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Epidemiology and clinical features of COVID-19: A review of current literature

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ABSTRACT

Coronavirus disease 2019 is a pandemic influencing the first half of the year 2020. The virus has rapidly spread to many countries. Studies are rapidly published to share information regarding epidemiology, clinical and diagnostic patterns, and prognosis. The following review condenses the surge of information into an organized format.

1. Introduction

In December 31, 2019, hospitals in Wuhan, Hubei, China reported a cluster of idiopathic pneumonia cases [1]. The Huanan Seafood Wholesale Market was identified as the origin of the infection, causing the area to shut down. However, a large fluctuation of visitors around the area during the Spring Festival caused the infection to rapidly spread to other regions of China. With the use of real-time reverse transcription polymerase chain reaction (RT-PCR), researchers identified the cause being a novel coronavirus labeled as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), later also called coronavirus disease 2019 (COVID-19) [2,3].

The number of RT-PCR—positive cases rapidly increased [4]. On January 30, 2020, the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern (PHEIC) and thus a pandemic. During February 2020, mainland China reported 77,780 cases. Thirty-three other countries also reported 2549 cases along with 34 fatalities. World-wide, 80,239 cases occurred with 2700 deaths [5].

2. Viral structure and life cycle

COVID-19 is a single, positive-stranded RNA virus enveloped in a lipid bilayer [6,7]. The lipid bilayer fuses with the host cell membrane, releasing RNA into the cytoplasm and causing translation of various viral proteins. The replicated RNA genome and synthesized viral proteins reassemble into new viruses, which burst out of the cell [8,9].

The virus enters via binding of two proteins. The viral counterpart is the spike-protein (S-protein), a glycoprotein expressed as a homotrimer on the viral envelope [10]. Each S-protein consists of two subunits. S1 subunit includes a receptor-binding domain that targets receptors on host cells, and S2 regulates the membrane fusion. This viral S-protein binds with the human protein receptor ACE2 [11]. ACE2 is abundant in lung, heart, kidney, and adipose tissue [12,13]. Binding of S-protein with ACE2 allows for membrane fusion and introduction of COVID-19 RNA into the cell. The binding of these two proteins serves as a target for potential treatments and vaccinations.

Compared to SARS, COVID-19 uses the same mechanism for entering host cells, but at slower speeds. However, COVID-19 accumulates more in the system compared to SARS. This explains why COVID-19 has a longer incubation period and is more contagious, while SARS presents with more symptoms and disease severity [14].

3. Transmission and infectivity

The spread of COVID-19 is rapid [4]. Transmission is from close contact and droplet. There is scarce evidence to suggest airborne transfer [15]. Very minimal to no RNA concentration is found in airborne samples [16]. No RNA is detected in urine or serum samples of positive patients [17]. Viral RNA can be detected on fomites including plastic [18].

The mean incubation period is about 3–9 days [19–23], with a range between 0–24 days (Fig. 1) [24]. The mean serial interval is about 3–8 days, presenting sooner than the end of incubation [21,23,25]. This suggests that one becomes contagious before symptoms present (about 2.5 days earlier from the start of symptoms) [21]. About 44 % of transmission is estimated to occur before symptoms arise [25].

Close contact with someone during their infectious period puts one

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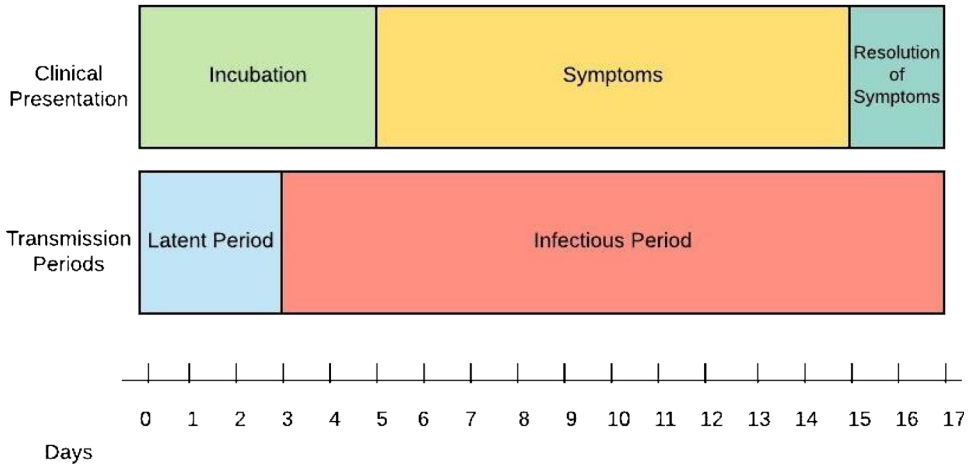

Fig. 1. Representation of COVID-19 Clinical and Transmission Periods.

at risk for acquiring the infection. However, the certainty of becoming infected is still unpredictable. Burke et al. tested 445 people that were in close contact (at least 6 feet from the source for a minimum of 10 min) with 10 COVID-19-confirmed patients. After two weeks of testing, only two subjects became positive. Both subjects were household members that practiced isolation from the infected individuals. Five subjects continued to expose themselves constantly with the infected individuals and never became positive. No healthcare workers (222 subjects) became positive [26]. These findings coincide with two other studies [23,27]. Evaluation of all positive cases from mainland China showed 3.8 % being from healthcare workers (1716/44672) [28].

About 18 % of cases remain asymptomatic [29–31]. The potential of asymptomatic patients infecting others is proven by multiple studies concerning clusters [32,33]. They can be asymptomatic and contagious regardless of lab or CT scan findings [20,32,34]. Younger patients tend to remain asymptomatic (even if constantly around an infected individual), while the elderly usually show symptoms [20,31]. It is calculated that about 86 % of infections have remained undocumented, and about 55 % of those cases were contagious [35]. This may be because of the infectious period presenting before symptoms, the frequency of asymptomatic cases, and the poor documented sensitivity of nasopharyngeal RT-PCR [36,37].

Symptoms tend to resolve after 10 days [38]. However, viral shedding continues despite symptoms disappearing [16,17,32,38]. COVID-19 RNA viral shedding persists for about 18 days (by nasopharyngeal swab) or 19 days (via feces) [39]. Mild and asymptomatic cases tend to shed 10 days (between 8–15 days) after symptom resolution [16,32,34], with 90 % resolving after 10 days and nearly all cases resolving after 15 days [16,32]. Severe cases continue shedding up until 25 days after initial symptoms arise. Severe cases also have 60 times more viral load than mild cases [40]. However, the infectious potential based on severity has not been discovered. Due to these findings, the Chinese Municipal Health Commission has recommended against discharging patients until the patient has remained afebrile for three days and RT-PCR becomes negative [41].

4. Clinical features

4.1. Age

Most cases present between ages 30–79 years. Table 1 organizes the prevalence based on age ranges as witnessed by mainland China [28]. These findings reflect a recent meta-analysis [42].

Table 1
Case Presentation Rate by Age Group.

Age Group (years)	Case Presentation Rate
< 10	1 %
10–19	1 %
20–29	8 %
30–79	87 %
80 +	3 %

Table 2
Comorbidity Rates Seen with COVID-19 Cases.

Comorbidity	Rate
Hypertension	30.7 %
Diabetes Mellitus	14.3 %
Cardiovascular Disease	11.9 %
Cerebrovascular Disease	6.6 %
Malignancy	4.3 %
Chronic Liver Disease	2.8 %
Chronic Lung Disease	2.4 %
Chronic Kidney Disease	2.1 %
HIV	1.4 %
Immunodeficiency	0.2 %

HIV – Human Immunodeficiency Virus.

4.2. Comorbidities

Table 2 presents the comorbidity rate seen with COVID-19 cases. The most common comorbidity is hypertension (30.7 %). This is followed by diabetes mellitus (14.3 %) and cardiovascular diseases (11.9 %) [24,43–47].

There is suspicion regarding whether angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) increase the risk of COVID-19 infection and severity [48]. Similar to SARS, COVID-19 binds to ACE2 to infiltrate cells [48,49]. ACE inhibitors and ARBs increase the level of ACE2 and could therefore increase the infectivity of COVID-19. However, animal models have shown that ACE inhibitors and ARBs modulate the ACE2 levels and therefore decrease the severity of SARS pneumonia [50]. While the question regarding increased infectivity of COVID-19 remains unanswered, the mortality benefits of ACE inhibitors and ARBs for cardiovascular diseases are well-established [49]. Therefore, experts recommend continuing the medications for COVID-19 patients [49,51,52].

Table 3
Rate of Symptoms Seen with COVID-19 Cases.

Symptom	Rate
Fever	82.2 %
Cough	61.7 %
Fatigue	44.0 %
Dyspnea	41.0 %
Anorexia	40.0 %
Productive Sputum	27.7 %
Myalgia	22.7 %
Sore Throat	15.1 %
Nausea	9.4 %
Dizziness	9.4 %
Diarrhea	8.4 %
Headache	6.7 %
Vomiting	3.6 %
Abdominal Pain	2.2 %

4.3. Symptoms

Table 3 shows the rate of symptoms presented with positive cases of COVID-19. The most common symptoms include fever (82.2 %) and cough (61.7 %) [43–46,53,54]. These symptoms are similar to other viral respiratory diseases. However, the presentation of myalgia, sore throat, nausea, vomiting, and diarrhea may suggest another infection instead. Viral respiratory co-infection is rare [17,55–58].

5. Laboratory findings

5.1. Common laboratory diagnostic tests

Laboratory values that suggest COVID-19 infection include lymphopenia, prolonged prothrombin time (PT), elevated lactate dehydrogenase (LDH), elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), elevated D-dimer, elevated neutrophils, eosinopenia, elevated C-reactive protein (CRP), and elevated troponin (including high-sensitivity troponin) [24,43–45,47,59,60]. Table 4 displays the frequency of most suggested labs. The most common findings are eosinopenia ($< 0.02 \times 10^{\wedge}9/L$) and lymphopenia ($< 1.5 \times 10^{\wedge}9/L$) with 78.8 % and 68.7 %, respectively.

While eosinopenia is linked with COVID-19 infection, its sensitivity and specificity are low at 82 % and 64 %, respectively. This equates to small positive and negative likelihood ratios of 2.29 and 0.28. The combination of lymphopenia and eosinopenia change the sensitivity and specificity to 38.5 % and 75.5 %. Positive and negative likelihood ratios worsen with 1.57 and 0.81, respectively [60].

Troponin elevation is suggestive of infiltration of cardiac tissue [61]. While respiratory-compromising symptoms are present in most cases, cardiac chest pain is also a possibility [59].

Table 4
Common COVID-19 Laboratory Findings.

Laboratory finding	Rate
Eosinopenia	78.8 %
Lymphopenia	68.7 %
Elevated AST	63.4 %
Elevated C-reactive protein	60.7 %
Elevated PT	58.0 %
Elevated LDH	47.2 %
Elevated D-dimer	46.4 %
Thrombocytopenia	36.2 %
Elevated ALT	21.3 %
Elevated HS-Troponin	12.5 %

LDH – Lactate Dehydrogenase; AST – Aspartate Aminotransferase; PT – Prothrombin time; HS-Troponin – High-sensitivity Troponin.

5.2. Reverse transcriptase – polymerase chain reaction

RT-PCR remains the gold standard for diagnosing COVID-19. While its specificity is nearly 100 % from having no reported false positive cases or cross-reactivity with other viruses or estranged oligonucleotides [62], the sensitivity is low at 64 % [36,37,63]. This correlates with a high positive likelihood ratio of 64, but a poor negative likelihood ratio of 0.3. Studies have started performing two sequential RT-PCRs to ensure true negative cases [36,37]. RT-PCR tends to present negative-to-positive at a mean of 5.1 days, and positive-to-negative at 6.9 days [36]. Recommendations are to acquire a repeat RT-PCR 3 days after an initial negative result. Factors that may contribute to the low sensitivity of one RT-PCR may be from immature technology, variation of detection by manufacturers, low initial viral load, and improper sampling [36].

While studies recommend two sequential RT-PCRs to ensure true negativity, testing kits are sparse during the pandemic. Some studies suggest employing chest CT scans if the initial RT-PCR is negative. CT scans have a sensitivity of 98 %, despite a lower specificity [37]. The Chinese General Office of National Health Committee initially allowed positive CT scan findings to be diagnostic for COVID-19 without RT-PCR, but this recommendation was removed in a more recent list of recommendations [64,65].

6. Image findings

Imaging modalities may serve as a surrogate to diagnose COVID-19. Chest x-ray abnormalities present in 33 %–60 % of patients, despite most having CT scan findings [66,67]. Chest CT scans hold more potential to diagnose COVID-19 cases.

Chest CT scans of COVID-19 cases present with bilateral ground-glass opacification or consolidation (Fig. 2). Ground-glass opacification is dominant during early stages and consolidation presents at later stages [68]. More than two lobes are frequently affected with most patients presenting with infiltration in all five lobes. Consolidation rarely present without ground-glass opacification [53,54]. The opacifications typically are rounded and present peripherally in the subpleural area [53,68]. Some studies suggest lower lobe predilection [54,69]. Severe cases present with more consolidation along with architectural distortion, traction bronchiectasis, lymph node enlargement, and pleural effusions [54,68–70].

CT scan findings, compared to RT-PCR, show a sensitivity of 84 %–98 % and specificity of 80.5 %–25 % [36,37,68]. Combining the data from two studies [36,37], the sensitivity and specificity for CT scans are 88 % and 25 %, respectively. This presents a positive likelihood ratio of 1.17 and a negative likelihood ratio of 0.48. Another study implemented a CT scan algorithm into a machine which produced positive and negative likelihood ratios of 4.3 and 0.2, respectively [68]. This suggests that a negative CT scan confers small-moderate confidence that the case is indeed negative.

CT scan interpretation by radiologists hold a sensitivity of 70–80 % and specificity of 90–100 % [71]. Bai et al. studied whether radiologists could discern COVID-19 cases based on CT scan findings. Using the medians from the study (sensitivity 80 %, specificity 93 %), the positive predictive value and negative predictive value are 92 % and 82 %, respectively. This suggests that during this pandemic, a radiologist stating a CT scan is COVID-19-positive is likely correct; however, if the CT scan is deemed negative, it only can be stated with moderate confidence.

7. Complications

7.1. Acute respiratory distress syndrome

Alveolar cells in the lung contain abundant amounts of ACE2, allowing COVID-19 to harbor within the alveoli [12]. About 41.8 % of

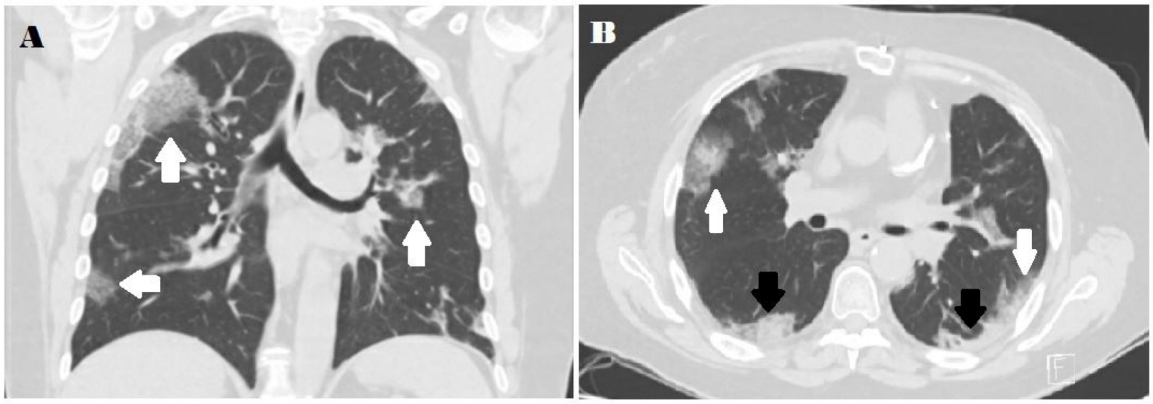

Fig. 2. A) Coronal thin-section unenhanced CT image showing ground-glass opacities with a rounded morphology (arrows). **B)** Axial thin-section unenhanced CT scan showing diffuse bilateral confluent and patchy ground-glass (white arrows) and consolidative (black arrows) pulmonary opacities. Note the peripheral propensity.

Table 5
Virus and Bacterial Co-infection Rate with COVID-19-Positive Cases.

Source	Lin et al. [57] (Shenzhen, China) 2020 (N = 92)	Xing et al. [58] (Qingdao, China) 2020 (N = 30)	Xing et al. [58] (Wuhan, China) 2020 (N = 38)	Chen et al. [56] (Hubei, China) 2020[a]	Woelfel et al. [17] (Munich, Germany) 2020 (N = 16)	Ai et al. [55] (Xiangyang, China) 2020 (N = 102)	Rate from Total
Viruses							
RSV	3	0	1	–	0	0	1.44 %
Flu A	0	18	0	–	0	0	6.47 %
Flu B	0	16	0	–	0	0	5.76 %
Corona NL63	0	–	–	–	0	–	0.00 %
Corona 229E	0	–	–	–	0	–	0.00 %
Corona HKU1	1	–	–	–	0	–	0.93 %
Corona OC43	0	–	–	–	0	–	0.00 %
Paraflu 1	0	0	0	–	0	–	0.00 %
Paraflu 2	1	–	–	–	0	–	0.93 %
Paraflu 3	0	–	–	–	0	–	0.00 %
H. Bocavirus	0	–	–	–	0	–	0.00 %
H. Metapneumovirus	1	–	–	–	0	–	0.93 %
Adenovirus	0	0	0	–	0	0	0.00 %
Rhinovirus	0	–	–	–	0	–	0.00 %
Bacteria							
Mycoplasma p.	–	7	1	29	–	2	17.30 %
Chlamydia p.	–	0	0	22	–	3	11.90 %
Legionella p.	–	6	0	–	–	–	8.82 %
Coxiella burnetii	–	0	0	–	–	–	0.00 %

[a] N = 44 for *Mycoplasma pneumoniae* evaluation and N = 40 for *Chlamydia pneumoniae* evaluation. RSV – Respiratory Syncytial Virus; Flu – Influenza; Corona – Coronavirus; Paraflu – Parainfluenza; H. – Human; p. - pneumoniae.

Table 6
Case-Fatality Rate Organized by Age Group.

Age group (years)	Case-Fatality Rate
Overall	1.6 %
0–9	0.0094 %
10–19	0.022 %
20–29	0.091 %
30–39	0.18 %
40–49	0.4 %
50–59	1.3 %
60–69	4.6 %
70–79	8.0 %
80 +	14.8 %

Table 7
Risk Stratification of COVID-19 Cases.

Severity	Description
Mild	COVID-19 positive
Severe	COVID-19 positive + RR > 30 or SaO_2 < 93 %
Critical	COVID-19 positive + mechanical ventilation, evidence of multiorgan failure, or shock

RR-Respiratory Rate; SaO_2-Oxygen Saturation; COVID-19-coronavirus infectious disease 2019.

patients develop acute respiratory distress syndrome (ARDS) [72]. Diabetes mellitus is a factor associated with the development of ARDS [72]. Other associated comorbidities include hypertension, cardiovascular disease, and chronic kidney disease [72,73]. Laboratory findings associated with the development of ARDS include neutrophilia, lymphopenia, elevated C-reactive protein (high-sensitivity and normal), elevated blood urea nitrogen, elevated d-dimer, prolonged PT, and elevated LDH [72,73]. Patients with ARDS present with higher lactate levels and score high in common risk stratification calculators [73].

About 35.8 %, 45.3 %, and 18.9 % of ARDS cases are mild, moderate, and severe; respectively [73]. Mortality increases with the severity of the disease. Patients greater than 65 years of age present with worse degrees of ARDS and have a higher mortality likelihood [73]. Laboratory markers predicting mortality of COVID-19 ARDS patients include low albumin, elevated blood urea nitrogen, and elevated LDH [72,73].

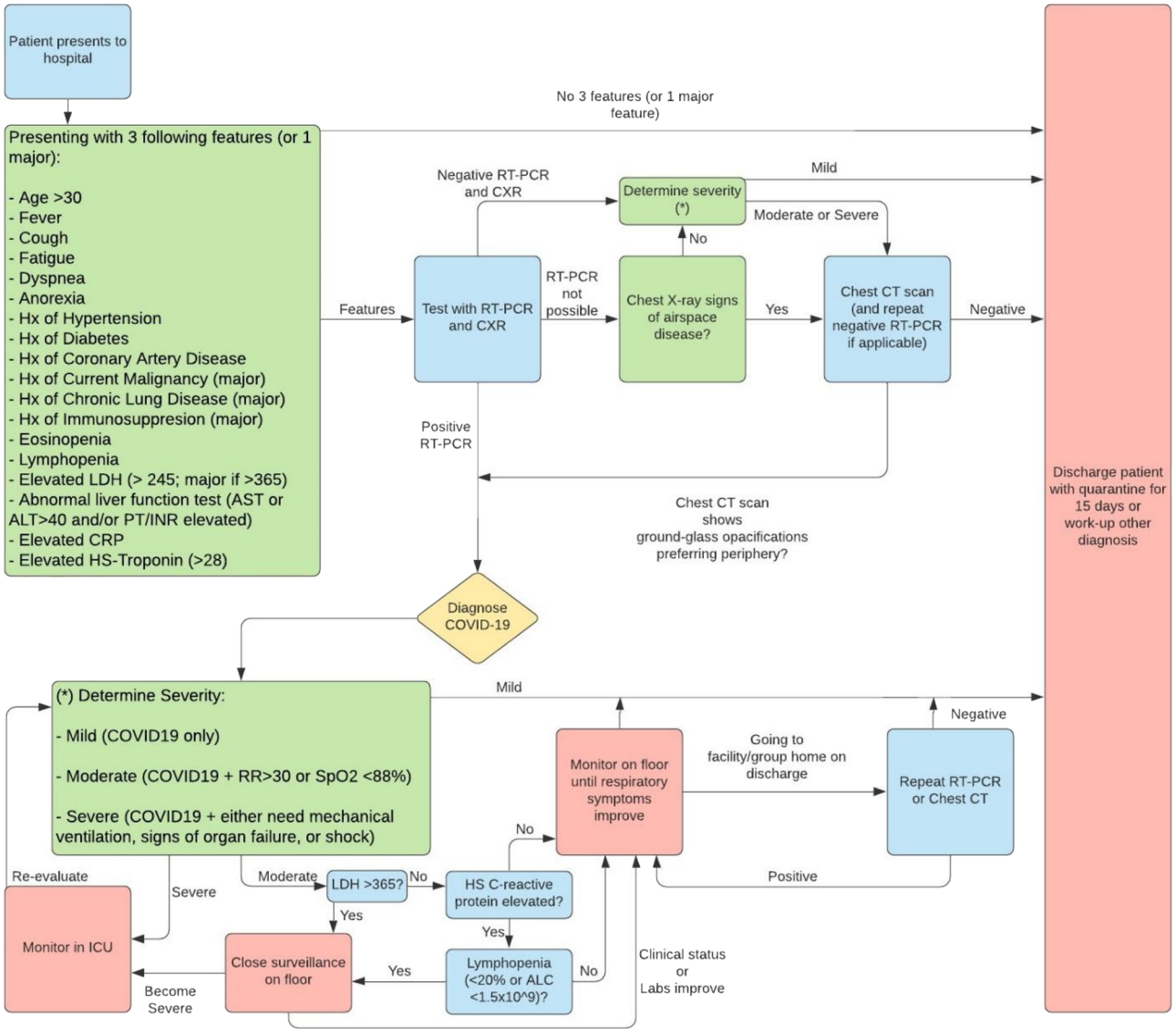

Fig. 3. COVID-19 Diagnostic and Risk-Stratification Algorithm.

7.2. Myocardial injury

The most common causes of COVID-19-related death are associated with the lungs and heart [45]. There are two theories explaining the mechanism of myocardial injury occurring with COVID-19. The first theory pertains to the heart having similar ACE2 levels as the lungs [12], allowing viral entry into the myocardial cells [52]. The secondary theory involves a cytokine storm causing myocardial injury [52]. Myocardial injury includes acute coronary syndrome, heart failure, myocarditis, hypotension or shock, and sepsis [74,75]. For definitive characterization of the injury, magnetic resonance imaging and possibly endocardial biopsy is required [74].

Arrhythmias arise with severe COVID-19 cases [61,74,76]. Malignant arrhythmias, including ventricular tachycardia and fibrillation, occur at a rate of 5.9 %, and arise more frequently in patients with elevated troponin levels (17.3 % of patients with elevated troponin) [76].

Heart failure is commonly encountered in severe cases of COVID-19, regardless of previous cardiac history [74,76]. This presents with elevated levels of N-terminal pro-B-type natriuretic peptide (NT pro-BNP) and troponin levels, especially in severe cases [77]. Some suspect pulmonary hypertension causing right heart failure also contributes to these cases [61,74].

Elevated high-sensitivity troponin (HS-troponin) and creatinine kinase – myocardial brand (CK-MB) levels can independently predict severe COVID-19 cases [75,76,78,79]. A recent meta-analysis showed troponin being more elevated in severe cases [80]. CK itself does not predict severity [78]. Patients with elevated HS-troponin (> 28 ng/L) and CK-MB are suspected to have myocarditis or heart failure [44,78].

7.3. Acute kidney injury

Acute kidney injury presents with elevated urea and cystatin-C levels in severe COVID-19 infection [72,73,81,82]. There are two hypotheses concerning the cause of acute kidney injury. One is from kidneys harboring more ACE2 levels than the lung or heart, especially in the proximal convoluted tubules. However, COVID-19 RNA is not encountered in the urine [17]. The other theory pertains to injury via a cytokine storm [82].

Patients may acquire continuous renal replacement therapy (CRRT) based on kidney injury severity. Speculation exists regarding CRRT potentially serving as a means of removing large cytokine levels from the system, regardless of kidney injury [81,82].

7.4. Co-infection rate

Table 5 presents the chance of co-infection with another microbe [17,55–58]. Bacteria are more frequently encountered with COVID-19 compared to other viruses.

The three most encountered co-infecting viruses were respiratory syncytial virus (RSV), Influenza A, and Influenza B. RSV presents with a rate of 1.44 %. Influenza A and B presents with a rate of 6.47 % and 5.76 %, respectively. However, the calculated rate of influenza A and B co-infection was heavily influenced by the study conducted in Qingdao, China. Removing the study reduces the rate to 0.00 % for both viruses.

The associated bacteria are those responsible for atypical pneumonia: *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumoniae*. No studies exist presenting the rate of other bacteria, including *Staphylococcus sp*. and *Streptococcus sp*. IgM against *Mycoplasma pneumoniae* is most frequently encountered with a rate of 17.30 % [55,56,58].

8. Prognosis

8.1. Risk stratification and survival rate

The case-fatality rate (CFR) continues to change as the pandemic continues. Table 6 presents the CFR in China via age groups [28,83]. Age greater than 60 years is considered a mortality risk factor [28,45,83].

Table 7 presents the risk stratification commonly used in studies [28,46,84,85]. About 81 % are mild cases, 14 % are severe, and 5 % are critical [28]. Mortality for mild, severe, and critical cases are 98 %, 52 %, and 6 % [84,85]. Severe cases have an unpredictable prognosis solely based on clinical presentation. Laboratory markers including LDH, high-sensitivity CRP, and lymphocyte count estimate the prognosis for these cases (Fig. 3) [85].

8.2. Prognosis predictors

Comorbidities associated with severe COVID-19 cases include elderly age, hypertension, cardiovascular disease, cerebrovascular disease, and chronic kidney disease [28,43,46,47]. Cardiovascular disease presents with a 10.5 % CFR. Other diseases that present with a high CFR include diabetes (7.3 %), chronic lung diseases (6.3 %), hypertension (6.0 %), and cancer (5.6 %) [28].

Laboratory values contribute to survival prediction. These include elevated LDH, elevated high sensitivity-CRP, and lymphopenia [85,85,86]. A significantly elevated LDH (> 365 units/L) presents a positive likelihood ratio of 58 for mortality based on the results by Yan et al. [85]. High sensitivity-CRP also has a positive likelihood ratio of 17, but a negative likelihood ratio of 0. Lymphopenia presents a small positive likelihood ratio of 2.65 and a small-moderate negative likelihood ratio of 0.37 [85,85,86]. Other laboratory values that suggest a high mortality risk if elevated include aspartate aminotransferase (AST), alanine aminotransferase (ALT), D-dimer, neutrophil count, prothrombin time, procalcitonin, and high-sensitivity and regular cardiac troponin [28,43–47,59,84–86]. Low monocytes, platelets, and albumin also suggest high mortality risk [28,44,45,47,87].

Some chest CT scan findings, although rare with COVID-19 respiratory disease, suggest a high-risk case. These include architectural distortion, traction bronchiectasis, intrathoracic lymph node enlargement, and pleural effusions [70].

9. Conclusion

The COVID-19 pandemic is rapidly spreading. Case rates and CFRs continue to change. Identifying clinical characteristics, developing and identifying pertinent diagnostic criteria, and providing effective treatment and care are vital for overcoming the pandemic.

Declaration of Competing Interest

No conflict of interest to report.

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