Multifactorial Predictors of Outcomes in COVID-19: Insights from Radiological, Laboratory, and Clinical Data

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Abstract

The COVID-19 pandemic has posed unprecedented challenges to healthcare systems worldwide, necessitating the identification of reliable predictors of patient outcomes to optimize resource allocation and clinical management. This review explores the radiological, laboratory, and clinical predictors of outcomes in hospitalized COVID-19 patients. Radiological findings, particularly chest imaging abnormalities, including bilateral ground-glass opacities and consolidation on CT scans, have emerged as critical indicators of disease severity and prognosis. Laboratory biomarkers, such as elevated D-dimer, CRP, ferritin, and lymphopenia, have been closely linked to poor outcomes, reflecting hyperinflammation and coagulopathy in severe disease. Clinical parameters, including age, comorbidities (e.g., diabetes, hypertension, cardiovascular disease), and oxygenation status, significantly influence patient trajectories, with older patients and those with comorbid conditions experiencing higher mortality and prolonged hospitalization. This review synthesizes the current evidence, highlighting the interplay between radiological, laboratory, and clinical factors in predicting outcomes and guiding treatment strategies. By integrating these predictors, clinicians can better stratify risk, identify patients requiring intensive care, and improve overall COVID-19 management outcomes.

Keywords: *Predictors of Outcomes, COVID-19*

1. Introduction

Coronaviruses comprise a vast family of viruses, seven of which are known to cause disease in humans. Some coronaviruses that typically infect animals have evolved to infect humans. SARS-CoV-2 is likely one such virus, postulated to have originated in a large animal and seafood market. (SARS) and (MERS) also are caused by coronaviruses that "jumped" from animals to humans. More than 8000 individuals developed SARS, nearly 800 of whom died of the illness (mortality rate, approximately 10%), before it was controlled in 2003. MERS continues to resurface in sporadic cases. In late February 2022, a total of 2585 laboratory-confirmed cases of Middle East respiratory syndrome (MERS) were reported worldwide (890 associated deaths;

case-fatality ratio, 34.4%). [1].

Route of Transmission

The principal mode by which people are infected with SARS-CoV-2 is through (generally within a space of 6 feet). Additional methods include contact transmission (eg, shaking hands) and airborne transmission of droplets that linger in the air over long distances (usually greater than 6 feet). Virus released in respiratory secretions (eg, during coughing, sneezing, talking) can infect other individuals via contact with mucous membranes. [2].

On July 9, 2020, the WHO issued an update stating that airborne transmission may play a role in the spread of COVID-19, particularly involving "super spreader" events in confined spaces such as bars, although they stressed a lack of such evidence in medical settings. Thus, they emphasized the importance of social distancing and masks in preventionThe WHO continues to support airborne transmission as a method of the disease's spread. The virus can also persist on surfaces to varying durations and degrees of infectivity, although this is not believed to be the main route of transmission. SARS-CoV-2 remained detectable for up to 72 hours on some surfaces despite decreasing infectivity over time. Notably, the study reported that no viable SARS-CoV-2 was measured after 4 hours on copper or after 24 hours on cardboard. [3].

Chin and colleagues found the virus was very susceptible to high heat (70°C). At room temperature and moderate (65%) humidity, no infectious virus could be recovered from printing and tissue papers after a 3-hour incubation period or from wood and cloth by day 2. On treated smooth surfaces, infectious virus became undetectable from glass by day 4 and from stainless steel and plastic by day 7. "Strikingly, a detectable level of infectious virus could still be present on the outer layer of a surgical mask on day 7 (~0.1% of the original inoculum)," the researchers write. Contact with fomites is thought to be less significant than person-to-person spread as a means of transmission. [4].

Viral shedding

The duration of viral shedding varies significantly and may depend on severity. A 2022 sytematic review and meta-analysis of 20 studies (866 participants) found that after symptom onset, the mean duration of RT-PCR positivity was 27.9 days, whereas the mean duration of isolation of replicant competent virus was 7.3 days. The mean duration of SARS-CoV-2 shedding was 26.5 days among immunocompetent individuals and 36.3 days among immunocompromised individuals. The mean duration of infectivity was 6.3 days among immunocompetent participants and 29.5 days among immunocompromised participants. The longest duration of infectivity was 18 days after symptom onset among immunocompetent patients compared with a maximum of 112 days among immunocompromised patients. [5].

Among 137 survivors of COVID-19, viral shedding based on testing of oropharyngeal samples ranged from 8 to 37 days, with a median of 20 days. repeated viral RNA tests using nasopharyngeal swabs were negative in 90% of cases among 21 patients with mild illness, whereas results were positive for longer durations in patients with severe COVID-19. In an evaluation of patients recovering from severe COVID-19, Zhou and colleagues found a median shedding duration of 31 days (range, 18-48 days). These studies have all used PCR detection as a proxy for viral shedding. [6].

Additionally, patients with profound immunosuppression (eg, following hematopoietic stem-cell transplantation, receiving cellular therapies) may shed viable SARS-CoV-2 for at least 2 months. SARS-CoV-2 has been found in the semen of men with acute infection, as well as in some male patients who have recovered. Asymptomatic/presymptomatic SARS-CoV-2 infection and its role in transmission [7].

Oran and Topol published a narrative review of multiple studies on asymptomatic SARS-CoV-2 infection. Such studies and news articles reported rates of asymptomatic infection in several worldwide cohorts, including resident populations from Iceland and Italy, passengers and crew aboard the cruise ship Diamond Princess, homeless persons in Boston and Los Angeles, obstetric patients in New York City, and crew aboard the USS Theodore Roosevelt and Charles de Gaulle aircraft carriers, among several others. Almost half (40-45%) of SARS-CoV-2 infections were asymptomatic. [8].

CDC assessed transmission from presymptomatic, never symptomatic, and symptomatic individuals across various scenarios to determine the infectious period of transmitting SARS-CoV-2. Results from their base case determined 59% of all transmission came from asymptomatic transmission, 35% from presymptomatic individuals and 24% from individuals who never developed symptoms. They estimate at least 50% of new infections came from exposure to individuals with infection, but without symptoms. Zou and colleagues followed viral expression through infection via nasal and throat swabs in a small cohort of patients. They found increases in viral loads at the time that the patients became symptomatic. One patient never developed symptoms but was shedding virus beginning at day 7 after presumed infection. [9].

Epidemiology

Coronavirus outbreak and pandemic

As of May 13, 2022, confirmed COVID-19 infections numbered over 517 million individuals worldwide and have resulted in over 6.2 million deaths. Additionally, the full death toll associated directly or indirectly with the pandemic is approximately 15 million. In the United States, over 85.9 million reported cases of COVID-19 have been confirmed as of June 17, 2022, resulting in more than 1 million deaths. The pandemic caused approximately 375,000 deaths in the United States during 2020. The age-adjusted death rate increased by 15.9% in 2020, making it the third leading cause of death after heart disease and cancer. During 2021, COVID-19 was associated with approximately 450,000 deaths in the United States, and was again the third leading cause of death. [10].

Racial health disparities

Communities of color have been disproportionally devastated by COVID-19 in the United States and in Europe. Data from New Orleans illustrated these disparities. African Americans represent 31% of the population but 76.9% of the hospitalizations and 70.8% of the deaths. A systematic review of 52 studies found racial and ethnic minority groups were at higher risk for COVID-19 infection and hospitalization, confirmed diagnosis, and death. Most of the studies listed factors such as low education level, poverty, poor housing conditions and overcrowded households, low household income, and not speaking the national language in a country as risk factors for COVID-19 incidence/infection, death, and confirmed diagnosis. [11].

Data suggest the cumulative effects of health disparities are the driving force. The prevalence of chronic (high-risk) medical conditions is higher, and access to healthcare may be less available. Finally, socioeconomic status may decrease the ability to isolate and avoid infection. A prospective cohort study surveyed 170 adult patients who had recovered from COVID-19 1 year prior, during March and April of 2020. The patients participated in a telephone survey during March and April of 2021.Almost half (79 patients; 46.5%) were of Hispanic ethnicity and 27.1% (46 patients) were African American. Job loss after COVID-19 diagnosis was highest among Hispanics (31/79; 39.2%) and African Americans (16/46; 34.7%). Hispanic individuals (31/79; 39.2%) and African Americans (17/46; 36.9%) also reported the most financial distress after COVID-19 diagnosis. Compared with Whites, Hispanics were more likely to experience job loss

(odds ratio, 4.456), as were African Americans (odds ratio, 4.465). [12].

Hobbs et al compared MIS-C cases (38 cases) and COVID-19 hospitalizations (74 children) among non-Hispanic Black and White children in a defined catchment 16-county area of Mississippi. Ward et al conducted a retrospective analysis of COVID-19 cases reported to the Alaska Department of Health and Social Services from March 12, 2020-December 31, 2021. The age-adjusted COVID-19 incidence among American Indian (AI)/Alaska Native (AN) individuals (26,583 per 100,000 standard population) was approximately twice the rate among White individuals (11,935). The age-adjusted COVID-19-associated hospitalization rate (273; rate ratio [RR], 2.72) and the age-adjusted COVID-19 related mortality rate (104; RR, 2.86) among AI/AN individuals were nearly three times those of White study participants. The overall age-adjusted death rate increased by 15.9% in 2020. Death rates were highest among non-Hispanic Black persons and non-Hispanic American Indian or Alaska Native persons. [13].

Young Adults

Outcomes from COVID-19 disease in young adults have been described by Cunningham and colleagues. Of 3200 adults aged 18 to 34 years hospitalized in the United States with COVID-19, 21% were admitted to the ICU, 10% required mechanical ventilation, and 3% died. Comorbidities included obesity (33%; 25% overall were morbidly obese), diabetes (18%), and hypertension (16%). Independent predictors of death or mechanical ventilation included hypertension, male sex, and morbid obesity. Young adults with multiple risk factors for poor outcomes from COVID-19 compared similarly to middle-aged adults without such risk factors. older children and adolescents are more likely to transmit SARS CoV-19 to family members than are younger children. The researchers reported that the highest infection rate (18.6%) was in household contacts of patients with COVID-19 aged 10 to 19 years, and the lowest rate (5.3%) was in household contacts of those aged 0 to 9 years. Teenagers have been the source of clusters of cases, illustrating the role of older children. [8].

COVID-19 in children

Data continue to emerge regarding the incidence and of COVID-19, especially for severe disease. A severe multisystem inflammatory syndrome linked to COVID-19 infection has been described in children. The American Academy of Pediatrics (AAP) reports children represent 19% of all COVID-19 cases in the 49 states reporting by age; over 13.1 million children have tested positive in the United States since the onset of the pandemic as of May 12, 2022. This represents an overall rate of 17,457 cases per 100,000 children. During the 2-week period of April 28 to May 12, 2022, there was an < 1% increase in the cumulated number of children who tested positive, representing 155,978 new cases. In the week from May 5-12, 2022, cases in children numbered 93,511 and represented 18.3% of the new weekly cases. Children were 1.3% to 4.6% of total reported hospitalizations, and 0.1% to 1.5% of all child COVID-19 cases resulted in hospitalization. [14].

In the United States, a modeling study found one child loses a parent or caregiver for every four COVID-19 associated deaths. From April 1, 2020 through June 30, 2021, more than 140,000 children younger than 18 years in the United States lost a parent, custodial grandparent, or grandparent caregiver who provided the child's home and basic needs, including love, security, and daily care. Overall, approximately one of 500 US children has experienced COVID-19-associated orphanhood or the death of a grandparent caregiver. Racial, ethnic, and geographic disparities in COVID-19-associated death of caregivers were also seen – children of racial and ethnic minorities accounted for 65% of those who lost a primary caregiver due to the pandemic. [14].

As of late June 2022, approximately 85,825,048 cases of SARS-CoV-2 infection and 1,007,964 associated deaths have been reported in the United States. Persons younger than 21 years constitute 26% of the US population. Clinical characteristics and outcomes of hospitalized children and adolescents aged 1 month to 21 years with COVID-19 in the New York City area have been described. These observations alerted clinicians to rare, but severe illness in children. Of 67 children who tested positive for COVID-19, 21 (31.3%) were managed as outpatients. Among 46 hospitalized patients, 33 (72%) were admitted to the general pediatric medical unit and 13 (28%) to the pediatric intensive care unit (PICU). Obesity and asthma were highly prevalent, but not significantly associated with PICU admission (P = .99). [15].

Admission to the pediatric intensive care unit (PICU) was significantly associated with higher C-reactive protein, procalcitonin, and pro-B type natriuretic peptide levels and platelet counts (P < .05 for all). Patients in the PICU were more likely to require high-flow nasal cannula (P = .0001) and were more likely to have received remdesivir through compassionate release (P < .05). Severe sepsis and septic shock syndromes were observed in seven (53.8%) patients in the PICU. ARDS was observed in 10 (77%) PICU patients, six (46.2%) of whom required invasive mechanical ventilation for a median of 9 days. Of the 13 patients in the PICU, eight (61.5%) were discharged home, and four (30.7%) patients remained hospitalized on ventilatory support at Day 14. One patient died after withdrawal of life-sustaining therapy associated with metastatic cancer. [16].

A case series of 91 children who tested positive for COVID-19 in South Korea showed 22% were asymptomatic during the entire observation period. Among 71 symptomatic cases, 47 children (66%) had unrecognized symptoms before diagnosis, 18 (25%) developed symptoms after diagnosis, and six (9%) were diagnosed at the time of symptom onset. Twenty-two children (24%) had lower respiratory tract infections. The mean (SD) duration of the presence of SARS-CoV-2 RNA in upper respiratory samples was 17.6 (6.7) days. These results lend more data to unapparent infections in children that may be associated with silent COVID-19 community transmission. [17].

Jiang and colleagues reviewed the literature on MIS-C noting the multiple organ system involvement. Unlike classic Kawasaki Disease, the children tended to be older and those of Asian ethnicity tended to be spared. A case series compared 539 patients who had MIS-C with 577 children and adolescents who had severe COVID-19. The patients with MIS-C were typically younger (predominantly aged 6-12 years) and more likely to be non-Hispanic Black. They were less likely to have an underlying chronic medical condition, such as obesity. Severe cardiovascular or mucocutaneous involvement was more common in those with MIS-C. Patients with MIS-C also had higher neutrophil to lymphocyte ratios, higher CRP levels, and lower platelet counts than those with severe COVID-19. [18].

COVID-19 in pregnant individuals and neonates

Pregnant women are at increased risk for severe COVID-19–related illness, and COVID-19 is associated with an increased risk for adverse pregnancy outcomes including intrauterine growth restriction, premature rupture of membranes and preterm delivery, fetal distress, spontaneous abortion, and stillbirth, and maternal and neonatal complications. The Centers for Disease Control and Prevention reported in November 2021 that maternal COVID-19 infection increases risk for stillbirth compared with women without COVID-19. From March 2020 to September 2021, 8154 stillbirths were reported, affecting 0.65% of births by women without COVID and 1.26% of births by women with COVID, for a relative risk of 1.90. The magnitude of association was higher during the period of SARS-CoV-2 B.1.617.2 (Delta) variant predominance than during the pre-Delta period. [19].

A multicenter study involving 16 Spanish hospitals reported outcomes of 242 pregnant patients diagnosed with COVID-19 during the third trimester from March 13 to May 31, 2020. They and their 248 newborns were monitored until the infant was 1 month old. Pregnant patients with COVID-19 who were hospitalized had a higher risk for cesarean birth (P = 0.027). Newborns whose mothers were hospitalized for COVID-19 infection had a higher risk for premature delivery (P = 0.006). No infants died and no vertical or horizontal transmission was detected. Exclusive breastfeeding was reported for 41.7% of infants at discharge and 40.4% at 1 month. [20].

A cohort study of pregnant patients (n = 64) with severe or critical COVID-19 disease hospitalized at 12 US institutions between March 5, 2020, and April 20, 2020 has been published. At the time of the study, most (81%) received hydroxychloroquine; 7% of those with severe disease and 65% with critical disease received remdesivir. All of those with critical disease received either prophylactic or therapeutic anticoagulation. One case of maternal cardiac arrest occurred, but there were no cases of cardiomyopathy or death. Half (n = 32) delivered during their hospitalization (34% severe group; 85% critical group). Additionally, 88% with critical disease delivered preterm during their disease course, with 16 of 17 (94%) pregnant women giving birth through cesarean delivery. Overall, 15 of 20 (75%) with critical disease delivered preterm. There were no stillbirths or neonatal deaths or cases of vertical transmission. [21].

Adhikari and colleagues published a cohort study evaluating 252 pregnant patients with COVID-19 in Texas. Maternal illness at initial presentation was asymptomatic or mild in 95% of them, and 3% developed severe or critical illness. Compared with COVID negative pregnancies, there was no difference in the composite primary outcome of preterm birth, preeclampsia with severe features, or cesarean delivery for abnormal fetal heart rate. Early neonatal SARS-CoV-2 infection occurred in six of 188 tested infants,(3%) primarily born to asymptomatic or mildly symptomatic mothers. There were no placental pathologic differences by illness severity. [18].

Breastfeeding

A study by Chambers and colleagues found human milk is unlikely to transmit SARS-CoV-2 from infected mothers to infants. The study included 64 milk samples provided by 18 mothers infected with COVID-19. Samples were collected before and after COVID-19 diagnosis. No replication-competent virus was detectable in any of their milk samples compared with samples of human milk that were experimentally infected with SARS-CoV-2. Mothers or birthing parents who have been infected with SARS CoV-2 may have neutralizing antibodies expressed in their milk. In an evaluation of 1-7 milk samples over 2 months from 64 women, 75% contained SARS-CoV-2-specific IgA and 7% persited for at least 2 months. These results support recommendations to continue breastfeeding/chestfeeding with masking during mild-to-moderate maternal COVID-19 illness. [1].

COVID-19 in patients with HIV

Data for people with HIV and coronavirus are emerging. A multicenter registry has published outcomes for 286 patients with HIV who tested positive for COVID-19 between April 1 and July 1, 2020. Patient characteristics included mean age of 51.4 years, 25.9% were female, and 75.4% were African-American or Hispanic. Most patients (94.3%) were on antiretroviral therapy, 88.7% had HIV virologic suppression, and 80.8% had comorbidities. Within 30 days of positive SARS-CoV-2 testing, 164 (57.3%) patients were hospitalized, and 47 (16.5%) required ICU admission. Mortality rates were 9.4% (27/286) overall, 16.5% (27/164) among those hospitalized, and 51.5% (24/47) among those admitted to an ICU. [4].

Multiple case series have subsequently been published. Most suggest similar outcomes in patients

living with HIV as the general patient population. Severe COVID-19 has been seen, however, suggesting that neither antiretroviral therapy of HIV infection are protective. A systematic review and meta-analysis of 43 studies including 692,032 COVID-19 cases found that 9097 (1.3%) were among people living with HIV (PLWH); the global prevalence of PLWH among cases of COVID-19 was 2%, and the highest prevalence occurred in sub-Saharan Africa. The relative risk (RR) for severe COVID-19 in PLWH was significant only in Africa, at 1.14 (95% CI, 1.05-1.24), whereas the relative risk for mortality was 1.5 (95% CI, 1.45-2.03) worldwide, suggesting that HIV infection may be associated with increased death from COVID-19. [10].

COVID-19 in clinicians

Among a sample of healthcare providers who routinely cared for patients with COVID-19 in 13 US academic medical centers from February 1, 2020, 6% had evidence of previous SARS-CoV-2 infection, with considerable variation by location that generally correlated with community cumulative incidence. Among participants who had positive test results for SARS-CoV-2 antibodies, approximately one third did not recall any symptoms consistent with an acute viral illness in the preceding months, nearly one half did not suspect that they previously had COVID-19, and approximately two thirds did not have a previous positive test result demonstrating an acute SARS-CoV-2 infection. [15].

Prognosis

During January to December 2020, the estimated 2020 age-adjusted death rate increased for the first time since 2017, with an increase of 15.9% compared with 2019, from 715.2 to 828.7 deaths per 100,000 population. COVID-19 was the underlying or a contributing cause of 377,883 deaths (91.5 deaths per 100,000). COVID-19 death rates were highest among males, older adults, non-Hispanic American Indian or Alaska Native (AI/AN) persons, and Hispanic persons. Age-adjusted death rates was highest among Black (1105.3) and AI/AN persons (1024). [18].

Mortality and diabetes

Type 1 and type 2 diabetes are both independently associated with a significant increased odds of in-hospital death with COVID-19. In a nationwide analysis in England of 61,414,470 individuals in the registry alive as of February 19, 2020, 0.4% had a recorded diagnosis of type 1 diabetes and 4.7% of type 2 diabetes. A total of 23,804 COVID-19 deaths in England were reported as of May 11, 2020; one third were in people with diabetes, including 31.4% with type 2 diabetes and 1.5% with type 1 diabetes. Upon multivariate adjustment, the odds of in-hospital COVID-19 death were 3.5 for those with type 1 diabetes and 2.03 for those with type 2 diabetes, compared with deaths among individuals without known diabetes. Further adjustment for cardiovascular comorbidities found the odds ratios were still significantly elevated in both type 1 (2.86) and type 2 (1.81) diabetes. [1].

Virology

The full genome of SARS-CoV-2 was first posted by Chinese health authorities soon after the initial detection, facilitating viral characterization and diagnosis. The CDC analyzed the genome from the first US patient who developed the infection on January 24, 2020, concluding that the sequence is nearly identical to the sequences reported by China. [SARS-CoV-2 is a group 2b beta-coronavirus that has at least 70% similarity in genetic sequence to SARS-CoV. Like MERS-CoV and SARS-CoV, SARS-CoV-2 originated in bats. [Viral variants emerge when the virus develops one or more mutations that differentiate it from the predominant virus variants circulating in a population. The CDC surveillance of includes US COVID-19 cases caused by variants. The site also includes which mutations are associated with particular variants. The CDC has launched a and a website tracking . Researchers are studying how variants may or may not

alter the extent of protection by available vaccines. For more information, see the Medscape topic. [4].

Variants of Concern in the United States

As mentioned, viruses such as SARS-CoV-2 are constantly changing. Among the hundreds of variants detected in the first year of the pandemic, the ones that are most concerning are the so-called . Researchers are continually studying how variants may or may not alter the extent of protection by avaible vaccines and antibody-directed therapies. [18].

Omicron

The omicron variant (B.1.1.529), initially identified in South Africa, was declared a variant of concern in the United States by the CDC November 30, 2021. This VOC contains several dozen mutations, including a large number in the spike gene, more than previous VOCs. These mutations include several associated with increased transmission. The omicron variant has quickly become dominant in the United States. As of January 8, 2022, it accounted for over 98% of circulating virus, compared with less than 8% on December 11, 2021. [15].

Antiviral agent effectiveness

An in vitro study published in December 2021 indicate that remdesivir, nirmatrelvir, molnupiravir, EIDD-1931, and GS-441524 (oral prodrug of remdesivir) retain their activity against the VOCs alpha, beta, gamma, delta, and omicron. [4].

Monoclonal antibody effectiveness

Data analyzed by the FDA and NIH in mid-December 2021 found tixagevimab plus cilgavimab (Evusheld) and sotrovimab retain their neutralizing activity against the omicron variant. However, casirivimab plus imdevimab (REGN-COV) and bamlanivimab plus etesevimab lose most of their effectiveness when exposed in laboratory tests to omicron. [10].

Vaccine effectiveness

A preprinted, nonpeer reviewed article of routine surveillance data from South Africa suggests the Omicron variant may evade immunity from prior infection. Among 2,796,982 individuals with laboratory-confirmed SARS-CoV-2 who had a positive test result for SARS-CoV-2 at least 90 days before November 27, 2021, there were 35,670 suspected reinfections identified. In another preprinted article, neutralization performed with sera from double or triple BNT162b2-vaccinated individuals (6, 0.5 or 3 months after last vaccination/booster) revealed an 11.4-, 37.0- and 24.5-fold reduction, respectively. Sera from double mRNA-1273-vaccinated and additionally BNT162b2-vaccinated individuals (sampled 6 or 0.5 months after last vaccination/booster) showed a 20- and 22.7-fold reduction in the neutralization capacity. [1].

Delta

The delta variant (B.1.617.2) that was first identified in India became the dominant variant in the United States in mid-July 2021. This variant increases ACE binding and transmissibility. An approximate 6.8-fold decreased neutralization for mRNA vaccines and convalescent plasma was observed with the delta variant. However, a study completed by Public Health England found the BNT162b2 vaccine was only slightly reduced from 93.7% with the B.1.1.7 variant to 88% for the delta variant 2 weeks after the second dose. As the omicron variant transmission increased rapidly in December 2021, the delta variant now accounts for less than 2% of cases in the United States. [18].

Alpha

The CDC tracks circulating in the United States and estimates the B.1.1.7 variant (Alpha) that was first detected in the United Kingdom accounted for over 44% of cases from January 2 to March 27, 2021. On April 7, 2021, the B.1.1.7 was the dominant strain circulating in the United

States. It was the dominant strain until mid-July 2021, when the Delta variant became the dominant strain. At the same time that the transmission of the wild type virus was dropping, the variant increased, suggesting that the same recommendations (eg, masks, social distancing) may not be enough. The UK variant is also infecting more children (aged 19 years and younger) than the wild type, indicating that it may be more transmissible in children. This has raised concerns because a relative sparing of children has been observed to date. This variant is hypothesized to have a stronger ACE binding than the original variant, which was felt to have trouble infecting younger individuals as they express ACE to a lesser degree. [15].

Beta

The E484K mutation was found initially in the South Africa VOC (B.1.351 [Beta]) and also with the Brazil variants in late 2020, and was observed in the UK variant in early February 2021. Position 484 and 501 mutations that are both present in the South African variant, and the combination is a concern that immune escape may occur. These mutations, among others, have combined to create the VOC B.1.351. [4].

Gamma

The Brazil VOC P.1 (Gamma) was responsible for an enormous second surge of infections. Sabino et al describe resurgence of COVID-19 in Manaus, Brazil in January 2021, despite a high seroprevalence. A study of blood donors indicated that 76% of the population had been infected with SARS-CoV-2 by October 2020. Hospitalizations for COVID-19 in Manaus numbered 3431 in January 1 to 19, 2021 compared with 552 for December 1 to 19, 2020. Hospitalizations had remained stable and low for 7 months prior to December 2020. Several postulated variables regarding this resurgence include waning titers to the original viral lineage and the high prevalence of the P.1 variant, which was first discovered in Manaus. In addition, researchers are monitoring emergence of a second variant in Brazil, P.2, identified in Rio de Janeiro. As of September 21, 2021, the CDC lists P.2 as a variant being monitored. [10].

Epsilon

VOCs B.1.427 (Epsilon) and B.1.429 (Epsilon) emerged in California. These variants accounted for 2.9% and 6.9% of variants circulating in the United States between January 2 to March 27, 2021. An approximate 20% increase in transmission has been observed with this variant. [18].

Clinical Presentation

Presentations of COVID-19 range from asymptomatic/mild symptoms to severe illness and mortality. Common symptoms include fever, cough, and shortness of breath. Other symptoms, such as malaise and respiratory distress, have also been described. Symptoms may develop 2 days to 2 weeks after exposure to the virus. A pooled analysis of 181 confirmed cases of COVID-19 outside Wuhan, China, found the mean incubation period was 5.1 days, and that 97.5% of individuals who developed symptoms did so within 11.5 days of infection. [1].

The following symptoms may indicate COVID-19 : Fever or chills, Cough, Shortness of breath or difficulty breathing, Fatigue, Muscle or body aches, Headache, New loss of taste or smell, Sore throat, Congestion or runny nose, Nausea or vomiting, Diarrhea, Other reported symptoms include the following:, Sputum production, Malaise, Respiratory distress, Neurologic (eg, headache, altered mentality). Among 72,314 COVID-19 cases reported to the CCDC, 81% were mild (absent or mild pneumonia), 14% were severe (hypoxia, dyspnea, >50% lung involvement within 24-48 hours), 5% were critical (shock, respiratory failure, multiorgan dysfunction), and 2.3% were fatal. These general symptom distributions have been reconfirmed across multiple observations. Clinicians evaluating patients with fever and acute respiratory illness should obtain information regarding travel history or exposure to an individual who recently returned from a

country or US state experiencing active local transmission. Williamson and colleagues, in an analysis of 17 million patients, reaffirmed that severe COVID-19 and mortality was more common in males, older individuals, individuals in poverty, Black persons, and patients with medical conditions such as diabetes and severe asthma, among others. [15].

A multicenter observational cohort study conducted in Europe found frailty was a greater predictor of mortality than age or comorbidities. Type A blood has been suggested as a potential factor that predisposes to severe COVID-19, specifically in terms of increasing the risk for respiratory failure. Blood type O appears to confer a protective effect. [4].

Patients with suspected COVID-19 should be reported immediately to infection-control personnel at their healthcare facility and the local or state health department. CDC guidance calls for the patient to be cared for with airborne and contact precautions (including eye shield) in place. Patient candidates for such reporting include those with fever and symptoms of lower respiratory illness who have travelled from Wuhan City, China, within the preceding 14 days or who have been in contact with an individual under investigation for COVID-19 or a patient with laboratory-confirmed COVID-19 in the preceding 14 days. A complete or partial loss of the sense of smell (anosmia) has been reported as a potential history finding in patients eventually diagnosed with COVID-19. A phone survey of outpatients with mildly symptomatic COVID-19 found that 64.4% (130 of 202) reported any altered sense of smell or taste. In a European study of 72 patients with PCR results positive for COVID-19, 53 patients (74%) reported reduced olfaction, while 50 patients (69%) reported a reduced sense of taste. Forty-nine patients (68%) reported both symptoms. [18].

Physical Examination

Patients who are under investigation for COVID-19 should be evaluated in a private room with the door closed (an airborne infection isolation room is ideal) and asked to wear a surgical mask. All other standard contact and airborne precautions should be observed, and treating healthcare personnel should wear eye protection. The most common serious manifestation of COVID-19 upon initial presentation is pneumonia. Fever, cough, dyspnea, and abnormalities on chest imaging are common in these cases. Huang and colleagues found that, among patients with pneumonia, 99% had fever, 70% reported fatigue, 59% had dry cough, 40% had anorexia, 35% experienced myalgias, 31% had dyspnea, and 27% had sputum production. [10].

Complications

Complications of COVID-19 include cardiac injury, arrhythmia, , liver dysfunction, , and multi-organ failure, among others.

Approximately 5% of patients with COVID-19, and 20% of those hospitalized, experience severe symptoms necessitating intensive care. The common complications among hospitalized patients include pneumonia (75%), ARDS (15%), AKI (9%), and acute liver injury (19%). Cardiac injury has been increasingly noted, including troponin elevation, acute heart failure, dysrhythmias, and myocarditis. Ten percent to 25 percent of hospitalized patients with COVID-19 experience prothrombotic coagulopathy resulting in venous and arterial thromboembolic events. Neurologic manifestations include impaired consciousness and stroke. [1].

Long COVID

As the COVID-19 pandemic has matured, more patients have reported long-term, post-infection sequelae. Most patients recover fully, but those who do not have reported adverse symptoms such as fatigue, dyspnea, cough, anxiety, depression, inability to focus (ie, “brain fog”), gastrointestinal problems, sleep difficulties, joint pain, and chest pain lasting weeks to months after the acute illness. Long-term studies are underway to understand the nature of these

complaints. Post-acute sequelae of SARS-CoV-2 (PASC) infection is the medical term for what is commonly called long COVID or "long haulers". The NIH includes discussion of persistent symptoms or organ dysfunction after acute COVID-19 within guidelines that discuss the clinical spectrum of the disease. [15].

Reinfection

COVID-19 reinfection is defined as an infected person who has undergone full vaccination, whether they have had a booster or boosters. According to the CDC, reinfection is COVID-19 infection of an individual with 2 different viral strains that occurs at least 45 days apart. It also may occur when an individual has 2 positive CoV-2 RT-PCR tests with negative tests between the 2 positive tests. It is essential to determine reinfection rates to establish the effectiveness of current vaccine prophylaxis. Reinfection in vaccinated and non-vaccinated persons probably is due to a variant. It is important to differentiate reinfection from reactivation or relapse of the virus, which occurs in a clinically recovered person within the first 4 weeks of infection, during which viral RNA testing has remained positive. During relapse, a tiny viral load of dormant virus reactivates, the reason of which often is unclear. [18].

Radiological Predictors of Outcome of Hospitalized COVID-19 Patients

In March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a global pandemic. Vietnam was a spectacular COVID-19 success story, reporting zero cases for months on end and maintaining life as normal as possible for the majority of the population. However, in late April 2021, the highly transmissible Delta variant began to spread across Vietnam. Especially, in the fourth wave of this pandemic, Ho Chi Minh City, the country's economic engine, where 13 million people live and work, became the epicenter of the virus's battle: hundreds of cases are documented daily amid extensive testing. As of August 2021, there were over 200,000 cases in the community of Ho Chi Minh City alone, with another 100,000 cases in other southern and central provinces. [22].

Several primary hospital wards were reorganized and exclusively dedicated to patients with COVID-19. The emergency department (ED) of the field hospital was overflowing with patients afflicted by COVID-19 symptoms; thus, providing adequate stratification was a life-saving urgency. In addition, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection rapidly changes, leading to an increase in confirmed cases in Vietnam. The progression of lung aberrations in COVID-19 patients requires fast radiological methods and appropriate treatment for infected patients. CT imaging was the best method of assessing the specific abnormalities of the disease in developed countries. However, the increasing number of hospitalized patients, lack of experienced radiologists, risk of cross-over infection, high cost, and increased radiological examinations make it challenging to use chest CT. Furthermore, due to its usefulness, convenience, wide availability, and ease of performance at the bedside, several studies demonstrated that CXR is a non-inferior, first-line triage substitute to diagnose COVID-19 and determine the severity as well as the progression of respiratory conditions. In addition, the interpretation of portable CXRs has always been utilized in medical fields to diagnose the causes of respiratory problems. [23].

Various objective measures have been applied to reduce the wide variability between observers in assessing lung involvement. Many descriptive reporting semi-quantitative scoring systems, such as Brixia and total severity score (TSS) on the severity of lung disease, were adopted for triage in ED combined with clinical data and to classify lung lesions, which helped assess the lung injury and correlated with adverse outcomes. The Brixia scoring system has been widely used to monitor the severity and progression of COVID-19 pneumonia in Tongji Hospital, Wuhan, and Azienda Socio Sanitaria Territoriale, Spedali Civili of Brescia, Italy . The authors

adapted and simplified the Radiographic Assessment of Lung (O)Edema (RALE) score proposed by Warren et al. in 2018. The Brixia score is another method to assess CXR, explicitly designed for patients with confirmed COVID-19. [24].

The Vietnamese Ministry of Health recommended the TSS to evaluate COVID-19 patient CXRs. Borghesi and Maroldi proposed it in March 2020. One of the most significant differences between the two scoring systems is that a general practitioner can perform TSS due to its ease of use. At the same time, the Brixia score is intended for use by a professional radiologist . Given the current conditions regarding the lack of distribution of resources in primary healthcare centers and the need for early stratification to optimize individualized treatment, non-radiologist clinicians have the responsibility to evaluate the portable CXR and make a final clinical decision. The purpose of this study is to determine the clinical utility of scoring systems through portable CXR in Vietnamese field hospitals and explore their potential hospitalized prediction of COVD-19 patient mortality. [25].

In adult patients with COVID-19, much research reveals that older people with underlying comorbidities (such as hypertension, diabetes, cardiovascular disease, and oncologic history) have the worst prognosis. They most often end up with worse outcomes such as acute respiratory distress syndrome (ARDS) and pneumonia. [26].

Imaging also plays a role in the predictive assessment and patient stratification in COVID-19 pneumonia. During this pandemic, in field hospitals, due to easy availability, faster results, less radiation exposure, easy disinfection procedure, and minimum risk of cross-infection, portable CXR plays a non-inferior role for an accurate radiological approach than chest CT-scan. To the best of our knowledge, this study is the first study to examine the relationship between CXR severity scores and all-cause mortality in COVID-19 patients who presented early to a Vietnamese primary health care center. Some CXR scoring systems have recently been developed as a semi-quantitative tool for evaluating lung abnormalities providing valuable help to clinicians, and improving the stratification of the disease's risk. In particular, higher disease scores at baseline have been associated with hospitalization, a requirement for mechanical ventilation, and in-hospital mortality . Nava-Munoz found that initial CXR can be helpful to use a scale of radiological severity to classify chest X-rays. The more significant the radiological severity or need for hospitalization, the more significant the alteration of laboratory parameters would be . While TSS scores have a relatively small association with recovery rate, the Brixia score has been ranked the most important, with the highest SHAP value. [27].

Moreover, the Brixia score positively correlated with other clinical indicators such as BMI, NEWS2, and age. The Brixia score improved clinical decision-making, especially in COVID-19 patients with moderate-to-severe signs and symptoms. The Brixia score should be included in a predictive model with other clinical factors. Both scoring systems have been demonstrated to be valuably prognostic in predicting ICU admission and mortality in resource-constrained scenarios. Compared to the Brixia score, the TSS score is quick and straightforward to calculate, reflected in its calculation speed. Thus, the Brixia score may be more difficult to understand for junior medical staff, and increased complexity may add to existing pressures on staff given the increasingly recognized risks of burnout. These pressures could be an obstacle for primary healthcare physicians who require an accurate and straightforward technique for the early diagnosis of COVID-19 pneumonia but lack the knowledge and experience to do so. A modified CXR scoring system designed by Dr. Soetomo, adopted from the Brixia score and TSS score, has a similar correlation with the clinical severity of the disease. Further study must be carried out to validate the modified score in the Vietnamese population. [28].

Ten months after the start of coronavirus disease (COVID-19) vaccination planning, the diffusion

and virulence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are progressively decreasing in many parts of the world. On October 21, 2021, the number of new SARS-CoV2 infections in Italy was 3794, with 22 new admissions to intensive care units (ICUs), and 36 new deaths. There was a decrease in new infections by 90.7%, in new admissions to ICU by 63.3% for new admissions to ICUs, and in new deaths by 93.5% as compared to the peak of incidence observed on November 13, 2020 during the second wave of COVID-19 in Italy. [29].
Despite the progressive reduction in hospitalization and fatality rates in patients with COVID-19, ICU admissions and deaths are still observed. Additionally, with the progressive lowering of temperatures in the coming months, an increase in new COVID-19 cases is anticipated. [30].
Chest X-ray (CXR) and chest computed tomography (CT) are the most commonly used imaging techniques for the management (diagnosis, hospitalization, and follow-up) of patients with COVID-19, and several authors have found that both modalities are useful predictors of patient outcome. Recently, in a simulated triage setting, the use of r-CXR (coronal image reconstructed from thin-section CT scan) in cases suspected of having COVID-19 was safe and helped optimizing both the use of radiology resources and patient management. However, to the best of our knowledge, the performance of CXR and chest CT for predicting adverse outcomes, such as invasive mechanical ventilation (IMV) and COVID-19 related mortality, has not yet been compared in the same cohort of hospitalized patients with COVID-19. Therefore, the aim of the present study was to retrospectively compare the prognostic value of CXR and chest CT at admission and during hospitalization in a group of patients with COVID-19. [23].
Chest imaging modalities, specifically CXR and chest CT, play a key role in the management of patients with COVID-19. In February 2021, the World Health Organization (WHO) published a simple guide on the use of chest imaging techniques in patients with confirmed or suspected COVID-19. For symptomatic patients with COVID-19, the WHO recommends chest imaging in addition to clinical and laboratory examinations to decide between patient discharge and hospitalization or to identify patients requiring specific therapeutic management. However, one of the most challenging questions about chest imaging in symptomatic patients with COVID-19 is which imaging modalities between CXR and chest CT are the most effective for improving risk stratification of infected patients and predicting disease progression. Until now, the answer to this question remains unresolved as the published data on chest imaging lack a comparative analysis of the prognostic value of CXR and chest CT. [23].
Although it is well known that chest CT is the most sensitive imaging technique for the detection of lung abnormalities, and quantitative CT analysis provides useful information for predicting disease progression, CXR has several advantages for the management of hospitalized patients with COVID-19. The main advantage is the possibility of using CXR as a diagnostic tool to monitor (“day by day”) the course of the disease, especially in the most critically affected patients. Hospitalized patients with COVID-19, in the multivariable analysis, the H-Brixia score (the highest score assigned on CXRs during hospitalization) was the only independent predictor of adverse outcomes in hospitalized patients with COVID-19. In particular, the H-Brixia score exhibited excellent power in predicting in-hospital mortality and the need for IMV. [30].
At admission, chest CT with the quantitative assessment of the extent of WAL (A-CT%WAL) did not provide substantial advantages in the risk stratification of COVID-19 patients compared to CXR with semiquantitative assessment of the disease severity (A-Brixia score) . Therefore, in symptomatic patients with COVID-19 (confirmed by RT-PCR), chest CT should not be considered the first-line imaging modality to evaluate the extent of pulmonary involvement and decide between discharge and hospitalization because its prognostic power does not differ substantially from that of CXR. [23].

Laboratory Predictors of Outcome of Hospitalized COVID-19 Patients

Over the past two decades, the SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) outbreaks have garnered public health emergencies against coronaviruses (CoV) in 2002 and 2012, respectively. At the end of 2019, an outbreak of pneumonia with unknown etiology was reported in Wuhan, the most populous city in central China with more than 11 million residents. SARS-CoV-2, formerly known as 2019-nCoV, is a newly emerging virus belonging to the Coronaviridae family, presumably derived from a bat SARS-like coronavirus and transmitted to humans after the emergence of mutations in the spike glycoprotein (protein S) and nucleocapsid N protein. [31].

This zoonotic pathogen, called coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO), is assumed to be the latest global biological human hazard. Although its mortality rate is lower than SARS and MERS, the long incubation period (up to 2 weeks) together with the relatively low pathogenicity increases the risk of SARS-CoV-2 contagion and facilitates its spread. According to the WHO's data, COVID-19 has already spread worldwide, with over 8,900,000 diagnosed cases in more than 210 different countries, causing more than 465,000 related deaths as of June 20, 2020. COVID-19 is a mysterious respiratory and systemic syndrome primarily presenting clinical symptoms of dry cough, dyspnea, and fever, which in some cases (8–15% depending on the geographical setting and individual characteristics) lead to a critical condition necessitating specialized management at intensive care units (ICU). [32].

This is not the first nor will it be the last time that a viral pneumonia pandemic has been described as a global health emergency by the WHO. Timely identification of virus carriers is vital not only to prevent their spread but also to more efficiently control disease progression. To the best of our knowledge, while most published articles have discussed the clinical features and imaging findings of COVID-19, few studies have addressed the diagnostic and prognostic value of abnormal laboratory findings. Irrespective of its inherent definition, the contributory role of laboratory medicine is far beyond etiological detection and it is now almost undeniable that this branch of medical science is effectively involved in epidemiologic surveillance, determination of prognosis, patient follow-up, and, last but not least, therapeutic monitoring of the wide range of human diseases, including COVID-19. [33].

To better represent how abnormal laboratory findings are important in COVID-19 diagnosis and prognosis, we searched the Scopus, PubMed, and Web of Science medical databases using the keywords "COVID-19," "2019-nCoV," or "coronavirus 2019." We ultimately selected 19 articles (totaling 2988 patients, 484 of whom (16.1%) were severely affected) that provided a panel of laboratory examinations in COVID-19 patients. Although when we wrote this article, some limitations such as low sample size, different applied methods, dissimilar reference ranges, non-synchronized methods of representing the results, and variety in the panels conducted may have adversely affected the ability to draw a clear conclusion, analyzing the current scientific literature will definitively shed light on the value of these patients' laboratory parameters. [34].

As presented, increased levels of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (Bili) and decreased levels of albumin are among the most common abnormal laboratory findings in COVID-19 patients. Changes were not limited to the indicated parameters since elevated creatine kinase (CK) and increased creatinine (Cr) were also demonstrated in earlier studies. Knowing that the primary site of the SARS-CoV-2 attack is the lower respiratory tract together with the fact that LDH is an important marker of lung damage may explain, at least partly, why this enzyme's level is elevated in most COVID-19 patients. The emergence of severe disease due to the injury of non-pulmonary organs may also instigate abnormal values of kidney- and liver-related biochemical parameters. Guan et. al.

reported that ALT and AST levels in COVID-19 patients were elevated in 21.3% and 22.2% of cases, respectively, which may mirror virus-mediated liver impairment. The results of a recent study also revealed that 2–11% of COVID-19 patients had liver comorbidities and 14–53% had abnormal levels of ALT and AST. Analysis of creatinine in 149 cases demonstrated that 28.8% of COVID-19 patients had an increased levels, representing SARS-CoV-2's ability to induce kidney injury. The results of multiple lines of evidence have indicated that measuring the biochemical parameters not only retains a specific diagnostic significance in this infection but their abnormalities may also correlate with unfavorable outcomes. [35].

Albeit lung tissue is the most common organ that is affected by SARS-CoV-2, the emergence of atypical clinical manifestations such as headache, nausea, vomiting, myalgia, dizziness, impaired consciousness, and the loss of the sense of smell and taste have demonstrated the neurotropism potential of this virus. This suggests that the virus may affect the nervous system of some COVID-19 patients, either through a direct or an indirect mechanism. As the first evidence of SARS-CoV-2's direct invasion of the nervous system, Zhou L. et al. detected SARS-CoV-2 in the CSF of a 56-year-old patient who was diagnosed with viral encephalitis. A 74-year-old patient who was positive for SARS-CoV-2 and presented with encephalopathy. In a strange case of COVID-19 in a 24-year-old man, while the molecular identification of SARS-CoV-2 was negative in a nasopharynx sample, it was positive in the CSF. In a report on two patients with COVID-19 and concurrent neurological symptoms, Al Saiegh et al. showed that the patients' CSF may have been devoid of viral particles even when they tested positive for COVID-19 via nasal swab. They concluded that whether SARS- CoV-2 is present in the CSF may depend on the systemic disease severity and degree of the virus' nervous tissue tropism. [36].

CSF analyses of a 60-year-old SARS-CoV-2 patient who developed akinetic mutism due to encephalitis showed that he was positive for pleocytosis and hyperproteinorrachia and displayed increased concentrations of IL-8 and TNF-α. Notably, applying high-dose steroid treatment results in progressive clinical improvement along with a reduction in CSF parameters, thus supporting inflammatory-mediated involvement within the brain in COVID-19. Intriguingly, a CSF analysis of a 41-year-old obese female with a history of diabetes showed 65 red blood cells and 70 white blood cells, 100% of which were lymphocytes. CSF protein was 100 and glucose was 120 (with serum glucose of 200) . Examination of CSF samples obtained from seven COVID-19 patients who underwent brain MRI and electroencephalography showed that oligoclonal bands were present in 2 patients, and the protein and IgG levels were elevated only in 1 patient. Notably, the RT-PCR results of the CSF samples were negative for SARS-CoV-2 in all 7 patients . The CSF sample of a 30-year-old COVID-19 patient who was admitted to the neurology emergency room with generalized tonic-clonic seizure showed normal protein and glucose levels with five cell counts (all lymphocytes) . [37].

Comparing the number of deaths to the total number of cases demonstrated that most COVID-19 patients recover; however, the increasing number of global fatalities is a reminder that SARS-CoV-2 continues to take its toll. Notwithstanding atypical pneumonia being the primary symptom. the occurrence of severe disease, mainly resulting from immune-mediated hyper-inflammation, may lead to death in some cases. Introducing potent biomarkers to timely predict disease outcomes is an essential field of research in a wide range of diseases from simple infections to human malignancies. Since the first description of COVID-19, several articles introduced some laboratory findings as valuable prognostic factors, which we will discuss in the next sections. [38].

The lymphocyte count is an important parameter to directly discriminate between COVID-19 patients with and without severe disease. Given that most COVID19 fatalities experienced

greater lymphopenia, it is reasonable to assume that the lymphocyte count is a rapid and commonly available laboratory parameter that can predict disease severity in COVID19. Leukocytes and neutrophils were also significantly higher in a severe group in a study conducted on 94 patients at Shenzhen Third People's Hospital. In agreement with these studies, Wang et al. reported that ICU patients had fewer lymphocytes and more leukocytes and neutrophils than non-ICU patients . [39].

While the lymphocyte counts lower than 0.8 × 109/L may be associated with COVID-19 severity, number of neutrophils higher than 3.5 × 109/L may reflect a poor clinical outcome. Yang et al. reported that the elevated neutrophil-to-lymphocyte ratio (NLR) may predict COVID-19 prognosis . Also, incidence of critical illness in COVID-19 patients aged more than 50 was 9.1% (1/11) for patients having NLR < 3.13, while it was 50% (7/14) for those with NLR ≥ 3.13. A meta-analysis of 9 studies totaling 1779 COVID-19 patients with 399 (22.4%) severe cases reported that a low platelet count was associated with an increased risk of severe disease and mortality. The authors proposed that thrombocytopenic COVID-19 patients will experience disease with a higher risk of adverse outcomes during hospitalization. 150 × 109/L as a cut-off level for platelet count to predict poor prognosis. [40].

Secondary hemophagocytic lymphohistiocytosis (sHLH), an immune disorder that causes uncontrolled systemic inflammation, is most commonly elicited by viral infections and is characterized by an overwhelming secretion of inflammatory cytokines leading to multi-organ failure. Acute respiratory distress syndrome (ARDS), fewer blood cells, lower fibrinogen levels, fever, and increased levels of serum aspartate aminotransferase and ferritin are among the most common features of sHLH , similar to COVID-19, especially in symptomatic patients. [41].

Dysregulation of the inflammatory cytokine expression profile is not limited to the novel coronavirus, since a significant correlation between cytokine storm and disease severity was reported in both SARS-CoV and MERS-CoV infections. In a study investigating the contributory role of cytokines in COVID-19 severity, Yang et al. examined 48 cytokines in plasma samples from 53 COVID-19 patients (34 were severe cases) and reported that 14 cytokines were significantly elevated upon admission. Of these cytokines, IL-1ra, IP-10 (interferon-gamma induced protein 10), and MCP3 (monocyte chemotactic protein-3) were independent predictors of the progression of COVID-19, and the combination of these cytokines showed the highest area under the curve (AUC) of the receiver-operating characteristic (ROC) calculations. In agreement, transcriptome sequencing of RNAs isolated from the bronchoalveolar lavage fluid (BALF) and peripheral blood mononuclear cell (PBMC) specimens of COVID-19 patients highlighted the association between COVID-19 pathogenesis and excessive cytokine release, such as CCL2/MCP-1, CXCL10/IP-10, CCL3/MIP-1A, and CCL4/MIP1B. Examination of inflammatory cytokines (including IL-1, soluble IL-2 receptor [sIL-2R], IL-6, IL-8, IL-10, and tumor necrosis factor-α [TNF-α]) within 24 h of admission of 47 COVID-19 patients revealed that the concentrations of sIL-2R and IL-6 in critically ill patients were significantly higher than those with severe disease, while the IL-10 and TNF-α levels were not statistically different between the two groups [40].

The clinical predictors of COVID-19 mortality, Ruan et al. suggested that COVID-19 mortality might be due to virus-activated cytokine storm syndrome. They reported higher levels of C-reactive protein (126.6 in fatal cases vs 34.1 in discharged cases, P < 0.001), IL-6 (11.4 in fatal cases vs 6.8 in discharged cases, P < 0.001), and serum ferritin (1297 in fatal cases vs 614 in discharged cases, P < 0.001), all suggesting that uncontrolled systemic inflammation can be considered one of the major causes of disease severity in SARS-CoV-2 infection. In a recent meta-analysis of IL-6 serum levels in COVID-19, Coomes et al. reported that the mean IL-6

concentrations were 2.9-fold higher in patients with complicated COVID-19 compared to those with non-complicated disease . [38].

COVID-19 patients who progressed to ARDS had significantly increased IL-6 levels (median 7.39 pg/mL vs median 6.29 pg/mL, P = 0.03). Xu et al. conducted a non-randomized clinical trial to investigate the therapeutic effects of IL-6 pathway blockade using tocilizumab. Notably, they reported that 15 of 20 patients (75%) had lower oxygen intake within 5 days after tocilizumab, further highlighting the fact that increased secretion of inflammatory cytokines may effectively contribute to COVID-19 pathogenesis. Notably, it has been reported that hyperferritinemia can activate macrophages, which increases the secretion of pro-inflammatory cytokines, and the subsequent inflammation is mainly responsible for organ damage. Although ferritin is a positive acute phase reactant and serum level of this intracellular protein increases during inflammation, dying cells may also release ferritin. Thus, it is reasonable to assume that higher serum ferritin levels in severely affected COVID-19 patients might indicate a greater extent of organ damage. [41].

Coronavirus disease-19 (COVID-19) is a novel coronavirus infection caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which was first detected in Wuhan, China, in December 2019 after a series of pneumonia cases of unknown aetiology had emerged. On 11 March 2020, WHO declared the rapid spread of this virus a pandemic. Since the initial detection of the virus, more than 25,000,000 cases of COVID-19 have been confirmed worldwide with over 850,000 fatal cases. [38].

In some patients, symptoms of severe respiratory infection can occur with rapidly developing acute respiratory distress syndrome and other serious complications, which may be followed eventually by multiple organ failure and death. Therefore, early diagnosis and timely treatment of critical cases are crucial. Despite some knowledge of the clinicopathological features of COVID-19, the correlation of changes in laboratory parameters and the prognosis of patients with COVID-19 is still unclear. [40].

However, studies on COVID-19 cases have shown that increased levels of white blood cells (WBC), decreased numbers of lymphocytes, especially CD8 + cells, increased levels of lactate-dehydrogenase (LDH), creatine kinase (CK), C-reactive protein (CRP), D-dimer, and levels of pro-inflammatory cytokines are associated with more severe inflammation and extensive lung damage with higher rates of admission to intensive care unit (ICU) and mortality. A better understanding of early prognostic clinical laboratory parameters could save many lives by enabling timely intervention and better resource allocation since ICU capacity is limited in most countries. In this meta-analysis, we aimed to explore the significance of changes in the laboratory parameters and assessed the correlation between clinical laboratory data and the clinical outcomes of patients with COVID-19. [41].

Clinical Predictors of Outcome of Hospitalized COVID-19 Patients

The coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 has been devastating compared to other viruses (seasonal, avian and swine influenza), in regard to both the morbidity and mortality and its economic impact, despite advancements in medical care since the Spanish Flu of 1918 . COVID-19 has had a dramatic impact on health systems globally and the US economy despite assistance from the US Federal government, via the CARES Act and other funding programs. [42].

The COVID-19 pandemic occurred quickly and was rapidly followed by a massive production of academic output, including prediction models for a variety of clinical outcomes; the initial models for hospital outcomes came from the city of Wuhan in the Hubei province of China,

where the initial cases were discovered. From there, models around the globe surged and were likely integrated into many hospital guidelines. However, it is unclear if those models could be applied to local cohorts. Having a rapidly available and accurate prediction model for COVID-19 patients being admitted from the emergency department (ED) would be useful for making accurate triage and prognostic assessments to inform decisions regarding treatment and resource allocation. While knowledge of the likelihood of death in those sent home from the ED would also be of interest, this requires longitudinal data which is often not as readily available. The value of appropriate triage decisions is important, especially in time when resources are stretched. [43].

The growth in the volume of readily available healthcare data has facilitated the development of artificial intelligence-based models; however, a significant factor limiting the utility of dissemination of such models is the issue of generalizability. For example, the earliest computer-aided decision models evaluating abdominal pain were not able to be replicated in different institutions. A mortality prediction tool in acute alcoholic pancreatitis (Ranson's criteria) developed in a small cohort has a wide acceptance compared to superior scoring tools. [44].

The features used in the models were surprisingly diverse. The number of variables in each model ranged from 2 through 11, with 19 different variables across the studies. The most common variables used were age, lymphocyte count, CRP and LDH. It is surprising that only 7 of the 10 models used age as a predicting variable, and the 3 models that did not use it did not perform well. In large multi-site cohorts examined in Britain, the US and internationally, age was a strong predictor of mortality. Three of the external models performed very well, with AUC's of 0.84–0.89. This demonstrates that although the patients were geographically distant, ethnically different, in different health systems and cultures, and at different times during the pandemic, reasonable prediction was possible. Our initial hypothesis was that these models would not work well, but this was not the case in all the models. [45].

It is likely that some of the models may have had better performance if retrained using our local cohort, but this was not done as the purpose was to see how they worked "out of the box". This appeared to be the intent of many of the authors of the published models as evidenced by the publishing of web calculators, nomograms and decision trees. One of the issues which may cause worse or better performance in a model is that the outcomes have been found to be a function of time during the pandemic, not just patient factors, with improving outcomes more recently. [46].

The average LDH was roughly 1/3 higher in our test cohort than in the average of the cohorts from China. It is not clear what the reason for this is. In a healthy multiethnic cohort from Hawaii there were at most minor differences between black, Hispanic, White and Asian patients in their LDH, suggesting that the differences in LDH are not likely due to racial factors. It is possible that a difference in the time of infection to presentation might explain the difference. The other models which used LDH predicted well, but this might be in part related to use of a logistic regression instead of a decision tree. [47].

The average CRP in our cohort is roughly 350% of the average in the external models, 99 mg/L vs. 27 mg/L. Four models used the CRP and only one model performed well, model C. The creatinine was significantly higher in our cohort than in any of the derivation cohorts and as well as the average of the studies, 0.84 mg/dL. Only one model used the creatinine, model H. Its derivation cohort average creatinine was 0.72 mg/dL. Thus, model H used both the CRP and creatinine, helping explain its poor performance. For creatinine, there are studies showing socioeconomic and ethnic variations in chronic kidney disease with one systematic review showing the prevalence of chronic kidney disease in China was less than a fourth of the rate in the US . The higher creatinine in the test cohort may not be related only to differences in illness

at presentation, but rather differences in the prevalence of CKD. [48].

It is not fully clear why the models produced at UIH using our training cohort did not perform better on our test cohort, though there are some likely factors. The AUC for mortality decreased from 0.98 to 0.84 and for criticality, from 0.97 to 0.83. In analysis of the entire cohort, we were able to determine that the mortality and criticality were associated with the admission date. This is consistent with publications showing an improved mortality rate over time. The WBC, lymphocytes and neutrophils were not all used in each model and all went up in the test cohort. Thus, it is possible that some variable not in the models changed over time, producing a worse fit compared to the first 60% of patients. [49].

The number of cases for which a model is unable to generate a prediction due to missing data is an important practical consideration for model implementation. The fraction of the test cohort for which predictions could not be generated due to missingness ranged between 17 and 31% for external models. The UI Health models could not generate predictions in 27% of the patients. Though retrospectively missing data can be imputed, this is not so easy in real time by clinicians during patient care, so was not done. This demonstrates non standardized test ordering, which is not surprising as our understanding of what is useful and necessary for testing in suspected COVID patients has evolved. [50].

The Kingdom of Saudi Arabia (KSA) is home to two of the circulating beta coronaviruses, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV-2 the causative agent of the COVID-19 pandemic. MERS-CoV was first discovered in KSA in September 2012 and has subsequently spread to 27 countries. Of the global total of the reported 2949 laboratory-confirmed cases through June 1, 2020, 74% (2167) cases including 842 deaths were reported by KSA. SARS-Cov-2, first reported in China in December 2019, received pandemic status on March 11, 2020, and since has caused over 10 million cases and over half a million deaths worldwide. In KSA, the first case of COVID-19 was reported on March 2, 2020; three different seeding patterns helped its spread to all areas and municipalities. With 170,639 cases including 1430 deaths by June 25, 2020, KSA is among the top 20 countries with highest total confirmed COVID-19 cases. The overall Case Fatality Rate (CFR) in KSA (0.70%), is much lower than that reported in other countries such as the USA (5.68%) and the UK (14.12%). Immunity due to past MERS-CoV exposure could be a potential reason. To describe the clinical picture of COVID-19 in KSA and assess potential interaction between MERS-CoV and SARS-CoV-2 infections, we reviewed data from hospitalized patients in the largest academic teaching hospital in KSA that serves also as a referral center for MERS-CoV. We describe the demographic, clinical characteristics and outcome in their 99 hospitalized COVID-19 infected patients and the outcome of MERS-CoV tests. [51].

This first detailed COVID-19 case series in KSA revealed that one-tenth of COVID-19 tests were positive and 16% required hospitalization. Of the hospitalized patients, 22% required ICU care. COVID-19 case fatality rate was 0.2% among all those who tested positive at this hospital, 12% among the hospitalized, and 50% among those admitted to the ICU. The hospitalized COVID-19 patients had no coinfection with MERS-CoV. [47].

Clinical presentation of patients with COVID-19 is variable between country reports. Compared to the high percentage of fever reported early from China (90%) during their peak of the epidemic, our cohort had a lower percentage of fever similar to the observation of 31% in New York, USA and 45% in Europe . This difference is likely due to increasing awareness about other symptoms which lead to early diagnosis. Similar to SARS and MERS , patient’s age, comorbid conditions and certain laboratory abnormalities were associated with poor in-hospital outcomes in COVID-19 patients. [43].

Underlying chronic medical conditions are commonly reported in hospitalized COVID-19 patients with variable proportions between studies probably due to variable hospitalization criteria (94% in USA, 77% in UK, 23% in China, 20% in KSA) . COVID-19 fatality rate among the hospitalized cases in this cohort is within the reported 12–15% range. The mortality among our critically ill cases (50%) was similar to case series from Seattle, USA (50%) and from Wuhan, China (52%) but was higher than in New York, USA (39%). Low COVID-19 mortality both overall and among the hospitalized patients may be due to relatively younger age of the Saudi population (≥65 years, 3%); and in our cohort one fourth of patients were young health care workers, asymptomatic for COVID-19, in which infection was detected through contact tracing, and are less likely to have co-morbidities. Potential benefit from past exposure to MERS-CoV cannot be ruled out. With a 50% genomic similarity between these two beta-coronaviruses, MERS-CoV exposure may provide partial immunity against severe disease. [49].

Inflammatory markers, which have been widely used in diagnosing infections and predict disease progression , were investigated in several reports since the beginning of the COVID-19 pandemic. CRP, which is a protein produced by the liver, was found to be a relatively good predictor for the development of pneumonia in MERS-CoV infections and has recently been found to be a valuable marker to anticipate the possibility of aggravation of non-severe adult COVID-19 patients, with an optimal threshold value of 26.9 mg/L. This association is also replicated in our cohort, in which we found an above-normal CRP is associated with severe disease requiring ICU admission (OR = 21.1, 95% CI: 1.19–374) but was not associated with mortality (p-value = 0.143). Other markers were reported to be helpful in predicting COVID-19 disease progression, namely, high d-dimer, ferritin, interleukin-6, hyperglycemia, and AST, is also reproduced in this case series. [49].

Similar to MERS-CoV, no high-quality evidence nor consensus agreement on directed therapy against COVID-19 has been established. Experimental therapies including HCQ, remdesivir, triple therapy (interferon-β 1b, lopinavir/ritonavir, and ribavirin) and favipiravir, which showed a potential in-vitro activity against SARS-CoV-2 with some anecdotal low/medium quality evidence in clinical trials. The best current approach is with source control of infection, proper use of personal protective equipment, early diagnosis and isolation of cases, with rapid contact tracing and quarantine, with supportive care for patients. Although from the 99 patients only nine had positive bacterial cultures; two from sputum and seven from blood with only one of those blood cultures considered a true pathogen; 53 (53.5%) patients received antibacterial therapy for a median of 4 days. [43].

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