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JACC FOCUS SEMINAR

Coronavirus Historical Perspective, Disease Mechanisms, and Clinical Outcomes

JACC Focus Seminar

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ABSTRACT

The emergence of a new coronavirus disease (coronavirus disease 2019 [COVID-19]) has raised global concerns regarding the health and safety of a vulnerable population. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) incites a profound inflammatory response leading to tissue injury and organ failure. COVID-19 is characterized by the bidirectional relationship between inflammation and thrombosis. The clinical syndrome is propelled by inflammation producing acute lung injury, large-vessel thrombosis, and in situ microthrombi that may contribute to organ failure. Myocardial injury is common, but true myocarditis is rare. Elderly patients, those with established cardiovascular disease, and mechanically ventilated patients face the highest mortality risk. Therapies for COVID-19 are evolving. The antiviral drug remdesivir, dexamethasone, transfusion of convalescent plasma, and use of antithrombotic therapy are promising. Most require additional prospective studies. Although most patients recover, those who survive severe illness may experience persistent physical and psychological disabilities. (J Am Coll Cardiol 2020;76:1999-2010)

In December 2019, a cluster of pneumonia cases of unknown etiology was reported in Wuhan, China (1). Initial data indicated an association with a wet market where live animals were sold (2). The causative agent was identified as a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the resultant clinical syndrome was termed coronavirus disease 2019 (COVID-19) (3). That December, a perfect epidemiological storm erupted. A highly virulent respiratory pathogen jumped species boundaries, landing in a major travel hub just before a holiday season, and spread rapidly

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ABBREVIATIONS AND ACRONYMS

ARDS = acute respiratory distress syndrome

BMI = body mass index

COVID-19 = coronavirus disease 2019

CS = cytokine storm

HCQ = hydroxychloroquine

IL = interleukin

MERS = Middle East respiratory syndrome

NIH = National Institutes of Health

RNA = ribonucleic acid

SARS = severe acute respiratory syndrome

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

TLR = toll-like receptor

TNF = tumor necrosis factor

TRIF = Toll/interleukin-1 receptor domain-containing adaptor-inducing interferon-β

throughout a susceptible population. On March 11, 2020, the World Health Organization declared COVID-19 a global pandemic, and by May 19, 2020, there were >5 million confirmed cases worldwide; by early August, that number had quadrupled to >20 million cases. Similar to the 2003 severe acute respiratory syndrome (SARS) epidemic, 3 critical issues quickly emerged. First, how was the virus transmitted; second, what was the clinical spectrum of COVID-19; and third, what were the risk factors for severe disease and death (4).

TRANSMISSION, CLINICAL SPECTRUM, AND RISK FACTORS

TRANSMISSION. SARS-CoV-2 is believed to be spread primarily via aerosol or droplet transmission (5). Both asymptomatic and presymptomatic transmission has been described and seems to be a major contributor to viral spread (6). In a study of asymptomatic infections, the median communicable period was 9.5 days, with a range up to 21 days (7). Unlike those with SARS and Middle East respiratory syndrome (MERS), asymptomatic patients with COVID-19 have high viral loads and an infection coefficient of 2.0 to 3.5 in the early disease phase (8). Community coronavirus transmission is influenced by a combination of jurisdiction-specific epidemiological and population factors, including: 1) timing of virus introduction; 2) population density; and 3) age distribution and prevalence of underlying health conditions in the local population (9). Population age structure may explain the remarkable variation in fatalities in China, South Korea, Italy, and Spain. Tight, intergenerational contacts in Italy may have accelerated infection within an older population, contributing to the observed high fatality rate. Conversely, the outbreak in South Korea was concentrated in the young Shinchenji religious group and contained with early detection and treatment (10). In Kings County, Washington, 19 of the first 22 deaths were in elderly nursing home patients, but recent analysis now suggests the virus was circulating in the community weeks earlier (11). Isolation is the most effective method for containing COVID-19. Effective surveillance to establish infection sources by testing and contact tracing are required to block infection transmission.

CLINICAL SPECTRUM. COVID-19 spans a wide clinical spectrum from asymptomatic infection, to mild-to-moderate illness with cough, fever, and fatigue, to severe disease with pneumonia and acute lung injury (**Table 1**) (12–19). The most critical disease is characterized by septic shock and multiorgan failure (13). Recent data indicate that upwards of 80% of infections may be asymptomatic (20). A recent report found that 13.7% of all pregnant patients presenting for delivery were positive for SARS-CoV-2, and 87.9% of these were asymptomatic (21). Most patients with COVID-19 experience mild disease and fully recover. In a study of 72,314 people, 81% had mild disease, 14% severe, and 5% critical (22). Although the COVID-19 case fatality rate is estimated to be 2.3%, it cannot yet be fully ascertained given the relative lack of testing in community populations. Mortality is highest in people >70 years of age (8% to 14.8%) (**Figure 1**) and in those with critical illness (49%).

RISK FACTORS. Recognition of risk factors for morbidity and mortality is critical to identifying high-risk populations. Multiple studies of the epidemic in China revealed male predominance (60% of cases), median age of 57 years, and co-morbidities in approximately one-half of the patients, with hypertension being most common, followed by diabetes and coronary heart disease (13,22,23). Several variables were associated with progression to severe disease and death, including age >60 years; having at least 1 comorbidity; lymphopenia; higher admission Sequential Organ Failure Assessment score; and elevated C-reactive protein, D-dimer (the breakdown product of cross-linked fibrin) >1 μg/ml, serum levels of interleukin (IL)-6, high-sensitivity cardiac troponin I, and lactate dehydrogenase (13,23). Younger patients, particularly those <60 years of age,

HIGHLIGHTS

- Severe acute respiratory syndrome coronavirus 2 infection (COVID-19) is a global pandemic affecting millions of people worldwide.
- Clinical sequelae result largely from an intense inflammatory response triggering large-vessel and microvascular thrombosis.
- No therapy has been universally effective for COVID-19, but systemic anticoagulation, remdesivir, and corticosteroids hold promise.
- Long-term sequelae of COVID-19 are variable and incompletely defined, but physical and psychological disabilities can persist.

TABLE 1 Clinical Characteristics and In-Hospital Outcomes in Selected Reports of Patients With COVID-19

	Guan et al. (12) (N = 1,099)	Zhou et al. (13) (N = 191)	Bhatraju et al. (14) (N = 24)	Goyal et al. (15) (N = 393)	Richardson et al. (16) (N = 5,700)	Cummings et al. (17) (N = 257)	Grasselli et al. (18) (N = 1591)	Paranjpe et al. (19) (N = 2,199)
Geographic region	China	China	Washington (United States)	New York (United States)	New York (United States)	New York (United States)	Italy	New York (United States)
Demographic characteristics								
Mean age, yrs	47.0	56.0	64.0	62.2	63.0	62.0	63.0	65.0
Male	58.1	62.0	63.0	60.6	60.3	67.0	82.0	58.8
Symptoms at presentation								
Fever	43.8	94.0	50.0	77.1	30.7	71.0	-	-
Cough	67.8	79.0	88.0	79.4	-	66.0	-	-
Fatigue	38.1	23.0	-	-	-	-	-	-
Shortness of breath	18.7	-	88.0	56.5	-	74.0	-	-
Nausea and/or vomiting	5.0	4.0	-	19.1	-	-	-	-
Diarrhea	3.8	5.0	-	23.7	-	12.0	-	-
Myalgia or arthralgia	14.9	15.0	-	27.2	-	26.0	-	
Chills	11.5	-	-	-	-	-	-	-
Headache	13.6	-	8.0	-	-	4.0	-	-
Time from symptoms to admission	-	11.0	7.0	5.0	-	5.0	-	-
Medical history								
Hypertension	15.0	30.0	-	50.1	56.6	63.0	49.0	37.0
Diabetes mellitus	7.4	19.0	58.0	25.2	33.8	36.0	17.0	26.5
Current or former smoker	14.5	6.0	22.0	5.1	15.6	13.0	-	-
Coronary artery disease	2.5	8.0	-	13.7	11.1	19.0	21.0	15.6
Cerebrovascular disease	1.4	-	-	-	-	-	-	7.0
Chronic kidney disease	0.7	1.0	21.0	4.6	5.0	14.0	3.0	9.4
Asthma	-	-	14.0	12.5	9.0	8.0	-	8.2
COPD	1.1	3.0	4.0	5.1	5.4	9.0	4.0	5.1
Cancer	0.9	1.0	-	5.9	6.0	7.0	8.0	6.9
Immunodeficiency	0.2	-	-	5.4	1.8	7.0		-
Laboratory findings			-					
Leukocytosis	5.9	21.0	38.0	13.0	-	-	-	25.0
Lymphopenia	83.2	40.0	75.0	90.0	60.0	-	-	11.0
Thrombocytopenia	36.2	7.0	-	27.0	-	-	-	-
Elevated troponin	-	17.0	-	4.5	22.6	-	-	-
Elevated creatinine	1.6	4.0	-	16.0	-	-	-	-
Elevated C-reactive protein	60.7	-	-	43.5	-	-	-	-
Elevated ferritin	-	80.0	-	66.2	-	-	-	-
Elevated interleukin-6	-	9.0	-	-	-	-	-	-
Elevated lactate dehydrogenase	41.0	67.0	-	-	-	-	-	-
Elevated D-dimer	46.4	42.0	-	36.4	-	-	-	33.0
Elevated procalcitonin	5.5	9.0	-	16.9	-	-	-	28.0
Elevated lactate	41.0	67.0	53.0	-	-	-	-	51.0
Elevated alanine aminotransferase	21.3	31.0	32.0	32.0	58.4	-	-	-
Elevated aspartate aminotransferase	22.2	-	41.0	46.5	39.0	-	-	-
In-hospital outcomes								
Death	1.4	28.3	50.0	10.2	21.0	39.0	26.0	29.0
ICU admission	5.0	26.0	100.0	-	14.2	100.0	100.0	36.0
Acute respiratory distress syndrome	3.4	31.0	75.0	-	-	-	-	-
Mechanical ventilation	6.1	17.0	75.0	33.1	12.2	79.0	88.0	-
Shock	1.1	20.0	-	-	-	-	-	-
Acute kidney injury	0.5	15.0	-	-	22.2	31.0	-	-
Cardiac injury	-	17.0	-	-	22.6	-	-	-
Arrhythmias	-	-	-	7.4	-	-	-	-
Use of ECMO	0.5	2.0	0.0	-	-	3.0	1.0	-

Values are % unless otherwise indicated.

COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit.

are generally believed to be a lower risk group. However, New York City has seen a disproportionately higher number of hospital admissions, disease severity, and death within this group. Obese patients are particularly vulnerable. In a study of 4,103 patients, body mass index (BMI) >40 kg/m^2 was identified as a major risk factor for hospitalization (24). In another study of 3,615 COVID-19 patients, 21% had a BMI of 30 to 34 kg/m^2 and 16% had a BMI >35 kg/m^2 (25). Patients <60 years of age with a BMI >30 kg/m^2 were 2.0 to 3.5 times more likely to be hospitalized for acute and critical care.

UNIFYING MODEL OF INJURY: INFECTION, INFLAMMATION, AND THROMBOSIS

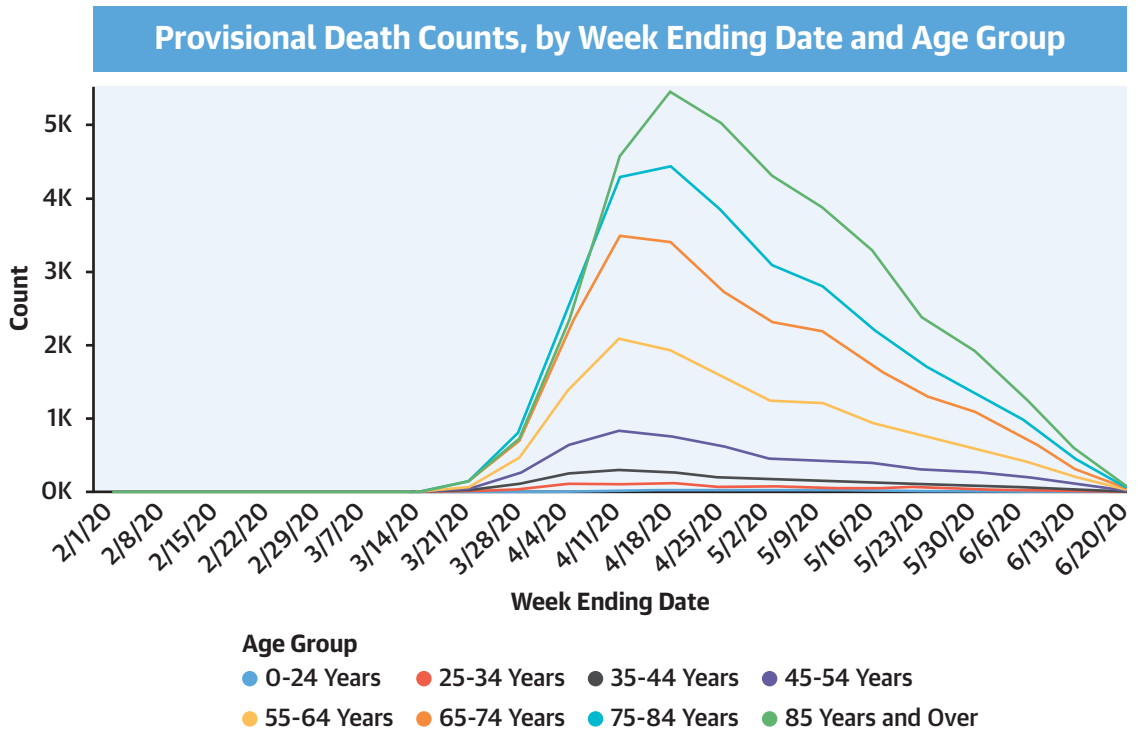
Viral illnesses, including the coronaviruses (SARS-CoV-1, SARS-CoV-2, and MERS-CoV), incite a profound systemic inflammatory response that leads to tissue injury and organ failure. The innate immune response to SARS-CoV and many other viruses involves Toll-like receptor (TLR)-3 signaling (26,27). TLR-3 is found on the surface of human alveolar, bronchial epithelial, and various immune cells (28), where it binds to endosome membranes recognizing double-stranded ribonucleic acid (RNA) from viral, bacterial, and fungal pathogens (29). After binding to double-stranded RNA, TLR-3 dimerizes and recruits the Toll/IL-1 receptor domain-containing adaptor-inducing interferon-β (TRIF) signaling cascade, whereas TLR-4 is signaled by either of the TLR adaptors TRIF or myeloid differentiation primary response 88. SARS-CoV-infected TRIF$^{-/-}$ mice have higher mortality, viral titers, and expression of cytokines, chemokines, and interferon-stimulated genes (26), mirroring the clinical sequelae of fatal SARS and MERS (30). The TRIF and MyD99 pathways contribute to host protection, whereas deletion of either pathway results in fatal SARS-CoV (26). The cellular immune response involves activation and proliferation of lymphocytes and macrophages, as well as increased levels of multiple proinflammatory cytokines, including monocyte chemoattractant protein-1, macrophage inflammatory protein-1 alpha, tumor necrosis factor (TNF)-α, IL-2, IL-7, and IL-10 (31).

Cytokine storm (CS) is a severe immune reaction in which the body releases excessive and overwhelming amounts of cytokines into the blood too quickly, causing harm. CS syndrome can be caused by a variety of diseases, including infectious diseases and autoimmune conditions (e.g., rheumatic diseases). CS may also occur after treatment with certain immunotherapies. Mediated by a CS syndrome, COVID-19 may cause severe, frequently lethal complications, such as progressive pneumonia, acute respiratory distress syndrome (ARDS), and organ failure. The proinflammatory cytokines involved in CS syndrome include IL-1, IL-6, interferon, and TNF-α (32,33). Binding of SARS-CoV-2 to the TLR causes the release of pro-IL-1β, which is cleaved by caspase-1, followed by inflammasome activation and production of active mature IL-1β (a mediator of lung inflammation), fever, and fibrosis (34).

COVID-19 is associated with dysregulation of the coagulation system, high incidence of venous and arterial thrombosis involving large and small vessels of various organs, and a poor prognosis (35). Among the frequent abnormalities are impaired fibrinolysis, elevated fibrinogen and factor VIII levels, and cross-talk between the intrinsic and extrinsic (contact) pathways in cases of disseminated intravascular coagulation (13,31,36,37). D-dimer levels are markedly elevated in many patients with COVID-19 and predictive of mortality (13). Although D-dimers are increased in a wide array of inflammatory disorders, levels are an order of magnitude higher in patients with COVID-19. Many patients also have elevated blood troponin levels, with or without clinical evidence of myocardial injury. Other correlates of thrombosis and mortality in this disease are thrombocytopenia, prolongation of prothrombin and partial thromboplastin times, hyperferritinemia, and hyperfibrinogenemia (13,37).

The balance between coagulation and fibrinolysis is complex, as is the bidirectional relationship between inflammation and thrombosis. The release of inflammatory molecules induced by the virus from damaged host cells activates the coagulation system, as does the host immune response (38). A dysregulated immune response in severe cases of COVID-19 promotes endothelial dysfunction, microvascular permeability, and thrombosis (39). Pulmonary endothelial damage is a characteristic feature of ARDS (40). Hypoxia induces transcription factors that activate tissue factor and plasminogen pathways (41). In addition to the typical risk factors for venous thromboembolism in hospitalized patients, acute pulmonary embolism in patients with COVID-19 (42) could also be triggered by both intrinsic thrombophilia and endothelial dysfunction (43). Hence, although COVID-19 is not primarily a thrombotic disease, thrombotic complications are frequent responses to inflammation and hypoxia. Although antiphospholipid antibodies have been identified in patients with COVID-19 and coagulopathy (44), transient antibodies of this type occur commonly in patients who become acutely ill from other causes and are often not thrombogenic.

FIGURE 1 Provisional Death Counts Involving COVID-19 From February 1, 2020, to June 20, 2020, as Reported to the CDC



Deaths involving coronavirus disease 2019 (COVID-19) are more prevalent in older age groups. CDC = Centers for Disease Control and Prevention. Adapted from the Centers for Disease Control and Prevention (99).

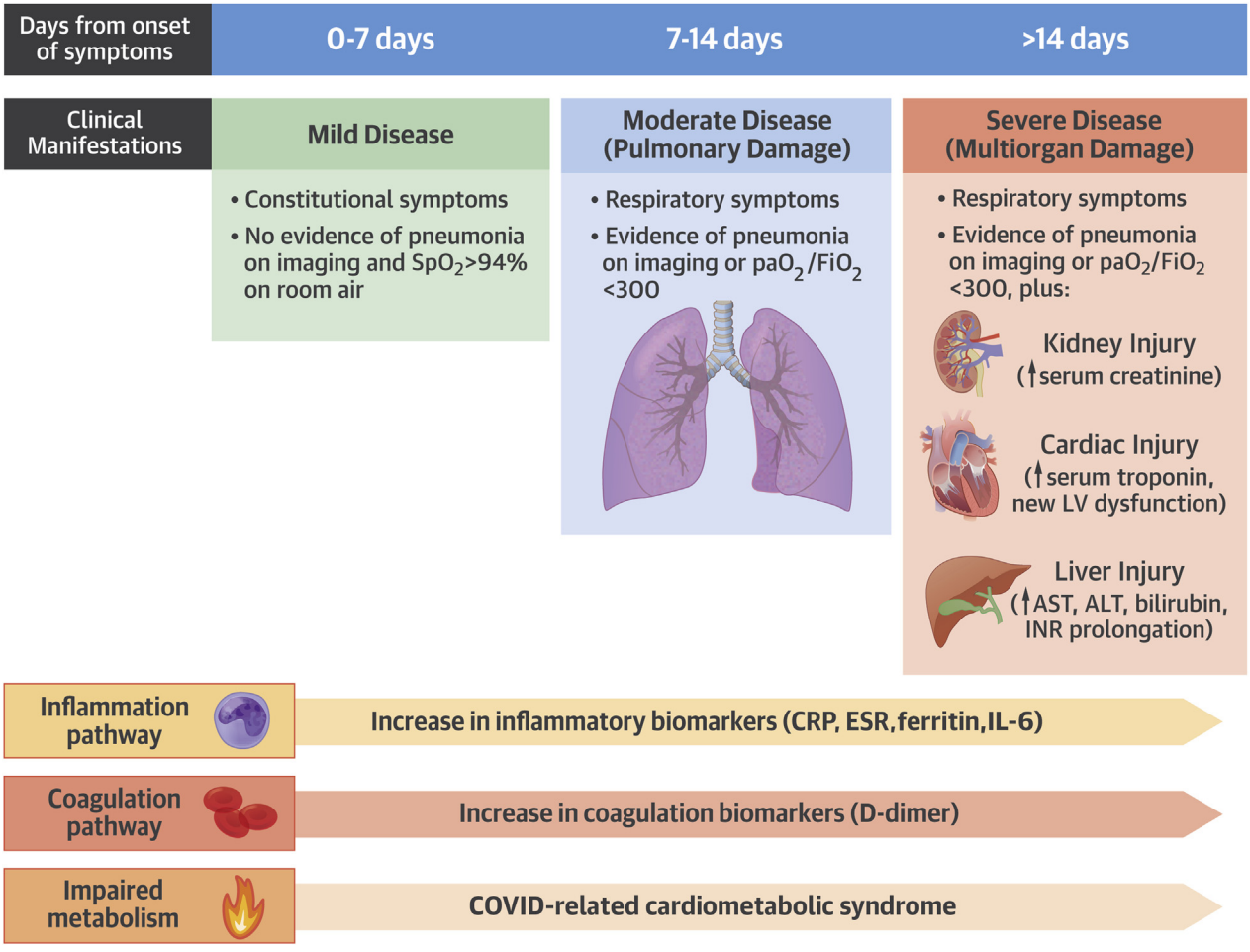
CLINICAL PRESENTATION AND OUTCOMES

The clinical manifestations of COVID-19 are highly heterogeneous (12-14,42,45-51). A summary of the clinical characteristics and hospital outcomes of patients with COVID-19 is listed in **Table 1**. In a multicenter registry from China including 1,099 patients from 552 hospitals, the most common presenting symptoms included cough (67.8%), fever (43.8%), and fatigue (38.1%) (12). Less common symptoms included headache, myalgias, sore throat, nausea, vomiting, and diarrhea. Anosmia and dysgeusia are possible symptoms as well (52). The median incubation period for COVID-19 is estimated to be 5 days, with >90% of patients developing symptoms within ~12 days from exposure (53). Patients with more severe disease requiring hospitalization frequently present with significant symptoms (e.g., shortness of breath) and are more likely to have concomitant co-morbidities, including chronic obstructive pulmonary disease, diabetes mellitus, hypertension, and coronary artery disease (12,13). Less frequently, patients may initially present with late COVID-19 complications, including thromboembolic events (e.g., stroke, peripheral limb ischemia, pulmonary embolism), or end-organ damage, including myocarditis with cardiogenic shock, and acute renal failure, without predominant respiratory symptoms (42,44,47,54).

A substantial proportion of patients have abnormalities on chest radiography and chest computed tomography imaging (12). The most frequent findings included bilateral multifocal opacities on chest radiography and ground-glass opacities on chest computed tomography imaging (56.4%); however, a number of patients with COVID-19 may not have radiological abnormalities (12,13). The extent of radiological abnormalities correlates with the severity of clinical presentation (12,13,45,48).

The most severe complications of COVID-19 include ARDS, acute kidney injury, cardiac injury, and both venous and arterial thromboembolic complications (12-14,42,45-51). The incidence of these complications is higher among elderly patients and those with pre-existing co-morbidities. ARDS is the most frequent COVID-19 complication, ranging

CENTRAL ILLUSTRATION **Proposed Severity Levels of Coronavirus Disease 2019**



Pinney, S.P. et al. J Am Coll Cardiol. 2020;76(17):1999–2010.

Coronavirus disease (COVID) 2019 produces a spectrum of clinical illness ranging from mild respiratory and constitutional symptoms to pneumonia with severe hypoxia and respiratory failure. Severe illness is associated with systemic inflammation and disturbances in coagulation leading to small- and large-vessel thrombosis. Myocardial injury when present is usually mild but associated with worse outcomes. ALT= alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; FiO_2 = fraction of inspired oxygen; IL = interleukin; INR = international normalized ratio; LV = left ventricular; paO_2 = partial pressure of oxygen; SpO_2 = blood oxygen saturation.

between 20% and 40% among hospitalized patients, and is strongly associated with a higher risk of in-hospital mortality (13,36,45,48). Patients who require mechanical ventilation are at higher mortality risk compared with those managed with noninvasive ventilation. However, mortality rates of patients requiring invasive mechanical ventilation seemed significantly worse in a retrospective series from China (13,55) compared with a more recent U.S. series (15). For example, among 393 patients who were admitted to 2 New York City hospitals, 130 (33.1%) required mechanical ventilation, of whom 19 (14.6%) died and 68 (52.3%) remained ventilated at time of publication. Other end-organ complications (e.g., acute kidney injury, cardiac injury) tend to occur late after symptom onset (8 to 14 days) and predict in-hospital mortality (13,36,45,48). COVID-19 can be staged from mild disease with only constitutional symptoms and no clinical evidence of lung injury, to severe disease with ARDS, multiorgan failure, and viral sepsis (**Central Illustration**) (56).

Mortality rates and need for intensive care (**Table 1**) are variable across published reports, reflecting differences in demographic factors and the prevalence

of pre-existing comorbidities (22,57). Based on data from the Chinese Center for Disease Control and Prevention Report, the overall COVID-19 case fatality rate is ~2.3% (22). This rate increases to 8.0% in patients 70 to 79 years of age, 14.8% in patients ≥80 years of age, and 49.0% in critically ill patients. Similar mortality trends have been reported in Italy (57) and the United States (58), with progressively higher case fatality rates per increase in age range, with most deaths occurring in patients ≥60 years of age.

THERAPEUTICS: ACCEPTED, EVOLVING, AND EXPERIMENTAL

There are currently no drugs or other therapeutics approved by the U.S. Food and Drug Administration to prevent or treat COVID-19 (59). Current guidelines emphasize the importance of infection prevention and control measures combined with supportive care. Beginning with the initial outbreak, patients have been treated with various off-label or compassionate-use medications with varying degrees of anecdotal success. Data continue to emerge at the time of this writing from clinical trials that are shaping treatment guidelines.

ANTIVIRAL THERAPIES. Remdesivir is a pro-drug that is metabolized to an analogue of adenosine triphosphate and inhibits viral RNA polymerases. It has shown in vitro activity against filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV-1, SARS-CoV-2, MERS-CoV) and has been well tolerated in clinical use (60). Results from a National Institutes of Health (NIH)–sponsored multinational clinical trial led to the emergency use authorization by the U.S. Food and Drug Administration for remdesivir in patients hospitalized with severe disease (61). This trial enrolled 1,063 patients with a mean age of 58.9 years, 52.1% of whom had 2 or more comorbidities, with a median time from symptom onset to randomization of 9 days. Remdesivir significantly reduced time to recovery compared with placebo (11 days vs. 15 days), with the clearest benefit observed in the subgroup who required supplemental oxygenation at study enrollment. Mortality at 14 days was lower for remdesivir-treated patients, but the difference failed to reach statistical significance. There was no observed benefit in patients with mild or moderate disease (small enrollment numbers), nor for those requiring mechanical ventilation or extracorporeal membrane oxygenation. A randomized, open-label trial of lopinavir/ritonavir enrolling 199 patients with severe COVID-19 illness failed to show an improvement in time to clinical improvement or survival beyond that of standard care (62).

ANTICYTOKINE AND IMMUNOMODULATORY DRUGS. IL-6 is a key inflammatory cytokine known to contribute to thrombo-inflammatory responses associated with acute and chronic inflammation (63). Elevated levels of IL-6 have been associated with increased immature platelet production, platelet adhesion, and thrombotic responses. Monoclonal antibodies targeting the IL-6 receptor, such as tocilizumab and sarilumab, are approved for rheumatoid arthritis treatment and have been used with varying success in small COVID-19 case series (64). The Italian Medicines Agency (AIFA), Italy's drug regulator, recently reported the results of a randomized study of tocilizumab, which failed to improve severe respiratory symptoms, reduce intensive care unit hospitalization, or lower mortality rates more than standard care alone (65). Whether there is a role for corticosteroids in treating COVID-19 lung injury continues to be a matter of debate (66). Steroids dampen nuclear factor-kB production of TNF-α, IL-1, and IL-6 but have not improved outcomes in ARDS (67). Initial clinical evaluation of their use in the most severe COVID-19 cases has shown a decreased rate of viral clearance, increased mortality, greater bacterial superinfections, and prolonged hospital stay (68). More recently, a British study reported that dexamethasone reduced 28-day mortality by one-third in ventilated patients and by one-fifth in those requiring oxygen only (69). Investigators randomized 2,104 patients to receive oral or intravenous dexamethasone 6 mg daily versus usual care. Results varied depending on the extent of respiratory support, with no benefit observed for those patients not requiring oxygen or mechanical ventilation.

ANTITHROMBOTIC AGENTS. SARS-CoV-2 infection has been associated with increased fibrinogen and decreased antithrombin levels, as well as both large-vessel and microvascular thrombosis. Several consensus statements recommend antithrombotic prophylaxis to prevent thromboembolism for hospitalized patients (70–73). Use of systemic anticoagulation remains uncertain. Citing a lack of sufficient data, the NIH does not recommend either for or against using therapeutic doses of antithrombotic or thrombolytic agents for COVID-19 in hospitalized patients (74). A retrospective, single-center study of 2,773 hospitalized patients reported an association between use of systemic anticoagulation and improved clinical outcomes (75). In-hospital mortality for patients treated with anticoagulation was 22.5% with a median survival of

21 days, compared with 22.8% and a median survival of 14 days in patients who did not receive systemic anticoagulation. Rates of major bleeding were higher (3.0% vs. 1.9%) with systemic anticoagulation, particularly among intubated patients. Conversely, a retrospective propensity-matched analysis of patients who were receiving systemic anticoagulation before COVID-19 infection showed no difference in survival or time to mechanical ventilation compared with those not receiving anticoagulant or antiplatelet therapy (76). The authors of this study expressed doubt as to whether systemic anticoagulation alone would be protective against COVID-19–related morbidity or mortality. Consensus opinion is that prospective randomized trials are needed to determine what role systemic anticoagulation should play in COVID-19 treatment.

Heparinoids have anti-inflammatory effects, which may be beneficial with COVID-19. Anticoagulation with heparin has been associated with better prognosis in patients with severe COVID-19 and coagulopathy (77). Unfractionated heparin may be the most effective anticoagulant, but there are several limiting considerations. Heparin therapy requires frequent monitoring of activated partial thromboplastin time to assure that anticoagulation intensity is in the therapeutic range. This monitoring exposes the nursing staff to patients with COVID-19 more frequently than would most other antithrombotic strategies. Sensitization is another potential risk, although the frequency of heparin-induced thrombocytopenia has not been reported in patients with COVID-19.

In acutely ill hospitalized patients with COVID-19, anticoagulant thromboprophylaxis with low-molecular-weight heparin or fondaparinux is preferred over unfractionated heparin (78). The benefit of low-molecular-weight heparin was established in several placebo-controlled trials involving medically ill patients well before the COVID-19 era (79). Dosing is problematic in patients with significant renal impairment. Monitoring of anti-factor Xa activity has been recommended. Bleeding is relatively uncommon in patients with COVID-19, but the relative frequency of hemorrhagic and ischemic stroke in this disease compared with other settings has not been established. In patients who develop deep vein thrombosis during hospitalization with COVID-19, full-dose oral anticoagulation is indicated for at least 3 months, and probably longer for those with pulmonary embolism.

The role of target-specific direct oral anticoagulants is unproven, but these are increasingly adopted, in part because of their ease of administration and wide acceptance among clinicians. Consideration may be given to extended (post-discharge) prophylaxis in certain high-risk individuals (age >75 years, D-dimer levels >2 times upper limit of normal, and previous thromboembolism) but is otherwise not recommended (74). Betrixaban compared favorably to enoxaparin when initiated before discharge and continued beyond (80). Also, rivaroxaban 10 mg daily for 31 to 40 days was superior to enoxaparin in subgroups of medical patients who had been hospitalized with infections and elevated D-dimer levels (81).

In patients with severe COVID-19, routine coagulation test results reflect the combined effects of coagulation dysfunction and anticoagulant administration, which makes it difficult to accurately assess coagulation activity (70). In patients with severe illness associated with disseminated intravascular coagulation, lupus anticoagulant, or variability in fibrinogen or factor VIII levels, inflammatory proteins may interfere with the association between activated partial thromboplastin time prolongation and anticoagulant efficacy. This can make anticoagulant dose regulation challenging without assays of anti-Xa, thrombin generation, and other indices that may not be readily available or rapidly reported (82).

CHLOROQUINE AND HYDROXYCHLOROQUINE. Chloroquine and hydroxychloroquine (HCQ), antimalarial drugs commonly used for treating rheumatological disorders, have in vitro activity against SARS-CoV-1 and SARS-CoV-2 (83). Results from 2 small studies, each with significant methodological limitations, suggested improvement with HCQ (84,85). These benefits have not been confirmed in larger observational and randomized trials (86,87). HCQ use among 1,376 patients hospitalized in a single New York City hospital was not associated with lower rates of intubation or death (86). In a British study, 1,542 patients were randomized to receive HCQ and then compared with 3,132 patients randomized to usual care alone (87). There was no significant difference in the primary endpoint of 28-day mortality (25.7% HCQ vs. 23.5% usual care) or evidence of beneficial effects on hospital stay duration or other outcomes. Significant concerns remain about the safety of HCQ and azithromycin due to QTc prolongation and susceptibility to ventricular arrhythmias. The NIH does not recommend use of chloroquine or HCQ outside a clinical trial (88).

CONVALESCENT PLASMA. Plasma obtained from recently recovered donors with protective immunity (antiviral titers >1:640) has now been administered to

>150 patients, including 15 in published reports (89,90). These patients were infused with 200 ml of convalescent plasma an average of 2 weeks after hospital admission. Infusions were safely tolerated and associated with viremia clearance, increased lymphocyte counts, reduced C-reactive protein levels, and radiographic improvement of lung injury within 7 days. Neutralizing antibodies were able to be maintained at a high level.

CLINICAL SEQUELAE AND LONG-TERM COMPLICATIONS

The majority of patients infected with SARS-CoV-2 experience asymptomatic or mild to moderate COVID illness and make a complete recovery. The sequelae for survivors of severe or critical illness remain uncertain, but some early observations are concerning. In 1 post-COVID-19 discharge clinic in Rome, almost 90% of patients had at least 1 persistent symptom 2 months after the onset of their illness, with fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%), and chest pain (21.7%) being most prevalent. Forty-four percent reported a measurable decline in their quality of life scores as a result of COVID-19 (91).

Additional insights can be gained from previous SARS and MERS epidemics. First, survivors of *Coronaviridae* infections develop neutralizing antibodies against a number of viral proteins, particularly the spike protein (92,93). Although passive transfer of antibodies from hyperimmune donors conferred immediate protection against SARS-CoV infection, it remains uncertain whether these antibodies retained long-lasting neutralizing capability (92). Isolation and immortalization of memory B cells from a SARS-CoV survivor produced several monoclonal antibodies with high viral neutralizing activity in vitro and in vivo, but due to the rich diversity in antigenic variants, cross-protection against different SARS-CoV strains cannot be certain (93).

Although cardiac dysfunction was relatively mild and mostly reversible in SARS, it is plausible to assume that COVID-19 survivors will be more vulnerable to long-term cardiac morbidity (94). Myocardial injury is frequently seen in hospitalized patients with COVID-19, particularly those with a history of or risk factors for cardiovascular disease (95). Serum troponin I elevations are generally low level but associated with worse clinical outcome (95,96). Myocardial injury, resulting from either microvascular thrombosis or direct viral myocyte injury, combined with insulin resistance and cardiometabolic syndrome may produce myocardial fibrosis, adverse diastolic relaxation, and a heart failure syndrome with either preserved or reduced ejection fraction. Autopsy findings are few but have identified mild, patchy interstitial fibrosis and myocyte hypertrophy indistinguishable from pre-existing cardiovascular disease (97). Longitudinal follow-up with multimodal imaging and physiological testing will be important to describe the full extent of acquired COVID-19 heart disease.

The impact of SARS on pulmonary function, exercise capacity, and quality of life is sobering (98). Roughly one-third of survivors had persistently abnormal pulmonary function 1 year after illness onset, with one-quarter exhibiting impaired gas exchange (reduced diffusing capacity for carbon monoxide). Survivors reported exercise capacity and health status that were below that of the general population and which seemed disproportionately reduced compared with the degree of pulmonary impairment. This scenario suggests that other contributory factors, such as steroid myopathy, critical illness neuropathy, and physical deconditioning, contribute to this disability. Given the extent of alveolar epithelial injury, microvascular angiopathy, and duration of deep intensive care unit sedation in survivors of severe or critical COVID-19, it seems reasonable to anticipate seeing similar or more severe disabilities in this population persisting beyond the current pandemic.

CONCLUSIONS

The emergence of a new viral pathogen (SARS-CoV-2) into an interconnected, vulnerable global population has produced a clinical syndrome (COVID-19) resulting from the intersection of infection, inflammation, and thrombosis. Most who are infected will experience mild symptoms and recover. The elderly and those with co-morbidities are particularly susceptible to infection and the development of severe illness. The development of ARDS and microthrombi in the lungs, heart, and kidneys seem to be drivers of fatal disease. There are currently no approved therapies for COVID-19, but remdesivir, convalescent plasma, dexamethasone, and antithrombotic agents seem promising.

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