



Clinical update on COVID-19 for the emergency clinician: Presentation and evaluation

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ABSTRACT

Introduction: Coronavirus disease of 2019 (COVID-19) has resulted in millions of cases worldwide. As the pandemic has progressed, the understanding of this disease has evolved.

Objective: This first in a two-part series on COVID-19 updates provides a focused overview of the presentation and evaluation of COVID-19 for emergency clinicians.

Discussion: COVID-19, caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), has resulted in significant morbidity and mortality worldwide. Several variants exist, including a variant of concern known as Delta (B.1.617.2 lineage) and the Omicron variant (B.1.1.529 lineage). The Delta variant is associated with higher infectivity and poor patient outcomes, and the Omicron variant has resulted in a significant increase in infections. While over 80% of patients experience mild symptoms, a significant proportion can be critically ill, including those who are older and those with comorbidities. Upper respiratory symptoms, fever, and changes in taste/smell remain the most common presenting symptoms. Extrapulmonary complications are numerous and may be severe, including the cardiovascular, neurologic, gastrointestinal, and dermatologic systems. Emergency department evaluation includes focused testing for COVID-19 and assessment of end-organ injury. Imaging may include chest radiography, computed tomography, or ultrasound. Several risk scores may assist in prognostication, including the 4C (Coronavirus Clinical Characterisation Consortium) score, quick COVID Severity Index (qCSI), NEWS2, and the PRIEST score, but these should only supplement and not replace clinical judgment.

Conclusion: This review provides a focused update of the presentation and evaluation of COVID-19 for emergency clinicians.

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1. Introduction

Coronavirus disease of 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic [1–4]. The initial outbreak in late 2019 consisted of 27 patients with pneumonia in Wuhan, Hubei Province, China [1,2]. The virus spread rapidly around the world and was initially declared a pandemic on March 11, 2020 [1–3]. Recent variants, including the Delta and Omicron variants, have resulted in significant increases in cases [4]. As

of December 31, 2021, over 287 million cases have occurred worldwide, with over 5.4 million deaths [4]. In the United States, there have been over 54.5 million confirmed cases and over 825,000 deaths [4]. This pandemic has resulted in significant challenges worldwide, and our understanding of this disease continues to evolve. This paper is the first in a two-part narrative review that will provide a focused update on the presentation and evaluation of COVID-19 for emergency clinicians.

2. Methods

A literature review of PubMed and Google Scholar databases was performed for articles up to December 31, 2021, using the keywords 'COVID' OR 'COVID-19' OR 'SARS-CoV-2' OR 'coronavirus' for this

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narrative review. The authors included retrospective and prospective studies, systematic reviews and meta-analyses, clinical guidelines, and other narrative reviews. Commentaries and letters were also included. The literature search was restricted to studies published or translated into English. Authors reviewed all relevant articles and decided which studies to include for the review by consensus, with focus on emergency medicine-relevant articles, including guidelines. A total of 194 resources were selected for inclusion in this review.

3. Discussion

3.1. Virology and variants

SARS-CoV-2 is an enveloped positive-stranded RNA virus, which binds to the angiotensin-converting enzyme 2 (ACE2) receptor and enters cells via the coronavirus spike proteins 1 and 2 [1,3,5]. These spike proteins possess multiple cleavage sites, which may increase the pathogenicity of the virus [1,3,5–7]. Gradual accumulation of small genetic changes in these viral spike proteins results in antigenic drift and different variants. There are three types of variant classifications, stratified as those of interest, those of concern, and those of high consequence [5–19] (Table 1). The current variants of greatest concern include the Delta (B.1.617.2 lineage) and the Omicron variant (B.1.1.529 lineage) [5–19].

Viral particles are present in respiratory droplets, aerosols, blood, ocular secretions, urine, and stool, but it is primarily spread through direct

person-to-person respiratory transmission [16–18,20–26]. The virus is spread from the mouth and nose as droplets and smaller aerosolized particles, which may become airborne and travel past 6 f. [17,18,20]. Of note, over 50% of viral transmission occurs in those with no symptoms, and viral shedding may occur 3 days before the onset of symptoms [20,27]. With symptom onset, viral load peaks [20,27]. While contaminated surfaces are not thought to be a significant cause of transmission, infection may still occur if a person touches their eyes, nose, or mouth with contaminated hands. The incubation period is typically 4 to 5 days, though it ranges from 1 to 14 days [13,28–30]. The initial estimate of the reproductive number, or R0, of the virus was 4.7–6.6 (the number of expected cases originating from a single infected individual) [29]. With early infection control and vaccines, this number decreased to approximately 1.5 [30]. The Delta variant is significantly more transmissible, with an estimated R0 ranging between 6 and 7 [13,28]. The Omicron variant is even more transmissible, approximately 3.2 times that compared to the Delta variant and has a 3-day doubling time [31,32]. Transmission after 7–10 days of symptoms is highly unlikely [28].

The Delta variant is associated with higher viral loads, up to 1000 times higher than other strains, with earlier and prolonged shedding [11,19,28]. It is also associated with higher rates of hospitalization and mortality [11,19,28]. One study found the Delta variant was associated with higher odds of oxygen requirement, need for intensive care unit (ICU) admission, or death (adjusted odds ratio [aOR] 4.90, 95% [confidence interval] CI 1.43–30.78) [19]; other studies have found approximately double the risk of hospitalization [33,34]. A study of over 40,000 patients infected with COVID-19 also found a higher risk of hospitalization associated with the Delta variant, with an adjusted hazard ratio of 2.26 (95% CI 1.32–3.89) [34]. Evidence suggests vaccinated patients with the Delta variant have similar nasopharyngeal viral loads compared to non-vaccinated patients, even though they demonstrate fewer or even no symptoms [11].

The most recent variant of concern, B.1.1.529, also known as Omicron, was identified in South Africa on November 9, 2021, and reported to the World Health Organization (WHO) on November 24, 2021 [14,15]. The WHO declared it a variant of concern on November 26, 2021 [14]. By November 28, 2021, the variant had been identified in South Africa, Belgium, Botswana, Hong Kong, Israel, Italy, Netherlands, and the United Kingdom. By December 25, 2021, the variant was present in over 90 countries and made up over 58% of all new infections in the United States [32]. The Omicron variant possesses over 50 mutations and has quickly become the predominant strain in many countries [14,15,32,35]. While prior infection with SARS-CoV-2 was thought to provide an estimated 80% reduction in infection with other strains, evidence suggests the Omicron variant is associated with increased ability to evade immunity from prior infection [32,36–40]. Fortunately, recent literature suggests vaccinated patients have strong protection against severe illness from the Omicron variant [41–43]. While two vaccine doses without a booster demonstrate less effectiveness in preventing infection with the Omicron variant compared with other strains, data suggest two doses still reduce the risk of severe disease [41–43]. Data are controversial whether the Omicron variant is associated with reduced disease severity [43–45]. Several reports announced a decrease in disease severity, with one finding a 29% reduction in hospitalization rate in those infected with the Omicron variant [43–45]. A report released on December 22, 2021, found a 20–25% reduced risk of any hospitalization and 40–45% reduced risk of multiday hospitalization [45]. Further studies are underway evaluating vaccine efficacy and the risk of severe disease associated with the Omicron variant.

3.2. Disease severity

COVID-19 infection is generally divided into symptomatic and asymptomatic, with symptomatic cases further categorized as critical, severe, and non-severe [2,46] (Table 2). The majority of patients have mild disease (over 80%) [2,3,46–48–33]. Clinically asymptomatic

Table 1
COVID-19 Variants [6,7,14,15]

Variant Classification	Definition	Specific Variants
Variant of interest	Predicted to affect transmission, diagnosis, treatment Evidence of increased transmission, outbreak clusters	–
Variant of concern	Attributes of variant of interest Evidence of increased transmissibility and/or disease severity	B.1.1.7 (Alpha) – first isolated in United Kingdom, 50% increased transmission, may increase mortality B.1.351 (Beta) – first isolated in South Africa, increased immune evasiveness, 50% increased transmission B.1.617.2 (Delta) – first isolated in India, likely 50% more transmissible than Alpha, may evade full vaccination and increase rate of infection, likely increases mortality B.1.427 and B.1.429 (Epsilon) – first isolated in California, 20% increased risk of transmissibility P.1 (Gamma) – first isolated in Brazil/Japan, likely increased disease transmissibility and severity B.1.526 (Iota) – first isolated in New York, likely increased transmissibility but not more severe disease B.1.1.529 (Omicron) - first isolated in South Africa, present in over 90 countries, predominant strain in U.S., over 50 mutations in spike protein
Variant of high consequence	Attributes of variant of concern Evidence of more severe infection, increased hospitalization, decreased vaccine and treatment efficacy, failure of diagnostics	None as of December 31, 2021

Table 2
COVID Severity Classifications [2,46]

Classification	Consideration
Critical	Acute respiratory distress syndrome, sepsis, septic shock, or other conditions requiring life-sustaining therapies (mechanical ventilation or vasopressor therapy)
Severe	Oxygen saturation < 90%, signs of severe respiratory distress (accessory muscle use, unable to speak in full sentences)
<i>*The 90% threshold is not definitive and should only be used as a component of the whole clinical picture</i>	
Non-severe	Any patient not meeting criteria for critical or severe

infection rates may approximate 33% of those testing positive for COVID-19 based on one meta-analysis, but this number varies [20,47,48]. However, literature suggests severe disease (defined as hypoxia or > 50% lung involvement) can occur in over 15% of patients and critical disease (consisting of respiratory failure, multiorgan injury, or shock) in up to 5%, though this depends on the patient population [1-3,26,48,49]. More recently a third category of pre-symptomatic proposes that as many as half of these persons who do not declare symptoms at the time of positive testing develop symptoms later [47,50,51].

Reported rates of hospitalization, mechanical ventilation, and mortality vary significantly due to several variables including patient age, healthcare and testing availability, and containment measures, among others. Initial studies suggested high rates of hospitalization and mortality, but with current therapies and vaccination, risks of hospitalization, mechanical ventilation, and mortality have declined [1,2,20,52–67]. Early in the pandemic, overall mortality rates for admitted patients reached 20%, but in those admitted to the ICU, mortality approximated 40% [1,2,20,52–67]. As the pandemic has progressed, ICU survival rates have improved from 58% to 80% [62]. Of those hospitalized with COVID-19, up to 35% require admission to an ICU [20,48,52]. More recent literature suggests the case fatality rate is under 2% in all patients with COVID-19, though this depends on age [20,48,57]. In those over age 60 years this rises to 6.4%, in those over age 80 years it is over 13%, and in those over age 90 years mortality is over 25% [57].

Several factors are associated with worse prognosis in patients with COVID-19. Risk factors for severe disease include age > 75 years, diabetes, cancer, history of transplant, hypertension, and prior cardiac or pulmonary disease [23,26,52,63–67]. Obesity is associated with increased mortality and need for intubation, independent of other factors including race, sex, and other comorbidities, especially in patients less than 65 years of age [68,69]. One study suggested mortality was four-fold higher in patients with a body mass index (BMI) > 45 [69]. Heart failure is associated with longer hospital length of stay, increased need for intubation and ventilation, and mortality [70]. Unfortunately, the Delta variant is also associated with worse outcomes, including need for hospitalization, ICU admission, and mortality [33,71]. Other poor prognostic factors include an initial oxygen saturation < 88%, lymphopenia, thrombocytopenia, acute kidney injury, elevated lactate dehydrogenase, C-reactive protein (CRP) > 200 mg/L, D-dimer > 2500 ng/mL, elevated troponin, and ferritin > 2500 ng/mL [23,26,52,63].

3.3. Clinical presentation

Approximately 98% of patients who develop symptoms will do so within 12 days of viral exposure [3,20]. Although symptomatic COVID-19 patients exhibit a variety of signs and symptoms, most present with fever, changes in taste and/or smell, myalgias, and respiratory tract symptoms such as cough [1-3,20,52,72–76]. However, there are no clinical features with high enough specificity to reliably differentiate COVID-19 from other infections for diagnosis [75]. Literature suggests that the most common symptoms include cough (60–86%), shortness of breath (53–80%), and change in taste or smell disturbance (64–80%) [72–76]. Fever can be present in approximately half of patients at the time of initial

presentation depending on the study, but overall, literature suggests 20–99% of patients experience fever during the course of the disease [1,2,18,23,49,53,72]. Literature varies on the definition of fever, with temperature thresholds as low as 37.1C [75,77,78].

Viral pneumonia, hypoxemic respiratory failure, and acute respiratory distress syndrome (ARDS) may result from COVID-19, with hypoxemic respiratory failure the most common reason for ICU admission [1-3,20,23,60,74,75]. Bacterial or fungal co-infections affect up to 8% of patients [79]. These are a major source of morbidity and mortality; in one study, half of those who died experienced a secondary infection [23,80,81]. Bacterial respiratory infections most commonly include *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Haemophilus influenzae*, though other infections such as pulmonary aspergillosis and mucormycosis may also occur [80–87]. Mucormycosis has primarily been documented in India, with diabetes and steroid treatment the most common risk factors [84–87]. Concurrent viral infections are also common, with one study finding 20.7% of patients with COVID-19 infected with at least one other virus [82].

3.4. Extrapulmonary presentations and complications

3.4.1. Cardiac

As the pandemic has progressed, a variety of extrapulmonary effects have been uncovered. Myocardial disease, manifested by dysrhythmias, acute coronary syndrome (ACS), heart failure, and myocarditis [22,88–90–76], occur in over 20% of patients admitted to the ICU with COVID-19 [22]. Dysrhythmias include AV blocks, bradycardia, and supraventricular and ventricular tachycardias [22,88–90]. Torsades de pointes may occur due to QT prolongation. The QT interval can be prolonged due to electrolyte changes (diarrhea, dehydration), systemic inflammation, and comorbidities (preexisting cardiac disease) [88,91,92]. ACS is likely associated with severe inflammation [88–96]. This may result in plaque rupture and ST elevation myocardial infarction [93–95]. Cardiomyopathy, heart failure, and myocarditis can also occur, with acute left heart failure occurring in 23% of patients [23,88,90,92]. Left heart failure is associated with increased mortality and was present in 52% of those who died in one study [23]. Right heart failure is more likely associated with lung injury and ARDS, as well as the hyperinflammatory state, thrombotic events, and viral damage [96,97]. Literature suggests right ventricular dilation occurs in 20–31% of cases [96,97]. Myocarditis is more likely in those with heart failure or shock who have no prior history of cardiac disease [88,90]. Myocarditis was the cause of death in 7% of patients and contributed to one third of deaths in one study [23]. However, cardiac involvement is likely more common than originally thought. One study of patients with mild to moderate COVID-19 who underwent cardiac magnetic resonance imaging found abnormal findings in 78%, most commonly cardiac inflammation [98], and a second study found 56% of patients had cardiac inflammation and edema [99]. Other studies suggest cardiac involvement is present even in patients with minimal or no symptoms [100].

3.4.2. Neurologic

Neurologic effects associated with the disease vary, ranging from mild illness to severe manifestations such as stroke. Up to 80% of patients experience neurologic symptoms during the course of the disease [101]. Mild symptoms such as headache and dizziness affect up to 40% of patients during acute illness, which may increase as the illness progresses [101–103]. Changes in smell and taste are common. This may be the first symptom in approximately one-third of patients [102,103]. Up to 80% of patients will experience a change in taste or smell during the course of illness, and almost half will have complete loss of taste or smell [72,75,103,104]. Literature suggests severe neurologic complications occur in a significant number of patients with COVID-19, including seizure, encephalopathy, and cerebral ischemia [105]. Mental status changes due to encephalopathy are more common in older patients with COVID-19 and associated with worse outcomes [101,105], with

delirium occurring in up to 55% of critically ill patients with COVID-19 [106]. Meningoencephalitis may occur due to direct central nervous system (CNS) invasion or systemic inflammation due to COVID-19. Immune-mediated complications such as Guillain-Barré Syndrome and myasthenia gravis have been reported [107]. Cerebral ischemia due to stroke may occur in up to 6% of critically ill patients with COVID-19 and can present as small or large vessel occlusion; however, the risk of cerebrovascular accident (CVA) is less than 1% in other populations with COVID-19 [108–110]. CVA most commonly occurs in the first several weeks after symptom development [108–110]. While rare, cerebral venous thrombosis has also been documented and is associated with high mortality rate in COVID-19 [111,112]. These patients can present with headache, seizure, focal neurologic deficit, or altered mental status. Acute disseminated encephalomyelitis and posterior reversible encephalopathy syndrome have also been reported. Finally, patients are at risk of psychiatric complications such as mood disorders, anxiety, insomnia, and psychotic disorders [103,113].

3.4.3. Gastrointestinal

Gastrointestinal (GI) symptoms are common, with up to one-third of patients with COVID-19 presenting first with GI symptoms [24,114,115]. Nausea and vomiting may be present in up to two-thirds of patients with COVID-19 [115]. Approximately 40% of patients with COVID-19 will have loss of appetite, and up to 50% will have diarrhea [24,115]. Abdominal pain is less common, occurring in less than 10% [24,115]. In critically ill patients, acute liver injury, cholecystitis, pancreatitis, ileus, pseudo-obstruction, and mesenteric ischemia may occur [116].

3.4.4. Dermatologic

Dermatologic manifestations of COVID-19 occur in 0.4–20% of cases but are often non-specific consisting of erythema or urticaria-like lesions on the trunk or, less frequently, the extremities [74,117–121]. Similarly, small case series and reports describe livedo reticularis, vesicular eruptions, maculopapular lesions, and areas of thickened erythema resembling chilblains [117–121]. New pernio-like lesions are also suggestive of COVID-19 [74,118].

3.4.5. Hematologic/thrombotic

Hematologic issues including thrombotic complications are common in critically ill patients with COVID-19. This risk is thought to be associated with systemic inflammation [122–132]. Initial studies suggested patients with COVID-19 were at a high risk of venous thromboembolic event (VTE), with rates of VTE reaching 31% in critically ill patients [122,124–126]. More recent studies have found that the overall risk of VTE, including pulmonary embolism (PE), in patients with COVID-19, no matter the severity of illness, is lower than initially suspected (< 1%), though the risk remains higher than the general non-COVID-19 population [132]. A second international study found COVID-19 was not an independent risk factor for PE, with 15% in the pandemic era and 15% of patients in the prepandemic era experiencing PE [132]. Routine evaluation for PE in all COVID-19 patients is not recommended [132]. Evaluation for PE should be considered in patients with other risk factors for PE; those with hypoxia, tachycardia, or hypotension out of proportion to clinical evaluation; sudden decompensation; or those whose symptoms are not explained by chest radiograph.

3.5. ED evaluation

3.5.1. SARS-CoV-2 testing

Evaluation in the ED setting primarily focuses on identification of COVID-19 and assessment for severe illness and end-organ injury [1–3]. Identification of COVID-19 infection continues to rely heavily on nucleic acid amplification tests (NAAT) for SARS-CoV-2 in nasopharyngeal specimens, with reverse transcription polymerase chain reaction (RT-PCR) assays comprising common methods recommended by the World Health Organization (WHO), Centers for Disease Control and

Prevention (CDC), and Infectious Diseases Society of American (IDSA) [1–3,20,74,133–139]. Initial concerns for suboptimal sensitivities of RT-PCR as low as 70% have been attributed to oropharyngeal sampling and poor sampling technique, while accuracy has significantly improved with nasal vestibular and middle turbinate swabs or the use of saliva [133–140]. Sensitivity may approach 100% when there is 500–5000 viral RNA/mL [135]. However, timing of testing can have significant impact on RT-PCR test characteristics, with the highest sensitivity at 2–3 days after symptom onset and the lowest sensitivity immediately after exposure [20,138].

Although RT-PCR can be performed in a condensed timeline, the sheer volume of tests performed in major centers has prompted examination of shorter-turnaround point-of-care testing, such as rapid SARS-CoV-2 antigen (Ag) testing to detect viral proteins. This process utilizes a nasal turbinate swab with a simple qualitative indicator when reagent is applied, with results available in approximately 15 min compared to the 60–120 min required for NAAT [140–145]. Despite generally high specificity, SARS-CoV-2 Ag testing demonstrates highly variable sensitivity (31–93%), likely due to varying viral loads, and it has less sensitivity at lower viral loads [20,133,137,140–145]. Most SARS-CoV-2 Ag tests demonstrate higher sensitivities with a lower cycle threshold (Ct), which describes the number of PCR cycles required to detect the virus [141–144]. SARS-CoV-2 Ag tests demonstrate higher sensitivities for those with a PCR Ct of ≤ 25 , compared to those with higher Ct values [133,137,140–145]. Due to this variability, SARS-CoV-2 Ag testing can be considered for rapidly screening patients who appear highly symptomatic with suspected or confirmed exposure. Current society guidelines recommend that SARS-CoV-2 Ag testing be employed in isolation only when NAAT is not available, or as screening for patients in conjunction with NAAT for definitive diagnosis (Fig. 1) [20,140,143]. Limited evaluation of SARS-CoV-2 Ag tests against Omicron variant infections do not demonstrate a significant decrease in overall sensitivity for symptomatic individuals [146,147].

3.5.2. Other laboratory testing

Patients with normal vital signs who appear well do not require laboratory assessment other than SARS-CoV-2 testing. However, additional laboratory testing can assist with risk stratification in determining the need for admission [1–3,20]. A complete blood count (CBC) can provide several markers of interest. For example, the CBC may reveal lymphopenia (absolute lymphocyte count $< 1.0 \times 10^9/L$), which can be found in up to half of patients overall and 83% of hospitalized patients, portending an increased risk for the combined outcome of severe disease course and mortality compared to those with normal levels (76% vs. 26%, $p < 0.001$) [20,38,148–155]. Lymphopenia tends to worsen with the severity of COVID-19 symptoms and is associated with an increased risk for respiratory failure (odds ratio [OR] 2.69, $p < 0.001$) [152–155]. Total leukocyte counts are variable but generally remain within a normal range of $4\text{--}10 \times 10^9/L$, though median values for more severe patients are more commonly below this lower limit at $3.7\text{--}3.9 \times 10^9/L$ [18,20,151,155]. Mild thrombocytopenia (platelet count $< 150 \times 10^9/L$) is seen in 12–33% of patients overall, with a higher proportion found in those with more severe illness (57.7% vs. 31.6%) [18,20,149,151,153,155].

Chemistry and liver function testing can be obtained to evaluate for organ injury and other complications in COVID-19 patients. Serum creatinine has been found to be elevated in less than 10% of patients, although one study found elevated creatinine in 28.8% of patients [18,154–159]. Common electrolyte derangements found in COVID-19 include hyponatremia (20.4–50%) and hypokalemia (15.1–62%), with most exhibiting mild depletion (Na 130–135 mmol/L, K 3.0–3.5 mmol/L) [53,156–159]. Lower sodium levels have been associated with more severe illness (139 mmol/L vs. 136 mmol/L, $p < 0.0001$) [53,157,160]. Those with severe hypokalemia (< 3 mmol/L) are also more likely to have severe COVID-19 ($p < 0.001$) [157,158]. Hyperglycemia is found in approximately half of patients, and in patients with diabetes, a venous blood gas panel should be considered to evaluate for COVID-19-

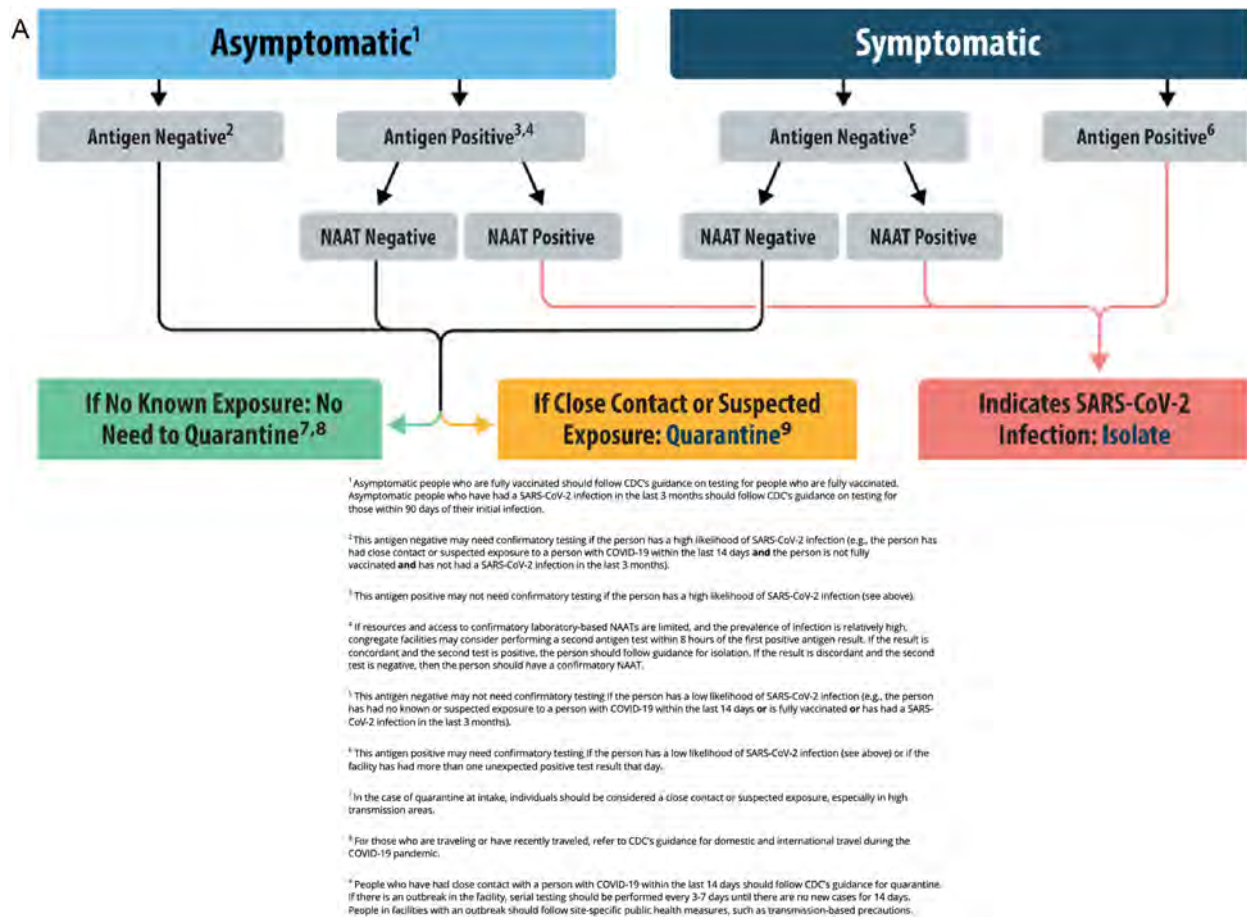


Fig. 1. CDC Antigen Testing Algorithm [134,140]. 1a) Testing for Congregate Living Settings. 1b) Testing for Community Settings. From <https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antigen-tests-guidelines.html#previous>

triggered diabetic ketoacidosis [153,161,162]. Lactate dehydrogenase (LDH) is elevated (>250 U/L) in 27–92% of COVID-19 patients [18,20,149,151–155].

Liver function tests demonstrate statistically significant elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in 10–28% and 9–36% of patients overall, respectively; however, at this time the clinical significance of this is not well established [20,148,153,155]. Scattered case reports suggest COVID-19 can present as acute hepatitis, while small studies show elevated AST and ALT in COVID-19 with preexisting hepatitis B infection [163,164]. However, there is no clear correlation at this time.

As in most inflammatory processes, inflammatory markers including CRP and erythrocyte sedimentation rate (ESR) tend to be elevated in COVID-19. This includes significant CRP elevation (≥ 10 mg/L) in 46–99% COVID-19 patients [18,20,53,149,155]. ESR is elevated (> 15 mm/h) in 24–96% of patients, albeit with less supporting studies relative to CRP [53,149,153,155]. CRP ≥ 10 mg/L demonstrates increased risk of respiratory failure (OR 5.91) and thrombotic events (OR 2.7) in COVID-19 patients, while ESR > 40 mm/h shows similar association with thrombosis (OR 2.64) in isolated studies [127,151,152].

Potential thrombotic complications may prompt evaluation for fibrinogen and coagulation studies, with serum D-dimer often elevated. While studies vary on D-dimer levels to define elevation, 46% of COVID-19 patients demonstrate levels >0.5 mg/L and 36% have levels >1.5 mg/L [20,127,149,153,165]. The predictive ability of elevated D-dimer for thrombotic events in these patients increases proportionally to the elevation, with increasing risk from 1 to 2.5 mg/L (OR 1.75) to >2.5 mg/L (OR 4.40), 5–10 mg/L (OR 5.55) and ≥ 10 mg/L (OR 7.09)

[127–130]. The degree of D-dimer elevation is also associated with severity of illness, with higher levels associated with more severe disease [155]. Less often, prolonged prothrombin (PT) and activated partial thromboplastin (aPTT) times are found in approximately 5–11% and 6–26% of patients, respectively, without significant correlation between abnormal levels and illness severity or bleeding complications [20,53,119,120,153,155].

3.5.3. Imaging

Chest radiography is generally employed for initial evaluation of COVID-19 patients with respiratory symptoms, although studies reveal significant variation in the frequency of their findings [1–3,18,166–172]. A normal chest X-ray (CXR) may be found in a significant proportion of patients with COVID-19 (5.6–53.6%), with 10.9% later progressing to abnormal findings on subsequent plain films [18,166–172]. The most common abnormal CXR findings include peripheral consolidations (5.3–88.9%) or ground glass opacities (14.1–63.1%), with the latter described as hazy increased attenuation with reticular consolidation [166–172] (Fig. 2). Patients most commonly have bilateral lung involvement (up to 76%) [166–172]. Computed tomography (CT) of the chest without contrast demonstrates improved sensitivity for detecting lung abnormalities (pooled sensitivity 87.9% to 90.6%) and should be considered in COVID-19 patients with severe respiratory symptoms despite unremarkable CXR [166,169,171–174] (Fig. 3). Up to 10% of patients can have a normal CT. A classification system has been proposed with 4 stages [173,174]. Stage 1 includes ground glass appearance (days 0–4), stage 2 is an increased crazy-paving pattern (days 5–8), stage 3

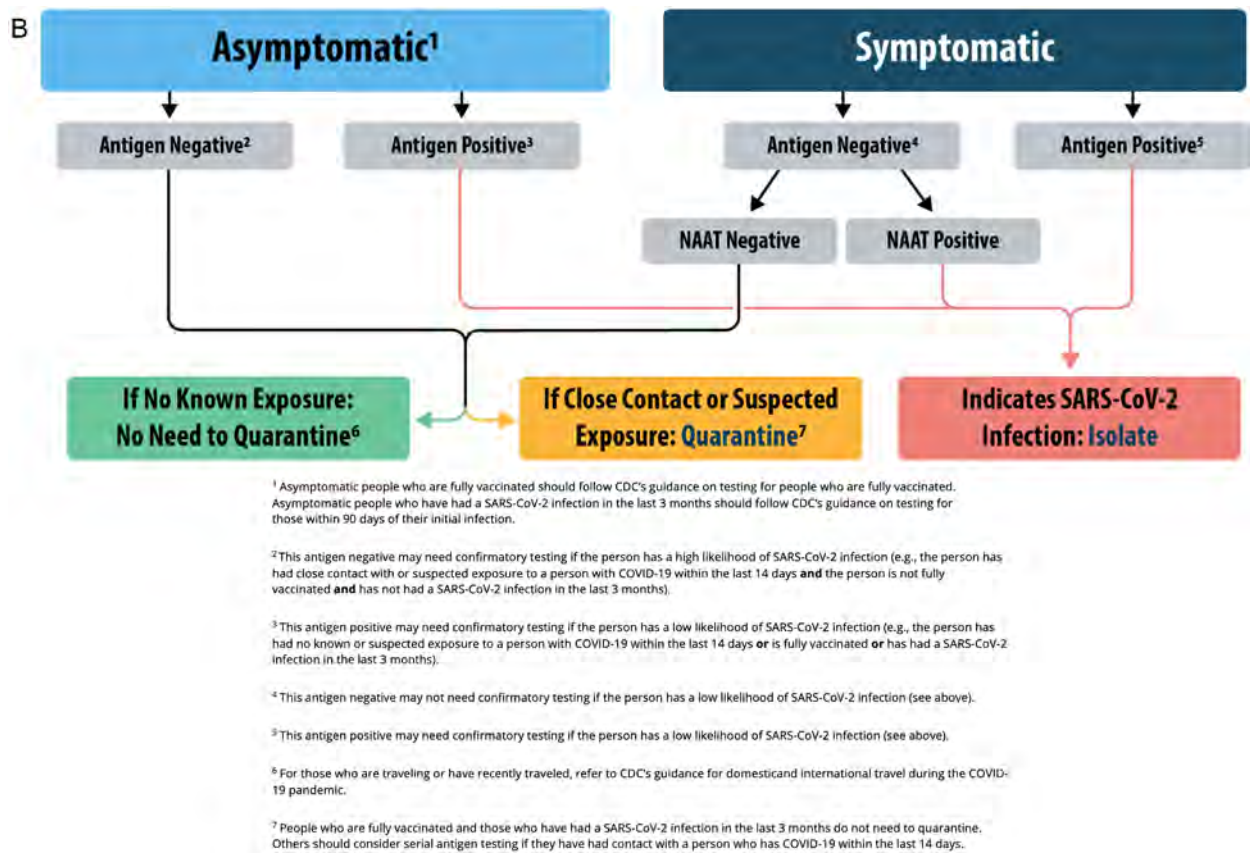


Fig. 1 (continued).

consists of consolidation (days 9–13), and stage 4 is gradual resolution (days ≥14) [174].

Lung ultrasound (LUS) is another tool in the evaluation of COVID-19 patients. A prospective cohort study found that LUS possessed a sensitivity of 94.4% for diagnosis and was able to identify false-negative cases on PCR [175]. A meta-analysis reported moderately high sensitivity (86.4%) but low specificity (54.6%) [172]. LUS findings in patients



Fig. 2. Chest x-ray with bilateral ground-glass opacities From: https://commons.wikimedia.org/wiki/File:COVID-19_Pneumonie_-_82m_Roe_Thorax_ap_-_001.jpg

with mild-to-moderate respiratory symptoms include abnormal pleural thickening and sliding, B-lines, skip lesions, and small areas of patchy consolidation, with the posterior lung fields most commonly affected (Fig. 4) [175–183]. B-line progression with enhanced consolidation suggests increasing disease severity and should raise concern for a potential need for enhanced respiratory support [176,177,179].

3.6. Risk scores

Over 20 prognostic scoring systems have been created for COVID-19. This review will not discuss all of these scores. Many of these scoring tools are a combination of clinical, laboratory, and imaging findings [184–194], and unfortunately, many of these have proven unreliable in the clinical setting. These scores are primarily derived from homogeneous, small populations of patients, and many lack extensive validation or are too complex for clinical use [184,185]. However, several demonstrate utility when used appropriately. When utilized, these scores should supplement clinical decision making, but they cannot replace clinical judgment [194].

One of the most robust and validated scores to predict mortality in patients with COVID-19 is the 4C (Coronavirus Clinical Characterisation Consortium) score. The 4C score has been validated in several settings in over 57,000 patients and considers age, sex, comorbidities, respiratory rate, oxygen saturation on room air, Glasgow Coma Scale, blood urea nitrogen, and CRP (Table 3) [186,187]. The derivation receiver-operator characteristic (ROC) curve was 0.79, with 0.77 in the validation cohort (ROC 0.5 suggests no discrimination, 0.7–0.8 suggests an acceptable level of discrimination, and greater than 0.8 is considered excellent) [186,187].

The quick COVID Severity Index (qCSI) is an effective physiological risk score that can be used at the bedside. It was initially created to



Fig. 3. Chest CT with bilateral, multilobar areas of airspace consolidations leaving ground-glass opacities, with some subpleural parenchymal bands already emerging. From <https://radiopaedia.org/cases/covid-19-pneumonia-158?lang=us>

determine risk of progressing to respiratory failure and critical illness within 24 h of hospital admission and is comprised of respiratory rate, pulse oximetry, and supplemental oxygen flow rate (Table 4) [188]. The initial ROC curve was 0.81, with other studies suggesting the score may be similar to the NEWS score and outperform other risk scores such as 4C and CURB-65 [188,189].

NEWS2 is another physiologic score comprised of respiratory rate, saturation, systolic blood pressure, pulse, consciousness, and temperature [190–192] (Table 5). This score demonstrates area under receiver operating characteristic (AUROC) curves of 0.78 for determining who will deteriorate over 24 h and for in-hospital mortality [192].

The PRIEST score, comprised of respiratory rate, oxygen saturation, heart rate, systolic blood pressure, temperature, alertness, inspired oxygen, sex, age, and performance status, reported a c-statistic of 0.80, with a score > 4 demonstrating a 98% sensitivity and 34% specificity to predict adverse events [193] (Table 6).

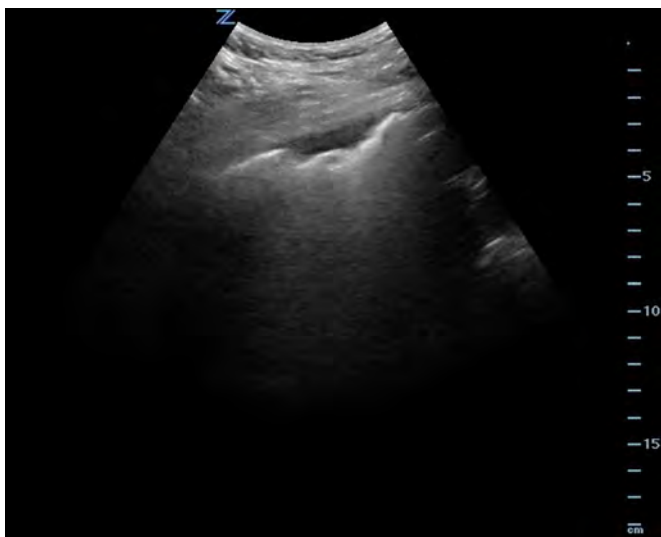


Fig. 4. Ultrasound demonstrating an irregular pleural line with a subpleural consolidation in a patient with COVID-19.

4. Conclusions

COVID-19 has resulted in millions of infections and deaths. The disease is primarily spread by respiratory droplets and aerosols. Several variants have arisen, including the Delta (B.1.617.2 lineage) and

Table 3
4C Score

Variable	Points
<i>Age in years</i>	
< 50	0
50–59	2
60–69	4
70–79	6
≥80	7
<i>Sex at birth</i>	
Female	0
Male	1
<i>Number of comorbidities</i>	
0	0
1	1
≥2	2
<i>Respiratory rate in breaths per minute</i>	
<20	0
20–29	1
≥30	2
<i>Peripheral oxygen saturation on room air</i>	
≥92%	0
<92%	2
<i>Glasgow coma scale</i>	
15	0
<15	2
<i>Urea/BUN</i>	
Urea <7 mmol/L or BUN <19.6 mg/dL	0
Urea 7–14 mmol/L or BUN 19.6–39.2 mg/dL	1
Urea >140 mmol/L or BUN >39.2 mg/dL	3
<i>CRP</i>	
< 50 mg/L	0
50–99 mg/L	1
≥100 mg/L	2
Score	Mortality
0–3 = Low risk	1.2–1.7%
4–8 = Intermediate risk	9.1–9.9%
9–14 = High risk	31.4–34.9%
≥15 = Very high risk	61.5–66.2%

Table 4
qCSI

Variable	Points
<i>Respiratory rate in breaths per minute</i>	
≤22	0
23–28	1
>28	2
<i>Peripheral oxygen saturation on room air</i>	
>92%	0
89–92%	2
≤88%	5
<i>O2 flow rate, L/min</i>	
≤2	0
3–4	4
5–6	5
Score	Risk of critical illness at 24 h
0–3 = Low risk	4%
4–6 = Low-intermediate risk	30%
7–9 = High-intermediate risk	44%
10–12 = High risk	57%

Table 5
NEWS2

Variable	Points
<i>Respiratory rate in breaths per minute</i>	
≤8	3
9–11	1
12–20	0
21–24	2
≥25	3
<i>SpO2 (on room air or supplemental)</i>	
≤91%	3
92–93%	2
94–95%	1
≥96%	0
<i>SpO2 (if patient has hypercapnic respiratory failure)</i>	
≤83%	3
84–85%	2
86–87%	1
88–92%, ≥93% on room air	0
93–94% on supplemental oxygen	1
95–96% on supplemental oxygen	2
≥97% on supplemental oxygen	3
<i>Oxygen</i>	
Supplemental oxygen	2
Room air	0
<i>Temperature</i>	
≤35.0 °C (95 °F)	3
35.1–36.0 °C (95.1–96.8 °F)	1
36.1–38.0 °C (96.9–100.4 °F)	0
38.1–39.0 °C (100.5–102.2 °F)	1
≥39.1 °C (102.3 °F)	2
<i>Systolic BP, mm Hg</i>	
≤90	3
91–100	2
101–110	1
111–219	0
≥220	3
<i>Pulse, beats per minute</i>	
≤40	3
41–50	1
51–90	0
91–110	1
111–130	2
≥131	3
<i>Consciousness</i>	
Alert	0
New onset confusion, responds to voice or pain, or unresponsive	3
Score	
0–4 = Low risk	
3 in any individual parameter = Low-medium risk	
5–6 = Medium risk	
≥7 = High risk	

Table 6
PRIEST score

Variable	Points
<i>Age in years</i>	
16–49	0
50–65	2
66–80	3
>80	4
<i>Sex</i>	
Female	0
Male	1
<i>Respiratory rate in breaths per minute</i>	
≤8	3
9–11	1
12–20	0
21–24	2
≥25	3
<i>Peripheral oxygen saturation</i>	
>95%	0
94–95%	1
92–93%	2
<92%	3
<i>Heart rate, beats per minute</i>	
≤40	3
41–50	1
51–90	0
91–110	1
111–130	2
≥131	3
<i>Systolic BP, mm Hg</i>	
≤90	3
91–100	2
101–110	1
111–130	0
≥130	3
<i>Temperature</i>	
≤35.0 °C (95 °F)	3
35.1–36.0 °C (95.1–96.8 °F)	1
36.1–38.0 °C (96.9–100.4 °F)	0
38.1–39.0 °C (100.5–102.2 °F)	1
≥39.1 °C (102.3 °F)	2
<i>Alertness</i>	
Alert	0
Confused or not alert	3
<i>Inspired oxygen</i>	
Air	0
Supplemental oxygen	2
<i>Performance status</i>	
Unrestricted normal activity	0
Limited strenuous activity, can do light activity	1
Limited activity, can self-care	2
Limited self-care	3
Bed/chair bound, no self-care	4

Omicron (B.1.1.529 lineage) variants. Most patients experience a mild infection with upper respiratory symptoms, fever, and change in taste/smell, but some may develop severe infection with respiratory failure and end organ injury. Aside from the respiratory system, SARS-CoV-2 can affect the cardiovascular, neurologic, gastrointestinal, and dermatologic systems. Evaluation includes identification of COVID-19 and assessment for end organ injury. Several risk scores may assist in prognostication.

CRedit authorship contribution statement

Brit Long: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Brandon M. Carius:** Writing – review & editing, Writing – original draft. **Stephen Y. Liang:** Writing – review & editing, Writing – original draft, Supervision. **Summer Chavez:** Writing – review & editing, Conceptualization. **William J. Brady:** Writing – review & editing, Conceptualization. **Alex Koyfman:** Writing – review & editing, Conceptualization. **Michael Gottlieb:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of Competing Interest

None

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