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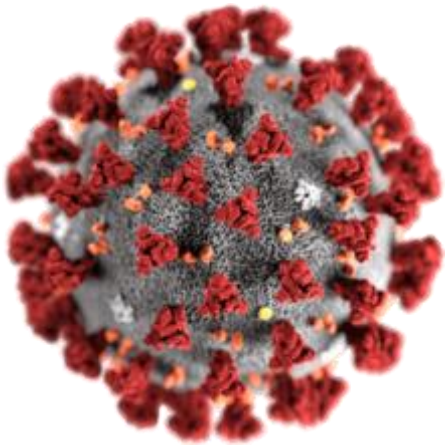

COVID-19 Science Report: Clinical Characteristics

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Announcement

We started the first of our COVID-19 Science Reports in the last week of January 2020, as the very first wave of the COVID-19 pandemic reached Singapore. It was a rapid scan for the current state of development of diagnostics, therapeutics and vaccines that could be useful against the novel coronavirus, as it was called then. It was an urgent request made on a Monday night, and we managed to deliver by that week Friday afternoon.

Since then, it has been a weekly saga (some might call it a nightmare), as we continued to scan and update these reports (highlighting the updated text and paragraphs each week) and added more chapters, first on symptoms and signs, then on laboratory and imaging findings, and then on containment measures. Each addition was responding to yet another urgent request and delivered in the same three to four days, and subsequently updated each week as we continued our scans.

By the fifth week, the Science Report had grown to well over a hundred pages (not counting of course the references) and had become somewhat unwieldy. This was also the same time we were requested to make the report available for downloading on the School's website. We broke up the report into five stand-alone Science Reports and launched them online on 28 February. We were pleasantly surprised by its reception. What started off as "national service" to support our local healthcare and government sector was praised, shared, and even tweeted about.

As the pandemic progressed, we did other reports as well, of course, for the government and for other agencies, not all of which made it online for various reasons. We summarised the available data on fomite-mediated transmission, the risks and management of persons in high density accommodations, how different countries are moving into lockdowns, the use of digital technologies in containment, business continuity measures for enterprises, stay home strategies, and more.

Through it all, our small team were able to deliver on time each week, working through weekends, juggling pieces of work in progress and helped by a group of enthusiastic and hardworking medical students and Public Health interns (some of whom were volunteering their vacations to help). It's been 19 weeks since we started the Science Reports and it is a good time to review and consolidate.

There are now many repositories that cover much of the same ground as our clinical characteristics, diagnostics, therapeutics and vaccines reports. There is also a lot more known about these aspects as clinicians around the world treat their patients. Our student interns have to move on as well, some to examinations, others back to their courses. We will therefore freeze our reports on 1 June 2020, enabling us to focus on the ones that continue to be of critical importance in the global and national responses to COVID-19.

For continuing information on the **clinical characteristics** of COVID-19, please see:

- **CDC Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease** *Outlines the latest evidence in clinical presentation, clinical progression, risk factors, illness severity, and laboratory and radiographic findings.*
- **COVIPENDIUM** *Provides information on the virus, immunity, clinical characteristics, fatalities, specific populations and many other issues.*
- **Medscape** *Provides a summary write up of the topics covered in our science report.*
- **UpToDate®**. *Outlines the epidemiology, virology, clinical features, diagnosis and prevention of COVID-19.*
- **BMJ Best Practice**. *Covers theory (Epidemiology, Aetiology), diagnosis, management and follow up with regard to COVID-19.*

Contents

Clinical Characteristics

In the case of an emerging infectious disease such as COVID-19, it can be difficult for medical practitioners to recognise and diagnose the disease because of the relative lack of knowledge around the presentation of the disease. This section reviews the literature that describe the clinical characteristics of patients with COVID-19, which will hopefully provide health authorities and medical practitioners with a better idea of how COVID-19 presents globally. Where possible, we compare the situation in Singapore to the global situation. Information about Singapore's COVID-19 patients are taken from the case series on the first 18 patients diagnosed between 23 January and 3 February 2020, with onset of symptoms occurring between 14 and 30 January 2020 All of these cases had a travel history to Wuhan city within 14 days prior to developing symptoms.

As of 25 March 2020, we found 223 published papers that reported the various clinical characteristics of COVID-19 patients (Table 4). A systematic search of pre-print articles was not carried out in view of the overwhelming number of papers, although selected pre-print papers were included in the report where relevant. These preprints are preliminary and yet to be peer reviewed, the results should be interpreted with caution. We recorded the various key clinical characteristics of patients and reported them as aggregates. We divided up the clinical characteristics into sociodemographic characteristics, clinical presentation, complications, morbidity and mortality. The report will continue to be updated weekly with the emergence of new studies and findings, and with continued expansion of our search strategy. From 26 March 2020, weekly updates to the report focused on highlighting novel presentations of COVID-19, risk factors for disease susceptibility and severity, as well as clinical characteristics in vulnerable sub-populations.

Caveat

The reported numbers and percentages for the various symptoms and signs should be interpreted with caution. There are multiple structural challenges in comparing the different reports, and these figures may change with the emergence of new studies and findings.

Variations in study design and data quality hinder our compilation. There is a risk of **selection bias** in particular in retrospective studies. Reported counts and percentages of sociodemographic characteristics, and clinical characteristics, incubation periods and mortality rates will vary by the selected sample of patients included in each study. Our analysis excludes individuals infected by SARS-CoV-2 for whom data has not been collected and analysed, including mild cases that did not receive treatment and follow-up in hospitals. Most of the studies were conducted in China, along with some studies in other countries such as Nepal, Singapore, South Korea, Taiwan, Vietnam, UK, USA and beyond. Thus, the findings will not be representative and predictive of the full spectrum of clinical disease, while morbidity and mortality rates will vary across different health care systems.

The current analysis (Table 2) involves summarizing patient counts for each included study. A key limitation of this is repetition and **double counting** of patients. Large scale studies such as that by the Chinese Centre for Disease Control and Prevention[1] involve data extracted from multiple sources and databases and are likely to include patients that have already been reported in the other studies (eg Chen et al 2020[2]) included in this analysis.

Several studies are **incomplete** in the sense that the final outcome for patients (discharged/survived vs. death) have not been determined. Patients may fail to present with signs and symptoms within the cut-off period even though they might subsequently go on to develop them. Moreover, most studies neither reported nor stratified findings by disease severity, or duration from the onset of symptoms or diagnosis. Time constraints may preclude thorough verification of data quality and accuracy.

There was also variation across studies, and within studies, in terms of **case definition**. The method of diagnosis was not reported in some studies[1]. While RT-PCR was the most commonly reported method, details such as the type of swab (throat or nasopharyngeal) were not included in some studies. One study used lower respiratory tract specimens[3], while another included any case picked up by at least one of three different diagnostic methods (SARS-CoV-2 isolation, at least two positive RT-PCR assay results, or genetic sequence match)[4]. The sensitivity and specificity of tests may vary across settings, and the rate of misclassification of false-positives and false-negatives cannot be determined. Variations also exist across studies in clinical practice and the use of terminology (eg classification of disease severity).

Finally, there is variation in the **range of coverage** of clinical presentations. Some studies report a wide range of clinical and laboratory parameters, while others focus only on specific parameters, such as chest X-ray findings, renal function, or T-cells. The effect of COVID-19 on specific organs and systems may not be fully captured in the existing studies.

Sociodemographic Characteristics

As of 25 March 2020, a total of 223 published papers were included in this report (Table 4).

Age

In China[1], the most commonly infected persons reported are those aged 50-59 years (22.4%), followed by those aged 60-69 years (19.2%) and 40-49 years (19.2%). Those aged 0-9 years are least commonly affected (0.9%). In Korea, the age distribution involves two peaks, with most cases aged 20-29 or 50-59[5]; children aged 19 and below accounted for 4.8% of all confirmed cases[5]. Among cases with data in US[6], 6% were aged 85 and above, 25% were aged 65-84 years old, 18% were aged 55-64 and 45-54 respectively, 29% were aged 20-44, and 5% were aged 0-19. In Italy[7], the median age reported was 64 years, with 37.6% above 70 years, 37.3% were aged 51-70, 24.0% were aged 19-50, and 1.2% were aged 0-18 (Table 1). An Italian study conducted in 783 COVID-19 positive patients concluded that males aged above 50-years and females aged above 80 years were at the highest risk of developing severe lung disease[8].

In Singapore[9], the median age of the first 18 cases reported was 47 (range: 31-73) years old.

Overall, it was suggested that adults aged 30-50 may tend to become infected as they are more active in social circles[4], and hence more likely to be exposed to someone who might transmit them the virus. Proposed explanations for the lower rate of infections among children include (1) lower exposure to the virus within their social circles, and (2) lack of testing among children[10]. A retrospective cohort study on 305 individuals in the US hypothesized higher risk in adults due to higher ACE2 expression in their nasal epithelium when compared to children[11].

Table 1 Age distribution of confirmed COVID-19 patients reported (%)

Country\ Age Range	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80+	Total number
China[1]	0.9	1.2	8.1	17.0	19.2	22.4	19.2	8.8	3.2	44672
Italy	1.2 (0-18yo)		24.0 (19-50yo)			37.3 (51-70yo)		37.6 (>70yo)		22512
USA[6]	5 (0-19yo)		29 (20-44yo)		18 (45-54yo)	18 (55-64yo)	25 (64-84yo)		6 (≥85 yo)	2449 (with known ages)

Gender

Out of the major epidemiological studies that took patient gender into account, some[1,2,12-21] reported a higher male to female ratio, while others reported otherwise[5,22-27]. Suggested reasons for the gender imbalance include lower susceptibility among females due to X chromosomes and sex hormone-related protective factors[2], and higher smoking rates among men[28]. However, it is more likely that there was a confounding effect (ie differential exposure to infected persons) that result in this gender imbalance. In Singapore, as of 27 March 2020, 393 out of 683 diagnosed cases (57.5%) in Singapore are male. In Italy, as of 15 March 2020, 59.8% of cases are male[7].

A study on 331 COVID-19 patients compared the IgG levels in male and female showed that the concentration of serum SARS-CoV-2 IgG antibody was higher in female patients than male patients, especially in early disease phase[29]. The authors postulated that this difference in antibody levels may be a potential cause leading to different disease outcomes based on sex.

Past Medical History

The most common comorbidities among patients with a confirmed diagnosis of COVID-19 in China[1] are hypertension (12.8%), followed by diabetes (5.3%), heart/cardiovascular disease (4.2%), chronic respiratory diseases such as COPD and/or asthma (2.4%), and ongoing malignancies (0.5%). A meta-analysis of 6 included studies noted that “the most prevalent cardiovascular metabolic comorbidities were hypertension (17.1%, 95% CI 9.9–24.4%) and cardia-cerebrovascular disease (16.4%, 95% CI 6.6–26.1%), followed by diabetes (9.7%, 95% CI 6.9–12.5%)”[30].

In Singapore[9], out of the first 18 patients diagnosed, 5 (28%) had hypertension, 2 (11%) of the cases had pre-existing diabetes, and 1 case (6%) had hyperlipidaemia.

Smoking Status

Out of 1085 patients with acute respiratory disease due to SARS-CoV-2 in China[16], 85% had no history of smoking, 13% were current smokers, and 2% had smoked in the past. This contrasts with the known high smoking prevalence in China of 27.7% (52.1% among men and 2.7% among women) in 2015[31]. There were no comments on this in the reviewed reports. There is no clear evidence on the association between smoking and the prevalence of COVID-19 currently,

and further studies may help to determine whether ACE2 expression contributes to disease susceptibility[28].

Predictive Factors of Disease Susceptibility

There is currently limited evidence on the factors that determine individuals' susceptibility to COVID-19. A pre-print article suggested that there is no gender difference in terms of susceptibility to SARS-CoV-2[32], while another suggested that children are as likely as adults to be infected[33], although disease severity and mortality may differ by age groups. In contrast, another pre-print study that has yet to be peer-reviewed[34] found that cigarette smoking is associated with elevated ACE-2 receptor expression in the respiratory tract, and thus potentially increases smokers' susceptibility to COVID-19. There is currently insufficient evidence to conclude that patients with cancer have a higher risk of SARS-CoV-2 infection[35], although one study in Wuhan found a higher risk of infection among cancer patients (OR 2.31, 95% ci 1.89-3.02)[36]. It has been hypothesized that patients with diabetes and hypertension who are treated with angiotensin converting enzyme (ACE) inhibitors and angiotensin II type-I receptor blockers are at a higher risk of SARS-CoV-2 infection, as the expression of ACE2 which facilitates the binding of SARS-CoV-2 to cells is increased, although there is no clear evidence at present[37]. Another study conducted on 12,594 patients reported no association of ACE 2 inhibitors and other five common classes of antihypertensive medications with a substantial increase in the likelihood of a COVID-19 positive test or a risk of severe infection among patients consuming antihypertensive medications[38]. Studies confirmed that though underlying cardiovascular disease is associated with an increased risk in mortality, it does not confirm association of ACE inhibitors or angiotensin receptor blockers (ARBs) with poor outcomes[39-41]. However an Italian study reported that ACE-inhibitor had no effect on risk of death[42]. This was confirmed by another large cohort study of 18,472 patients whereby ACE-inhibitor or ARBs were not associated with COVID-19 disease[43]. It was also proposed that the increased susceptibility of patients with diabetes, stroke and hypertension to COVID-19 may be due to ACE2 polymorphism, although this requires further investigation[37]. An analysis suggested that SARS-CoV-2 has a receptor-binding domain that may bind well to human ACE-2, and that pericytes in cardiac cells with a high expression of ACE2 may be targeted[44]. Another yet to be peer-reviewed Finnish study compared genetic differences in the human angiotensin-converting enzyme 2 (hACE2) gene on 56,885 Non-Finnish Europeans and 9,197 east Asians. The study reported small yet insignificant genetic differences.[45]

There is said to be no increased risk of infection among patients with inflammatory bowel disease (IBD)[46,47]. However, an Italian study reported that active IBD was independently associated with negative COVID-19 outcome whereas IBD treatments were not associated with COVID-19 outcomes[48]. Thus, further research is needed on IBD patients co-infected with SARS-CoV-2.

A study that has yet to be peer-reviewed, noted that among 1559 individuals tested for SARS-Cov-2 (of which 682 tested positive) the New York Presbyterian Hospital, individuals with blood group A have a higher odds of testing positive for COVID-19, and individuals with blood group O have lower odds of testing positive[49]. This association was only noted in patients who are Rh+[49]. Another study also yet to be peer-reviewed, reported similar findings where risk of COVID-19 infection was higher in patients with blood group A compared to other blood groups with an OR value of 1.40 (1.01-1.96) in mild cases and an OR of 1.63 (1.10-2.42) in critical cohorts[50]. However, the blood type distribution was not relevant in predicting severe outcomes of acute

respiratory distress syndrome (ARDS), acute kidney infection (AKI) and mortality rate. Similar to previous study, COVID-19 with blood group O were less likely to progress to severe infection.

Clinical Presentation

Initial Presentation

As of 25 March 2020, a total of 42 published studies discussed the initial presentation of COVID-19 patients. Most papers reported fever and cough as the most common symptoms reported at initial presentation. A dry cough is more commonly reported than productive cough among patients diagnosed with COVID-19[51].

Chen et al[2] found that the top three signs and symptoms upon admission include fever (83%), cough (82%) and shortness of breath (31%). Liu et al[22] reported that the fevers were typically "high fevers" that "occurred within several days and were not alleviated by routine anti-infective drugs", although some patients, in particular middle-aged and older patients with co-morbidities, did not have any fever. Huang et al[3] reported that fever was the most common presenting symptom in 40 (98%) of 41 patients, followed by cough (76%) and myalgia or fatigue (44%). Only 43.8% of patients showed signs of fever upon hospital admission in the study by Guan et al[16]. Myalgia and fatigue was also reported in 34.8% and 69.6% of patients respectively in a study by Wang et al[23]. Early clinical manifestations noted by Han et al[52] include fever (87%), dry cough (60%) and fatigue (60%). Two studies reported acute onset of olfactory and taste disorders (OTD) to be more frequent among COVID-19 patients compared with influenza patients[53,54]. While less common, other reported symptoms include sputum production, haemoptysis and diarrhoea (Table 2). One study of 116 patients in California noted that 31.9% of patients had gastro-intestinal symptoms (in particular loss of appetite, nausea/vomiting and diarrhoea), of which 89.2% described it as mild[55]. A study of 59 patients in Hong Kong found the proportion of patients with gastrointestinal symptoms to be 25.4%[56]. In Singapore[9], the most common presenting symptoms were cough (83%), fever (72%), and sore throat (61%). In another case report, a man showcased atypical symptom of constant stabbing testicular and abdominal pain with no accompanying respiratory symptoms but was later tested positive for COVID-19[57].

In Singapore[58], earlier cases had a median of 2 (1-10) days of symptoms and 1 (0-8) day of fever before admission. In Beijing, patients attend the hospital on average 4.5±3.7 days after the onset of symptoms[26], while the median interval was noted to be 6.8 days in a study in Wenzhou[17]. In Taiwan, the first 10 cases averaged 4.2 ± 2.9 days before diagnosis confirmation following symptom onset[59].

Both children and adults can be infected by SARS-CoV-2, although the disease was concentrated among adults 15 years and above during the initial stages of the epidemic[60].

Stronger clinical predictors for a positive SARS-CoV-2 test in a study in Singapore[61] included elevated body temperature (Adjusted OR: 4.81, 95% CI: 1.97-13.12), gastrointestinal symptoms (Adjusted OR: 3.73, 95% CI: 1.23-12.45), and elevated respiratory rate (Adjusted OR: 1.21, 95% CI: 0.93-1.5). A model including male gender, exposure risk factors (eg contact with COVID-19 case), body temperature, heart rate, respiration rate, diastolic blood pressure, sore throat, sputum production, gastrointestinal symptoms, CT X-ray findings suggestive of pneumonia, neutrophil count, eosinophil count, creatinine levels, sodium levels performed well with an area under the receiver operating characteristics curve (AUC) of 0.91[61]. In few cases,

patients initially presented with fever and a distinctive febrile rash[62], acute urticaria[63] or in peculiar cases as petechial rash[64] which in a case has been misdiagnosed as dengue[65]. Another study reported two COVID-19 positive cases with initial herpes zoster-like lesions.[66]

A yet to be reviewed study reported changing clinical presentations over the course of time[67]. Those presenting before 23 January had more systemic symptoms such as fever, fatigue and myalgia. Also, a greater proportion of the earlier patients had small amount of sputum production compared to the those admitted after 23 January. The earlier group also had greater proportion of patients with reduced lymphocyte, CD3 and CD8 counts and elevated serum amyloid.

In rare cases, patients have reported with solely ocular symptoms as the initial presentation of infection. A case report described a 62-year-old man presenting with persistent diplopia and a droopy left eyelid with no fever or respiratory symptoms who was eventually tested positive for COVID-19[68]. In another case, a 2 years-10 months old child presented with conjunctivitis and eyelid dermatitis as the only signs of COVID-19 infection[69]. A New York City study reported five cases of stroke in patients younger than 50-years of age who were later tested to be COVID-19 positive[70].

Asymptomatic Presentation

It is noteworthy that for cases outside of China, 27 out 804 cases (3.36%) were detected while apparently asymptomatic[71]. A study[72] found that out of 24 cases that did not present with symptoms before laboratory test confirmation, 5 eventually developed symptoms in hospital, including fever (38°C and below), cough, nasal congestion, fatigue, dizziness and arthralgia. High levels of “alanine aminotransferase, aspartate aminotransferase, creatine kinase, C-reactive protein and D-dimer were uncommon” and 4 patients had lymphopenia and leukopenia on admission. Seven out of 24 patients had normal CT images and remained asymptomatic during follow-up. While most cases received initial antiviral therapy, none of the cases developed severe pneumonia, and 18 cases were cleared of the virus (after two consecutive negative nucleic acid tests) by the end of the study. One important caveat is that 21 of these patients – including all 5 symptomatic patients – were started on specific antiviral therapy (details of therapy were otherwise unavailable) upon hospitalization. Of 55 cases that were initially asymptomatic, 12 cases eventually developed symptoms of cough or fever[73].

A study in Beijing found that 5% of cases were asymptomatic[26]. 46.5% of COVID-19 cases on the “Diamond Princess” cruise ship were reported to be asymptomatic at the point of testing[74], although a statistical modelling study estimated the true asymptomatic proportion to be 17.9% (95% CI 15.5-20.2)[75]. Based on data from Japanese evacuees from Wuhan, the estimated asymptomatic ratio is 30.8% (95% CI 7.7%-53.8%)[76]. It was reported that 78% of new infections in China recorded over 24 hours up to 1st April 2020 were asymptomatic, although the data is preliminary[77]. In Korea, 3 of the 28 initial laboratory confirmed COVID-19 cases were asymptomatic[78]. In Singapore, pre-symptomatic cases accounted for 6.4% of the 157 locally acquired cases recorded between January 23 and March 16[79]. As of 15 March 2020, 6.7% of patients in Italy were asymptomatic, while 10.6% had unspecified symptoms[7]. However, a study in an isolated village in Italy (Vo’Euganeo) with testing of the entire population found that 50-75% of cases were asymptomatic[80].

15.8% of children treated in Wuhan Children’s Hospital were asymptomatic[81], while 12.9% of children confirmed to have COVID-19 were asymptomatic in a retrospective study[82]. One infant

was asymptomatic in spite of a positive test result on admission, and remained generally afebrile during hospitalization[83]. In another retrospective study of 36 children, 28% were asymptomatic[84].Approximately 50% of residents who tested positive for COVID-19 in a skilled nursing facility were asymptomatic or pre-symptomatic at testing[85].

There have been reports of pre-symptomatic transmission[79,86], as well as suggested asymptomatic transmission[85]. One study found rapid transmission of COVID-19 by an initially asymptomatic youth, to a cluster of youngsters, with a median incubation period of 2 days (range 1-4) and median serial interval of 1 day (range 0-4)[87]. The international WHO mission report noted that most asymptomatic cases go on to develop symptoms, thus truly asymptomatic infections are rare although the true proportion of asymptomatic cases is unclear[88].

In a study of 1012 non-critically ill patients in Wuhan, 30 patients (3.0%) were asymptomatic from exposure to admission, of which 53.3% developed symptoms during follow-up. 14 patients (1.4%) remained asymptomatic during the follow-up period lasting a median of 24 days (IQR 22-27)[89]. Another study of 58 patients in Wuhan found that 27.6% of asymptomatic patients eventually developed symptoms[90], including fever, fatigue, shortness of breath and diarrhoea.

A study in Shanghai[91] classified 13 patients who tested positive for COVID-19 on RT-PCR but with no symptoms into 4 categories: (1) patients in incubation period, (2) patients with signs of disease (eg chest CT findings) but no subjective symptoms, (3) patients with subclinical infection, and (4) asymptomatic chronic carriers. Out of 13 patients who did not have subjective symptoms, 3 patients fell under both category 1 and 2, 10 under category 2 only, 1 patient under category 3, and none under category 4 as all patients tested negative within 3 weeks.

Incubation Period

In total, 26 out of the 223 published papers included as of 25 March 2020, discussed the incubation period. The incubation period for SARS-Cov-2 has been reported to range from 0-24 days. One of the first estimations of mean incubation period published on January 29, 2020, based on a small sample size of 10 cases, was 5.2 days (95% CI 4.1-7.0)[34]. A subsequent report[13] suggested published on February 6, 2020 estimated that incubation times, based on 88 cases, are between 6.4 days (95% CI 5.6-7.7 days). A study by Guan et al[16] suggested that the median incubation period time of SARS-Cov-2 is 4.0 days (IQR 2.0-7.0), while a statistical analysis by Linton et al suggested the mean incubation period (including Wuhan residents) is 5.6 days (95% CI 5.0-6.3)[92]. Lauer et al suggested that the median incubation period is 5.1 days (95% CI 4.5-5.8) based on a pooled analysis, and that 97.5% of patients who eventually became symptomatic developed symptoms in 11.5 days (95% CI 8.2-15.6). It was estimated that 101 of every 10,000 cases will develop symptoms after 14 days of quarantine[93]. A recent preprint study broke down the incubation time of the 132 patients into two age groups: 110 patients in 15 to 64 and 22 patients in 65 to 86[94]. It was found that the median incubation time for the 15 to 64 age group was 7.00 (+1.10 - 0.9) days whereas it was significantly higher in the 65-86 age group, 10.9 (+2.7 - 2.0) days. In a peculiar case in Wuhan, China, a patient reported with an incubation period of 38 days which is the longest reported incubation period so far[95]

A study of 10 children[96] suggested a mean incubation period of 6.5 days (range 2-10). There is said to be no observable difference between the mean incubation period of SARS-CoV-2 and that of SARS and MERS[97].

Symptoms Reported over the Course of Illness

As of 25 March 2020, 137 published studies reported symptoms reported by their patients. Across studies, fever, cough, expectoration, fatigue, and myalgia or arthralgia were the most common symptoms reported. In a large-scale study by Guan et al[16] involving 1099 patients, the percentage of confirmed cases with fever was highest (88.7%), followed by cough (67.8%), fatigue (38.1%) and expectoration (33.7%). The list of reported symptoms among adults can be found in Table 2 below.

There is preliminary evidence that anosmia, hyposmia, and dysgeusia are symptoms of SARS-CoV-2 infection[98,99]. Approximately two thirds of 100 patients in a university hospital in Germany were reported[100] to have anosmia, while this figure is approximately 30% in South Korea in mild cases[101]. A survey of 59 hospitalized COVID-19 patients in Italy found that 33.9% reported at least one olfactory or taste disorder (OTD), with 18.6% reporting both. OTDs were more commonly reported in females, and younger patients[102]. A study of 417 mild-to-moderate COVID-19 patients in Europe[103] found that 85.6% of patients had infection related olfactory dysfunction, of which 79.6% were anosmic and 20.4% were hyposmic. 12.6% of patient developed phantosmia, while 32.4% developed parosmia[103]. The majority of patients (65.4%) developed olfactory dysfunction after general or ENT symptoms, although 11.8% olfactory dysfunction before other symptoms. On the other hand, 88.0% of patients reported gustatory dysfunctions. Olfactory and gustatory dysfunctions were found to have a statistically significant association[103]. 44.0% of patients recovered their olfactory in the short-term, of which 72.6% recovered within 8 days following disease resolution[103]. In a preprint study, 78 patients investigated the COVID-19 status of patients with initial sudden olfactory anosmia (ISOA) using nasopharyngeal swabs for RT-PCR analysis[103]. In patients with anosmia duration ≤12 days, 42 patients (87.5%) had a positive viral load while in those with duration >12 days, 7 patients (23%) had positive viral load. Among the 46 patients whom psychophysical olfactory evaluation was performed, anosmia was observed in 52% (N=24), hyposmia in 24% (N=11) and normosmia in 24% (N=11) of patients. In a Korean study over 3,191 patients in Daegu, researchers reported that anosmia or ageusia were significantly more prevalent in females and younger patients ($p = 0.01$, $P < 0.001$ respectively)[104].

A study reported that neurological symptoms occurred in 36.4% of patients, including central nervous system manifestations (24.8%) such as dizziness (16.8%) and headache (13.1%), peripheral nervous system manifestations (8.9%) such as taste impairment (5.6%) and smell impairment (5.1%) as well as skeletal muscular injury (10.7%)[105]. Nervous system manifestations were more common in patients with severe infections[105]. In a case report, a COVID-19 positive patient was reported to have suffered interstitial pneumonia and seizures and showed demyelinating lesions on an MRI[106]

In a study in China, out of 38 patients with clinically confirmed COVID-19 (of which 73.7% tested positive based on RT-PCR from nasopharyngeal swab), 31.6% (95% CI 17.5-48.7) had ocular abnormalities consistent with conjunctivitis[107]. However only one of 30 patients had conjunctivitis in another study[108], and only 9 out of 1099 patients had conjunctival congestion in the study by Guan et al[16]. In a meta-analysis study, ocular symptoms were reported to have relatively low prevalence in COVID-19 patients[109], however, conjunctivitis and other ocular symptoms were associated with severe disease[109,110].

Other manifestations may include cutaneous manifestations (20.4% of 88 patients), including erythematous rash, urticaria, and chickenpox-like vesicles[111] and chilblain like lesions with our

without Raynaud's phenomenon[112,113]. A French observational study also reported vascular lesions such as macules with "porcelain-like" appearance, livedo, non-necrotic purpura, necrotic purpura, and eruptive cherry angioma[113]. A 32-old-woman COVID-19 positive case in China was reported with a rare case of immune thrombocytopenic purpura nearly two weeks after developing COVID-19 symptoms[114]. Another study reported a digitate papulosquamous eruption in an elderly patient on the second day of hospitalization[115]. A new pattern of erythema multiforme-like eruption was reported in four women patients in the older age group (range: 58-77 years) with COVID-19 infection[116]. A 57-year-old woman presented with erythema nodosum on day 8 of hospital admission[117]. A review study speculated that clinical features such as viral exanthems have low specificity and thus poor diagnostic and prognostic value for COVID-19 disease, however, vasculopathy-related skin manifestations such as chilblain-like lesions, vasculitis among others may provide prognostic values by indicating severe COVID-19 disease. Early detection of cutaneous signs may help in predicting severe disease and help in improving patient outcomes[118].

Among children, a study of 9 infants[32] under the age of 1 infected with SARS-CoV-2 found that the most common symptoms reported were fever (44%), and upper respiratory tract symptoms (22%). Fever (80%), cough (60%) and sore throat (40%) were the most common symptoms in another study of 10 children[96], although fevers tend to resolve within a day, with peak temperatures ranging from 37.7-39.2°C. The predominance of fever and cough was noted in another study[119]. In a study of 171 children in Wuhan[81], 48.5% of patients had a cough, 46.2% had pharyngeal erythema, and 41.5% had fever lasting a median of 3 days (range 1-16). On admission, tachycardia (42.1%) and tachypnoea (28.7%) were also noted[81]. Other reported symptoms among neonates and children include nausea[120], vomiting[81,120,121], diarrhoea[81,120], abdominal pain or discomfort[120], fatigue[81], rhinorrhea[81], nasal congestion[81], and shortness of breath[121]. In a peculiar case, a 10-year old COVID-19 positive child with mild respiratory symptoms presented with gross haematuria which on analysis showed normally shaped red blood cells[122]. However, renal function and renal ultrasound were both normal in this case.

Progression of Disease

While only 43.8% of patients showed signs of fever upon hospital admission in the study by Guan et al[16], 88.7% of the patients exhibited signs of fever during their hospital stay, with the median highest temperature going up to 38.3°C (IQR 37.8 -38.9). This is similar across patients of varying disease severities at admission (classification based on clinical practice guidelines by the American Thoracic Society and Infectious Disease Society of America)[16].

Another study reported that a self-reported anosmia was strongly and independently associated with outpatient care and a milder clinical course[123].

The highest recorded body temperatures of patients in the study by Huang et al[3] were in the range of 38.1-39.0°C (44%), 39.0°C and above (34%), and 37.3-38.0°C (20%). Most patients who required ICU care eventually had their highest body temperature recorded at 38.1-39.0°C (54%); the number of remaining patients with ICU care were split equally between the other two temperature ranges. Chen et al reported that the median duration of fever in patients with fever was 10 days (95% CI: 8-11) following the onset of symptoms[124], and patients transferred to intensive care units have fevers for a longer period of time (31 vs 9 days).

Huang et al[3] noted that above half (55%) of patients eventually developed dyspnoea, and that the median duration from "illness onset to dyspnoea was 8.0 days (IQR: 5.0–13.0)". The time

from initial symptoms to the development of shortness of breath is similar in the report by Wu et al[24]. Liu et al[22] reported that this duration was 7 days (range 1.0 – 20.0).

Physician-diagnosed pneumonia was common (91.1%[16], 100%[3]) among patients in a few studies in China. The median time from symptom onset to pneumonia development is said to be 3.0 days (IQR 1.0-6.0)[16]. In a rare case, a 47-year-old man presented with bowel necrosis in the setting of patent mesenteric vessels[125].

The median duration of hospitalization is said to be 12.0 days (IQR 10.0-14.0)[16].

In the study of 44,672 cases in China[1], 80.9% were mild (with mild pneumonia or no pneumonia), 13.8% were severe (with "dyspnea, respiratory frequency ≥30/minute, blood oxygen saturation ≤93%, PaO_2/FiO_2 ratio <300, and/or lung infiltrates >50% within 24–48 hours") and 4.7% were critical (with "respiratory failure, septic shock and/or multiple organ dysfunction/ failure"). In a study of 2143 suspected and confirmed children with COVID-19 in China, 50.9% of cases were mild, 38.8% were moderate, 5.2% were severe, and 0.6% were critical[82]. Polypnea was the most common symptom, followed by fever and cough in a case series of 8 children with severe COVID-19[126]. However, a three-week-old new-born showed a late-onset neonatal sepsis which was complicated by pneumothorax[127]. The patient was successfully managed in PICU with mechanical ventilation and appropriate antibiotic course. A brain MRI studying brain imaging features on 27 critically ill COVID-19 patients reported 4 patients presenting with leukoencephalopathy, one with microhaemorrhages and 6 with a combination of both[128].

Recovery

The median duration from symptom onset to first negative RT-PCR results is said to be 9.5 days (IQR 6.0-11.0)[129]. Mo et al[130] found that 45.2% of patients showed clinical and radiological signs of remission within 10 days of hospitalization.

There have been case reports of patients who tested positive for SARS-CoV-2 after discharge from hospital in China[131,132]. While delayed viral clearance and viral reactivation have been suggested, further studies are required to verify these postulations[131]. A prospective cohort study of 131 patients discharged after COVID-19 disease reported readmission in 2.29% of cases because of fever or positive SARS-CoV-2 retest[133]. Majority of the cohort patients were self-quarantined and were in the course of recovery.

Hong Kong's Hospital Authority reported that some patients showed signs of 20-30% reduction in lung function, and abnormal lung scans after recovery from COVID-19. Nonetheless, the long-term effect on recovered patients, including the risk of pulmonary fibrosis, is uncertain[134]. Lei et al[135] found that 46.9% of 49 patients studied showed evidence of lung fibrosis in a follow-up CT after an average of 15.8 days after hospital discharge (range 7 – 25 days). Patients who developed fibrosis tended to be older (Mean age 45.4 vs 33.8 years), had a longer length of stay in hospital (19.1 vs 15.0 days), and had ICU admission (17.4% vs 3.8%)[135]. A preprint case study on 34 ICU patients reported complications rate (including acute liver injury, acute cardiac injury and acute kidney injury) were higher in invasive mechanical ventilation (IMV) cases than non-invasive ventilation (NIV) cases[136]. Lymphocytopenia, neutrophilia, and increase of IL-6 and IL-10 occurred in SARS-CoV-2 infected on admission day of patients in ICU, however, the progression of those was significantly different in IMV cases and NIV cases during hospitalization.

Table 2 Selected studies on signs and symptoms of COVID-19 ("-" indicates Not Reported)

Study	Chen N et al[2]	Liu K et al[22]	Wang D et al[23]	Wu J et al[24]	Huang C et al[3]	Guan W et al[16]
Time point	On admission	On admission	On admission	On admission	On admission	Throughout hospital stay
Study sample (n)	99	137	138	80	41	1099
Fever	-	-	-	-	-	88.7%
(on admission)	83%	81.8%	98.6%	78.8%	98%	43.8%
Cough	82%	48.2%	59.4% (dry)	63.8%	76%	67.8%
Fatigue	-	32.1%	69.6%	-	44%	38.1%
Myalgia/ Arthralgia	11%	-	34.8%	22.5%		14.9%
Sputum production/ Expectoration	-	4.4%	26.8%	-	28%	33.7%
Dypsnoea/ Shortness of breath	31%	19.0%	31.2%	37.5%	55%	18.7%
Nasal congestion/ Rhinorrhea	4%	-	-	6.1%	-	4.8%
Headache	8%	9.5%	6.5%	16.3%	8%	13.6%
Dizziness	-	-	9.4%	-		-
Sore throat/ Pharyngalgia	5%	-	17.4%	13.8%	-	13.9%
Chills	-	-	-	-	-	11.5%
Diarrhoea	2%	8.0%	10.1%	1.3%	3%	3.8%
Nausea	1%	-	10.1%	1.3%	-	5.0%
Vomiting		-	3.6%			
Haemoptysis	-	5.1%	-	-	5%	0.9%
Abdominal pain	-	-	2.2%	-	-	-
Anorexia	-	-	39.9%	-	-	-
Chest pain	2%	-	-	3.8%	-	-
Confusion	9%	-	-	-	-	-

Study	Chen N et al[2]	Liu K et al[22]	Wang D et al[23]	Wu J et al[24]	Huang C et al[3]	Guan W et al[16]
Conjunctival congestion	-	-	-	-	-	0.8%
Heart palpitations	-	7.3%	-	-	-	-
Throat congestion	-	-	-	-	-	1.8%
Tonsil Swelling	-	-	-	-	-	1.8%

Radiographic Findings

123 out of 223 published studies included as of 25 March 2020, discussed chest X-ray and CT findings.

Zhang et al[137] and Chen et al[138] highlighted that chest CT scans show pulmonary lesions more clearly than chest X-rays[137], while She et al[139] cited that elderly patients may show more “diffuse and extensive” chest CT imaging than younger patients, with more consolidated lung lesions in persons aged 50 and above[27].

Chest X-ray

An early case report[140] suggested the presentation of bilateral lung opacities eight days after admission, which became more extensive in a chest radiograph taken three days later, especially in the lower lung. The patient died nine days later. In terms of disease progression, for a COVID-19 case in the US[141], while no abnormalities were noted on Day 7, signs of pneumonia developed in the lower left lobe by Day 9 along with a fall in oxygen saturation to 90% and “basilar streaky opacities” were seen on Day 10. This coincided with rales on bilateral lungs during auscultation. Extension of opacities and “basilar predominant consolidation” were noted in a patient who died subsequently[142]. In Singapore[9], 12 of the first 18 patients showed no radiographic signs on admission. Three subsequently developed “bilateral diffuse airspace opacities”. 5 of 9 patients showed radiographic anomalies on baseline chest X-rays in Korea[143]. In a study of 64 patients, using three RT-PCR tests as a gold standard, baseline chest X-ray had a sensitivity of 69% (95% CI 56-80) compared to 91% (95% CI 83-97) for initial RT-PCR in patients with COVID-19 infection[144]. Chest X-ray severity scores peaked at 10-12 days[144], and the common presentation was bilateral lower zone consolidation[144]. In Italy, a chest X-ray scoring system was studied for quantifying and monitoring disease progression. In a preliminary validation study on 100 hospitalized patients the CXR scoring of higher scores correlated with higher mortality[145].

In children[138], early stages of pneumonia may show up as “small patchy shadows and interstitial changes”, in particular in the “lung periphery” on Chest X-rays, which develop into “bilateral multiple ground-glass opacity, infiltrating shadows, and pulmonary consolidation, with infrequent pleural effusion”. Unilateral patchy infiltrates were noted in 40% of children with COVID-19 in a study[96].

Chest CT Scans

Across major studies[2,16,19,22,24,25,146-153], bilateral lung involvement occurred in the majority of cases (range: 36[153]-90%[148]), with all five lobes commonly affected (range 27[149]-36%[153]). Ground glass opacities (GGO) were common (range: 56[16]-90%[148]), and may be accompanied by consolidation (range: 13[153]-44%[150]). Ground glass opacities are predominantly distributed in the posterior[27,143] and peripheral regions[18,27,143,146,150,152], and have been noted in the perihilar and subpleural regions bilaterally[154]. A summary of radiographic findings across selected studies is presented in Table 3. In one study of 21 symptomatic patients[155], a rounded morphology was reported in 33% of cases. Linear opacities and a "crazy-paving pattern" were less common at 14% and 19% respectively, although linear opacities was found to be more common (61%) in another study[153]. No lung cavitation, pulmonary nodule, pleural effusion, lymphadenopathy, emphysema, and pulmonary fibrosis was detected in the study[155]. Nonetheless, a small cavity has been reported in a case report[156], and bronchiectasis was reported in another[157]. Air bronchogram was noted in 62.5% of patients with early phase disease, and 90.9% of patients with advanced-phase disease[152].

In terms of the prevalence of abnormal CT findings, a study of 121 symptomatic patients[149] found that 56% of patients reviewed early (0-2 days from symptom onset) did not have any abnormal CT findings. However, bilateral lung involvement with more extensive opacities become more common with time from initial presentation[149], while consolidation became more common 5 or more days after the onset of symptoms[27]. Pleural effusion, pericardial effusion and lymphadenopathy were less common, occurring in 8%, 6% and 6% of patients respectively[27], but may be more common in severe or critical cases[18]. An enlarged subsegmental vessel (>3mm diameter) was noted in 89% of 58 patients in Italy[158]. 2 out of 21 cases[159] recruited from Hong Kong and Shenzhen had normal chest CT scans, while 14-23% of patients in other studies in China had normal CT scans at baseline[153,155].

Shi et al[19] reported that CT features of patients who are preclinical may involve unilateral ground glass opacification. In the first week from symptom onset, lesions may become bilateral and diffuse, with potential pleural effusion and lymphadenopathy. In the second week of symptom onset, consolidation patterns may be noted, although ground glass opacities are still predominant. In the third week, reticular patterns may also become predominant, with thickening of adjacent pleura. Based on findings of patients with mild COVID-19 pneumonia, Pan et al[146] defined four stages of lung involvement: early stage (0-4 days from onset of symptoms), progressive stage (5-8 days from onset), peak stage (9-13 days from onset) and absorption stage (14 days and above after onset). Wang et al[160] suggested that CT abnormalities rapidly progressed after symptom onset, and peaked after approximately 6-11 days, followed by sustained high levels. While ground glass opacities were predominant initially, mixed patterns became second most prevalent and peaked after 12-17 days of symptom onset[160]. Similarly, Han et al[161] noted rapid increase in mean CT score from first to third week, with a peak of 8.2 in the second week, as well as increasing presentation of consolidation and mixed patterns in the second week, which become less prevalent as compared to ground glass opacities again in the third and fourth week during recovery.

Shi et al[19] also observed 4 patterns of radiographic changes: (1) progression to peak before improvement (46%), (2) radiographic deterioration (32%), (3) radiographic improvement (14%), and (4) unchanged (9%). Chen et al found that upon repeat imaging after a median of 3 days, 65.7% patients showed progression or worsening, 22.6% showed improvement, and 12.1%

remained stable[124]. Lei et al found that 89.8% of patients followed a typical transition from early to advanced followed by dissipating stages[135].

In a study of 41 patients[3], on admission, ICU patients had “bilateral multiple lobular and subsegmental areas of consolidation” compared to non-ICU patients that typically had “bilateral ground-glass opacity and subsegmental areas of consolidation”. For the latter, the consolidation resolved over time. Patients with severe or critical illness over the course of the disease were said to have higher CT scores, and more frequently present with linear opacities, consolidation, crazy-paving pattern, bronchial wall thickening, lymph node enlargement, and pleural effusion with right upper and middle lobe involvement on chest CTs at baseline[162]. Similar findings were reported in another study observing 93 cases and correlating CT characteristics with disease severity[163]. The study reported that multiple lobe involvement, presence of consolidation, crazy-paving sign, interlobular septal thickening and pleural thickening and effusion was more common in severe infections ($p < 0.05$) and have potential prognostic value[164] whereas ground-glass opacities, involvement in one-two lobes and the halo sign were more likely to be seen in mild cases.

16 of 20 children studied in China presented with chest CT abnormalities, with 10 children (50%) with bilateral pulmonary lesions[119]. Twelve children (60%) showed ground glass opacities, and 10 children (50%) showed consolidation with halo signs on chest CT[119]. In children[138] with severe infection, “multiple lobar lesions”, ground glass opacities and segmental consolidation, may be present bilaterally. A study of 10 children found that chest X-rays showed largely normal or coarse lung markings without signs of pneumonia, although ground glass opacities were noted in the chest CT scans of 5 children[165]. In a study of 171 children under 16 years old with COVID-19 in Wuhan, 32.7% had ground glass opacities, 18.7% had local patchy shadowing, 12.3% had bilateral patchy shadowing and 1.2% had interstitial abnormalities[81]. A case series reported that children had milder CT findings than adults with smaller and mainly ground-glass nodules, with rare larger consolidations and white-outs [166,167].

It was found that on chest CT, pure ground glass opacities were less commonly noted among pregnant women than non-pregnant women, while consolidation was more commonly noted among pregnant women[168].

A study[72] found that out of 24 cases that did not present with symptoms before laboratory test confirmation, 50% had chest CT scans that showed patchy shadows or a ground-glass appearance while approximately 21% showed stripe shadows. The rest had normal radiographic findings. Similarly, a study found unremarkable CT findings in an asymptomatic COVID-19 patient[169]. 54% of the asymptomatic COVID-19 patients on the “Diamond Princess” cruise ship had lung opacities on chest CT, as compared to 80% among symptomatic patients[170]. On chest CT, ground glass appearance predominance was noted in 80% of asymptomatic cases, with milder CT severity score as compared to symptomatic cases[170].

One report suggested that ground glass changes on chest CT scans may appear before positive RT-PCR test results[139]. In one study[171], five out of 167 (3%) cases who were tested positive for COVID-19 after initial negative test results had initial chest CT scans with ground-glass opacities indicative of viral pneumonia, although seven patients who were tested positive (4%) did not have positive CT findings. Other studies noted the limited sensitivity of chest CT scans in the early stages of disease[149], and lack of evidence of the “prognostic role of chest CT”[153]. One study found that 17 out of 149 (11.4%) symptomatic patients did not show radiographic abnormalities on chest CT on admission, of which 12 remained negative for chest

CT findings after 10 days. Another study found a relatively high proportion of patient with normal chest CT (30.8%), and suggested it is not suitable as an independent screening modality[172]. Nonetheless, one study recommended the use of chest CT for screening among patients with clinical findings suggestive of SARS-CoV-2 infection, but negative RT-PCR results[147]. Using RT-PCR as a gold standard for diagnosis, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of chest CT were found to be 97% (95% CI 95-98), 25% (95% CI 22-30), 65% (95% CI 62-68), 83% (95% CI 76-89), and 68% (95% CI 65-70), respectively[173]. Another study in Rome, Italy, found the sensitivity, specificity and accuracy of CT to be 97% (95% CI 88-99), 56% (95% CI 45-66), and 72% (95% CI 64-78)[158]. Another study analysed CT findings over a period of 0-28 days since symptom onset and showed the radiological changes occurred rapidly in early disease and lasted for a long time[174].

The presentation on chest X-rays and CT scans after full recovery from COVID-19, including the presence of residual fibrotic changes, is uncertain at present[155]. Nonetheless, it was noted that improvements in chest CT signs[146] began approximately 14 days after the onset of symptoms in patients with mild pneumonia.

On four ^{18}F-FDG PET/CT scans, similar ground-glass appearances (with potential lung consolidations), and high ^{18}F-FDG uptake were noted[175]. No disseminated lesions were noted[175]. It should be highlighted that these scans should not be performed routinely[175] for COVID-19 cases. A case report noted a diagnosis of COVID-19 in an initially asymptomatic patient after findings of “bilateral, diffuse and intense FDG uptake” on a ^{18}F-FDG PET/CT scan for malignancy, which correlated with ground-glass opacities seen on a low-dose CT scan[176].

One study[177] found weak associations between clinical and CT findings at baseline. Nonetheless, significant positive associations were noted between CT features (eg sum score, lesion size, and air bronchogram) and CRP, ESR and LDH levels. High fevers above 38.1-39°C (4.06, 95% CI 0.39-7.73) were associated with a higher risk of a change in opacification size sum score, as compared to those with temperatures below 37.3°C, after adjustment for age and gender.

In a preprint study, an advanced 3-dimensional virtual histological imaging of a single gross sample of lung tissue was taken from a COVID-19 patient at the time of autopsy. The true extent of cytopathic viral changes and damage to the lung from COVID-19 were visualized[178]. Notably, there was activated mature megakaryocytes in the small vessels of the lung, pulmonary microangiopathy independent of diffuse alveolar damage and the pathologic extent of fibrin deposition and clot formation with inflammatory cell attachment, which was far more extensive than previously visualised in 2D. In a case of a 68-year-old COVID-19 positive male patient, non-smoker, with no history of lung disease, a lung scintigraphy showed signs of tracheobronchitis[179].

A CT scan-based scoring system was developed for COVID-19 infections[180]. The scoring system has a sensitivity of 56.67% and a specificity of 95.35% for a score > 4, a sensitivity of 86.67% and a specificity of 67.44% for a score > 2, and a sensitivity of 100% and a specificity of 23.26% for a score > 0.

Table 3 Selected studies on common chest CT findings

Study	Chung M et al (2020)[155]	Bernheim A et al (2020)[149]	Song F et al (2020)[27]	Ng M-Y et al (2020)[87]	Xu X et al (2020)[153]
N	21	121 (includes the 21 patients in Chung et al's study)	51	21	90
Ground Glass Opacities	86%	44% (early), 88% (intermediate), 88% (late)	77%	86%	72%
Consolidation		17% (early), 55% (intermediate), 60% (late)	55%	62%	13%
Number of lobes affected					
1	5%	15%	8%	15%	13%
2	10%	12%	16%	12%	4%
3	14%	9%	12%	9%	14%
4	19%	15%	24%	15%	9%
5	38%	27%	39%	27%	36%
Bilateral lung disease	76%	60% (overall) 28% (early) 76% (intermediate) 88% (late)	86%	60%	59%
Lobe involvement					
Right upper lobe	67%	44%	84%	67%	53%
Left upper lobe	67%	48%		76%	53%
Right middle lobe	57%	41%	59%	48%	44%
Right lower lobe	76%	65%	90%	76%	66%
Left lower lobe	67%	63%		81%	61%
Opacification distribution and pattern					
Rounded morphology	33%	54%	-	-	-
Linear opacities	14%	7% (overall) 0% (early) 20% (late)	-	-	61%

Crazy-paving pattern	19%	5% (overall) 0% (early) 20% (late)	-	-	12%
Peripheral distribution	33%	52% 22% (early) 72% (late)	86% (80% posterior)	86%	51%
Cavitation	0%	0%	-	-	0%
Reverse halo	-	2% (overall) 0% (early) 4% (late)	-	-	-
Reticulation	-	-	22%	-	-
Pleural Effusion	0%	1%	8%	0%	4%

Lung Ultrasound

In a study of 30 patients using bedside ultrasound, 90% of patients had interstitial pulmonary edema and pulmonary consolidations[181]. Taking chest CT as a reference standard, bedside lung ultrasound had high diagnostic efficacy for patients with severe disease (but not for mild-to-moderate disease)[181]. Another study described the use of Lung Ultrasound (LUS) in patient triage based on a typical artefact named “light beam”[182]. This sign was observed invariably in most (48 of the 49) patients with pneumonia from COVID-19 and corresponded to the early appearance of ‘ground glass” alterations in CT scan. The sign was described as a broad, lucent, band-shaped, vertical artefact arising from a regular pleural line interspersed within areas of normal pattern or with separated B-lines. The artefact moved rapidly with sliding, creating an “on-off” effect as it appeared and disappeared from screen. This sign was never observed in 12 patients with negative COVID-19 swab test.

Laboratory Findings

As of 25 March 2020, 113 published studies reported laboratory findings.

Haematology

Coagulation Function/Activated Partial Thromboplastin Time (APTT)/Prothrombin Time/D-dimer

In a study of 99 patients in China[2], APTT was lower than normal in 16% of patients and higher than normal in 6% of patients. Prothrombin times were reduced in 30% of patients but increased in 5% of patients[2]. This was 2.7% and 11.4% respectively in another study[155]. Prothrombin times on admission[3] were longer in ICU patients (Median:12.2s, IQR 11.2-13.4) as compared to non-ICU patients (Median: 10.7s, IQR 9.8-12.1). A longer prothrombin time was also noted in those who died (Median: 15.5s, IQR 14.4-16.3) as compared to those who survived (Median: 13.6 s, IQR 13.0-14.3)[15]. Elevated D-dimer has been reported in some cases[2,16,155,183], however other case reports have suggested normal D-dimer concentration levels[157]. D-dimer levels were higher in ICU patients as compared to non-ICU patients on admission[3], and during hospital stay[23], as well as among the non-survivors as compared to survivors[15]. Non-survivors also had

higher levels of fibrin degradation products[15]. It was suggested that coagulation parameters were associated with prognosis; disseminated intravascular coagulation (DIC) was noted in non-survivors, and rarely in survivors[15].

In a study with 94 patients and 40 healthy controls[184], antithrombin, and prothrombin time activity (PT-act) values are lower in COVID-19 patients as compared to healthy individuals, while D-dimer, fibrinogen, and fibrin/fibrinogen degradation product (FDP) levels were higher in patients as compared to controls. D-dimer and FDP levels are also said to be higher in patients who have more severe or critical conditions[184]. Nonetheless, no significant difference could be observed for APTT, prothrombin time-international normalized ratio (PT-INR), and PT between COVID-19 patients of different disease severities (ordinary, severe, critical).

Complete Blood Count/Full Blood Count

Chen et al[2] found that 51% of patients had lowered haemoglobin counts. While 36.2% had thrombocytopenia on admission in one study[16], this was less common (12-14%) in others[2,24], and no difference in platelet counts[3] was noted between patients requiring ICU and non-ICU care in another study. In another pre-print study of 271 COVID-19 patients, 11.8% experienced COVID-19 associated delayed phase thrombocytopenia, which was significantly associated with increased length of stay and ICU admission rate[185].

Leukopenia (WBC <3.5-4 x10^9/L)[3,16,24,155,183,186] has been reported in some COVID-19 patients. A case report in US reported leukopenia and lowered absolute neutrophil count on day 7 and 9 illness[141]. Another case report noted elevated neutrophil ratio (81.2%, normal range 40.0-75.0%)[157], although others reported normal neutrophil counts[183,186]. A study of 99 patients reported that 9% of patients had lower leucocyte levels, and 24% had higher than normal leucocyte levels[2], with 38% of patients having higher than normal neutrophil counts[2], while another study suggested that most cases have normal white blood cell and neutrophil counts[27]. Elevated neutrophil ratios (OR 9.679, 95% CI 3.278-28.577) were associated with severe/critical disease in one study[162]. Although no statistically significant difference was found between white blood cell counts of ICU and non-ICU patients in Singapore[21], peak absolute neutrophil counts were higher in ICU patients (Median 11.6 x 10^9/L, IQR 9.3-13.8) as compared to non-ICU patients (Median 3.5 x 10^9/L, IQR 2.6-4.4).

Studies noted that between 31%[153] and 75%[148] of patients had lowered lymphocyte counts. One study on peripheral blood smear consult for haemolysis observed atypical lymphocytes in 14/15 (93.33%)[187]. One study of 51 patients noted low lymphocyte count in 65% of patients, while the remaining 35% were normal[27]. A positive correlation was noted between eosinophil and lymphocyte counts[148]. A lower lymphocyte ratio was noted in a case report (12.8%)[157], although another reported lymphocytosis[186]. Severe cases[16] had more prominent leukopenia and lymphopenia as compared to non-severe cases, and patients with acute respiratory distress syndrome (ARDS) are more likely to have lymphopenia at admission compared to those without ARDS[188]. Similarly, another study[162] found that patients with severe or critical illness had lower lymphocyte counts (OR 12.000, 95% CI 3.213-44.819), lower lymphocyte ratios (OR 7.6000, 95% CI 2.481-23.284), and lower monocyte ratios (OR 18.000, 95% CI 2.035-159.153). Lymphopenia as indicated by a low lymphocyte percentage (LYM%) was said to be associated with disease progression and poor prognosis[189]. Proposed explanations for lymphocytopenia among severe cases include direct viral cytotoxic action[2,20], and endothelial dysfunction due to existing co-morbidities (eg hypertension) among older ICU patients[190]. Nonetheless, a study did not find a statistically significant difference between rates of lymphocytopenia between survivors

and non-survivors who were in critical condition[20]. In Singapore[21], 39% of patients had lymphopenia during admission[9], with a lower baseline absolute lymphocyte count in ICU patients (Median 0.5 x 10^9/L, IQR 0.48-0.8) as compared to non-ICU patients (Median 1.3 x 10^9/L, IQR 0.9-1.7). ICU patients also had a lower Nadir ALC count during the hospital stay. One study involving 10 participants suggested that an increase in lowered eosinophil counts back to normal was associated with recovery from SARS-CoV-2 infection[191]. A meta-analysis of 15 studies showed that severe patients had higher neutrophils and neutrophil-to-lymphocyte ratio with fewer lymphocytes than non-severe patients suggesting that monitoring these markers might assist in predicting the severity and prognosis of patients with COVID-19[192]. A study showed that data involving neutrophil count, lymphocyte count and platelet count (NLP score) as a clinically predictive tool can be used in improving risk stratification and management of COVID-19 patients[193]. On monitoring the Concordance index (C-index), calibration curve, decision curve and clinical impact curve concurrently with the NLP score showed that the nomogram can be used to predict prognosis in COVID-19 patients accurately.

A study noted that NKG2A expression in COVID-19 patients may be associated with early stage functional exhaustion of cytotoxic lymphocytes, resulting in disease progression[194].

T cell counts are said to be lowered in COVID-19 patients[195], in particular the elderly and those in ICU. Another study found that T cells, in particular helper and suppressor T cells were reduced significantly, especially in severe cases of SARS-CoV-2 infection[196]. One study noted that multi-functional CD4+ T cells are significantly reduced in the severe group[197]. A study[198] found that lower levels of lymphocytes, CD4+ T-cells, CD8+ T cells, B cells and NK cells were noted in severe cases as compared to milder cases, with a decrease in CD8+ T cells and B cells, as well as an increase in CD4+/CD8+ ratio, associated with poor recovery and clinical efficacy[198]. A study with similar findings suggested that counts of CD4+T and CD8+T cells could be used as diagnostic markers and predictors of COVID-19 disease severity[199].

Leukoerythroblastic reaction was noted in one case report[200].

Among children with COVID-19, white blood cell count is said to be either normal or lowered, with reduced lymphocyte counts, and increasing lymphocytopenia for severe conditions[138]. One study found elevated lymphocyte counts and CRP levels in a 10-month-old boy with co-infection with Influenza A[201].

Lymphopenia was noted in 4 out of 24 COVID-19 patients who were asymptomatic[72], and in 5 out of 9 pregnant patients[202]. Leukocytosis, elevated neutrophil ratio, and lymphopenia were said to be more common among pregnant patients than non-pregnant adults in a study[168].

C-reactive protein (CRP)/Erythrocyte sedimentation rate (ESR)/IL-6/Procalcitonin/Serum ferritin/Presepsin

Elevated C-reactive protein was said to be an important presentation in COVID-19[137]. In Singapore, 38% of patients had elevated CRP upon admission[9]. Elevated CRP levels[24,124,153,183,186] were reported in multiple case reports of COVID-19, particularly among older patients[203]. Up to 55%[155]-99%[52] of cases have been reported to have elevated CRP levels. CRP levels may be normal or increased in children[138]. 75% of pregnant patients[202] had elevated CRP levels. In a multivariate analysis[204], higher CRP levels (>8.2 mg/L) were associated with disease progression (OR 10.530, 95% CI 1.224-34.701), while in another study[162], increased CRP levels were associated with greater disease severity (OR 13.204, 95% CI 2.847-61.237). Another study reported that soluble cluster of differentiation (CD) 14 subtype (sCD14-ST) also termed as

presepsin (PSP) helps in modulating immune responses and found to be useful for early diagnosis, prognosis and risk stratification prediction[205].

Higher erythrocyte sedimentation rates[2,124,157,183,186] (>15-20 mm/h) have also been reported in case reports, and in up to 85.5%[124] of cases with COVID-19. One study noted elevated ESR levels in all patients in the early phase[206]. Lymphokine IL-6 was increased (27.47 pg/ml, 413.6pg/ml) in two case reports[157], while this was reported in 52% of cases in another study[2]. One study suggested that multiorgan and tissue damage is caused by SARS-Cov-2 itself, rather than due to a "cytokine storm"[207].

Most patients[2,3,24] have normal procalcitonin levels at admission. This is similar for children[138], although another study noted common procalcitonin elevation in children[119]. Nonetheless, one study found that elevated procalcitonin levels were associated with greater disease severity[162] (OR 7.989, 95% CI 2.426-26.305). One case report noted elevated serum amyloid A protein levels[186] although this has not been verified in larger-scale studies. In one study[2], most patients (63%) had higher than normal serum ferritin levels.

Cytokines

Prior studies showed that elevated serum proinflammatory cytokines was "associated with pulmonary inflammation and extensive lung damage" in patients with SARS-CoV and MERS-CoV infection[3]. Similarly, for SARS-CoV-2, baseline plasma IL1-B, IL1RA, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNF-α, and VEGF concentrations were higher in both ICU patients and non-ICU patients than in healthy adults. Among COVID-19 patients, plasma concentrations of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα were also higher in ICU patients than non-ICU patients. This suggests that disease severity is associated with a cytokine storm[3]. Another study supported the finding of higher levels of "pro-inflammatory cytokines (TNF-α, IL-1 and IL-6), and chemokines (IL-8)" among patients with severe disease as compared to mild disease[196,208]. It was noted that unlike SARS-CoV infection, secretion of T-helper-2 cytokines was noted in SARS-CoV-2 infection, although more studies should be carried out to determine the pathogenesis of COVID-19[3]. One study of the dynamic immune response following SARS-CoV-2 infection found that the expression of most inflammatory genes, except those on the IL1 pathway, "peaked after respiratory function nadir" in one severe case[209]. This appears to deviate from the "cytokine storm hypothesis". Another finding of attenuated cytokine response in patients with mild infection suggests a delay in T-cell immunity against SARS-CoV-2, which may prolong infection and potentially increase virus spread in the community[209].

Mehta suggests that "a cytokine profile resembling secondary haemophagocytic lymphohistiocytosis (sHLH) is associated with COVID-19 disease severity"[210].

In an ex-vivo study, SARS-CoV-2 infection upregulated the expression of 5 out of 13 pro-inflammatory cytokines and chemokines, as compared to 11 by SARS-CoV infection, although the SARS-CoV-2 replicated more efficiently in human lung tissue[211].

On admission, 7 out of 10 children in a study showed elevated IL-17F (of which, 5 had elevation of IL-22 as well), while 5 showed elevation of IL-6[165].

Liver Function

Alkaline Phosphatase (ALP)/Alanine aminotransferase (ALT)/Aspartate aminotransferase (AST)/Lactate Dehydrogenase/Albumin/Total bilirubin/Gamma-Glutamyl Transpeptidase

Alterations in liver function were noted on day 9 from the onset of symptoms in the first case of COVID-19 in USA[141]. Alanine aminotransferase levels on admission were higher in ICU patients (Median: 49.0 U/L, IQR 29.0-115.0) as compared to non-ICU patients (Median: 27.0 U/L, IQR 19.5-40.0)[3]. Aspartate aminotransferase levels were also elevated in 37% of patients in the study by Huang et al[3], including 62% of patients who were admitted to ICU patients. In another study[2], 35% and 28% of patients had higher than normal levels of aspartate and alanine aminotransferase respectively. The elevations were also documented in other case reports and studies[16,24,155,186]. Increased lactate dehydrogenase levels were reported in 21%[24] of patients , in particular older patients[2,203]. Another study reported that lactose dehydrogenase was associated with two-fold higher risk of severe infection (OR: 2.21; 95%CI, 1.64-2.99)[212]. Among pregnant patients[202], 33% reported elevated ALT/AST levels. In Singapore[21], baseline lactate dehydrogenase counts (Median 1684 U/L, IQR 1053-2051) were higher in ICU patients, as compared to non-ICU patients (Median 401 U/L, IQR 352-513). Similarly[21], peak lactate dehydrogenase counts during hospitalisation were higher (Median 1081 U/L, IQR 752-1460 vs Median 451 U/L, IQR 367-629). In a longitudinal study, liver function tests were monitored as markers of liver injury and their association with mortality[213]. The study reported that in severe patients, AST elevated first, followed by ALT, whereas ALP increased modestly and mostly remained in the normal range. AST abnormality was significantly associated with mortality risk compared to other liver profile indicators. A meta-analysis of 20 studies reported that deranged liver profile markers were associated with a significant increase of severe COVID-19 infection[214].

98% of patients were reported to have hypoalbuminemia[2], although this was much lower (6%) in another study[155]. Lower albumin levels[204] (< 40g/L) are said to be associated with disease progression (OR 7.353, 95% CI 1.098-50.000). Total bilirubin levels were higher than normal in 1-18% of patients[2,24,155]. A study also found elevated Gamma-glutamyl Transpeptidase (GGT) in 5 of the 14 patient cohort[215].

Kidney Function

3 studies discussed kidney function in detail[2,216,217].
Acute renal impairment is said to be a strong indicator of subsequent mortality from SARS[218]. Similarly, kidney impairment was found to be associated with mortality in patients with COVID-19[217].

The three proposed aetiologies[217] of kidney impairment in patients with COVID-19 include (1) direct cytopathic effect of SARS-CoV-2 on renal cells, following viral entry through highly expressed ACE2 in the kidney, (2) renal damage by immune complexes triggered by viral antigens, and (3) renal damage caused by “hypoxia, shock or rhabdomyolysis” as a result of viral induced cytokines and mediators. Li et al[15] suggested close monitoring of renal functions in patients with severe disease, and recommended early interventions including the use of continuous renal replacement therapy.

Proteinuria/Haematuria

In one study[15], 32 out of 51 (63%) of patients presented with proteinuria. Out of this group, based on semiquantitative analysis, approximately 75% had 1+ protein, 16% had 2+ protein, and 9% had 3+ protein. Most cases (64%) had signs of proteinuria upon admission, although no information was given on the severity of disease among study participants at admission.

Cheng et al[217] noted that 43.9% of patients had proteinuria, with 26.7% exhibiting haematuria. After adjustment for age, gender, disease severity, comorbidity and leukocyte count, proteinuria 2+ (HR 4.84, 95% CI 2.00-11.70), haematuria 1+ (HR 2.99, 95% CI 1.39-6.42), and haematuria 2+~3+ (HR 5.56, 95% CI 2.58-12.01) were found to be associated with mortality[217] and could predict severe or critical COVID-19[219].

Blood urea nitrogen (BUN)

While only 2-11% of patients were found to have elevated BUN levels in various studies[2,24,155], 27% of patients showed elevated BUN levels in the study by Li Zhen et al[15]. Among this group, values before normalization ranged from 1.7-12.8. In addition, Li found that among 43% of patients who had BUN data over time, an increase in BUN levels occurred between 2 to 10 days (median: 4 days) after hospital admission. After adjusting for age, gender, disease severity, comorbidity and leukocyte count, higher baseline BUN (HR 3.97, 95% CI 2.57-6.14) was found to be associated with mortality[217]. Patients in ICU have statistically higher BUN levels than patients who are not admitted to ICU[23].

Plasma/Serum Creatinine (Cre)

19% of patients showed elevated Cre levels in the study by Li Zhen et al[15]. Among this group, values before normalization ranged from 40-115 μmol/L. In addition, Li found that an increase in Cre levels occurred between 1 to 10 days (median: 5 days) after hospital admission. In contrast, Cheng et al[217] found that peak Cre was 91±67 μmol/L. Another study[2] found that 21% of patients had lower than normal Cre levels, and only 3% of patients had elevated Cre levels. This is echoed in studies by Guan et al[16] and Wu et al[24] which found that only a small percentage (~2.%) of patients had elevated Cre.

It was noted that Cre levels were high (209-286 μmol/L) in all three patients who died[15]. High Cre levels may predict mortality in patients infected with coronavirus[15]. After adjustment for age, gender, disease severity, comorbidity and leukocyte count, higher baseline Cre at admission (HR 2.10, 95% CI 1.36-3.26), AKI stage 2 (HR 3.51, 95% CI 1.49-8.26), and AKI stage 3 (HR 4.38, 95% CI 2.31-8.31) were found to be associated with mortality[217].

Wang et al reported that although 10.8% of patients without chronic kidney disease showed mild increase of blood urea nitrogen or serum creatinine, and 7.2% of patients showed trace or 1+ albuminuria, the patients “did not meet the diagnostic criteria of AKI”[220].

Others/Cardiology/Endocrinology/Musculoskeletal

Hypersensitive troponin I/Creatine kinase/Myoglobin

Hypersensitive troponin I levels were elevated in 12% of patients, who had a diagnosis of virus-associated cardiac injury[3], which potentially suggests viral-related myocardial injury. Results of a meta-analysis[221] showed that cardiac troponin I (cTnI) levels were significantly elevated in patients with severe SARS-CoV-2 infection as compared to those without (standardized mean difference, 25.6 ng/L, 95% CI 6.8–44.5). Patients with elevated cardiac troponin T levels (TnT) and underlying cardiovascular disease were found to have higher mortality rates (69.4%), as compared to those with elevated TnT levels without CVD (37.5%), those with normal TnT levels with CVD (13.3%), and those with normal TnT levels and no underlying CVD (7.5%)[222]. Similar finding was reported in another study where initial cardiac Troponin I (cTnI), senior age, comorbidities, and elevated C-reactive protein (CRP) were predictors of myocardial injury which was highly associated with in-hospital death[223].

Elevated creatine kinase (>200 U/L) was noted in a case in the USA on days 7 and 9 of illness[141], and in approximately 8[155]-20[24]% of patients based on studies in China, although both elevated and depressed creatine kinase levels were reported among a group of 99 patients[2]. Myoglobin levels were elevated in 15% of patients in one study[2].

Viral Load and Seroconversion

SARS-CoV-2 viral loads in two patients, were said to be high early after the onset of symptoms[224]

Among the first 18 COVID-19 patients in Singapore[9], viral shedding from the nasopharynx is said to last a median of 12 days (range 1-24 days), with viral shedding for 7 or more days in 83% of patients. Viral loads are said to peak within the initial days of the presentation symptoms[9], around 5-6 days after symptom onset[225], and decline thereafter[9]. Another study noted that salivary viral load peaked in the first week after symptom onset and declined with time thereafter (–0·15, 95% CI –0·19 to –0·11). It was noted that older age was associated with a higher viral load (Spearman's ρ=0·48, 95% CI 0·074–0·75; p=0·020)[226]. Based on testing using RT-PCR cycle threshold (Ct) and droplet digital PCR (ddPCR), viral loads are said to be higher in the "early and progressive stages" (46800 ± 17272) as compared to the recovery stage (1252 ± 1027)[227]. A recent preprint study has provided evidence that the SARS-CoV-2 acquired mutations capable of changing its pathogenicity substantially due to the variation in cytopathic effects and viral load between viral isolates[228].

Severe cases have higher viral loads (60 times the mean for mild cases), and longer virus shedding periods (100% positive tests at 10 day post-onset vs 10% remaining positive at 10 day post-onset for mild cases)[229]. The time to PCR conversion is longer in patients admitted in ICU compared to the others[124]. Amongst survivors, the median duration of viral shedding was 20·0 days (IQR 17·0–24·0); viral shedding lasted till death in non-survivors[230]. In another study of 161 patients, the median duration from exposure to source of infection and last positive test for COVID-19 was 20 days (IQR 16- 26 days) among patients with non-severe disease, and 27 days (IQR 19 −33 days) in patients with severe disease[231].

The longest observed duration of viral shedding in survivors was 37 days[230]. In a case series, three patterns were noted: (1) high nasopharyngeal titres of virus within 24 hours of illness onset in paucisymptomatic individuals (2) decreasing viral loads from the nasopharynx in spite of worsening of respiratory conditions after approximately 10 days following mild symptoms, and (3) persistently high viral load in the upper respiratory tract in a patient with critical illness[232]. Patients with prolonged viral shedding were reported to be older (p = 0.011) and have comorbidities such as diabetes (p = 0.016) and hypertension (p = 0.006)[233].

Among 16 patients with severe disease, 69% showed prolonged viral shedding (>28 days after symptom onset) from the lower respiratory tract[234]. Lower respiratory tract specimens (sputum/ endotracheal aspirate) also had a higher viral RNA load as compared to specimens taken from nasal and throat swabs[234].

A study found that the median duration of viral shedding was 17 days (IQR 13-22) from illness onset[235]. The male gender (OR 3.24, 95% CI 1.31-8.02), delayed hospital admission of more than 5 days following illness onset (OR 1.30, 95% CI 1.10-1.54), and invasive mechanical ventilation (OR 9,88, 95% CI 1.11-88.02) were risk factors for prolonged SARS-CoV-2 RNA shedding (≥15 days)[235]. Patients with longer viral shedding took a longer time for their body

temperatures to return to normal, and had slower recovery of focal absorption on radiographs[235]. A study reported that using a system of RT-PCR, patients with cycle threshold (CT) values equal or above 34 are not contagious and can be de-isolated[236].

Male sex (odds ratio [OR], 3.24 [95% CI, 1.31–8.02]), delayed hospital admission (OR, 1.30 [95% CI, 1.10–1.54]), and invasive mechanical ventilation (OR, 9.88 [95% CI, 1.11–88.02]) were independent risk factors for prolonged SARS-CoV-2 RNA shedding. Another preprint study discovered the high expression of ACE2 in testes, and proposed the possibility of testicular viral reservoirs resulting in viral persistence in males[237]. A study comparing viral loads at different stage of disease progression found that the virus persisted longer in male patients and patients aged above 60 years[238]. The study also found that the viral load peaks in the third week in respiratory tissue of patients with severe disease compared to second week peaks in patients with mild disease.

Viral loads are higher in sputum as compared to throat swab samples[225,227]. There are reports of lower but positive viral loads in stool samples among some patients[225]. Live virus may be present in stools of COVID-19 patients who do not have diarrhoea[239]. One study did not find an association between disease severity and fecal sample viral RNA positivity[240]. In another study, viral shedding was detected in 50% of patients with stool samples (regardless of presence of diarrhoea) and one out of 12 patients with whole blood samples, but not in urine[9]. A cohort study in China found the viral persistence significantly longer in stool samples than in the respiratory and serum samples[238]. A study in Singapore found no detectable virus from tear samples taken between day 3 and 20 of symptom onset, suggesting a low risk of ocular transmission[241]. Nonetheless, a study detected SARS-CoV-2 from conjunctival swabs from 2 patients with ocular manifestations suggestive of conjunctivitis[107], and another yielded positive RT-PCR results from tear and conjunctival secretions from a patient with conjunctivitis[108]. In another study on 43 patients with severe COVID-19, RT-PCR confirmed 3 tear samples positive for viral RNA of which only one patient showed conjunctivitis[242]. A study of 10 female postmenopausal patients with severe COVID-19 disease in China did not find the presence of SARS-CoV-2 virus in vaginal fluids obtained from vaginal swab samples taken 17-40 days after onset of infection[243]. In a cohort study, 38 male patient's semen was collected for SARS-CoV-2 testing[244]. Result was positive in 4/15 (26.7%) patients in an acute stage of infection and in 2/23 (8.7%) cases who were recovering. Further studies are recommended for acquiring detailed information about virus shedding, survival time and viral load in semen.

Asymptomatic patients have returned negative PCR results on average 2 days after admission[124]. The viral load of an asymptomatic patient was said to be similar to that of other symptomatic patients in a study[224]. In a study in a nursing facility, there was said to be no statistically significant difference in the range of RT-PCR testing cycle threshold (Ct) values among COVID-19 patients with typical symptoms (fever, cough and shortness of breath) (18.6-29.2), patients with atypical symptoms (24.3-26.3), pre-symptomatic patients (15.3-37.9) and asymptomatic patients (21.9-31.0)[85]. Low Ct values are representative of large amounts of viral RNA"[85].

Recent reports have suggested that viral loads may still be detectable in a small number of patients who have been previously discharged based on 2 consecutive negative RT-PCR results and chest CT findings[245]. The Korea Centers for Disease Control and Prevention reported that 51 people tested positive again for COVID-19 after discharge, likely due to viral reactivation, although further studies are required[246]. There are reports that between 3-10%[247],

and approximately 14% of patients[248] test positive after recovery in China. In another case, viral RNA reappeared and persisted in throat swabs and in extremely high titers in saliva 40 days after showing negative on throat swabs[249]. A study in Shenzhen found that 14.5% of 172 discharged patients (after achieving two consecutive negative RT-PCR test results 24 hours apart) in Shenzhen tested positive again without symptom aggravation after 2-13 days[250]. In another study of 66 patients who had “recovered” based on negative RT-PCR test results from oropharyngeal swabs, while the majority of patients had negative stool specimens in a median of 11.0 days (IQR 9.0-16.0 days) from symptom onset, 16.7% were found to still have positive stool samples[177]. One study of 69 patients found that 4 patients had anal swabs that tested positive for SARS-CoV-2 infection after recovery, suggesting the risk for fecal-oral transmission[251]. In another case report, a patient initially found to be SARS-CoV-2 negative on plasma testing was positive for the virus from lung biopsy samples[252]. This suggests that despite disappearance from other clinical samples, SARS-CoV-2 virus may still persist in lungs. One limitation of this study as stated by authors is the inability to culture the lung biopsy sample and the resultant uncertainty on correlating positive lung sample with infectiousness.

Viral RNA in the nasopharynx and throat could be detected among children within 4 to 48 hours of symptom development[96]. Viral clearance took between 9-12 days in an analysis for three children[121], and the mean time was noted to be 12 days in another study[96]. Similar to adults, there was a detectable viral load in stool samples of an asymptomatic infant[83], but not in urine samples[83]. This applied to children of other ages as well[96]; 5 out of 6 fecal samples tested positive, although all urine and serum samples tested negative. Another preprint study suggested that younger patients, less than 14 years old, with milder symptoms seem to be re-detectable positive (RP) for the virus after discharge[253]. They showed no obvious clinical symptoms and disease progression upon re-admission. Retrospectively, the RP patients displayed fewer symptoms, more sustained remission of CT imaging and earlier RNA negative-conversion but similar plasma antibody levels during their hospitalization period as compared to those non-RP patients. In a retrospective study on 94 patients at Shenzhen hospital, mRNA clearance ratio was significantly correlated with the decline of serum creatine kinase (CK) and LDH levels[254].

Eight out of 10 pediatric patients in a study had persistent positive RT-PCR results from rectal swabs, even after they had negative RT-PCR results[165]. In another report, cases with negative pharyngeal or bronchoalveolar swabs tested positive for salivary samples[255]. In another study, sputum specimens were tested instead of nasopharyngeal and oropharyngeal swabs where sputum viral load was positively correlated with disease severity and risk progression[256].

Seropositivity was noted after 14 days or more in serum samples, for anti-NP IgG (94%), anti-NP IgM (88%) anti-RBD IgG (100%), anti-RBD IgM (94%)[226].In a study of 173 patients, less than 40% of patients had antibodies from 1 week of symptom onset, although the percentage of patients with antibodies increased to 100.0% (Ab), 94.3% (IgM) and 79.8% (IgG) 15 days from symptom onset[257]. The median time to Ab, IgM and IgG seroconversion was 11, 12 and 14 days respectively[257]. In a longitudinal study on 338 COVID-19 patients, IgG and IgG antibody levels were assessed specifically[29]. The study reported that severe and critical cases had higher IgM levels and lower IgG levels than mild cases. IgM levels were also slightly higher in deceased patients than recovered patients whereas IgG levels did not differ significantly.

Cerebrospinal fluid (CSF) was tested negative for viral particles in two patients with neurological symptoms and stroke[258]. In another study, a COVID-19 infected patient was operated for

laparoscopic appendicectomy and his peritoneal fluid and washings tested negative for COVID-19 on PCR.[259]

Complications/Morbidity

As of 25 March 2020, 48 published papers reported on the complications in patients with COVID-19. The most common complications reported by Huang et al[3] are Acute Respiratory Distress Syndrome (ARDS) (29%), RNAemia (15%), acute cardiac injury (12%), secondary infection (10%), septic shock (7%) and acute kidney injury (7%). Chen et al[2] noted that up to 33% of patients had complications, with 17% of patients developing ARDS, and a lower percentage of patients with septic shock (4%) and acute renal injury (3%). These percentages are much lower in another study of 1099 patients by Guan et al[16]– 3.4% with ARDS, 1.1% with septic shock and 0.5% with acute kidney injury. Acute kidney injury was noted in 5.1% of patients in a prospective cohort study of 701 patients[217]. Other less commonly reported complications include hepatic insufficiency[260], liver dysfunction[20], acute pancreatitis[261], renal insufficiency[260], cardiac injury[20], cardiac failure[260], disseminated intravascular coagulation[16], rhabdomyolysis[16], hyperglycemia[20],subcutaneous emphysema[262] and pneumothorax[20]. 33.3% of critically ill patients in a study in US had cardiomyopathy[263]. It was noted in a case series that hypercapnia was common in patients with ARDS on low-tidal volume ventilation[264]. A study in China found that males were more likely to have liver injury and such patients with liver injury had higher WBC counts, neutrophils, CRP, CT score and had a longer length of stay[265]. The study reported that extent of pulmonary lesions on CT was a predictor of liver function damage.

Pulmonary embolism has been reported to occur in patients with COVID-19 without notable risk factors for venous thromboembolism (VTE) [266,267]. In a study, 22.2% of ICU patients suffering from interstitial pneumonia had venous thrombotic events[268]. Pulmonary embolism may be associated with respiratory deterioration[269], elevated serum D-dimer levels[266,269,270], and hemoptysis[266]. There are also case reports of clinically significant coagulopathy and antiphospholipid antibodies (anticardiolipin IgA, anti- β_2-glycoprotein I IgA and IgG) in COVID-19 patients in ICU[271]. While there has been a report of acute necrotizing hemorrhagic encephalopathy in a patient with COVID-19, this has not been proven to be a result of the infection[272]. In a retrospective study in French ICUs, proportion of VTE was higher in patients with prophylactic anticoagulation therapy (doses of low molecular weight heparin (LMWH)) compared to patients on therapeutic anticoagulation (either LMWH, or unfractioned heparin with anti-Xa monitoring) (100% vs 56%)[273]. A study compared thrombotic risk based on ethnicity where they found that Chinese had a 3-4-fold lower risk compared to Caucasians and a significantly higher risk in African-Americans[274]. A study on 388 patients requiring ICU from Milan, Italy reported a high number of arterial, and in particular, VTE diagnosed within 24 hours admission suggesting there is an urgent need to improve on VTE diagnostic strategies and investigate further the efficacy and safely of thromboprophylaxis in COVID-19 patients[275]. A study found heparin resistance in critically ill patients[276]. Such patients had sub-optimal peak anti-Xa following therapeutic Low molecular weight Heparin (LMWH). In another study, two patients were diagnosed with acute thrombotic occlusion of infra-renal aorta extending into common iliac artery and intraluminal thrombus in descending thoracic aorta with embolic occlusion of superior mesenteric artery respectively[277]. A case series reported two patients in older age group (70 and 81-years) with pathological sinus node dysfunction most likely caused by cardiac inflammation or SARS-CoV-2 infiltration and suggested monitoring of patients for bradyarrhythmia and haemodynamic instability[278]. In another case series of five patients, 4/5

COVID-19 patients presented with profound haemodynamic instability, cardiac arrest and acute right ventricular failure most likely caused by acute pulmonary thromboembolism though this was not definitively confirmed in all cases[279]. In Iran, a COVID-19 female patient suffering from severe dyspnea reportedly had a large saddle pulmonary embolism in the main pulmonary artery (MPA), right pulmonary artery (RPA) and left pulmonary artery (LPA) on a computed tomography angiography (CTA)[280]. In another case report, a 64-year-old-male with no risk factors for cardiovascular disease presented with ST-elevation myocardial infarction (STEMI). A coronary angiography revealed a critical thrombotic stenosis of proximal right coronary artery as well as a non-occlusive filling defect in left anterior descending (LAD) artery[281].

Complications are more common in severe cases at baseline compared to non-severe cases[16], with 2.9% of severe patients requiring extracorporeal membrane oxygenation and 5.2% of severe patients requiring continuous renal-replacement therapy, as compared to 0% of non-severe patients. In a single study that has yet to be peer reviewed, renal dysfunction was noted in up to 63% of patients in a study of 59 patients, of which 28 were severe cases[15].

Co-infections including other viral, bacterial and fungal infections were not commonly found among patients with COVID-19[2]. Similar findings were reported in Singapore where rate of co-infection with SARS-CoV-2 was 1.4%.[282] The study conducted at one of the major hospitals in Singapore reported low in-hospital mortality and proportion of patients requiring invasive ventilation (1%) in comparison with community-acquired respiratory virus infections over the same period. A study of 92 SARS-CoV-2 positive patients in Shenzhen, China found that common respiratory viruses were concurrently detected in 6 patients (3.2%), with 4 of them testing positive for two or more of the detected viruses[283]. Based on a case series of 5 patients, it was noted that patients with a concurrent influenza infection may also report symptoms of nasal tampon and pharyngalgia, and authors suggested that there is no clear evidence of more severe illness in patients with co-infection[284]. None of the first 18 patients in Singapore developed concomitant infections[9]. It has been highlighted that SARS-CoV-2 infections can occur concurrently with dengue virus infections[285].

Huang et al[3] reported that the median time from onset of illness “to Acute Respiratory Distress Syndrome was 9.0 days (IQR 8.0–14.0), to mechanical ventilation was 10.5 days (IQR 7.0–14.0), and to ICU admission was 10.5 days (IQR 8.0-17.0)”. Liu et al[22] reported that the median time from initial symptoms to severe symptoms (including dyspnea and acute respiratory distress syndrome) was 7 days (range 1-20 days), while Wang et al[23] reported that the median time to dyspnea and ARDS were 5.0 (IQR 1.0-10.0) and 8.0 (IQR 6.0-12.0) days respectively.

In Singapore[9], 6 of 18 initial patients (33%) had oxygen saturation levels that fell below 92% and required oxygen supplementation. In a study of 149 patients in Wenzhou, China[155], 9.4% of patients had oxygen saturation levels that fell below 95% while 15.4% of patients had a lowered partial pressure of oxygen. Supplemental oxygen was used in 41%[16] to 76%[2] of patients. 3 of 80 patients had severe symptoms in a study in Jiangsu[24], while 17.6% of 262 patients were classified as “severe”, with dyspnea or respiratory failure in Beijing[26]. A study reported case report of two patients with COVID-19 pneumonia who presented with syndrome of inappropriate antidiuresis (SIADH).[286]

5% of 1,099 patients required intensive care unit (ICU) admission in the study by Guan et al[16], while 6.1% required mechanical ventilation[16]. This is in contrast to Huang et al’s study[3] where 13 out of 41 patients (31.7%) were admitted to ICU, and 4 patients (9.8%) required invasive mechanical ventilation, including 2 patients that required extracorporeal membrane oxygenation.

26.1% of patients received ICU care in the study by Wang et al[23]. Two of the first 18 patients in Singapore required ICU admission, of which one required mechanical ventilation[9]. Wang et al[23] noted that patients who received ICU care were more likely to be older, and have underlying comorbidities. In a case-series in Italy, Guillain-Barré Syndrome was reported in five COVID-19 positive patients, however, it is yet to be determined whether the neuromuscular deficits and axonal involvement were typical features of COVID-19[287]. In a similar case study, Guillain- Barré Syndrome was reported in a 54-year-old Caucasian female, with no previous fever or respiratory symptoms, except transient loss of smell and taste. This finding along with recent literature suggests that COVID-19 may present as immunological processes regardless of the prodromic symptoms[288]. In a separate case report Evans syndrome was observed in a 39-year-old COVID-19 positive man[289].

Potential At-Risk Populations

Pregnant Women

For pregnant mothers in late stage (third trimester) pregnancy, potential pregnancy-related complications are foetal distress and premature rupture of membrane[202]. These occurred in 2 out of 9 patients studied. Most of the 13 pregnant patients with COVID-19 in a study outside Wuhan in China[290] had mild to moderate symptoms. 10 patients underwent caesarean section, of which 5 were emergency procedures due to pregnancy complications, while 3 were discharged with an uncomplicated ongoing pregnancy after recovery from COVID-19[290]. Late pregnancy complications are said to be due to both the viral infection and hypoxia intolerance[290]. One of the 10 patients developed severe pneumonia and multiple organ dysfunction syndrome in the third trimester[290]. 46% of the cases had preterm labour between 32-36 weeks of gestation[290]. Studies suggest that there is no current evidence of vertical transmission among women with COVID-19 during late pregnancy[202,290,291]. There was a case reported of uncomplicated spontaneous vaginal delivery in a pregnant mother diagnosed with COVID-19 in US[292]. In the WHO-China joint mission report, based on findings for 147 pregnant women, pregnant women did not appear to have a higher risk of severe disease"[88]. Nonetheless, there was a case report of a 27-year-old, 30 and 3/7 week pregnant patient with COVID-19 who died in Iran following respiratory distress and multi-organ failure, and delivered a cyanotic fetus (Apgar score of 0 at 1st and 5th minute, with no change after CPR)[293]. Another maternal mortality was reported in UK caused by pulmonary embolism and basilar artery thrombosis, in a 29 year old female with pre-existing T2DM and obesity[294] A study reported miscarriage in a COVID-19 positive woman during the second trimester of pregnancy related to placental infection with SARS-CoV-2[295]. A tertiary care obstetric hospital observed a rise in incidence of hydatidiform mole (HM) coinciding with the onset of COVID-19 pandemic. Majority of these cases were in primigravidae with no other known risk factors for HM[296].

Children

None of the 9 infected infants described by Wei et al developed severe complications or required ICU care[32]. Although 1 out of 10 births studied in other parts of China beyond Wuhan ended in a still birth, the other infants had a 1-minute Apgar score of 10 and did not develop severe asphyxia[290]. While there was a case report of a neo-natal infection 36 hours after birth in China, it could not be ascertained if the case was a vertical transmission[297]. Among 19 neonates who were separated from mothers with COVID-19 immediately after birth who had their throat swabs, gastric fluid samples, urine samples and faeces samples tested, only one neonate had a

positive SARS-CoV-2 RT-PCR test result from a throat swab, which was negative upon re-testing[298]. However, another preprint systematic review reported evidence of vertical transmission of SARS-CoV-2 in 11% cases[299]. Two case reports from Wuhan, China reported presence of IgM antibodies in new-borns born to COVID-19 positive mothers immediately after birth suggesting vertical transmission[300,301]. A preprint rapid review on breastfeeding of infants born to COVID-19 positive mothers reported that SARS-CoV-2 viral nucleic acid had not been detected in breast milk and mothers taking hand hygiene precautions before breastfeeding showed that no neonate was infected with influenza during one-month follow-up[302]. The study thus concluded that the benefits of breastfeeding could outweigh the risk of COVID-19 infection in infants. However, in another study, a new-born that tested negative on discharge was tested positive at 2-week follow-up though he remained asymptomatic[303]. In this case, the mother was COVID-19 positive at discharge, however, the breast milk samples tested negative for SARS-CoV-2. The study implies that long-term follow-up and testing is necessary in new-borns. In Brussels, a preterm baby born at 26-weeks' gestation was tested SARS-CoV-2 positive following his mother[304]. At the time of publication, the baby was stable and did not show signs of severe disease.

In a Shenzhen family cluster[203], a 10-year-old was asymptomatic but confirmed infected by RT-PCR. He also had CT changes suggestive of lung infection. While there have been reports of respiratory distress among children with pre-existing medical conditions[121], the clinical course of viral infection is said to be "milder" in children than adults[81,121], with uneventful recovery[96]. In China, only 2 critical COVID-19 cases among children were reported as of early March 2020 – a 7 month old with congenital heart disease, and a 13 month old with "bilateral hydronephrosis and calculus of left kidney"[291]. These two children required invasive mechanical ventilation after deteriorating to respiratory failure rapidly following disease onset[291]. Nonetheless, another recent case report noted that an otherwise healthy 55 day old infant developed pneumonia, liver injury, and cardiac damage from SARS-CoV-2 infection[305]. The prevalence of severe and critical disease reported in confirmed and suspected COVID-19 cases in children in China was 10.6% in those aged below 1, 7.3% in children 1-5 years, 4.2% in children 6-10 years, 4.1% in children 11-15 years and 3.0% in children 16 years and above[82]. In another study at Wuhan Children's hospital, 171 children (171/1391, 12.3%) were confirmed to have SARS-CoV-2 infection[306]. Fever, cough and pharyngeal erythema were common signs and symptoms, however 15.8% (27/171) of children patients were asymptomatic and no radiological features. The study reported three patients, all with coexisting conditions, requiring intensive care support and invasive mechanical ventilation and one death, a 10-month old child with intussusception and multiorgan failure. In a cross-sectional study across North-American PICUs, 40/48 (83%) children that tested positive for SARS-CoV-2 had preexisting underlying medical conditions, 35 (73%) presented with respiratory symptoms and 18 (38%) required invasive ventilation[307]. The hospital mortality rate was 4.2%. The study concluded that severe illness in children is less frequent and early hospital outcomes are better in children than adults.

A paper in the Lancet highlighted a much higher rate of hyperinflammatory shock in children during this COVID-19 period than usual. They had 8 children presented with such symptoms in a period of 10 days (compared to the usual 1-2). These children presented with hyperinflammatory shock with multiorgan involvement, showing features similar to Kawasaki disease shock syndrome or toxic shock syndrome. All 8 children tested negative for SARS-CoV-2 while in hospital (via bronchoalveolar lavage or nasopharyngeal aspirates), but 2 of them tested positive post-discharge. Pre-hospitalization, 5 out of 8 children had contact with people

with confirmed COVID-19. This study suggests that this Kawasaki disease-like syndrome might be a novel phenomenon affecting previously asymptomatic children with SARS-CoV-2 infection[308]. An Italian cohort study also observed a high incidence of a severe form of Kawasaki disease during the SARS-CoV-2 epidemic[309]. Recent reports of children affected by severe mix of symptoms similar to Kawasaki and toxic shock syndrome with fever and cardiac involvement has been termed 'Pediatric Inflammatory Multisystem Syndrome (PIMS)' and is hypothesized to be associated with COVID-19 as some of the affected children were tested positive[310].

A French study on pediatric oncology children patients with COVID-19 suggested that children with malignancies may have a more severe form of disease requiring intensive care more often than immunocompetent children[311].

Immunocompromised Persons

COVID-19 patients with cancer are said to have a higher risk of complications, including ICU admission and death, compared to those without cancer[312]. This may be due to an increased susceptibility to infection due to immunosuppression[312]. The time to the development of complications was also shorter among patients with cancer (median: 13 days, IQR 6-15 days), as compared to those without (median: 43 days, IQR 20 days-not reached)[312]. In two COVID-19 patients who underwent lobectomies for adenocarcinoma[313], "edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells" were noted upon pathological examination of lung tissues. A cancer patient cohort study, yet to be peer-reviewed, noted that anti-tumour treatment within the previous 14 days and patchy consolidation on CT scan on admission significantly increased the risk of developing severe events such as ICU admission, mechanical ventilation and death with HR: 4.1, 95% CI 1.1-15.3 and HR 5.438, 95% CI 1.5-19.7 respectively[314]. In contrast, another preprint study conducted in London, found that the mortality rate of cancer and non-cancer patient cohort was the same, with a median age of mortality being 80 years[315].

There are a few case reports on the impact of COVID-19 on other patients who are significantly immunocompromised, eg patients with hemophilia[316], and with solid organ[317] transplants. It was noted that the clinical and laboratory signs of COVID-19 may be atypical[317], or in part masked by existing conditions in patients with immunosuppression[318]. A case report noted that a man with HIV recovered from SARS-CoV-2 infection[319], while another noted delayed antibody response in a COVID-19 patient with existing co-infection with HIV-1 and HCV[320]. A retrospective study on 47 HIV patients reported that HIV patients were at a lower risk of severe disease compared to HIV negative patients[321]. An elderly man in Japan passed away after co-infection with SARS-CoV-2 and Legionella[322]. An adult COVID-19 patient with sickle cell disease developed Acute Chest Syndrome, and underwent exchange transfusion before recovery[323].

Among 34 patients who underwent elective surgeries during their incubation period of COVID-19, 15 (44.1%) were admitted to ICU, and 7 patients (20.5%) died[324]. ICU patients were more likely than non-ICU patients to be older, have underlying co-morbidities, have undergone more difficult surgeries, and have more severe laboratory abnormalities (eg hyperleukocytemia)[324]. Periera et al reported severe outcomes in organ transplant recipients infected by COVID-19[325,326].

Guidelines have also been published on the management of patients with medical conditions (eg hematology patients[327], patients with gastro-intestinal issues[328], cancer[329]) during this outbreak.

Predictive Factors of Disease Severity

In a multivariate analysis, Liu et al[204] found that the risk factors for disease progression 2 weeks after hospital admission include a higher age of 60 and above, with an odds ratio of 8.546 (95% CI 1.628-44.864). A history of smoking (OR 14.285, 95% CI 1.577-25.000), and high maximum body temperature at admission of 37.3°C and above (OR 8.999, 95% CI 1.036-78.147) were also associated with disease progression. A pre-print meta-analysis of 12 papers with a collective pool of 9,025 patients reported significant association between smoking and progression of COVID-19 (OR: 2.25, 95% CI 1.49-3.39)[330].

A preprint ecology study conducted in London demonstrated a strong correlation between increased air pollution and increased risk of COVID-19 transmission within London boroughs (R2>0.7)[331]. The study along with another English study[332] predicted higher risk of mortality in regions with higher NO_2 and PM2.5 pollution concentrations (R2> 0.72). The study thus showed the possibility of employing air pollution as another indicator to rapidly identify the vulnerable regions within a city. Another preprint cross-sectional study from United States, reported that after adjusting for confounders, a small increase in long-term exposure to PM2.5 leads to a large increase in COVID-19 death rate[333].

Another study[334] found that independent risk factors for disease progression include comorbidity (HR 3.9, 95% CI 1.9-7.9), age above 60 years (HR 3.0, 95% CI 1.4-6.0), lower lymphocyte levels ≤1.0 x 10^9/L (HR 3.7, 95% CI 1.8-7.8), and higher lactate dehydrogenase levels between 250-500 U/L (HR 2.5, 95% CI 1.2-5.2) and above 500 U/L (HR 9.8, 95% CI 2.8-33.8) at presentation. The study proposed the use of a CALL scoring model incorporating the risk factors, for the prediction of risk of progression of disease. Based on ROC analysis, the AUC was 0.91 (95% CI 0.6-0.94)[334].

Wu et al[335] found that the risk factors associated with the development of ARDS included older age (HR 3.26, 95% CI 2.08-5.11), neutrophilia (HR 1.14, 95% CI 1.09-1.19), and organ and coagulation dysfunction such as higher lactate dehydrogenase (HR 1.61, 95% CI 1.44-1.79) and D-dimer (HR 1.03, 95% CI 1.01-1.04). High fever (≥39 °C) was associated with a higher likelihood of ARDS development (HR 1.77, 95% CI 1.11-2.84).

Chen et al[124] found that older age (OR 1.06, 95% CI 1.00-1.12) and lower CD4 T cell counts (OR 0.55 per 100 cells/uL increase, 95% CI 0.33-0.92) were independently associated with ICU admission. In a meta-analysis[30], the proportion of ICU patients with hypertension was higher than that among non-ICU patients (RR 2.03, 95% CI 1.54-2.68). This is similar for cardio-cerebrovascular diseases (RR 3.30, 95% CI 2.03-5.36). The difference in proportion of diabetics among ICU patients and non-ICU patients was not statistically significant (RR 2.21, 95% CI 0.88-5.57).

Zhang et al found that older age (OR 1.086, 95% CI 1.020-1.157) and elevated neutrophil-to-lymphocyte ratio (OR 1.490, 95% CI 1.012-2.192) was associated with severe COVID-19[336]. Another preprint Italian study on 2653 COVID-19 positive, symptomatic patients reported a higher susceptibility to infection in females compared to males in the under-50 age group with Hazard ratio (HR) 2.61 vs 1.84 per 1000, but were less susceptible than males in the over 50 age group[42]. Men were reported to have an increased risk of hospitalization (HR 1.4, 95% CI 1.2-2.1). in addition, the study reported that immigrants were more likely to be hospitalized but has no significant difference in mortality. A study focused on patients with obesity and metabolic

associated fatty liver disease (MAFLD) found that such patients exhibited a ~ 6 fold increased risk of severe COVID-19 illness[337].

After adjusting for other factors, Mo et al[130] found that patients that did not show signs of clinical and radiographical remission after ten days of hospitalization (ie “refractory” patients) were more likely to be male (OR 2.206, 95% CI 1.012-4.809) and show signs of anorexia upon admission (OR 3.921, 95% CI 1.144-13.443). In contrast, patients with signs of fever on admission were less likely to be “refractory” patients (OR 0.331, 95% CI 0.116-0.945)[130]. In addition, refractory patients tended to receive oxygen treatment (OR 3.065, 95% CI 1.189-7.897), expectorant (OR 2.688, 95% CI 1.204-6.003), corticosteroid (OR 2.232, 95% CI 1.030-4.838), lopinavir and ritonavir (OR 13.975, 95% CI 3.274-59.655), and immune enhancers (OR 8.959, 95% CI 1.724-46.564)[130].

A higher percentage of patients with GI symptoms were found to have severe/critical disease (22.97%), as compared to those without GI symptoms (8.14%)[338]. Risk factors for severe/critical disease in patients with GI symptoms include sputum production (OR 11.40, 95% CI 1.89-68.73) increased lactate dehydrogenase (OR 24.77, 95% CI 4.60-133.33) and increased glucose levels (OR 2.42, 95% CI 1.43-4.10)[338].

For haematological parameters, statistically significant differences were noted between mild and severe groups for IL-6, D-dimer, glucose, thrombin time, fibrinogen and C-reactive protein[339]. The combination of IL-6 (>24.3pg/mL) and D-dimer (>0.28µg/L) provided the highest specificity (96.4% - parallel testing) and sensitivity (93.3% - tandem testing) for early prediction of disease severity[339]. In another preprint study, mycoplasma IgG positivity was indicated to be a potential protective factor against COVID-19 infection[340]. Patients with mycoplasma iGG positivity had significant better lab indicators of disease severity and needed fewer nasal catherisation and oxygen mask (p=0.029) than those without mycoplasma IgG.

In a meta-analysis, risk factors for severe disease could include hypertension (pooled OR 2.36, 95% CI 1.46-3.83), respiratory diseases (OR 2.46, 95% CI 1.76-3.44), and cardiovascular diseases (OR 3.42, 95% CI 1.88-6.22)[341]. In a univariate analysis[162], risk factors associated with severe/critical illness, as compared to a milder condition, include older age above 50 years old (OR 7.596, 95% CI 2.664-21.659), a longer time period between symptom onset and hospitalization (Median 8.00 days, IQR 6.00-12.00 vs Median 6.00 days, IQR 3.00-8.50), the presence of co-morbidities (OR 10.607, 95% CI 2.930-38.399) in particular diabetes and COPD, and cough (OR 9.951, 95% CI 1.245-79.554), expectoration (OR 4.875, 95% CI 1.505-15.789), dyspnea (OR 10.899, 95% CI 2.073-57.198), chest pain (OR 10.857, 95% CI 1.147-102.773), and a higher body temperature (Mean 38.0°C, SD 0.9 vs 37.6°C, SD 0.6) at baseline. ICU patients (Median 54 years, IQR 47-62), were noted to be approximately a decade older than non-ICU patients (Mean 41, IQR 32-53) in Singapore[21].

A systematic review of prediction models for disease severity noted that the most commonly reported predictors of severe disease include age sex, features derived from computed tomography scans, C reactive protein, lactic dehydrogenase, and lymphocyte count. C index estimates ranged from 0.85 to 0.98 for prognostic models. However, most studies had a high risk of bias due to “non-representative selection of control patients, exclusion of patients who had not experienced the event of interest by the end of the study, and high risk of model overfitting”[342]. In another retrospective study of 276 patients diagnosed with severe/fatal pneumonia following an acute exacerbation reported that such patients were likely to have severe clinical symptoms ($p < 0.01$) and abnormal laboratory changes ($p < 0.01$). Also, the

numbers of affected lobes and CT score increased significantly. The study concluded that combining an assessment of clinical and laboratory changes with CT changes could help clinical teams with evaluating the prognosis[343].

The US Center for Disease Control and Prevention noted that individuals at higher risk of severe illness include elderly aged 65 and above, individuals living in nursing home and long-term care facilities, people with chronic lung disease, moderate-to-severe asthma, serious heart conditions, severe obesity (BMI 40 and above), underlying uncontrolled medical conditions, and/or people who are immunocompromised[344]. France has added obesity to its list of risk factors for severe disease, on top of older age, and co-morbidities including hypertension, diabetes, and coronary artery disease[345]. Based on RNA sequencing, patients with heart failure were found to have increased myocardial ACE2 expression which may result in a higher risk of heart attack[44]. Another yet to be peer reviewed study reported that lipogenesis dysregulation and the subsequently high ACE2 expression in obese patients increased risk for severe complications in COVID-19 patients[346]. In a retrospective study on 182 patients with confirmed COVID-19 in Singapore, a sub-group analysis on patients aged <60 years-old found that BMI ≥25 was significantly associated with pneumonia on chest radiograph on admission, requiring low-flow supplemental oxygen and higher serum lactate dehydrogenase levels which are all predictors of severe disease. These findings suggest the importance of a lower BMI cut-off for risk stratification in Asian populations, similar to a lower BMI cut-off in metabolic and cardiovascular diseases[347]. Furthermore, a review study reported that increasing one's aerobic capacity may improve pulmonary functions and immune functions thus conferring some protection against severe COVID-19 disease[348].

In a small longitudinal study in Germany, urine samples of COVID-19 positive patients who became very sick within few days were used to detect systemic capillary leak syndrome for predicting fluid overload, respiratory failure, severe disease requiring ICU admission and death[349]. In patients with severe outcomes the authors observed low serum antithrombin III concentrations (26-62% [reference > 70%]), severe hypoalbuminaemia (serum concentration 1.4-1.9 mg/dL [reference 3.4-5.0 mg/dL]), and urine samples positive for blood, albumin and leucocytes which suggested COVID-associated nephritis. The study concluded that screening by urine sample analysis might help predict complications.

While there were reports suggesting that ibuprofen can exacerbate COVID-19, there is no clear evidence on the effect of NSAIDs on disease progression currently[350].

A longitudinal study explored the association of serial viral loads in 308 COVID-19 positive patients that included general patients (n = 70), severe patients (n = 195) and critical patients (n =43)[351]. The study reported higher viral loads in sputum samples compared to nasal and pharyngeal swab samples. Also, the SARS-CoV-2 viral load was negatively associated with blood parameters and positively associated with cardiovascular system features. The study concluded that resurgence of virus during treatment should be treated as a warning sign of severe illness.

Mortality

The COVID-19 Situation Report[352] released by the Centre for Infectious Disease Epidemiology and Research (CIDER) provided figures of reported deaths globally. As of 8 April 2020, the total number of deaths in the world directly attributable to COVID-19 was 82,085, bringing the overall

case-fatality rate to 5.73%[352]. The case fatality rate outside of China stands at 5.83%[352]. The case fatality rate in Italy as of 17 March 2020 was 7.2%[353]. Within China, the overall case fatality rate based on an analysis of 44,672 confirmed cases was 2.3%[1]; the case fatality rate in Beijing was reported to be lower than the national average[26]. The estimated hospital fatality risk in a study published on 23 January 2020 was 14%[354]. The case fatality rate reported among 101 residents in a nursing facility in Washington was 33.7%[355]. Studies carried out earlier in the outbreak may have excluded milder cases, which may result in an overestimation of the risk of complications and mortality.

In Singapore, the majority (67%) of the first 18 reported cases had an uncomplicated disease course, with only mild, predominantly respiratory symptoms[9]. There have been no deaths attributable to COVID-19 in Singapore, although one patient with pre-existing co-morbidities, including pneumonia, is in a “very critical state” as of the report[356].

In one study, the interval between the onset of symptoms and ventilator-assisted breathing is said to be between 3 and 10 days, with rapid disease progression to multiple organ failure among patients who died[2]. An early analysis found that the median interval from first symptoms to death was 20.0 days (range 10-41) for those below 70 years old[357], and is shorter (Median: 11.5 days, range 6-19 days) among elderly aged 70 and above[357]. Linton et al[92] estimated that the mean time from reported disease onset to death is 15.0 days (95% CI 12.8-17.5). In contrast, the mean number of days from symptom onset to death was reported to be 23.7 days (95% CI 22.0-25.3) for SARS[358]. Another study[359] found that there were two peak timings for death, approximately 14 days, and 22 days from disease onset.

Factors affecting Mortality

Mortality rates are higher among elderly. As of 11 Feb 2020, the case fatality rates among all confirmed cases in China[1] is highest among those aged 80 and above (14.8%), followed by those aged 70-79 (8.0%), and those aged 60-69 (3.6%). In contrast, the case-fatality rate for individuals aged 10-39 was 0.2%. Similarly in Korea, the case fatality rates of those was 3.7% for those aged 80 and above, 3.1% for those aged 70-79, 1.1% for those aged 60-69, 0.6% or below for those aged 50-59, and 0.2% for those aged between 30-49[5]. Case fatality rates increase with age based on preliminary data from US[6]. No foetal or neonatal deaths were reported in a study involving 9 live births under caesarean section where the mothers have been diagnosed with COVID-19[202], although one study reported a stillbirth[297], and another reported death of an infant after 9 days[360]. A preprint study found a higher median R0, infection rate, critical disease rate and death rate in the European region (median age: 41.7 years) than the African region (median age: 18.9 years), indicating that countries with sizable elderly populations may experience large and rapid epidemics in absence of interventions[361]. In another preprint meta-analysis of 31,864 COVID-19-related deaths in 13 European countries (range: 27-14,381 per country), the summary proportions of persons < 40, 40-69, and ≥ 70 years of age among all COVID-19-related deaths were 0.1% (0.0-0.2%; I2 24%), 12.8% (10.3-15.6%; I2 94%), and 84.8% (81.3-88.1%; I2 96%), respectively[362].

Although death is rare among children, there were reports of a 10 month old who passed away with intussusception and multi-organ failure in Wuhan[81], and 14 year old boy from Hubei who died of COVID-19[82]. A child under the age of 18 was reported to have died in Los Angeles, USA[363], while a 16 year old girl passed away in France[364], and a 13 year old boy passed away in UK[365]. The youngest victim reported in Europe is a 12 year old girl in Belgium[366]. The

youngest reported COVID-19 related death in US is that of a six-week-old infant who died due to complications of COVID-19[367].

Mortality rates were higher in males (2.8%) than females (1.7%)[1] in a study in China, although a study in Wuhan found no statistically significant differences in gender distribution between survivors and non-survivors[359]. However, another preprint systematic review and meta-analysis comprising 32 studies reported a significantly higher mortality in males compared to females (OR 3.4, 95% CI 1.2-9.1)[368].

The presence of comorbidities[1] was associated with increased mortality, in particular for patients with pre-existing cardiovascular diseases (10.5%), diabetes (7.3%), chronic respiratory diseases (6.3%), hypertension (6.0%) and cancer (5.6%). A study showed that diabetics on metformin treatment reported reduced in-hospital mortality caused by COVID-19 compared to diabetic patients on non-metformin treatment[369]. One paper suggested that smoking is associated with mortality[2] (which contrasted with the lower than expected number of smokers among the patients with ARDS). In another study in Wuhan, 63% of patients who died had comorbidities as compared to 41% of patients who were discharged[359], and a medical history of hypertension and cardiovascular disease was associated with mortality[359]. 58.2% of patients that met a composite end point of admission to ICU, use of mechanical ventilation or death had co-morbidities, compared to 21.5% of those who did not[16]. In another study by Guan[370], the risk factors of meeting composite end points include COPD (HR 2.681, 95% CI 1.424-5.048), diabetes (HR 1.59, 95%CI 1.03-2.45), hypertension (HR 1.58, 95% CI 1.07-2.32) and malignancy (HR 3.50, 95%CI 1.60-7.64). Patients with at least one comorbidity had a HR of 1.79 (95% CI 1.16-2.77), while those with two or more co-morbidities had a HR of 2.59 (95% CI 1.61-4.17)[370]. In an early report of 775 patients in critical care in UK, mortality rates were higher in overweight individuals (BMI ≥30: 60.9%) as compared to those who were not (BMI <25: 42.1%, BMI 25-<30: 41.7%)[371].

An Italian study reported that patients with heart failure, arrhythmia, dementia, ischemic heart disease, DM and hypertension had an increased risk of death whereas patients with COPD had an increased risk of hospitalization but no increase in mortality[42].A preprint meta-analysis on sixteen papers with 3743 ICU patients and mortality outcomes indicated a significant association between acute cardiac injury, (OR: 15.94, 95% CI 2.31-110.14), hypertension (OR: 1.92, 95% CI 1.92-2.74), heart failure (OR: 11.73, 95% CI 5.17-26.60), other cardiovascular diseases (OR: 1.95, 95% CI 1.17-3.24) and overall CVDs (OR: 3.37, 95% CI 2.06-5.52) and mortality in COVID-19 patients[372]. The same study reported arrhythmia (OR: 22.17, 95%CI 4.47-110.04), acute cardiac injury (OR: 19.83, 95%CI 7.85-50.13), coronary heart disease (OR: 4.19, 95%CI 1.27-13.80), cardiovascular disease (OR: 4.17, 95%CI 2.52-6.88) and hypertension (OR: 2.69, 95%CI 1.55-4.67) were also significantly associated with ICU admission in COVID-19 patients.

A multivariable regression analysis[230] found that older age is associated with higher odds of in-hospital death (OR 1·10, 95% CI 1·03–1·17). A higher Sequential Organ Failure Assessment (SOFA) score (OR 5·65, 95% CI 2·61–12·23), and d-dimer level greater than 1 µg/mL (OR 18·42, 95% CI 2·64–128·55) on admission were also associated with higher odds of death[230].

In a bivariate Cox regression analysis of 201 patients in China[335], the risk factors associated with progression from ARDS to death included older age (HR 6.17, 95% CI 3.26-11.67), neutrophilia (HR 1.08, 95% CI 1.01-1.17), and organ and coagulation dysfunction such as higher lactate dehydrogenase (HR 1.30, 95% CI 1.11-1.52) and D-dimer (HR 1.02, 95% CI

1.01-1.04). High fever (≥39 °C) was associated with a lower risk of death (HR, 0.41; 95% CI, 0.21-0.82). Among patients with ARDS, treatment with methylprednisolone decreased the risk of death (HR 0.38, 95% CI 0.20-0.72).

More of the non-survivors (81% vs 45%) out of those who were in critical condition had developed acute respiratory distress syndrome, with significantly lower PaO_2 to FiO_2 ratios[20]. This is supported in another study that found that a higher percentage of non-survivors had acute respiratory distress syndrome (81% vs 9%), respiratory failure (85% vs 16%), acute kidney injury (31% vs 2%), and infection (16% vs 1%)[359]. Patients with cardiac injury had a higher risk of death, from the time of symptom onset (HR 4.26, 95% CI 1.92-9.49) and from hospital admission (HR 3.41, 95% CI 1.62-7.16)[373].

The mean duration from onset of symptoms to hospital admission was 9.7 days (95% CI 5.4-17.0) for survivors, as compared to 6.6 days (95% CI 5.2-8.8) for survivors in the study by Linton et al[92], although this duration may have been affected by triaging processes and hospital admission criteria. Leung et al[374] modelled that the time from symptom onset to hospital admission among 46 people who died of COVID-19 in China, is normally distributed with mean 6.2 days (95% CI 5.1-7.3). He also found that the time from hospital admission to death is log-normally distributed (mean 11 days, median 8 days (IQR 5.0-12.0))[374]. It was reported that the duration from symptom onset to death is shorter in those aged 70 and older (median 11.5 days), as compared to younger adults (median 20 days)[375].

49.0% of patients who were in critical condition (defined as signs of “respiratory failure, septic shock, and/or multiple organ dysfunction/failure”) eventually succumbed[1]. In contrast, another study that defined acute respiratory distress severity based on the American Thoracic Society guidelines found that 8.1% of patients with severe disease died, as compared to 0.1% of those with non-severe disease[16].

Non-survivors had higher white blood cell counts, lymphocyte counts, platelet counts, levels of albumin, total bilirubin, blood urea nitrogen, creatinine, cardiac troponin, myoglobin, C-reactive protein, interleukin-6 and serum ferritin[359]. While “most patients” had marked lymphopenia, non-survivors were said to develop more severe lymphopenia with time[23]. High CT scores (24.5 and above) are said to predict mortality (sensitivity 85.6%, specificity 84.5%)[98]. After adjustment for age, gender, BMI, co-morbidities, smoking status, respiratory rate, ALT levels, creatinine levels, prothrombin time and D-dimer levels, neutrophil-to-lymphocyte ratio is associated with an 8% increased risk of mortality (OR 1.08, 95% CI 1.01-1.14)[376].

A study recommended a N terminal pro B type natriuretic peptide (NT-proBNP) cut-off value of 88.64pg/mL for the prediction of in-hospital death among patients with severe COVID-19, with a sensitivity of 100% and specificity of 66.67%[377]. Another study found that peak cardiac troponin I level (HR 8.9, 95% CI 1.9-40.6) and peak NT-pro BNP levels (HR 1.2, 95% CI 1.1-1.3) are associated with a composite endpoint (requiring ICU admission, mechanical ventilation and/or ECMO, or death), although no statistically significant association was found between cardiac troponin I levels at baseline (“first test”) and the attainment of the composite endpoint[378].

A higher proportion of survivors were given antiviral agents (65%), as compared to non-survivors (31%) in the study[20]. This was echoed in Ruan et al’s study, where 67% of survivors received antivirals as compared to 49% of non-survivors[359]. Yang et al found that more of the survivors received high flow nasal cannula treatment (85% vs 50%), while more of the non-survivors received mechanical ventilation (94% vs 35%)[20]. This is in contrast to Ruan et al’s

study where the percentage of non-survivors that received high flow nasal cannula treatment (as well as mechanical ventilation) was higher than that of survivors[359]. Treatment modalities and clinical management affect mortality rates but an in-depth discussion is beyond the scope of this report.

A preprint study reported BCG vaccination to be protective by comparing the median doubling time of the death toll in four countries using “Tokyo 172-1” strain (Japan, Iraq, Malaysia, and Pakistan). The median doubling time of death toll in these four countries was significantly higher than that of the other 28 vaccinated countries (6.8 and 3.8 respectively, $p = 0.024$)[379]. Another yet to be reviewed Dutch study used modelling to investigate BCG provided protection from COVID-19[380]. The study found a positive correlation between BCG vaccination and protection from mortality by the heterologous effect of BCG vaccination conferring ‘trained immunity’ to its recipients.

Causes of Death

Based on the included studies, the reported causes of deaths are severe (bilateral) pneumonia, septic shock, respiratory failure, and sudden cardiac arrest. The three pathologic mechanisms leading to death have been said to be neutrophilia due to cytokine storms triggered by SARS-Cov-2 infection, coagulation activation, and acute kidney injury due to hypoxia and shock[23]. In one study with 68 deaths[359], 53% of patients succumbed to respiratory failure, 7% had circulatory failure, while 33% died of both causes. The study[359] highlighted the potential of death from fulminant myocarditis.

Deaths were found in one study to be consistent with Multilobular infiltration, Lymphopenia, Bacterial coinfection, Smoking history, hyperTension and Age (MuLBSTA) scores that predict mortality[2].

A study of 92 patients who died from COVID-19 found that common complications reported were ARDS (73/91), myocardial injury (31/91), liver injury (15/91), renal insufficiency (14/91), multiple organ dysfunction syndrome (MODS) (14/91), and pneumothorax (1/91)[381].

One study reported a death in spite of 6 days of IV methylprednisolone treatment[22]. Corticosteroids have been reported to have no effect on mortality rates[3], and may delay viral clearance, as with patients with SARS and MERS[3]. High corticosteroid doses in the management of influenza are associated with higher rates of mortality and hospital-acquired infection[382].

A study reported that African Americans may be at a higher risk of sudden cardiac death from COVID-19 due to variance in cardiac ion channel variance[383].

Certification and Classification of COVID-19 as Cause of Death

The World Health Organization (WHO) issued the “International Guidelines for Certification and Classification (Coding) of COVID-19 as a Cause of Death” based on ICD International Statistical Classification of Diseases on 20 April 2020[384]. The main purpose of this report is to provide standardized mortality surveillance, crucial information on population-level disease progression and assessment of public health interventions impact.

For this purpose, the official terminology, “**COVID-19**” and not ‘*coronavirus*” should be used for all certification of this cause of death. The report states that COVID-19 should be recorded as a cause of death on the medical certification for ALL decedents the disease caused, or is

assumed to have caused that contributed to death, unless there is an alternate cause of death unrelated to COVID disease (e.g. trauma). The deceased should not have completely recovered from COVID-19 preceding his death. Death in patients with chronic conditions (e.g. cancer) should be counted as pre-existing conditions that are suspected of triggering a severe form of COVID-19 disease. Based on ICD-10 codes, U07.1 COVID-19 should be used when the virus is identified and U07.2 COVID-19, when the virus is not identified i.e. probable or suspected COVID-19. Inclusion of 'probable' or 'suspected' cases without laboratory confirmation is however not consistent across all states of the United States (US)[385], and few states such as Florida have continued to report only fatalities with a confirmed positive test[386].

United Kingdom's Office of National Statistics has issued guidelines during the COVID-19 pandemic emergency relaxing some of the previous legislations concerning completion of the medical certificate cause of death (MCCD)[387]. Without diagnostic proof, the medical practitioners can specify that MCCD section "information from post-mortem may be available later". If the patient had typical COVID-19 infection symptoms, then the certifying medical practitioner needs to indicate ante-mortem investigations on MCCD. In the absence of swab, it is satisfactory to apply clinical judgement. Many other countries such as Australia[388], India[389] and European CDC[390] have released their 'Death certification' guidelines based on WHO report.

Search method

On 18 February 2020, a systematic search was carried out on PubMed to identify published studies on the clinical characteristics of COVID-19. Key words used include "clinical characteristics", "epidemiological", "COVID-19", "2019-nCov", "novel coronavirus", and "SARS-Cov-2". Only articles in English were included in our analysis. Given that most articles have yet to be indexed, hand searching of major journals, official websites and clinical trial sites, including BMJ, Lancet, and NEJM, was conducted. The search was updated on 26 February, 2 March, 9 March and 16 March 2020. Updated weekly searches from 25 March, up to 9 April 2020 focused on articles highlighting novel presentations of COVID-19, risk factors for disease susceptibility and severity, as well as clinical characteristics in vulnerable sub-populations.

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Xu Ang

Appendix A

As of 25 March 2020, the following papers on the COVID-19 outbreak were included following a systematic search.

Table 4 List of published papers included in report

No.	Author	Title	Date Published (online)
1	Wu P et al	Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan	January 23, 2020
2	Chan JF et al	A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster	January 24, 2020
3	Huang C et al	Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	January 24, 2020
4	Phan L T et al	Importation and human-to-human transmission of a novel coronavirus in Vietnam	January 28, 2020
5	Li Q et al	Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia	January 29, 2020
6	Wang W et al	Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV in Wuhan, China)	January 29, 2020
7	Chen N et al	Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study	January 30, 2020
8	Rothe C et al	Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany	January 30, 2020
9	Holshue M L et al	First case of 2019 novel coronavirus in the United States	January 31, 2020
10	Lei J et al	CT Imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia	January 31, 2020
11	Chen Z-M et al	Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus	February 2, 2020
12	Chung M et al	CT Imaging features of 2019 novel coronavirus (2019-nCov)	February 4, 2020
13	Kanne JP et al	Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: Key points for the radiologist	February 4, 2020
14	Liu P et al	2019 novel coronavirus (2019-nCoV) pneumonia	February 4, 2020
15	del Rio C et al	2019 novel coronavirus – important information for clinicians	February 5, 2020

16	Backer J A et al	Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28 January 2020	February 6, 2020
17	Ryu S et al	An interim review of the epidemiological characteristics of 2019 novel coronavirus	February 6, 2020
18	Song F et al	Emerging coronavirus 2019 n-CoV pneumonia	February 6, 2020
19	Chang D et al	Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China	February 7, 2020
20	Fang Y et al	CT manifestations of two cases of 2019 novel coronavirus (2019-nCov) pneumonia	February 7, 2020
21	Liu K et al	Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province	February 7, 2020
22	Shi H et al	Evolution of CT manifestations in a patient recovered from 2019 novel coronavirus (2019-nCoV) pneumonia in Wuhan, China	February 7, 2020
23	Wang D et al	Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China	February 7, 2020
24	Liu YX et al	Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury	February 9, 2020
25	Moran Ki	Epidemiologic characteristics of early cases with 2019-nCoV disease in Republic of Korea	February 9, 2020
26	Wang Z et al	Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment	February 9, 2020
27	Bastola A et al	The first 2019 novel coronavirus case in Nepal	February 10, 2020
28	Zhu H et al	Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia	February 10, 2020
29	Diao K et al	HRCT imaging features in representative imported cases of 2019 novel coronavirus pneumonia	February 11, 2020
30	Chen H et al	Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records	February 12, 2020
31	Duan Y et al	Pre- and posttreatment chest CT findings: 2019 novel coronavirus (2019-nCoV) pneumonia	February 12, 2020
32	Huang P et al	Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion	February 12, 2020
33	Li X et al	COVID-19 infection presenting with CT halo sign	February 12, 2020

34	Liu Y-C et al	A locally transmitted case of SARS-CoV-2 infection in Taiwan	February 12, 2020
35	Sahin A R et al	2019 novel coronavirus (COVID-19) outbreak: a review of the current literature	February 12, 2020
36	Xie X et al	Chest CT for typical 2019-nCov pneumonia: relationship to negative RT-PCR testing	February 12, 2020
37	Jiang X et al	Does SARS-CoV-2 has a longer incubation period than SARS and MERS?	February 13, 2020
38	Liu T et al	Spectrum of chest CT findings in a familial cluster of COVID-19 infection	February 13, 2020
39	Kong W et al	Chest imaging appearance of COVID-19 infection	February 13, 2020
40	Ng M-Y et al	Imaging profile of the COVID-19 Infection: radiologic findings and literature review	February 13, 2020
41	Pan F et al	Time course of lung changes on chest CT During recovery from 2019 novel coronavirus (COVID-19) pneumonia	February 13, 2020
42	Pan Y et al	Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China	February 13, 2020
43	Silverstein WK et al	First imported case of 2019 novel coronavirus in Canada, presenting as mild pneumonia	February 13, 2020
44	Zhang J et al	Therapeutic and triage strategies for 2019 novel coronavirus disease in fever clinics	February 13, 2020
45	China Centre for Disease Control	Vital Surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) – China, 2020	February 14, 2020
46	Kay F et al	The many faces of COVID-19 – spectrum of imaging manifestations	February 14, 2020
47	Liang W et al	Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China	February 14, 2020
48	Qian L et al	Severe acute respiratory disease in a Huanan seafood market worker: images of an early casualty	February 14, 2020
49	Wei M et al	Novel coronavirus infection in hospitalized infants under 1 year of age in China	February 14, 2020
50	Wu Y et al	Longitudinal CT findings in COVID-19 pneumonia: case presenting organizing pneumonia pattern	February 14, 2020
51	Lai C-C et al	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges	February 17, 2020
52	Linton NM et al	Incubation period and other epidemiological characteristics of 2019 novel coronavirus infections with right truncation: a statistical analysis of publicly available case data	February 17, 2020

53	Van Cuong L et al	The first Vietnamese case of COVID-19 acquired from China	February 18, 2020
54	Xu Z et al	Pathological findings of COVID-19 associated with acute respiratory distress syndrome	February 18, 2020
55	Fang Y et al	Sensitivity of chest CT for COVID-19: comparison to PCR	February 19, 2020
56	Huang W-H et al	2019 novel coronavirus disease (COVID-19) in Taiwan: reports of two cases from Wuhan, China	February 19, 2020
57	Kim JY et al	Viral load kinetics of SARS-CoV-2 infection in first two patients in Korea	February 19, 2020
58	Pan X et al	Asymptomatic cases in a family cluster with SARS-CoV-2 infection	February 19, 2020
59	Tang N et al	Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia	February 19, 2020
60	Zhang J et al	Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China	February 19, 2020
61	Zou L et al	SARS-CoV-2 viral load in upper respiratory specimens of infected patients	February 19, 2020
62	Xu XW et al	Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series	February 19, 2020
63	Bernheim A et al	Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection	February 20, 2020
64	She J et al	2019 novel coronavirus of pneumonia in Wuhan, China: emerging attack and management strategies	February 20, 2020
65	Sun K et al	Early epidemiological analysis of the coronavirus disease 2019 outbreak based on crowdsourced data: a population level observational study	February 20, 2020
66	Wong J et al	COVID-19 in Singapore – current experience: critical global issues that require attention and action	February 20, 2020
67	Zhu N et al	A novel coronavirus from patients with pneumonia in China, 2019	February 20, 2020
68	Bai Y et al	Presumed asymptomatic carrier transmission of COVID-19	February 21, 2020
69	Hao W	Clinical features of atypical 2019 novel coronavirus pneumonia with an initially negative RT-PCR Assay	February 21, 2020
70	Yang X et al	Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study.	February 21, 2020
71	Zu ZY et al	Coronavirus disease 2019 (COVID-19): a perspective from China	February 21, 2020

72	Meo SA et al	Novel coronavirus 2019-nCoV: prevalence, biological and clinical characteristics comparison with SARS-CoV and MERS-CoV	February 24, 2020
73	Pan Y et al	Viral load of SARS-CoV-2 in clinical samples	February 24, 2020
74	Patel A & Jernigan D	Initial public health response and interim clinical guidance for the 2019 novel coronavirus outbreak — United States, December 31, 2019–February 4, 2020	February 24, 2020
75	Qin C et al	^{18}F-FDG PET/CT findings of COVID-19: a series of four highly suspected cases.	February 22, 2020
76	Shi H et al	Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study	February 24, 2020
77	Wu Z et al	Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention	February 24, 2020
78	Xu YH et al	Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2	February, 25, 2020
79	Liang W et al	Diarrhoea may be underestimated: a missing link in 2019 novel coronavirus	February 26, 2020
80	Wei J et al	2019 novel coronavirus (COVID-19) Pneumonia: serial computed tomography findings	February 26, 2020
81	Yang W et al	Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China	February 26, 2020
82	Yoon SH et al	Chest radiographic and CT Findings of the 2019 novel coronavirus disease (COVID-19): analysis of nine patients treated in Korea	February 26, 2020
83	Huang Y et al	Clinical characteristics of laboratory confirmed positive cases of SARS-CoV- 2 infection in Wuhan, China: A retrospective single center analysis	February 27, 2020
84	Lan L et al	Positive RT-PCR test results in patients recovered from COVID-19	February 27, 2020
85	Tian S et al	Characteristics of COVID-19 infection in Beijing	February 27, 2020
86	Cai J et al	A case series of children with 2019 novel coronavirus infection: clinical and epidemiological feature	February 28, 2020
87	Guan et al	Clinical characteristics of coronavirus disease 2019 in China	February 28, 2020
88	Huang R et al	A family cluster of SARS-CoV-2 infection involving 11 patients in Nanjing, China	February 28, 2020

89	Kam K-q et al	A well infant with coronavirus disease 2019 (COVID-19) with high viral load	February 28, 2020
90	Lillie PJ et al	Novel coronavirus disease (Covid-19): the first two patients in the UK with person to person transmission	February 28, 2020
91	Ling Y et al	Persistence and clearance of viral RNA in 2019 novel coronavirus disease survivors	February 28, 2020
92	Liu W et al	Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease	February 28, 2020
93	Sun P et al	Clinical characteristics of 50466 hospitalized patients with 2019-nCoV infection	February 28, 2020
94	Tian S et al	Pulmonary pathology of early phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer	February 28, 2020
95	Xu X et al	Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2	February 28, 2020
96	Li K et al	The clinical and chest CT features associated with severe and critical COVID-19 pneumonia	February 29, 2020
97	Wu J et al	Clinical characteristics of imported cases of COVID-19 in Jiangsu province: a multicenter descriptive study	February 29, 2020
98	Lu Q and Shi Y	Coronavirus disease (COVID-19) and neonate: What neonatologist need to know	March 1, 2020
99	Bae JM	A Chinese case of COVID-19 did not show infectivity during the incubation period: based on an epidemiological survey	March 2, 2020
100	Cao Q et al	SARS-CoV-2 infection in children: transmission dynamics and clinical characteristics	March 2, 2020
101	Ruan Q et al	Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China	March 3, 2020
102	Xiong Y et al	Clinical and high-resolution CT features of the COVID-19 infection: comparison of the initial and follow-up changes	March 3, 2020
103	Yang P et al	Coronavirus disease 2019, a growing threat to children?	March 3, 2020
104	Young BE et al	Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore	March 3, 2020
105	Zhao W et al	Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: a multicentre study	March 3, 2020
106	Zhu Y et al	Clinical and CT imaging features of 2019 novel coronavirus disease (COVID-19)	March 3, 2020
107	Fan B E et al	Hematologic parameters in patients with COVID-19 infection	March 4, 2020
108	Hu Z et al	Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China	March 4, 2020

109	Jiang F et al	Review of the clinical characteristics of coronavirus disease 2019 (COVID-19)	March 4, 2020
110	Li Y & Xia L	Coronavirus disease 2019 (COVID-19): role of chest CT in diagnosis and management	March 4, 2020
111	Liu Y et al	Clinical manifestations and outcome of SARS-CoV-2 infection during pregnancy	March 4, 2020
112	Yan G et al	Covert COVID-19 and false-positive dengue serology in Singapore	March 4, 2020
113	Zhang C et al	Liver injury in COVID-19: management and challenges	March 4, 2020
114	Bermejo-Martin J F et al	Lymphopenic community acquired pneumonia as a sign of severe COVID-19 infection	March 5, 2020
115	Lake MA et al	What we know so far: COVID-19 current clinical knowledge and research	March 5, 2020
116	Liang H & Acharya G	Novel corona virus disease (COVID-19) in pregnancy: What clinical recommendations to follow?	March 5, 2020
117	Lin D et al	Co-infections of SARS-CoV-2 with multiple common respiratory pathogens in infected patients	March 5, 2020
118	Wang L et al	The clinical dynamics of 18 cases of COVID-19 outside of Wuhan, China	March 5, 2020
119	Wang Y et al	Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures	March 5, 2020
120	Xia W et al	Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults	March 5, 2020
121	Zhou S et al	CT Features of coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan, China	March 5, 2020
122	Burke R M et al 2020	Active monitoring for persons exposed to patients with confirmed COVID-19 – United States, January – February 2020	March 6, 2020
123	Yang W & Yan F	Patients with RT-PCR confirmed COVID-19 and normal chest CT	March 6, 2020
124	Zhou C et al	COVID-19 with spontaneous pneumomediastinum	March 9, 2020
125	Gupta R et al	Clinical considerations for patients with diabetes in times of COVID-19 epidemic	March 10, 2020
126	Lauer SA et al	The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases- estimation and application	March 10, 2020
127	Lippi G et al	Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19)- evidence from a meta-analysis	March 10, 2020

128	Soong YG et al	COVID-19, a clinical syndrome manifesting as hypersensitivity pneumonitis	March 10, 2020
129	Cai Hua	Sex difference and smoking predisposition in patients with COVID-19	March 11, 2020
130	Chen J et al	Clinical progression of patients with COVID-19 in Shanghai, China	March 11, 2020
131	Chen R et al	Chest computed tomography images of early coronavirus disease (COVID-19)	March 11, 2020
132	Fang L et al	Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?	March 11, 2020
133	Li B et al	Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China	March 11, 2020
134	Liu H et al	Clinical and CT imaging features of the COVID-19 pneumonia: focus on pregnant women and children	March 11, 2020
135	Liu K et al	Clinical feature of COVID-19 in elderly patients: a comparison with young and middle-aged patients	March 11, 2020
136	Mao R et al	Implications of COVID-19 for patients with pre-existing digestive diseases	March 11, 2020
137	Wang W et al	Detection of SARS-CoV-2 in different types of clinical specimens	March 11, 2020
138	Zhou F et al	Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study	March 11, 2020
139	Zhu F et al	Co-infection of SARS-CoV-2 and HIV in a patient in Wuhan city, China	March 11, 2020
140	Chen Q et al	A report of clinical diagnosis and treatment of 9 cases of coronavirus disease 2019	March 12, 2020
141	Garnier-Crussard A et al	Novel coronavirus (COVID-19) epidemic: what are the risks for older patients?	March 12, 2020
142	Ghinai I et al	First known person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA	March 12, 2020
143	Li LQ et al	2019 novel coronavirus patients' clinical characteristics, discharge rate and fatality rate of meta-analysis	March 12, 2020
144	Liu F et al	Patients of COVID-19 may benefit from sustained lopinavir-combined regimen and the increase of eosinophil may predict the outcome of COVID-19 progression	March 12, 2020
145	Liu W et al	Detection of COVID-19 in children in early January 2020 in Wuhan, China	March 12, 2020
146	Ng OT et al	SARS-CoV-2 Infection among travelers returning from Wuhan, China	March 12, 2020

147	Pongpirul W et al	Journey of a Thai taxi driver and novel coronavirus	March 12, 2020
148	Qin C et al	Dysregulation of immune response in patients with COVID-19 in Wuhan, China	March 12, 2020
149	Wang S et al	A case report of neonatal COVID-19 infection in China	March 12, 2020
150	Xing Y et al	Post-discharge surveillance and positive virus detection in two medical staff recovered from coronavirus disease 2019 (COVID-19), China, January to February 2020	March 12, 2020
151	Ye G et al	Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation	March 12, 2020
152	Zhao D et al	A comparative study on the clinical features of COVID-19 pneumonia to other pneumonias	March 12, 2020
153	Chan KW et al	An update on the epidemiological, clinical, preventive and therapeutic evidence and guidelines of integrative Chinese-Western medicine for the management of 2019 novel coronavirus disease	March 13, 2020
154	Guo Y-R et al	The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak – an update on the status	March 13, 2020
155	Henry B M	COVID-19, ECMO, and lymphopenia- a word of caution	March 13, 2020
156	Mehta P et al	COVID-19: consider cytokine storm syndromes and immunosuppression	March 13, 2020
157	Rodriguez-Morales A J et al	Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis	March 13, 2020
158	Shi F et al	2019 novel coronavirus (COVID-19) pneumonia with hemoptysis as the initial symptom: CT and clinical features	March 13, 2020
159	Sun Q et al	Evolution of computed tomography manifestations in five patients who recovered from coronavirus disease 2019 (COVID-19) pneumonia	March 13, 2020
160	Wu C et al	Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China	March 13, 2020
161	Xu T et al	Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19	March 13, 2020
162	Xu Y et al	Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding	March 13, 2020
163	Zhu W et al	Initial clinical features of suspected coronavirus disease 2019 in two emergency departments outside of Hubei, China	March 13, 2020
164	COVID-19 National Incident Room	National incident room surveillance team COVID-19, Australia, epidemiology report 7	March 14, 2020

	Surveillance Team		
165	Cheng Z et al	Clinical features and chest CT manifestations of coronavirus disease 2019 (COVID-19) in a single-center study in Shanghai China	March 14, 2020
166	Salehi S et al	Coronavirus disease 2019 (COVID-19): a systematic review of imaging findings in 919 patients	March 14, 2020
167	Su Y-J et al	Comparison of clinical characteristics of coronavirus disease (COVID-19) and severe acute respiratory syndrome (SARS) as experienced in Taiwan	March 14, 2020
168	Willan J et al	Care of haematology patients in a COVID-19 epidemic	March 15, 2020
169	Dong Y et al	Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China	March 16, 2020
170	Han H et al	Prominent changes in blood coagulation of patients with SARS-CoV-2 infection	March 16, 2020
171	Henry B et al	Laboratory abnormalities in children with novel coronavirus disease 2019	March 16, 2020
172	Ji L-N et al	Clinical features of pediatric patients with COVID-19: a report of two family cluster cases	March 16, 2020
173	Korean society of infectious diseases	Report on the epidemiological features of coronavirus disease 2019 (COVID-19) outbreak in the Republic of Korea from January 19 to March 2, 2020	March 16, 2020
174	Leung C et al	Clinical features of deaths in the novel coronavirus epidemic in China	March 16, 2020
175	Mo P et al	Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China	March 16, 2020
176	Pung R et al	Investigation of three clusters of COVID-19 in Singapore: implications for surveillance and response measures	March 16, 2020
177	Thevarajan I et al	Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19	March 16, 2020
178	Wang Z et al	Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China	March 16, 2020
179	Adhikari SP et al	Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review	March 17, 2020
180	Cui Y et al	A 55-Day-Old Female Infant Infected With 2019 Novel Coronavirus Disease: Presenting with Pneumonia, Liver Injury, and Heart Damage	March 17, 2020
181	Gao Y et al	Diagnostic Utility of Clinical Laboratory Data Determinations for Patients with the Severe COVID-19	March 17, 2020

182	Han R et al	Early clinical and CT Manifestations of Coronavirus Disease 2019 (COVID-19) Pneumonia	March 17, 2020
183	Inui S et al	Chest CT findings in cases from the cruise ship “Diamond Princess” with coronavirus disease 2019 (COVID-19)	March 17, 2020
184	Lei P	The progression of computed tomographic (CT) images in patients with coronavirus disease (COVID-19) pneumonia: The CT progression of COVID-19 pneumonia	March 17, 2020
185	Livingston E & Bucher K	Coronavirus Disease 2019 (COVID-19) in Italy	March 17, 2020
186	Qian GQ et al	Epidemiologic and Clinical Characteristics of 91 Hospitalized Patients with COVID-19 in Zhejiang, China: A retrospective, multi-centre case series	March 17, 2020
187	Qu R et al	Platelet-to-lymphocyte ratio is associated with prognosis in patients with Corona Virus Disease-19	March 17, 2020
188	Ran L et al	Risk factors of healthcare workers with corona virus disease 2019: a retrospective cohort study in a designated hospital of Wuhan in China	March 17, 2020
189	Wang Y et al	Clinical outcome of 55 asymptomatic cases at the time of hospital admission infected with SARS-COV-2 in Shenzhen, China	March 17, 2020
190	Zheng H-Y et al	Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients	March 17, 2020
191	Driggin E et al	Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) pandemic	March 18, 2020
192	Lu X et al	SARS-CoV-2 Infection in children	March 18, 2020
193	Sun Q et al	Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu province	March 18, 2020
194	Zhou Z et al	Effect of gastrointestinal symptoms on patients infected with COVID-19	March 18, 2020
195	Arentz M et al	Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state	March 19, 2020
196	Liu Y et al	Viral dynamics in mild and severe cases of COVID-19	March 19, 2020
197	Lu S et al	Alert for non-respiratory symptoms of Coronavirus Disease 2019 (COVID-19) patients in epidemic period: A case report of familial cluster with three asymptomatic COVID-19 patients.	March 19, 2020
198	Sun D et al	Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study	March 19, 2020

199	Wang Y et al	Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study	March 19, 2020
200	Wu Y et al	Prolonged presence of SARS-CoV-2 viral RNA in faecal samples	March 19, 2020
201	Ye Z et al	Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review	March 19, 2020
202	Yuan M et al	Association of radiologic findings with mortality of patients infected with 2019 novel coronavirus in Wuhan, China	March 19, 2020
203	Zheng M et al	Functional exhaustion of antiviral lymphocytes in COVID-19 patients	March 19, 2020
204	Ding Q et al	The clinical characteristics of pneumonia patients co-infected with 2019 novel coronavirus and influenza virus in Wuhan, China	March 20, 2020
205	Guillen E et al	Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation?	March 20, 2020
206	Luo S et al	Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19)	March 20, 2020
207	Zhang X et al	Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings	March 20, 2020
208	Wan S et al	Clinical features and treatment of COVID-19 patients in northeast Chongqing	March 21, 2020
209	Liu X et al	Ventilatory ratio in hypercapnic mechanically ventilated patients with COVID-19 associated ARDS	March 23, 2020
210	Luvigsson et al	Systematic review of COVID-19 in children show milder cases and a better prognosis than adults	March 23, 2020
211	Onder G et al	Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy	March 23, 2020
212	Qian G et al	A COVID-19 transmission within a family cluster by presymptomatic infectors in China	March 23, 2020
213	To K et al	Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study	March 23, 2020
214	Seah YJI et al	Assessing Viral Shedding and Infectivity of Tears in Coronavirus Disease 2019 (COVID-19) Patients	March 24, 2020
215	Yu N et al	Clinical features and obstetric and neonatal outcomes of pregnant patients with COVID-19 in Wuhan, China: a retrospective, single-centre, descriptive study	March 24, 2020
216	Lian J et al	Analysis of Epidemiological and Clinical features in older patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan	March 25, 2020
217	Mitra A et al	Erythroblastic reaction in a patient with COVID-19 infection	March 25, 2020

218	Shi S et al	Association of Cardiac Injury with Mortality in Hospitalized Patients With COVID-19 in Wuhan, China	March 25, 2020
219	Sun Y et al	Epidemiological and Clinical Predictors of COVID-19	March 25, 2020
220	Yu J et al	SARS-CoV-2 Transmission in Patients with Cancer at a Tertiary Care Hospital in Wuhan, China	March 25, 2020
221	CDC	Severe outcomes among patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12 - February 16, 2020	March 26, 2020
222	Monteleone G & Ardizzone S	Are patients with inflammatory bowel disease at increased risk for Covid-19 infection?	March 26, 2020
223	Jin X-H et al	COVID-19 in a patient with chronic lymphocytic leukaemia	April 1, 2020

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