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Risk factors for severe disease and poor prognosis in COVID-19 patients - A rapid review of the evidence

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COVID19 Canberra Health Service and ANU College of Health and Medicine – Predictors of severity and poor prognosis

LKIRK, 6 April 2020

Acronyms:

- CFR: case fatality rate, ARDS: acute respiratory distress syndrome, ICU: intensive care unit, WHO: World Health Organization, CDNA: Communicable Diseases Network Australia, PPE: Personal protective equipment, HCW: Healthcare worker, IMV: invasive mechanical ventilation, NIV: non-invasive ventilation, HFNC: high-flow nasal cannula, PP: prone position

Summary:

- *This summary does **not** cover the predictors of prognosis of specific conditions such as ARDS or AKI, and does not cover the use of pre-established scoring systems such as CURB-65 or APACHE II in COVID19 patients, it does not provide a comprehensive view of overall CFRs*
- Distribution of clinical severity **among symptomatic patients: 81% mild, 14% severe, 5% critical** → CFR of critical patients is around 50%
- Overall CFR is thought to be about 1.38% (adjusted for likely missed cases in China)
 - o CFR is heavily impacted by **age and comorbidities** → both the number of comorbidities and the type
- Factors that have been found to be significantly associated with disease severity and ICU admission include:
 - o Comorbidities: **Age, COPD, HTN, coronary artery disease, diabetes, CKD**
 - o **Dyspnoea** → this is the only Sx associated with disease severity and is a strong predictor of severity and ICU admission
 - o Anaemia, **elevated WCC and neutrophils**
 - o **Lymphopaenia**
 - o Elevated PTT and **D-dimer**
 - o Decreased albumin, increased ALT, increased total bilirubin, increased LDH, elevated creatinine
 - o **Elevated troponins, elevated ferritin, elevated CRP**
 - o **Increasing SOFA score and increasing CURB-65 score**

SOURCE

SUMMARY

24/02/20, Letter/comment: **Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China¹**

<https://jamanetwork.com/journals/jama/fullarticle/2762130>

- Descriptive study of 72 314 COVID19 patients from mainland China
- Severity: 81% mild, 14% severe, 5% critical
- Case fatality rate (CFR): 2.2% overall, 49.0% in critical
- Healthcare personnel infection rate: 3.8%
- Risk factors for severe disease:
 - o Increasing age 70-79yrs CFR 8.0%, ≥80yrs CFR 14.8%
 - o Cardiovascular disease CFR 10.5%
 - o Diabetes CFR 7.3%
 - o Chronic respiratory disease CFR 6.3%
 - o HTN 6.0%
 - o Cancer 5.6%

15/02/20, Article: **Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China²**

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30183-5/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30183-5/fulltext)

- Descriptive study of 41 confirmed cases of COVID19 in Wuhan - six deaths (15%)
- Sx at onset: fever 98%, cough 76%, myalgia or fatigue 44%, sputum 28%, headache 8%, haemoptysis 5%
- 55% developed dyspnoea, median duration from illness onset to dyspnoea of 8.0 days
- Median time from onset to admission of 7.0 days, 8.0 days to dyspnoea, 9.0 days to ARDS, 10.5 days for ICU admission and mechanical ventilation
- All had CT abnormalities on admission (commonly bilateral ground-glass opacities and subsegmental consolidation)
- Complications: all had pneumonia, 29% ARDS, 12% acute cardiac injury, 10% secondary infection
- 5% refractory hypoxaemia with ECMO salvage
- Factors significantly associated with ICU admission
 - o Dyspnoea
 - o Increased neutrophil count, lymphopaenia
 - o Elevated prothrombin time, elevated D-dimer
 - o Decreased albumin, increased ALT, increased total bilirubin, increased LDH

03/04/20, Guideline: **National COVID-19 Living Guidelines³**

<https://covid19evidence.net.au/#living-guidelines>

- *Consortium guidelines on a range of issues – just information on disease severity presented here*
 - o References handbook from China, and guidelines from Italy as main sources⁴
- **Mild** → not presenting with any clinical features suggesting a complicated course
 - o No symptoms or mild upper respiratory tract symptoms, stable clinical pictures
- **Moderate** → stable w/ respiratory and/or systemic Sx or signs → maintain O2 sat >92% with ≤ 4L/min O2 via NP
 - o Prostration, fever >38dC, persistent cough
 - o Clinical or radiological signs of lung involvement
 - o BUT no clinical or laboratory indicators of clinical severity or respiratory impairment
- **Severe** → if they meet any criteria:
 - o **RR ≥30/min, SpO2 ≤92% at rest, PaO2/FiO2 ratio ≤300**
- **Critical** → any of the criteria:

11/03/20, Article: **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study**⁵

[https://doi.org/10.1016/s0140-6736\(20\)30566-3](https://doi.org/10.1016/s0140-6736(20)30566-3)

30/03/20, Article: **Estimates of the severity of coronavirus disease 2019: a model-based analysis**⁶

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30243-7/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30243-7/fulltext)

02/03/20, Letter: **Critical care crisis and some recommendations during the COVID-19 epidemic in China**⁷

<https://link.springer.com/article/10.1007/s00134-020-05979-7#citeas>

07/02/20, Article: **Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China**⁸

<https://jamanetwork.com/journals/jama/fullarticle/2761044>

- **Respiratory failure:** severe respiratory failure, resp. distress, ARDS, requiring increasing resp. support or mechanical ventilation
- Hypotension or shock, impairment of consciousness, other organ failure

- ***This is probably the most comprehensive work I can find and would be worth looking at the figures...***
- Retrospective study of 191 confirmed cases of COVID19 in Wuhan – 54 deaths (2.8%)
- Factors associated with increased risk of mortality:
 - Comorbidities: Age, HTN, diabetes, coronary artery disease, COPD, chronic kidney disease
 - Sx and signs: RR>24/min, HR≥125/min, SOFA score, CURB-65 score, disease severity
 - Labs: lymphopenia, anaemia, decreased platelets, D-dimer >1ug/mL, elevated cardiac troponins, ferritin, LDH,
- Sx on admission: fever 94%, cough 79%, sputum 23%, myalgia 15%, fatigue 23%
- Disease severity: 35% severe, 11% critical
- Median time from onset to admission of 11.0 days, med. time to ventilation 14.5, med to death 18.5 days
 - ECMO used in three – none survived
 - Med time to dyspnoea 7.0
 - Med time to ARDS 12.0
- Imaging features: consolidation 59%, ground-glass opacities 71%, bilateral infiltrating pneumonia 75%
- Complications: sepsis 59%, resp fail 54%, ARDS 31%, heart failure 23%, septic shock 20%, coagulopathy 19%, AKI 15%
- Mean onset of Sx to death **17.8 day** (95% credible interval 16.9-19.2), **onset to discharge 24.7 days** (22.9 -28.1)
- **Crude CFR from China 3.67%** (3.56-3.80) → **adjusted for demography and missed cases CFR 1.38%** (1.23-1.53)
- CFR, adjusted for under-ascertainment: **<60yrs 1.01%, ≥60yrs 9.49%** (see article for full breakdown, table 1.)
 - CFR increase substantially with age → those infected due to their travel history are then likely to have a different crude CFR compared to a population wide epidemic
- ~15% developed severe pneumonia, ~6% needed non-invasive or invasive ventilatory support → massive shortfall of resources → beds, staff, monitors, machines, PPE, oxygen → lead to only about 25% of initial deaths occurring in those who were intubated (ie. Patients were dying from not receiving the support they needed)
- Reports may patients had “silent hypoxaemia” → hypoxaemia without signs of respiratory distress
- **“Our unpublished data demonstrate that severe lymphopenia and high levels of CRP correlated with the severity of hypoxaemia and predicted hospital mortality”**
- HTN was the most common comorbidity in non-survivors (48.2%), diabetes (26.7%), IHD (17.0%)
- High mortality of patients who received ECMO → total 28, 14 died, 5 weaned successfully, 9 still on ECMO
- 26.1% of hospitalised patients were admitted to ICU → ARDS (61.1%), arrhythmia (44.4%), shock (30.6%)
- Med. time to dyspnoea was 5.0 days, to hospital admission 7.0 days, ARDS 8.0 days
- Patients in the ICU were older, were more likely to have comorbidities, more likely to have dyspnoea and anorexia
- Laboratory results significantly associated with **ICU admission:**
 - Decreased lymphocyte count

27/03/20, Letter: **Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study**⁹

<https://www.nature.com/articles/s41392-020-0148-4#citeas>

03/03/20, Letter: **Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China**¹⁰

<https://link.springer.com/article/10.1007/s00134-020-05991-x#citeas>

16/03/20, Preprint: **Systematic review and meta-analysis of predictive symptoms and comorbidities for severe COVID-19 infection**¹¹

<https://www.medrxiv.org/content/10.1101/2020.03.15.20035360v1>

- Elevated D-dimer, CK-MB, LDH, ALT, ALP, creatinine, Trop I
- **Factors associated with non-survivors: increasing lymphopenia, elevated WCC and neutrophils, elevated D-dimer**
- Those in ICU → 41.7% receive NIV → 47.2 received invasive ventilation

- **Good article – worth the read**
- Tracked lymphocyte levels over time for cohorts of moderate-cured patients, severe-cured, and severe-died
 - Used **blood lymphocyte percentage (LYM%)**
- Suggests the use of two time points:
 - Day 10-12 after SYMPTOM onset
 - If LYM% >20% → MODERATE → high likelihood of cure
 - If LYM% <20% → SEVERE → still in “danger” and require high supervision
 - Day 17-19 after symptom onset → Recheck severe patients
 - If LYM% >20% → in recovery
 - If LYM% 5-20% → still in “danger” and require high supervision
 - If LYM% <5% → critically ill → high mortality rate → should be in intensive care if not already...

- Factors significantly associated with being a non-survivor were:
 - Dyspnea
 - Underlying disease/comorbidity → particularly cardiovascular disease
 - Secondary infection, ARDS, AKI
 - WWC (elevated), absolute lymphocytes (low), platelets (low), albumin (low), BUN (elevated), total bilirubin, creatinine, troponin, myoglobin, CRP, IL6, ferritin (high)

- **Appears to be a high quality SR and MA → 7 studies with 1813 COVID19 patients**
 - Comparison of ICU vs non-admission
- **Dyspnoea was the only symptom strongly predictive for severe disease (OR=3.70,95%CI:1.83-7.46) and ICU admission (OR=6.55,95%CI:4.28-10.0)**
 - Cough was associated with severe disease (OR=1.63,95%CI:1.03-2.60), but not ICU admission
 - Remaining symptoms were not significant
- Comorbidities associated with severe disease, and ICU admission were:
 - COPD (severe OR=6.42,2.44-16.9, ICU OR=17.8,6.56-48.2)
 - Cardiovascular disease (severe OR=2.70,1.52-4.80, ICU OR=4.44,2.64-7.47)
 - Hypertension (severe OR=1.97,1.40-2.77, ICU OR=3.65,2.22-5.99)

Figure 1. Clinical course of symptoms²

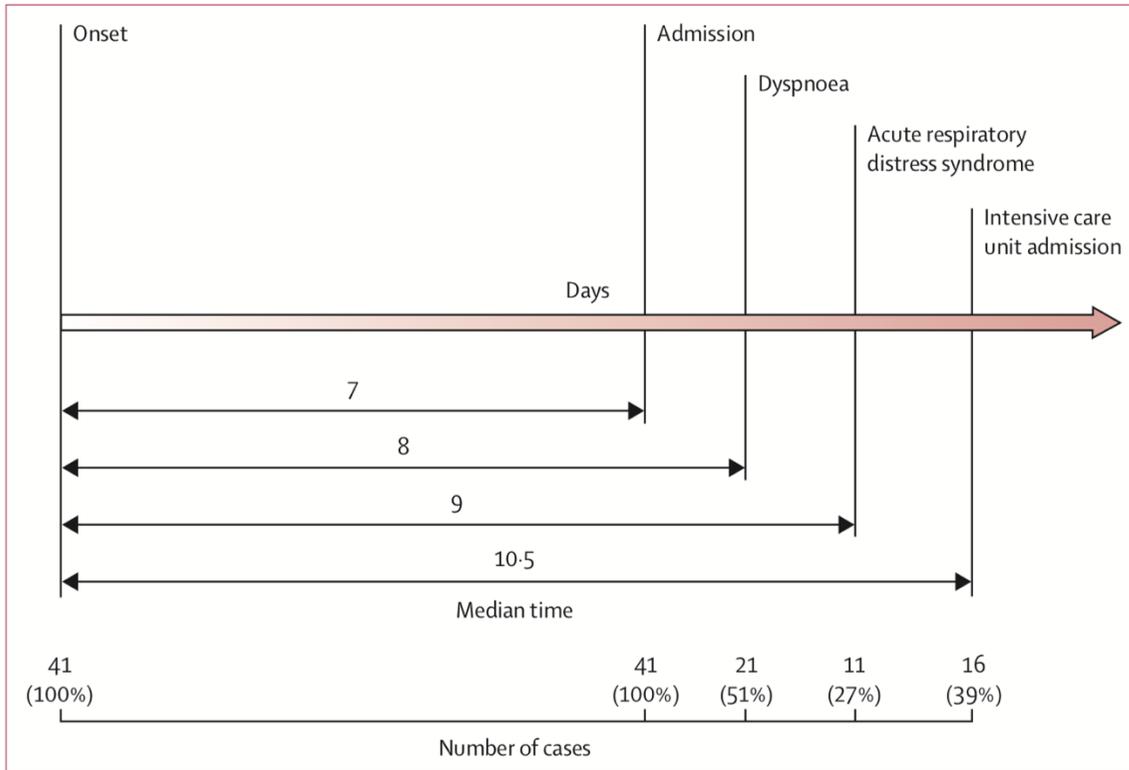


Figure 2: Timeline of 2019-nCoV cases after onset of illness

Figure 2. Clinical course of symptoms and duration in both hospitalised survivors and non-survivors⁵

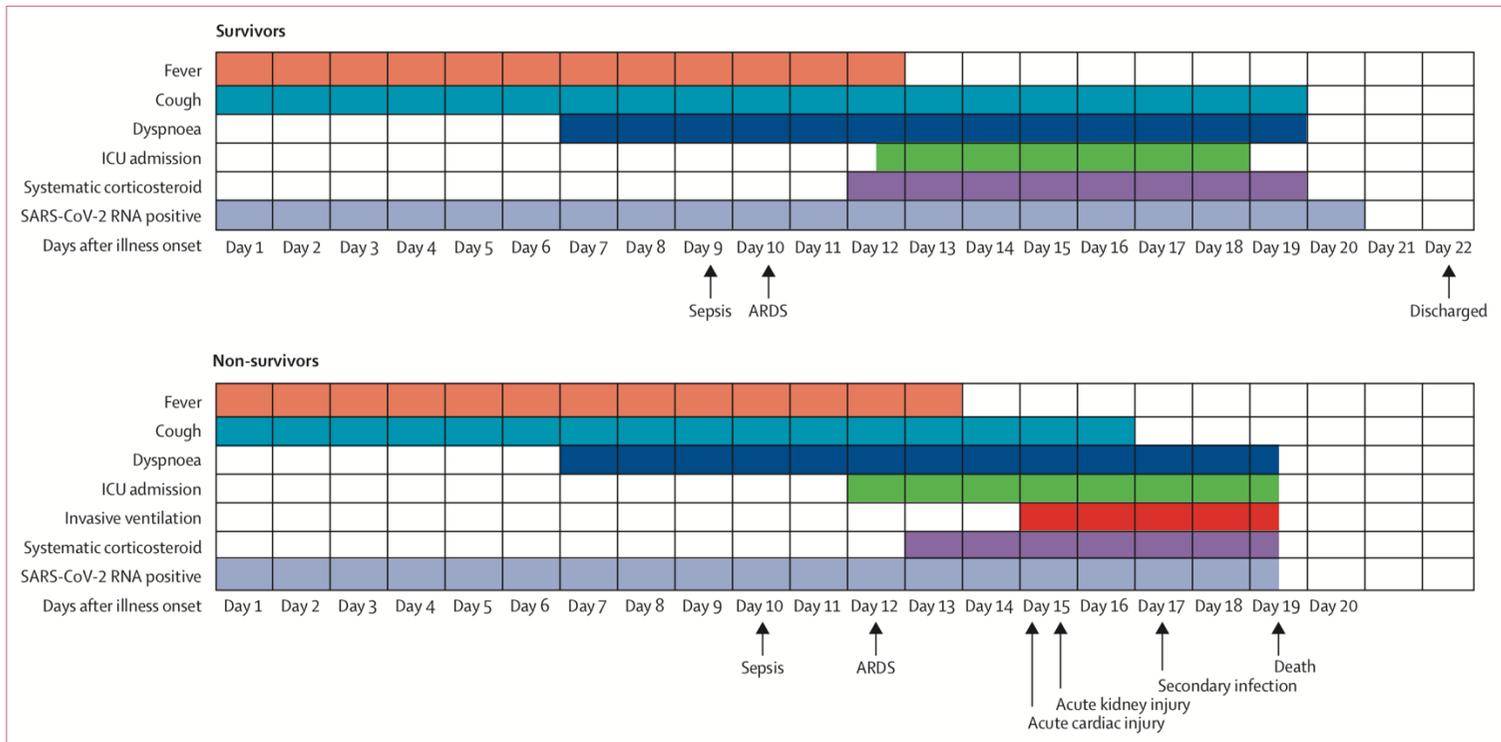


Figure 1: Clinical courses of major symptoms and outcomes and duration of viral shedding from illness onset in patients hospitalised with COVID-19

Figure shows median duration of symptoms and onset of complications and outcomes. ICU=intensive care unit. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ARDS=acute respiratory distress syndrome. COVID-19=coronavirus disease 2019.

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