk of developing progressive CKD after the initial infection [86]. The risk CKD is associated with the severity of the AKI and the presence or absence of tubular damage [94]. These results suggest that early recognition of kidney dysfunction in patients with SARS-CoV-2 is important for disposition and monitoring for potential decompensation and to reduce the progression to chronic kidney impairment.

3.4.2. Acute Kidney Injury and mortality

In addition to being a predictor of severe disease, Li et al. demonstrated that patients who developed an AKI had a 5.3-fold increased risk of mortality compared to those without kidney abnormalities, illustrating the importance of renal dysfunction as a negative prognostic indicator for survival [87]. Chen et al. also determined that 25% of non-survivors had developed an AKI during hospitalization [43]. One study noted that the kidney was the third most commonly damaged organ after the lungs and heart in those who died due to COVID-19 [89]. A consecutive cohort study of 710 COVID-19 positive patients confirmed that markers of kidney dysfunction such as elevated BUN and creatinine were independent risk factors for in-hospital death even after adjusting for potential confounders [91]. Mortality for those who presented with evidence of renal failure on admission was 33.7% vs. 13.2% in those without kidney dysfunction [91]. Similarly, Pei et al. demonstrated that patients with renal involvement had higher overall mortality compared to those without (11.2% vs 1.2%) [88]. Patients with chronic kidney disease are particularly vulnerable to negative outcomes. A recent meta-analysis confirmed that those with pre-existing renal dysfunction appeared to have significantly higher pneumonia-related mortality than those without underlying renal disease and are at increased risk for severe COVID-19 infection [95,96].

When comparing SARS-CoV-2 with SARS-CoV, AKI was a much less common finding (6%) during the 2003 outbreak of SARS, but it was recognized as a significant indicator of mortality (92% of SARS patients with AKI died) [92]. Similarly, renal dysfunction was also associated with increased risk of death in patients infected with H1N1 [93]. Evidence of the prognostic implications of kidney injury in other serious respiratory viruses highlights the importance of recognizing dysfunction early in the disease course in order to improve morbidity and mortality. Early recognition and treatment of renal dysfunction may help to improve the prognosis of those infected with COVID-19.

3.5. Dermatologic symptoms

Based on a study of 1099 confirmed COVID-19 cases in Wuhan, China, the most common symptoms included fever (43.8% of patients were febrile on admission, and 88.7% of patients became febrile during their hospital stay), cough (67.8%), and fatigue (38.1%). However, the study did note that 2 patients (0.2%) had rashes but did elaborate further [5]. There are several mentions in the literature of the dermatologic manifestations of SARS-CoV-2, but a predictable pattern has yet to emerge in the research.

3.5.1. Cutaneous symptoms in COVID-19 patients

Dermatologists have become increasingly involved in caring for COVID-19 patients due to shifting clinical responsibilities during the pandemic, thus sparking an interest in the possible cutaneous manifestations of SARS-CoV-2. Recalcati, an Italian dermatologist, looked at a cohort of 88 COVID-19 positive patients and determined that 18 (20.4%) developed skin symptoms [97]. The manifestations reported were erythematous rash (15.9%), generalized urticaria (3.41%) and chicken pox-like lesions (1.14%) [97]. Dermatologists in Rome identified 2 of 130 patients with COVID-19 who presented with isolated herpetiform lesions on their trunk during their inpatient stays [98]. A patient in Barcelona exhibited vesicular lesions on her back 8 days

after COVID-19 diagnosis [98]. A multicenter case series of 22 patients in Italy described a varicella-like exanthem as a specific cutaneous manifestation of the virus [99]. Furthermore, the study showed that median time from onset of systemic symptoms (fever, fatigue, or cough) to presentation of the exanthem was 3 days with a median duration of 8 days [99]. 54.5% of patients had vesicular lesions on the trunk, and the lesions were scattered in the majority of cases (72.7%) [99]. 7 of the 22 patients underwent skin biopsy and demonstrated histology consistent with viral infection.

Several case reports have also described the potential skin manifestations of COVID-19. A cluster of eight children in the U.K. presented with features similar to atypical Kawasaki including the archetypal skin rash appearance [100]. Following this report, additional cases with similar presentation were observed across the globe. Henry et al. outlined the case of a 27-year-old female who presented with pruritic disseminated erythematous plaques without cough or fever. Two days later she tested positive for COVID-19 after the onset of chest pain and fever [101]. Another case report discussed a 28-year-old female who developed confluent “erythematous-yellowish” papules that progressed to pruritic, hardened plaques 13 days after testing positive for COVID-19 [102]. Joob and Wiwanitkit detailed the case of a petechial eruption and thrombocytopenia initially thought to be Dengue fever, but ultimately proven to be COVID-19 after the development of respiratory symptoms [103]. Amatore et al. discussed a 39-year-old male who complained of fever and exhibited “erythematous and edematous non-pruritic annular fixed plaques involving the upper limbs, chest, neck, abdomen and palms, sparing the face and mucous membranes” without cough or dyspnea [104]. The patient was tested for and diagnosed with COVID-19 after reporting exposure to a family member with the virus. Similarly, Van Damme et al. examined cases of disseminated urticaria in two febrile patients who later developed respiratory symptoms and tested positive for COVID-19 [105].

3.5.2. Cutaneous reactions secondary to drug exposure

Dermatologists have been challenged with differentiating between infectious and allergic etiologies of rashes associated with COVID-19, since they are both clinically and histologically similar. Many of the medication combinations currently under investigation for the treatment of the virus may lead to drug eruptions [106]. In a study of 140 COVID-19 patients by Zhang et al., drug hypersensitivity (11.4%) and urticaria (1.4%) were the most prevalent cutaneous symptoms associated with the virus [16]. Jimenez-Cauhe et al. described a patient with “erythematopurpuric, millimetric, coalescing macules, located in flexural regions” that developed 3 days into treatment with hydroxychloroquine and lopinavir/ritonavir [107]. It was unclear whether these lesions were a manifestation of SARS-CoV-2 or an adverse reaction to the medications; however, there are no additional reports of dermatological symptoms in patients treated with this combination therapy [107]. Another report described sterile pustules, similar to the typical findings of acute generalized exanthematous pustulosis (AGEP), as a cutaneous manifestation of COVID-19 [108]. Although AGEP is classically associated with drugs, it is possible that COVID-19 can predispose certain patients to develop AGEP-like cutaneous eruptions as a late-onset manifestation of the infection.

3.5.3. Cutaneous reactions secondary to hypercoagulable states

In addition to potential drug hypersensitivity or direct viral infection of the skin, Manalo et al. hypothesized that underlying DIC and microthrombi may contribute to cutaneous symptoms [109]. The study described two cases of unilateral transient livedo reticularis in non-critically ill COVID-19 positive patients. Similarly, a retrospective study of 7 critically ill patients in Wuhan, China exhibited significant limb ischemia with plantar plaques and acral cyanosis as dermatologic manifestations of their underlying hypercoagulable state [110].

While the cutaneous manifestations of COVID-19 can vary, early identification of unusual lesions in those without a known trigger is crucial to limiting the spread of COVID-19.

3.6. Neurologic symptoms

Recent studies have indicated that the SARS-CoV-2 is similar in taxonomy and sequence to the SARS-CoV virus [111]. The virus utilizes a spike protein S1 to attach to the host membrane by interacting with host ACE-2 receptor, which is found on neurons, endothelial cells, kidneys, lungs, and small intestine [112]. Upon entering the cell, it initiates an immune cascade which stimulates CD4⁺ T cells, and this sequence of events activates macrophages to produce IL-6, leading to a cytokine storm and eventual systemic destruction of tissues [113]. There are several neurological manifestations of the virus that are important to recognize and treat early.

3.6.1. The Nervous System & Respiratory Distress

The SARS-CoV-2 virus is known to cause severe respiratory distress through direct invasion into the lung parenchyma as evidenced by the destructive pattern seen on imaging of COVID-19 positive patients. However, some patients with evidence of significant lung damage and severe hypoxic do not develop tachypnea [114]. Scientists have hypothesized that there is an abnormal response of the peripheral afferent fibers in the lungs and airways that stimulate respiration [114]. Direct entry of the virus into brain tissue, notably the brainstem, may also result in the loss of involuntary control of breathing [115,116].

3.6.2. Neurologic Manifestations

SARS-CoV-2 is believed to enter the nervous system via hematogenous spread, directly through the cribriform plate, or through retrograde neuronal synapses from the olfactory bulb and vagal afferents [111,113,117,118]. Upon entering the nervous system, it can manifest as a viral encephalitis, cerebrovascular disease, or peripheral nerve symptoms [117,119,120].

3.6.2.1. Viral Encephalitis. Various case reports summarized in Table 3 suggest that COVID-19 causes symptoms consistent with meningoencephalitis [121-124]. Some COVID-19 positive patients presented with altered mental status and fever, and CSF studies showed elevated lymphocyte count but a negative viral biofire [121-124]. Though these presentations could not be definitively linked to the virus due to the lack of CSF SARS-CoV-2 testing at the time, no other etiology for the viral meningoencephalitis was found in this COVID-19 positive cohort. A study conducted at the Beijing Ditan Hospital did confirm the presence of SARS-CoV-2 in the cerebrospinal fluid of patients with known COVID-19 and symptoms consistent with encephalitis by genome sequencing [125]. Evidence of infectious toxic encephalitis was also found when cerebral edema was identified during autopsy of COVID-19 patients [38]. A recently published report detailed the case of serious neurologic damage and mental abnormalities in a patient whose infection was confirmed by IgM and IgG antibodies in the CSF despite negative nasopharyngeal swabs. After the initial presentation of fatigue and headaches, the patient suddenly developed the inability to walk, uroclipsia, coprolalia, and delusions. His CSF studies were strongly positive for SARS-CoV-2 antibodies, and after weeks of antiviral and antipsychotic treatment, he was discharged with mild hand tremors and fatigue [126].

3.6.3. Cerebrovascular disease

A large retrospective study of 221 patients with COVID-19 at the Union hospital in Wuhan found that 5% of patients presented with acute ischemic stroke, one patient developed cerebral venous sinus thrombosis (CVST), and one had cerebral hemorrhage [127,128]. Those with cerebrovascular disease were significantly older (71.6 ± 15.7 years vs 52.1 ± 15.3 years; $p < 0.05$) and had cardiovascular risk factors. Lab evaluation of this cohort determined that they were

more likely to have elevated CRP and d-dimer, lymphopenia, thrombocytopenia, and uremia [127-129].

Cerebral hemorrhage is thought to be a consequence of the virus binding to ACE-2 receptors on endothelium, contributing to break down of the blood brain barrier [117,120]. Ischemic changes and CVST are likely secondary to a hypercoagulable and pro-inflammatory state, further supported by elevation in CRP and d-dimer in these patients [117,128,129]. Numerous other studies summarized in Table 2 discuss presentations of cerebrovascular disease in COVID-19 patients [120,128,129].

While it is theorized in many of the aforementioned studies that patients who are COVID-19 positive are at increased risk for cerebral ischemia, research out of Piacenza, Italy noted decreased rates of admission for stroke. They reported only 6 admissions for CVA from February 21, 2020 to March 25, 2020 compared to their normal monthly average of approximately 51 cases [130]. The authors put forth a number of theories for these findings, such as thrombocytopenia or the potential neuroprotective role of IL-6. Research related to CVA incidence in the time of COVID is currently mixed, and further studies need to be conducted to corroborate these findings.

3.6.3.1. Seizures. Since many studies have demonstrated that COVID-19 patients are at increased risk for encephalopathy and cerebrovascular disorders, it has been theorized that these clinical scenarios could lead to seizures [127-129]. However, a large multi-center retrospective study of 304 COVID-19 positive patients in China study evaluated seizure activity in a cohort of patients with no prior history of epilepsy [121]. Only two patients were identified as having seizure-like activity despite the presence of potentially predisposing hypoxia or electrolyte abnormalities in the majority of the cohort. Both patients were later found to have severe electrolyte abnormalities, and symptoms improved with correction [121]. A study of 111 COVID-19 patients within the New York academic hospital system investigated EEG abnormalities among infected patients. This study showed that the most frequent EEG finding was generalized slowing (57%) and epileptiform findings were observed in 30% and seizures in 7% (4% were non-convulsive seizures). The study also concluded that only a history of epilepsy and definite clinical seizures prior to EEG testing independently predicted epileptiform findings on EEG [131].

3.6.3.2. Peripheral nervous system. Though most research efforts have been focused on identifying CNS dysfunction in SARS-CoV-2, some studies have discussed the effect on the peripheral nervous system. One case series reported on a patient with COVID-19-related Miller-Fisher syndrome and another with polyneuritis cranialis. The first patient developed characteristic features with external ophthalmoplegia, ataxia, and loss of tendon reflexes and recovered after being treated with IVIG [132]. The second had ageusia, areflexia, and abducens palsy consistent with polyneuritis cranialis, which spontaneously and rapidly improved [132]. A large retrospective study by Mao L et al. determined that 5% of patients had hypogeusia and another 5% had hyposmia [129]. Several Chinese studies indicated that up to 70% of patients complained of myalgias with increases in creatine kinase (CK) present in up to 33%, suggesting a possible SARS-CoV-2 viral myositis [2,3,28,124,133]. A recently published report details the case of acute transverse myelitis after a complicated SARS-CoV-2 infection. The patient developed hypotonia in both lower limbs with absent distal reflexes. An MRI with gadolinium contrast showed increased T2 signal between C7-T12 with an LP significant for an elevated IgG index and a positive RT-PCR for SARS-CoV-2. He recovered one week later after treatment with IVIG [134].

3.7. Psychiatric symptoms

With the rise of COVID-19 cases in the US, social distancing measures have continued significantly past their predicted duration, likely contributing to increased anxiety, depression, and loneliness. Prior epidemics have negatively impacted the psychological health of the

Table 3
Studies with COVID-19 patients presenting with neurologic symptoms.

Study (locations, date)	Methods	Number of Patients	Neurologic Manifestations (% of patients)	Lab Abnormalities
Mao L, et al. (Wuhan China, 2020) [129]	Retrospective Analysis	214	CNS: Dizziness (16.8%) Headache (13.1%) Impaired consciousness (8%) Acute cerebrovascular problems (3%) Ataxia (0.5) Seizures (0.5%) PNS: Hypogeusia (5.6%) Hyposmia (5.1%)	CNS: Lower Lymphocyte count, lower platelet count and higher BUN PNS: Higher CK
Li, Y. et al. (Wuhan, China 2020) [128]	Retrospective Analysis	221	Acute ischemic stroke (5%) Cerebral venous sinus thrombosis (0.5%) Cerebral hemorrhage (0.5%)	Elevated CRP and D Dimer: C-reaction protein
Lu, L et al. (Hubei, Sichuan, and Chongqing China 2020) [121]	Retrospective Multi-Centered Study	306	Encephalopathy (2.6%) Seizure (0.7%)	N/A
Gutiérrez-Ortiz C, et al. (Madrid, Spain 2020) [132]	Case Report	2	Miller-Fisher syndrome Polyneuritis Cranialis	Albuminocytologic dissociation
Duong L, et al. (Los Angeles, USA, 2020) [122]	Case Report	1	Meningoencephalitis	CSF: High lymphocyte count, protein elevated and glucose was normal. Negative HSV PCR
Yin R, et al. (Wuhan, China, 2019) [123]	Case Report	1	Encephalitis	Lymphocyte count: $3.3 \times 10^9/L$ and C-reactive protein (CRP) level, 10.74 mg/L
Zhang J et al. (Wuhan, China 2020) [124]	Retrospective Analysis	603	Headache (3%) Dizziness (3.5%) Unconsciousness (1.5%)	Decreased Lymphocyte Counts, Elevated CRP, Increased LFTs, Elevated Creatinine
Huang C et al. (Wuhan, China 2019) [3]	Prospective Study	41	CNS: Headache (8%) PNS: Myalgias (44%) Dizziness (9%) Headache (7%)	Low lymphocyte count, Elevated D dimer, Elevated LFTs, normal procalcitonin
Wang et al. (Wuhan, China 2020) [2]	Retrospective Analysis	138	Headache (7%)	Low lymphocyte count, Elevated Prothrombin Time, Increased LDH
Yang X et al. (Wuhan, China 2020) [28]	Retrospective Analysis	52	Headache (6%) PNS: Myalgia (10%)	Low lymphocyte count
Chen N et al. (Wuhan, China 2020) [4]	Retrospective Analysis	99	Confusion (9%) Headache (8%)	Low Lymphocyte count, Low platelets, Low hemoglobin, Increased LDH, Increased D dimer, Increased CRP

population. A prospective study conducted during the 2003 SARS epidemic in Hong Kong demonstrated that stress, dysphoria, impaired sleep and concentration were much greater among infected individuals than controls, and 25% of the patients requested follow-up for the negative psychological effects of being infected [135]. A study examining psychiatric symptoms in SARS survivors one year later indicated that these patients experienced persistent distress with 64% scoring above the GHQ12 threshold for psychiatric morbidity [136]. Additionally, infected healthcare workers who survived showed significantly higher stress levels, more depression, and symptoms consistent with PTSD [136]. Based on this research, it is possible we will see similar patterns of anxiety, depression and other psychiatric symptoms in those currently affected by COVID-19.

3.7.1. Cause of psychiatric symptoms

The psychological impact of this pandemic is likely multifactorial, due in parts to self-isolation, fear of infection, uncertainty, financial woes, job insecurity, and pre-existing mental health conditions. A recent study out of China using online surveys determined that 16.5% of respondents exhibited moderate to severe depressive symptoms, and 28.8% reported severe anxiety [137]. Of

these respondents, 75.2% attributed their increased anxiety to fear that they or their family members could contract COVID-19 [137]. Misinformation and uncertainty can raise anxiety levels in both healthy individuals and those with preexisting psychiatric conditions [138]. Lunn et al. observed that the absence of effective disease treatment and the uncertainty regarding outcomes for those infected has led to mass panic and anxiety [139]. In addition, the rapid spread of misinformation and bias has induced fear, prejudice, and xenophobia [140,141].

3.7.2. Social isolation and mental health

One of the major consequences of the pandemic is increased social isolation, a risk factor that is strongly associated with depression, self-harm, and suicide [142-144]. Older adults are especially vulnerable to the mental health ramifications of social isolation, particularly those in residential care [145]. Mental health experts have stressed the importance of research examining the rates of anxiety, depression, and other psychiatric symptoms to inform interventions during this public health crisis [142]. An analysis of emotional indicators on the Chinese social media platform Weibo during the height of their COVID-19 crisis demonstrated

that anxiety and depression increased while positive emotional indicators (Oxford happiness) decreased [146]. The study also analyzed linguistic expression and determined that there was an increase in the use of the words “health” and “family” and a decrease in “leisure” and “friend”, highlighting the rapidly evolving priorities in this population during the pandemic [146].

Patients with pre-existing mental health conditions are both more vulnerable to the psychological impacts of the pandemic and at increased risk of infection, likely due to cognitive impairment, diminished efforts for personal protection, lack of awareness of their personal risk, and discrimination [147]. Patients with severe mental illness are also more vulnerable due to significantly higher rates of both homelessness and smoking [148]. Many patients have reported poor adherence to medication during this time, disruption of mental health services, and suspension of substance abuse treatment [149]. Lastly, the close proximity with which many homeless patients with mental illness live is a significant risk factor for the spread of the virus.

3.7.3. Psychiatric Manifestations of COVID-19 Infection

There is some emerging research that suggests a link between COVID-19 infection and severe psychiatric symptoms. A cross-sectional study of 112 patients with COVID-19 reported higher levels of somatization, depression, anxiety, phobias, sleep disturbances, and eating disorders in infected patients compared to the healthy population [150]. Case reports have detailed the psychiatric presentations of patients with SARS-CoV-2 both during their acute infections and post-clinical recovery. One such patient presented to the hospital with extreme anxiety, suicidal ideation, agitation, and hallucination [151]. A case series out of Spain examined viral involvement in new-onset psychiatric symptoms. They discussed several patients who presented to the hospital with psychosis and concomitant infection with SARS-CoV-2 without any known history of prior mental health disorders [152]. While neither of these reports was able to establish whether the patients' psychoses were primary or secondary (related to treatment or acute delirium), these findings suggest the need for additional research on the neuropsychiatric manifestations of COVID-19 infection.

Effective management of mental health problems during the pandemic has proven challenging, especially as infectious concerns inhibit face to face evaluation, and the influx of COVID-19 cases has consumed healthcare resources. The rapid spread of infection has led to increased rates of depression, anxiety, and feelings of self-isolation within the community. Additionally, some evidence suggests that COVID-19 can present with primary or secondary psychiatric symptoms. More research needs to be performed to fully assess the mental health burden of this crisis, particularly with regard to vulnerable populations.

4. Conclusions

The COVID-19 pandemic has resulted in massive, widespread economic and public health hardships. While several therapies are still under investigation, there remains no definitive treatment for SARS-CoV-2. Many clinical trials are ongoing, and treatment of COVID-19 currently includes supportive care and symptomatic management. Community-wide public health containment strategies consist of social isolation, distancing, face coverings, and travel restrictions. Despite these efforts, the virus continues to spread, highlighting an even greater need for additional research into the pathophysiology, clinical presentations, and treatment modalities for SARS-CoV-2. Ultimately, it is critical for frontline healthcare workers to understand and recognize the many clinical manifestations of COVID-19 in order to better protect themselves, efficiently identify potentially infected patients, and prevent nosocomial outbreaks.

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