

Clinical course, prognostication, and palliative care considerations for COVID-19 patients who are not ICU candidates

Author: Lawrence Chow, MD, FRCPC. Division of General Internal Medicine and Palliative Care. Vancouver General Hospital. University of British Columbia. Contact: lsjchowmd@gmail.com

PREAMBLE

As we prepare for COVID-19 cases to ramp up, the number of patients who will be managed with a non-invasive strategy, whether that be on the basis of being a poor ICU candidate, or on the basis of limited resources, will begin to rise, and we need to be prepared to manage them.

Understanding the expected clinical course and prognosis of severe COVID-19 infections will aid in patient and family counselling, determining goals of care, and appropriate timing and intensity of symptom management.

There is extremely limited published literature on the topic of patients managed with a non-invasive strategy; much of the information here been extrapolated from the published information from full-code patients, as well as anecdotal experiences circulating online and discussions with colleagues.

Dec 2020 Update

Since this initial document was prepared, there have been advances in the understanding of COVID-19 and in particular, advances in treatments, most notably the use of dexamethasone for clinically severe disease (patients requiring oxygen). Published case fatality rates from CDC and Canadian statistics have not deviated significantly from initial dataset in Wuhan, and the risks associated with severe disease remain similar (age and comorbidities).

What has changed is the clinical course in those with severe disease in the era of dexamethasone. In the randomized control trial published from the UK, the dexamethasone group show an overall risk reduction in 28 day mortality of -17% (22.9 vs 25.7%) among those requiring supplemental oxygen (7) Those on mechanical ventilation had the largest relative risk reduction of -36% (29.3 vs 41.5%) (7).

The rapid deterioration, need for mechanical ventilation, and progression to ARDS around days 8-12 seems to be less frequent and more attenuated in the era of dexamethasone. Unless there is a compelling contraindication, for any patient with COVID-19 infection requiring supplemental oxygen, the current guidelines recommend treatment with low-dose dexamethasone. Please see local guidelines on dosing and the most up to date other treatments.

What is the overall mortality rate of COVID-19 infections?

The majority (81%) of patients have mild disease, 14% develop severe symptoms requiring hospitalization, and 5% are critically ill (eg. respiratory failure, shock, or multiorgan dysfunction) (1).

Published case fatality rate is 2.3 and 7% in China and Italy, respectively. In those over the age 80, case fatality rate is 14.8 and 20.2% respectively (2).

What is the mortality rate of patients admitted to hospital?

Being hospitalized indicates severe disease and portends a worse prognosis. A retrospective Wuhan study from two hospitals in the area study revealed 54 out of 191 admitted patients died (28%) (3).

What is the clinical course and complications of severe COVID-19 infections?

A retrospective review of patients in Wuhan describes the clinical course of fulminant disease well (see figure below) (3). From anecdotal reports, this clinical course is mirrored in other centers.

After exposure, there is an approximate 5 day incubation period. Illness is then heralded by fever and dry cough, and GI symptoms (Day 0). On day 5, patients develop dyspnea and may be admitted for viral pneumonia with variable level of hypoxia. From this point, patients seem to go one of two ways, at day 10 they rapidly decompensate “in front of your eyes” with ARDS (worsening hypoxemic respiratory failure with bilateral infiltrates), +/- multiorgan dysfunction and cytokine storm, or they do not. The rate of ARDS among hospitalized patients was 20% and 41% in two different Wuhan studies (3) (4); Age greater than 65 years, diabetes mellitus, and hypertension were each associated with ARDS. 52% of the patients who developed ARDS died, despite all having received mechanical ventilation. Average duration of mechanical ventilation is 11-21 days.

For those who do not evolve into ARDS, the outcome is less clear. Ostensibly, these patients fair better but may still have severe viral pneumonia or develop COVID-19 related complications such as secondary infections, arrhythmias, acute cardiac injury, and cardiomyopathy.

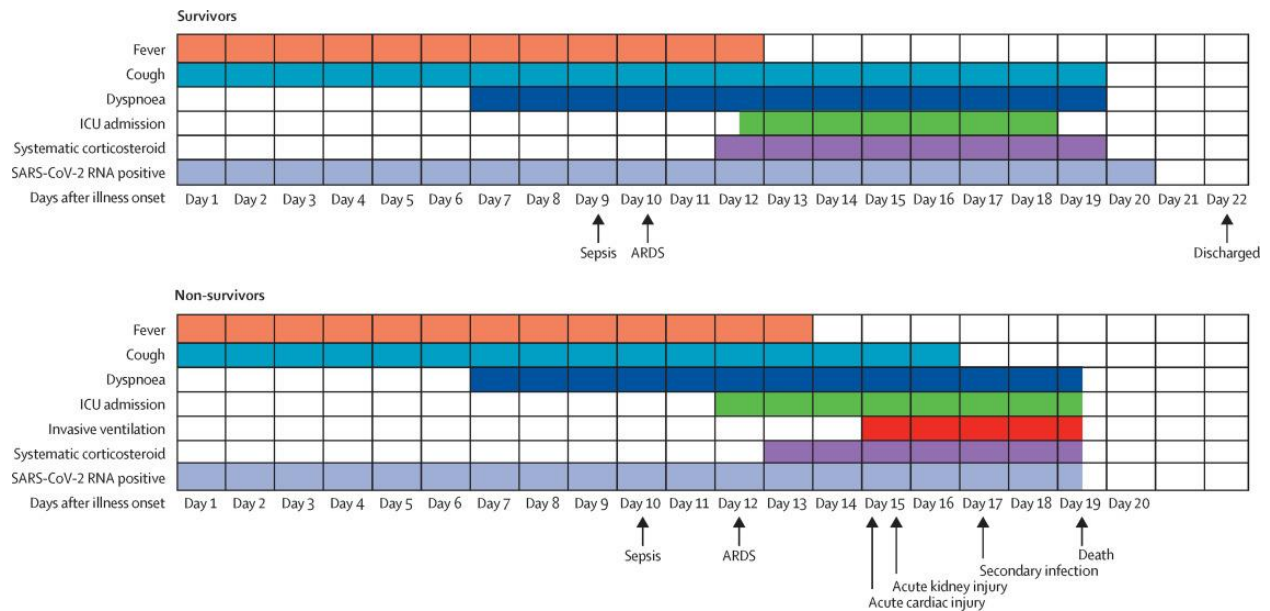


Figure 1. Clinical course amongst survivors and non-survivors from a study in Wuhan, China (3)

Are there any markers of prognostication?

A study based on two hospitals in Wuhan described increased odds of in-hospital death associated with older age, higher SOFA score, and d-dimer levels higher than 1.0ug/mL at the time of admission (3). During the clinical course, the temporal changes of the following lab markers are also associated with worse outcomes (See figure below) (3).

- Worsening lymphopenia
- Elevated LDH
- Elevated D-dimer and PT
- Elevated inflammatory markers: CRP, ferritin, IL-6
- Elevated troponin

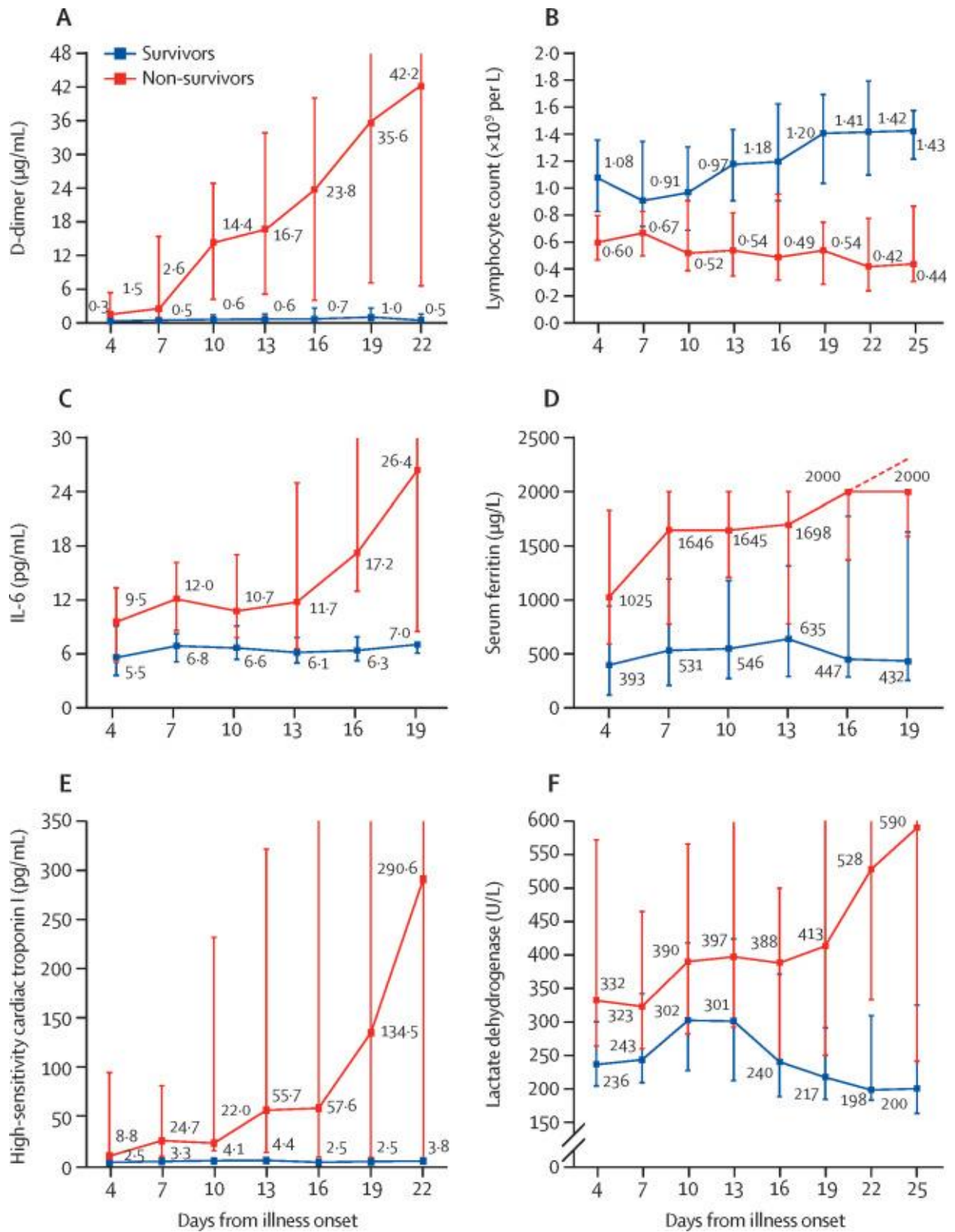


Figure 2. Temporal changes in laboratory markers from illness onset in patients hospitalised with COVID-19. Red line = non-survivors, blue line = survivors. (3)

What is the natural history/prognosis of patients who are not ICU candidates?

Not much has been published on this specific group of patients, and our local experience amongst physicians on the front lines is limited, so there is no specific data to draw upon.

Patients who are not ICU candidates are more likely to be frail, co-morbid, and elderly and are at high risk of mortality if admitted to hospital with hypoxia. That being said, a trial of supportive medical therapy is warranted if within their goals of care (ie. HFNP). Survival will depend greatly on whether or not they develop ARDS or other complications of severe disease, their pre-morbid state, and the duration of their illness.

Anecdotal experiences shared is that when patients develop ARDS, they evolve quickly, and likely die within 8-12 hours if not intubated.

When should a DNR-M3 (medical management) patient be transitioned to M1 (comfort care)?

As with any illness, goals of care based on patient and family's goals/values, quality of life factors, prognosis, and clinical judgement must be individualized and best discussed early while the patient is capable and not in distress.

While we cannot predict the clinical trajectories for all patients admitted with a non-invasive strategy, the syndrome that would denote a rapid clinical decline associated with significant burden of symptoms would be ARDS. It's important to recognize the syndrome and differentiate from other causes of worsening respiratory status, as ARDS is unlikely survivable without invasive ventilation, and a quick switch to comfort care would be most appropriate.

For all other scenarios, it would be best left to the discretion of the treating physician.

Please note, a patient does not need to be DNR M1 or develop ARDS in order to provide medications to relieve symptoms of pain and dyspnea. If a patient remains dyspneic despite medical management, strongly consider starting low dose opioids (eg. Hydromorphone 0.25-0.5mg q1h prn).

What considerations are needed for symptom management?

Please refer to the COVID-19 specific PPO for comfort care orders. Call palliative care consult service for phone advice if needed. To limit exposure and preserve man-power, an in-person consultation will likely be reserved for complex cases.

The primary symptoms to prepare at end of life would include dyspnea, cough, agitation, and delirium. In the absence of ARDS, standard terminal care orders with drugs available on a PRN basis would be appropriate. These can be changed to regular dosing if the PRN use is high.

If patients develop ARDS, or are at high risk of developing it, the management strategy should include moderate doses of regularly scheduled opioids, with adjunctive sedative medications PRN (nozinan and benzodiazepines), and rescue midazolam for refractory symptoms or respiratory crisis. VCH is currently

in the process of removing midazolam restrictions for COVID-19 patients so it can be ordered by any practitioner for end-of-life.

Other than symptom management, what considerations are needed for end-of-life management?

- Observing infection control precautions
 - o Limiting frequent nursing checks and unnecessary exposure is an important consideration. As such, comfort care medication doses should be thoughtfully considered, and err'ed on the generous side.
 - o Do not use fans or open windows in COVID-19 patient rooms for management of dyspnea
- Oxygen therapy
 - o Consider stepping the patient down from HFNP to 6L NP to reduce risk of aerosolization. If you do this, pre-medicate before stepping down. If patients are on significant high flow nasal prongs, it may be reasonable to continue on this, with no further escalation, to minimize abrupt precipitation of dyspnea.
- Family communication with patients
 - o Families will need to observe infection control precautions which may mean that they are unable to be in the same room with their loved ones. One idea from Italian palliative physicians was to purchase iPads and cell phones to be kept on the COVID wards (5).
- Counselling and psychological support for families
 - o Recognize that these are not normal times and end-of-life may be quite traumatic. Families may be at high risk of complex grief following the death of a loved one in these circumstances. Having social worker involvement and grief counselling is recommended.
- Surge mode
 - o At some point, we will all be stretched thin. We must be ready to be flexible and adapt. Remember, we are all in this together and are here to look after those who need it most.

References

1. *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.* **Wu Z, McGoogan JM.** s.l. : JAMA, 2020.
2. *Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy.* **Onder G, Rezza G, Brusaferro S.** 2020, JAMA, p. published online.
3. *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.* **Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al.** 2020, The Lancet, p. published online.
4. *Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China.* **Wu C, Chen X, Cai Y, et al.** 2020, JAMA.
5. **European Association for Palliative Care.** *From the front line: Palliative care in Bologna during the COVID-19 crisis.* [Online] March 22, 2020. <https://eapcnet.wordpress.com/2020/03/22/from-the-front-line-palliative-care-in-bologna-during-the-covid-19-crisis/>.
6. *Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China.* **Wang, Dawei, et al.** 2020, JAMA, pp. 1061-1069.
7. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med. 2020 Jul 17:NEJMoa2021436. doi: 10.1056/NEJMoa2021436