COVID-19 Evidence Update

COVID-19 Update from SAHMRI, Health Translation SA
and the Commission on Excellence and Innovation in Health

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Predictors of admission to ICU

Executive Summary[1]

The evidence base: about patient characteristics and other prognostic indicators of severity of COVID-19 consist of 7 systematic review/meta-analysis studies, and over 40 studies and reports reporting retrospective case report data. Outcome measures were not consistent across all studies. Definitions of what constituted severe disease varied somewhat, with ICU admission and/or death included in many, but not all, definitions of 'severe'. The studies were predominantly from China.

Symptoms: Cough and fever were the most prevalent symptoms among ICU patients. **Prevalence of Dyspnoea** was significantly higher in the ICU group compared to the non-ICU group. High fever is common but is not the most important indicator of disease severity. Clinical guidelines recommend monitoring respiratory rate, heart rate, SpO2, and signs of organ failure.

Patient characteristics: Severity of COVID-19 (including critical status, ICU admission and death) was associated with **older age** (aged 60+; higher still for aged 80+), **male** gender, and **all (measured) medical comorbidities**. Four factors used to identify high-risk patients include age, lymphocyte count, oxygen supplementation and aggressive pulmonary radiographic infiltration.

Medical Comorbidities: Among comorbidities, chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), Diabetes, Chronic Kidney Disease (CKD), and hypertension were significantly predictive for both severe disease and ICU admission, with the associations stronger for ICU admission than with severe disease. Although COPD was a relatively uncommon comorbidity, even in ICU patients, **COPD** was by far the most strongly predictive comorbidity (among those measured) for ICU admission.

Laboratory reports and lung-related diagnostics: Numerous studies have investigated lab results as markers for disease severity, including ICU admission. Few laboratory results prognosticated consistently. However, it does appear that **Neutrophil/ lymphocyte ratio (NLR)**; **CRP** (elevated) and **CT** results are most consistently prognostic.

[1] *Note: we refer to the virus as SARS-CoV-2 and the disease as COVID-19*

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Clinical Guides:

National COVID-19 Clinical Evidence Taskforce (Australia) is a large coalition of peak health professional groups that will providing updated evidence-based guidance to clinicians (https://covid19evidence.net.au/#living-guidelines). Launched on 4 April 2020, the first set of recommendations cover definition of disease severity, monitoring and markers of clinical deterioration, antivirals and other disease modifying treatments and respiratory support, as well as decision flowcharts for managing patients with severe to critical COVID-19.

Kings Critical Care (UK) provides a summary of evidence to assist with the clinical management of COVID-19, documenting pathophysiology, stages of illness, prevalence of signs and symptoms; typical disease course; chest x-ray and CT findings, sensitivity of investigations, evaluation for competing diagnoses, treatment and therapy, and prognostic indicators. Epidemiological risk factors were: older age, male gender, Medical Comorbidities highlighted: (COPD, CVD, incl hypertension), cerebrovascular disease, Diabetes). Laboratory risk stratification: Prolonged or worsening lymphopenia portends poor outcome. Neutrophil/ lymphocyte ratio (NLR) appears to be a superior prognosticator when compared to either lymphopenia or C-reactive protein. Higher levels of C-reactive protein. Higher levels of troponin.

Chinese Clinical Guidelines (7th ed), report that the warning signs for severe and critically ill patients are: i) Progressive decline in the number of peripheral lymphocytes; ii) Progressive increase in the levels of peripheral inflammatory biomarkers (e.g. IL-6, CRP; iii) Progressive increase in lactic acid concentration; iv) Pulmonary lesions progress rapidly in a short time.

In **Jiangsu Province**, where outcomes were observed to be better, early recognition of high-risk and critically ill patients was reported to be important to prognosis. Four factors were used to identify high-risk patients: i) age, ii) lymphocyte count, iii) oxygen supplementation and iv) aggressive pulmonary radiographic infiltrations. High risk patients were screened twice per day and respiratory rate (RR), heart rate (HR) and SpO2 were monitored.

Documents providing guidance for clinicians

- **Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition** [1] provides information on clinical features and classifications for disease severity (dated 4 March 2020). However, these classifications have not been routinely used in studies aimed at identifying patient characteristics that predict outcomes such as ICU admission or death.
    - Clinical manifestation: Incubation period of 1-14 days, most patients show clinical symptoms in 3-7 days. Fever, dry cough and fatigue are the main manifestations.
        - Mild: clinical symptoms are mild, no sign of pneumonia on chest imaging
        - Moderate: fever and respiratory symptoms, signs of pneumonia through imaging
        - Severe: any of: shortness of breath (RR>=30 times/min), oxygen saturation <=93% at rest, Alveolar oxygen partial pressure/fraction of inspiration 02 <=300mmHg
        - Critically severe: any of: respiratory failure requiring mechanical ventilation, shock, organ failure
        - Note: critically severe cases should be admitted to ICU as soon as possible
    - Warning signals for severe and critically severe types
        - Progressive decline in the number of peripheral lymphocytes
        - Progressive increase in the levels of peripheral inflammatory biomarkers (e.g. IL-6, CRP)
        - Progressive increase in lactic acid concentration
        - Pulmonary lesions progress rapidly in a short time

- **King's Critical Care** [2] provided a summary based on the available evidence on clinical management of COVID-19 (dated 9 March 2020)
    - Pathophysiology:
        1. Acute Respiratory Distress Syndrome (ARDS);
        2. Cytokine storm
    - Stages of illness:
        1. replicative stage (innate immune response occurs but does not contain the virus; mild symptoms may occur);
        2. adaptive immunity stage (immune response reduces virus load [terminology?] but may increase inflammatory cytokines, which in some patients, may lead to tissue damage causing clinical deterioration)
    - Signs and Symptoms:
        - Fever: The frequency of fever is variable between studies (ranging from 43% to 98%)
        - Gastrointestinal presentations: up to 10% of patients can present initially with gastrointestinal symptoms (e.g. diarrhea, nausea), which precede the development of fever and dyspnea
        - "Silent hypoxemia" – some patients may develop hypoxemia and respiratory failure without dyspnea (especially elderly)
        - Physical examination is generally nonspecific.
    - Typical Disease course:
        - White blood count tends to be normal
        - Lymphopenia is common, seen in ~80% of patients
        - Mild thrombocytopenia is common (but platelets are rarely <100). Lower platelet count is a poor prognostic sign
        - Coagulation labs are generally fairly normal upon admission, although elevated D-dimer is commonly seen
        - Disseminated intravascular coagulation may evolve over time, correlating with poor prognosis
        - COVID-19 does not appear to increase the procalcitonin. Elevated procalcitonin may suggest an alternative diagnosis (e.g. pure bacterial pneumonia). This seems to track with disease severity and prognosis.
        - COVID-19 increases C-reactive protein (CRP).
    - Chest X-ray and CT Thorax
        - The typical finding is patchy ground glass opacities, which tend to be predominantly peripheral and basal. The number of involved lung segments increases with more severe disease. Over time, patchy ground glass opacities may coalesce into more dense consolidation. Infiltrates may be subtle on chest X-ray. CT scan abnormalities might emerge before symptoms.
    - Epidemiological risk factors were: older age, male gender, Medical Comorbidities highlighted: (COPD, CVD, incl hypertension), cerebrovascular disease, Diabetes).
    - Laboratory risk stratification: Prolonged or worsening lymphopenia portends poor outcome. Neutrophil/ lymphocyte ratio (NLR) appears to be a superior prognosticator when compared to either lymphopenia or C-reactive protein. Higher levels of C-reactive protein. Higher levels of troponin.
    - Implications: initial clinical symptoms are not necessarily predictive of future deterioration

- **Sun et al.** [3] (Letter to the editor; Annals of Intensive Care) investigated why outcomes were better in the province of Jiangsu and Hubei province and stated that **early recognition of high-risk and critically ill patients is important since the severity of disease is closely related to the prognosis**. In the Jiangsu province critical care was shifted forward and early screening measured:
    - Patients were screened twice per day and respiratory rate (RR), heart rate (HR) and SpO2 (room air) were monitored regularly. Once SpO2<93%, RR>30/min, HR>120/min or any signs of organ failure were observed, patients were transferred to ICU.
    - Four factors were used to identify high-risk patients: age, lymphocyte count, oxygen supplementation and aggressive pulmonary radiographic infiltrations; patients in the high risk category were monitored continuously.

Key summary from the evidence

A systematic review [4] noted the current limitations in the evidence base. Definitions of what constituted severe disease, and whether this included ICU admission was inconsistent across studies. Furthermore, studies varied in how they determined the severity of disease (e.g. on hospital admission or later as the disease progressed), the timing of measurements of symptoms (e.g. from illness onset [via recall] versus clinical presentation) and were retrospective in design.

Review studies

- A systematic review and meta-analysis of 7 published studies (all from China;[2] up to 5 March 2020) identified symptoms and comorbidities predictive of severe illness and ICU admission associated with COVID-19 [4]. Outcome measures were not consistent across all 7 studies. Only 3 of 7 studies reported on ICU admission vs non-admission [5-7]. Both disease severity (severe and critical disease vs non-severe disease) and ICU status (admission vs non-admission) are included below:
    - Cough and fever were the most prevalent symptoms in both the severe and ICU admission groups.
    - Dyspnoea was the only symptom that was significantly associated with both severe disease and ICU group, being more strongly associated with the latter. Dyspnoea is not a common symptom in COVID-19 patients, but the prevalence was much higher in the ICU group (67.2%) compared to the non-ICU group (10.2%), suggesting that its presence may help to discriminate between severe and non-severe COVID-19 cases.
    - Among comorbidities, chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), and hypertension were significantly predictive for both severe disease and ICU admission, with the associations stronger for ICU admission than with severe disease.
    - Although COPD was relatively uncommon, even in ICU patients, it was by far the most strongly predictive comorbidity for ICU admission.
- A systematic review [8] that aimed to identify risk factors for severity of disease and COVID-19 related death. Risk factors for severity of disease were assessed using 30 studies[3] which used a range of definitions and criteria for assessing severe versus non-severe cases (including critical status, ICU

[2] Note that all studies were from China, whose population may differ to others in terms of health-seeking behaviour, symptom reporting, prevalence of comorbidities and access to high quality health services

[3] Note that there was considerable heterogeneity across studies, the majority of studies were from China and were published prior to 25 February 2020.

admission and death). To avoid potential duplication of cases used in analyses from multiple sources, risk factors for death were assessed using data from a single source, the Chinese Centers for Disease Control.

- Disease severity was associated with older age (over 50 years), male gender, smoking and any comorbidity. Of the comorbidities, there were larger risks associated with CKD (Chronic Kidney Disease), COPD, cerebrovascular diseases, diabetes and hypertension.
- Lab results differed between severe and non-severe cases on: PLT; lymphocyte count; LDH; D-dimer; and CRP. The authors suggested that lymphopenia, thrombocytopenia and elevated D-dimer could act as effective predictors of the COVID-19 severity.
- COVID-19 related death was associated with older age (over 60 years of age), male gender, and any comorbidity, most notably CVD, hypertension and diabetes. The onset-to-admission time was closely related to mortality, which increased about 1.27% with every day of delay in admission.
- Other reviews based on similar studies had similar findings [9, 10].

- Two meta-analyses were conducted to identify specific biomarkers that could be used to differentiate between COVID-19 patients with or without severe disease (including ICU admission and/or death) [11, 12].
  - One meta-analysis of 4 studies found that increased procalcitonin values were associated with a higher risk of severe infection (defined as needing admission to ICU or use of mechanical ventilation). This study also showed the following laboratory abnormalities in patients with severe disease: Increased white blood cell count; neutrophil count; lactate dehydrogenase (LDH); alanine aminotransferase (AST); aspartate aminotransferase (AST); total bilirubin; creatinine; cardiac troponin; D-dimer; prothrombin time (PT); procalcitonin; C reactive protein (CRP); decreased lymphocyte count; and albumin [11].
  - The other meta-analysis of 9 studies, found that platelet count was significantly lower in patients with more severe COVID-19 (defined as either ICU admission, use of mechanical ventilation, death or progression towards ARDS), although there was high heterogeneity across studies. It was also reported that thrombocytopenia was associated with an increased risk of severe disease [12].

- Regarding smoking status being a predictor, existing studies show a trend toward an association between smoking and severity of COVID-19 [5, 13-16], but a meta-analysis that pooled the data of these individual studies found that the association was not significant [17]. This may reflect the small numbers of smokers recorded in each study. While a significant association has not been consistently demonstrated for COVID-19, smoking is known to be a major risk factor for acute respiratory tract infections in general [18]. Smoking hinders the immune system's responsiveness to infections [19], and smokers have been found to be more susceptible to influenza and more likely to have severe symptoms [18], as well as having higher mortality in the earlier MERS-CoV outbreak [20].

Other studies with similar findings as the review studies

Studies and reports published since the above reviews were conducted have found similar results.

- A report from the World Health Organization included data from 55,924 laboratory confirmed cases (as of 20 February 2020), of which 2114 had died [21].
  - Those at the highest risk for severe disease and death included people aged 60 years and over (and was highest among people over 80 years of age), males, and those with underlying

conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer.
    - Similar findings were observed in other studies, including findings related to clinical symptoms such as fatigue, shortness of breath, vomiting and lung lesions [22-31].

Additional noteworthy findings regarding patient characteristics

- As shown in the figure used in the WHO report [21], cases in all disease categories can have ICU and death as an outcome.
  Note: The size of the arrows indicates the proportion of cases who recovered or died.

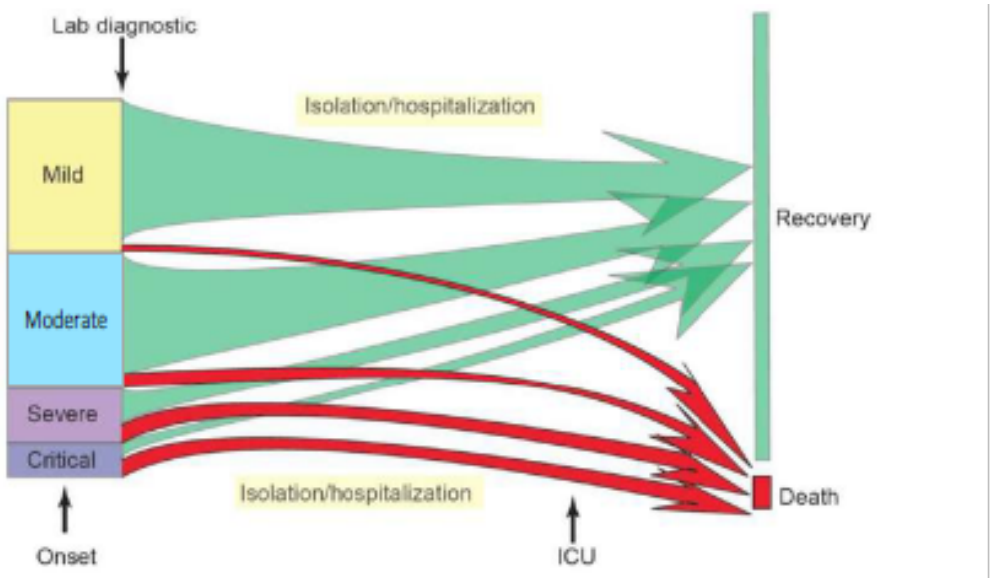

Figure 5. Pattern of disease progression for COVID-19 in China
Note: the relative size of the boxes for disease severity and outcome reflect the proportion of cases reported as of 20 February 2020. The size of the arrows indicates the proportion of cases who recovered or died. Disease definitions are described above. Moderate cases have a mild form of pneumonia.

- A study on disease progression among 78 hospitalised patients in Wuhan, China (Outcome: stabilised/improved or deteriorated) found that predictors of poor outcome were: older age, smoker, higher maximum body temperature on admission, respiratory failure, lower albumin and higher c-reactive protein [13].
- A study on 249 confirmed COVID-19 cases in Shanghai, China, comparing ICU (n=22) to non-ICU (n=227) cases found that, when variables were compared simultaneously, older age and lower CD4 T cell counts were independently associated with ICU admission, which were noted to be indicators of immunosuppression [32].
- In a study of 201 patients from China, risk factors associated with the development of ARDS and progression from ARDS to death included older age (the authors attribute this potentially to less rigorous immune response), neutrophilia, and organ and coagulation dysfunction (eg, higher lactate dehydrogenase and D-dimer). High fever (≥39 °C) was associated with higher likelihood of ARDS development and lower likelihood of death. Among patients with ARDS, treatment with methylprednisolone decreased the risk of death. In a sub-group of patients who developed ARDS, patients who ultimately died were older and had lower proportion of high fever than those who survived. They also had higher proportions of hypertension and were less likely to be treated with antiviral therapy.

In terms of most intense oxygen support, among the 44 ARDS patients who died, 86.4% received NMV, 5 11.4% received IMV, and 1 (2.3%) received IMV with ECMO [23].

- A single-centred, retrospective, observational study described the clinical course and outcomes of 52 critically ill adult patients with SARS-CoV-2 pneumonia admitted to ICU. 28 day mortality was the primary outcome with data presented as frequencies only. Critically ill patients that died were more likely to be older, have ARDS, receive mechanical ventilation, had lower PaO2/FiO2 ratio and had a history of cerebrovascular disease, than critically ill patients who survived [16].
- A retrospective analysis and case-control study, paired by age, of 116 hospitalised patients (Tongji Hospital China) confirmed COVID-19 pneumonia and SARS-CoV-2-specific immunoglobulins. 15 of 116 patients died. Serum IgM levels were negatively correlated with clinical outcome (Serum IgM levels were higher in deceased patients than mild-moderate patients but not IgG, both in the sample overall and in case-controls, paired by age) [26].
- Patients with severe COVID-19 (including ICU admission) were observed to have a higher viral load and longer period of virus-shedding compared to patients with mild COVID-19 [33].
- A single centred, retrospective study of 155 consecutive confirmed COVID-19 patients compared general vs refractory patients found that those with anorexia, males and those with no fever on admission predicted poor outcomes. It was suggested that those without fever had a slow or meagre response to the virus and were more likely to have a severe disease [30].
- A small study (n=12) showed that viral load of COVID-19 was positively associated with lung disease severity [34].

Laboratory indicators

- Numerous studies have investigated lab results as markers for disease severity, including ICU admission. Many of the analyses were done without controlling for other factors and larger samples are needed to confirm the trends that have been observed. See [13, 14, 22-24, 26-28, 30, 32, 34-37] for details.
- Key differentiators of mild-moderate and severe (including critically ill or ICU groups) identified by authors of the studies included:
    - Lower
        - Albumin (ALB)
        - Lymphocyte %
        - CD4 T cell counts
        - estimated glomerular filtration rate
        - Serum total protein
        - High-density lipoprotein cholesterol (HDL-C)
        - ApoA1
        - CD3+T%
        - CD4, 100/ml
        - CD8+T%
        - Eosinophil
        - Platelets
    - Higher
        - C-reactive protein (CRP)
        - Lactate dehydrogenase (LDH)
        - White blood cell count
        - NEU (%)
        - D-dimer

    - Aspartate aminotransferase
    - Leucocyte count

- Research is ongoing regarding cellular responses to the disease. Authors of a study of 16 patients indicated that “COVID-19, similar to some chronic infections, damages the function of CD4+ T cells and promotes excessive activation and possibly subsequent exhaustion of CD8+ T cells. Together, these perturbations of T cell subsets may eventually diminish host antiviral immunity” [38].

- Results of a study of 54 patients in China where NT-proBNP was tested “found that patients with higher NT-proBNP (above 88.64 pg/mL) level had more risks of in-hospital death. After adjusting for potential confounders in separate modes, NT-proBNP presented as an independent risk factor of in-hospital death in patients with severe COVID-19.”[39]

- A database of blood samples from 404 infected patients in Wuhan, China were screened via machine learning; three biomarkers that predicted patient survival with more than 90% accuracy were lactic dehydrogenase (LDH), lymphocyte and high-sensitivity C-reactive protein (hs-CRP). The authors commented that “in particular, relatively high levels of LDH alone seem to play a crucial role in distinguishing the vast majority of cases that require immediate medical attention.” [40]. Similar findings were obtained in another machine learning study [41].

Lung-related diagnostics

- Lesions on lungs were investigated in a number of studies, with authors from four studies noting that evaluation of CT images can accurately assess clinical severity of COVID-19 [42-45], and authors of other studies noting “white lung” appearance, diffuse lesions and increased density of lungs increasing when a patient’s condition worsened [46, 47].

Indications for ICU treatment

- Studies have reported that acute pneumonia, ARDS, sepsis and septic shock are indications for ICU treatment [48].
    - One study showed that, of ICU patients, 40% had ARDS, 6% acute kidney damage and 13% had septic shock [5].
    - Another study showed that, of ICU patients, 67% had ARDS, 29% had acute kidney damage and 29% had liver dysfunction [16].

Authors: Prof Caroline Miller, Dr Jacqueline Bowden, Jo Dono

Searchers: Nikki May & Dr Ingrid Lensink (Commission on Excellence and Innovation in Health)

Expert input: Prof Steve Wesselingh

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