King's Critical Care – Evidence Summary
Clinical Management of COVID-19

This is not a clinical guideline or Standard Operating Procedure. This is a summary of the evidence available internationally on the management of COVID-19 disease which clinicians may find useful.

Pathophysiology

- (1) ARDS
  - The primary pathology is ARDS, characterized by diffuse alveolar damage (e.g. including hyaline membranes). Pneumocytes with viral cytopathic effect are seen, implying *direct* virus damage (rather than a purely hyper-inflammatory injury; Xu et al 2/17).
- (2) Cytokine storm
  - Emerging evidence suggests that some patients may respond to COVID-19 with an exuberant "cytokine storm" reaction (with features of bacterial sepsis or hemophagocytic lymphohistiocytosis).
  - Clinical markers of this may include elevations of C-reactive protein and ferritin, which appear to track with disease severity and mortality (Ruan 3/3/20).

Stages of illness

- There seem to be different stages of illness that patients may move through.
  - (#1) Replicative stage – Viral replication occurs over a period of several days. An innate immune response occurs, but this response fails to contain the virus. Relatively mild symptoms may occur due to direct viral cytopathic effect and innate immune responses.
  - (#2) Adaptive immunity stage – An adaptive immune response eventually kicks into gear. This leads to falling titres of virus. However, it may also increase levels of inflammatory cytokines and lead to tissue damage – causing clinical deterioration.
- This progression may explain the clinical phenomenon wherein patients are relatively OK for several days, but then suddenly deteriorate when they enter the adaptive immunity stage (e.g. Young et al. 3/3/2020).
- This has potentially important clinical implications:
  - Initial clinical symptoms aren't necessarily predictive of future deterioration. Sophisticated strategies may be required to guide risk-stratification and disposition (see below section on prognosis).
  - Anti-viral therapies might need to be deployed *early* to work optimally (during the replicative stage).

Signs and Symptoms

Symptoms near the time of presentation in various cohorts

	Guan et al. NEJM (largest cohort)	Shi et al Lancet	Yang et al. Lancet (critically ill pts)	Chen et al.	Huang et al.	Xu et al. BMJ
Constitutional						
Fever	473/1081 (43%)	18/21 (86%)	46/52 (88%)	82/99 (83%)	40/41 (98%)	48/62 (77%)
Myalgia	164/1081 (15%)		6/52 (12%)	11/99 (11%)		
Headache	150/1081 (14%)	2/21 (10%)	3/52 (6%)	8/99 (8%)	2/38 (8%)	21/62 (34%)
Upper respiratory						
Rhinorrhea	53/1081 (5%)	5/21 (24%)	3/52 (6%)	4/99 (4%)		
Sore throat	153/1081 (14%)			5/99 (5%)		
Lower respiratory						
Dyspnea	205/1081 (19%)	9/21 (43%)	33/52 (64%)	31/99 (31%)	22/40 (55%)	2/62 (3%)
Chest tightness		5/21 (24%)				
Cough	745/1081 (68%)	15/21 (71%)	40/52 (77%)	81/99 (82%)	31/41 (76%)	50/62 (81%)
Sputum	370/1081 (34%)	3/21 (14%)			11/39 (28%)	35/62 (56%)
Hemoptysis	10/1081 (1%)				2/39 (5%)	2/62 (3%)
Gastrointestinal						
Nausea/Vomiting	55/1081 (5%)	2/21 (10%)	2/52 (6%)	1/99 (1%)		
Diarrhea	42/1081 (4%)	1/21 (5%)		2/99 (2%)	1/38 (3%)	3/62 (8%)

-The Internet Book of Critical Care, by @PulmCrit

COVID-19 may cause constitutional symptoms, upper respiratory symptoms, lower respiratory symptoms, and, less commonly, gastrointestinal symptoms. Most patients will present with constitutional symptoms and lower respiratory symptoms (e.g. fever and cough).

- Fever:
  - The frequency of fever is *variable* between studies (ranging from 43% to 98% as shown in the table above). This may relate to exact methodology used in various studies, different levels of illness severity between various cohorts, or different strains of the virus present in various locations.
  - Regardless of the exact numbers – *absence of a fever does not exclude COVID-19*.
- 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 (Wang et al. 2/7/20).
- "Silent hypoxemia" – some patients may develop hypoxemia and respiratory failure without dyspnea (especially elderly)(Xie et al. 2020).
- Physical examination is generally nonspecific. About 2% of patients may have pharyngitis or tonsil enlargement (Guan et al 2/28).

Typical Disease Course

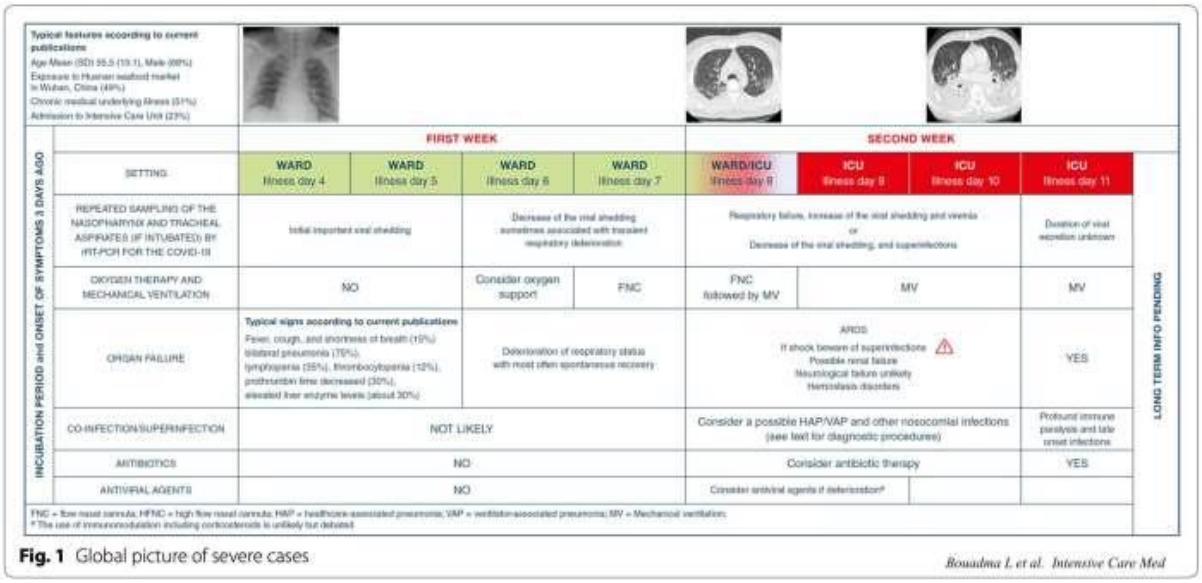


Fig. 1 Global picture of severe cases

Bouadma L et al. Intensive Care Med

Admission laboratory pattern in patients with COVID-19

	Guan et al NEJM (largest cohort)	Shi et al Lancet	Chen et al Lancet	Huang et al. Lancet	Xu et al. BMJ
WBC count	4.7 (3.5-6)	7.8 (2.5)	7.5 (4)	6.2 (4-10.5)	4.7 (3.5-5.8)
Platelet count	168 (132-207)	213 (100)	214 (79)	164 (132-263)	176 (136-215)
Lymphocyte count (normally >1)	1 (0.7-1.3)	1 (0.3)	0.9 (0.5)	0.8 (0.6-1.1)	1 (0.8-1.5)
Hemoglobin	13.4 (12-15)	12.7 (1.3)	13 (1.5)	12.6 (11.8-14)	13.7 (12.9-15.2)
ALT (U/L)		51 (25)	39 (22-53)	32 (21-50)	22 (14-34)
AST (U/L)		48 (21)	34 (26-48)	34 (26-48)	26 (20-32)
Bilirubin uM/L (normal range 5-22 uM/L)		14 (4)	15 (7)	12 (10-14)	
Creatinine (normal range up to ~80-100 uM)		68 (15)	76 (25)	74 (58-86)	72 (61-84)
Prothrombin time (normal range ~12.7-15.4)		10.5 (0.4)	11 (2)	11 (10-12.4)	
APTT (normal range ~21-37 seconds)		34 (7)	27 (10)		
Thrombin time (normal range ~15-18.5)		32 (8)			
Fibrinogen mg/dL		192 (350)			
D-dimer (mg/L) – (Nl range seems to vary?)		6.9 (1.1)	0.9 (0.5-2.8)	0.5 (0.3-1.3)	0.2 (0.2-0.5)
Creatinine kinase			85 (51-184)		
LDH (normal range up to 250 U/L)			336 (260-447)	286 (242-408)	205 (184-260)
C-Reactive Protein mg/L		61 (40)	51 (42)		
Procalcitonin	<0.5 in 95% patients		0.5 (1)	0.1 (0.1-0.1)	0.04 (0.03-0.06)
Erythrocyte sedimentation rate (ESR)			50 (23)		
Ferritin			808 (490)		

Laboratory findings are generally nonspecific. Substantial *deviation* from these values might argue *against* a diagnosis of COVID-19. However, in most cases, laboratory findings are unlikely to be tremendously helpful.

-The Internet Book of Critical Care, by @PulmCrit

White blood count

- WBC count tends to be normal.
- Lymphopenia is common, seen in ~80% of patients (Guan et al 2/28, Yang et al 2/21).
- Mild thrombocytopenia is common (but platelets are rarely <100). Lower platelet count is a poor prognostic sign (Ruan et al 3/3).

Coagulation studies

- Coagulation labs are generally fairly normal upon admission, although elevated D-dimer is commonly seen (table above).
- Disseminated intravascular coagulation may evolve over time, correlating with poor prognosis (figure below)(Tang et al. 2020).

Inflammatory markers

- **Procalcitonin**
  - COVID-19 does *not* appear to increase the procalcitonin. For example, the largest series found that procalcitonin levels were <0.5 in 95% of patients (Guan et al 2/28).
  - Elevated procalcitonin may suggest an alternative diagnosis (e.g. pure bacterial pneumonia). For patients who have been admitted with COVID-19, procalcitonin elevation may suggest a superimposed bacterial infection.
- **C-reactive protein (CRP)**
  - COVID-19 increases CRP. This seems to track with disease severity and prognosis. In a patient with severe respiratory failure and a *normal* CRP, consider non-COVID etiologies (such as heart failure).
  - Young et al. 3/3 found low CRP levels in patients not requiring oxygen (mean 11 mg/L, interquartile range 1-20 mg/L) compared to patients who became hypoxemic (mean 66 mg/L, interquartile range 48-98 mg/L).
  - Ruan et al 3/3 found CRP levels to track with mortality risk (surviving patients had a median CRP of ~40 mg/L with an interquartile range of ~10-60 mg/L, whereas patients who died had a median of 125 mg/L with an interquartile range of ~60-160 mg/L)(figure below in the section on prognosis).

Evaluation for competing diagnoses

- PCR for influenza and other respiratory viruses (e.g. RSV) may be helpful. Detection of other respiratory viruses doesn't prove that the patient *isn't* co-infected with COVID-19. However, an alternative explanation for the patient's symptoms might reduce the index of suspicion for COVID-19 *substantially*.
- Conventional viral panels available in some hospitals will test for “coronavirus.”
  - This test does *not* work for COVID-19!
  - This PCR test for “coronavirus” is designed to evaluate for four coronaviruses which usually cause mild illness.
  - Ironically, a positive conventional test for “coronavirus” actually makes it *less likely* that the patient has COVID-19.
- Blood cultures should be performed as per usual indications.

Sensitivity of investigations

- Sensitivity compared to CT scans
  - In a case series diagnosed on the basis of clinical criteria and CT scans, the sensitivity of RT-PCR was only ~70% (Kanne 2/28).
  - Sensitivity varies depending on assumptions made about patients with conflicting data (e.g. between 66-80%; figure above)(Ai et al.).
- Among patients with suspected COVID-19 and a negative initial PCR, repeat PCR was positive in 15/64 patients (23%). This suggests a PCR sensitivity of <80%. Conversion from negative to positive PCR seemed to take a period of days, with CT scan often showing evidence of disease well *before* PCR positivity (Ai et al.).
- Bottom line?
  - PCR seems to have a sensitivity somewhere on the order of ~75%.
  - A single negative RT-PCR *doesn't* exclude COVID-19 (*especially* if obtained from a nasopharyngeal source or if taken relatively early in the disease course).
  - If the RT-PCR is negative but suspicion for COVID-19 remains, then ongoing isolation and re-sampling several days later should be considered.

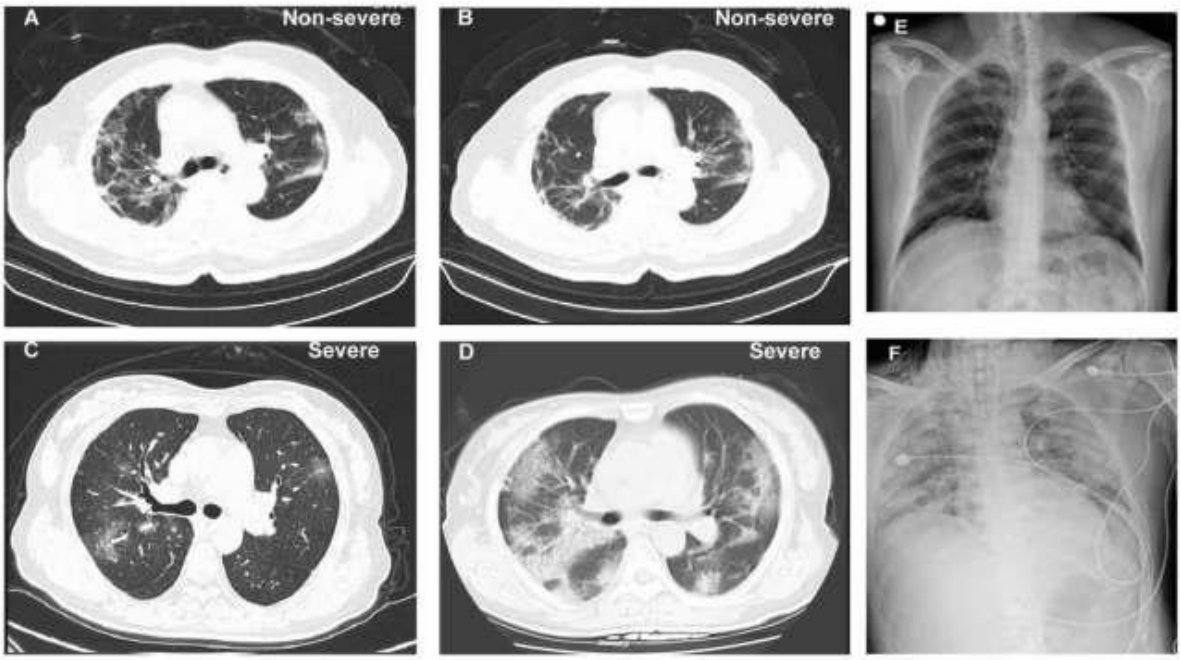
Chest X-Ray and CT Thorax

General description of imaging findings on chest x-ray and CT scan

Figure: First case of 2019 novel coronavirus in Canada
Chest x-ray shows bilateral, peribronchovascular, ill-defined opacities in all lung zones.

- The typical finding is patchy ground glass opacities, which tend to be predominantly peripheral and basal (Shi et al 2/24). 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 (example above from Silverstein et al).
- Findings which *aren't* commonly seen, and might argue for an alternative or superimposed diagnosis:
  - Pleural effusion is uncommon (seen in only ~5%).
  - COVID-19 doesn't appear to cause masses, cavitation, or lymphadenopathy.

Figure S1. Representative chest radiographic manifestations in a non-severe and a severe case with COVID-19



Transverse chest computed tomography imaging from a 50-year-old male with non-severe COVID-19, at 8 days after hospital admission (Panel A) and at 15 days after hospital admission (following the receipt of supportive treatment) (Panel B) showing multilobular and subpleural ground-glass opacity and consolidation. The transverse chest computed tomography imaging from a 60-year-old female with severe COVID-19 at 1 day after hospital admission (Panel C) showing multilobular ground-glass opacity and consolidation and at 4 days after hospital admission (following the receipt of supportive treatment) showing rapid radiologic progression, evidenced by multilobar subsegmental consolidation (Panel D).
Chest X-ray imaging from a 39-year-old male with non-severe COVID-19 after hospital admission demonstrating minor infiltrates in the right lower lobe (Panel E) and from 49-year-old male with severe COVID-19 after hospital admission demonstrating diffuse patchy shadowing and consolidation (Panel F).

W Guan Z et al, NEJM 2020

Sensitivity and time delay

- Limitations in the data
  - Data from different studies conflict to a certain extent. This probably reflects varying levels of exposure intensity and illness severity (cohorts with higher exposure intensity and disease severity will be more likely to have radiologic changes).
- Sensitivity of CT scanning?
  - Sensitivity among patients with positive RT-PCR is high. Exact numbers vary, likely reflecting variability in how scans are interpreted (there currently doesn't seem to be any precise definition of what constitutes a "positive" CT scan).
    - Sensitivity of 86% (840/975) in Guan et al.
    - Sensitivity of 97% (580/601) in Ai et al.
  - Among patients with *constitutional* symptoms only (but *not* respiratory symptoms), CT scan may be less sensitive (e.g., perhaps ~50%)(Kanne 2/27).
- CT scan abnormalities might emerge *before symptoms?*
  - Shi et al. performed CT scanning in 15 healthcare workers who were exposed to COVID-19 *before* they became symptomatic.

    - Ground glass opacification on CT scan was seen in 14/15 patients! 9/15 patients had peripheral lung involvement (some bilateral, some unilateral).
    - Emergence of CT abnormality *before* symptoms could be consistent with the existence of an asymptomatic carrier state (discussed above).
- Chest X-ray
    - Sensitivity of chest X-ray is lower than CT scan for subtle opacities. In Guan et al., the sensitivity of chest x-ray was 59%, compared to 86% for CT scan.

Bronchoscopy

- Risks of bronchoscopy:
    - May cause some deterioration in clinical condition (due to instillation of saline and sedation).
    - Enormous risk of transmission to providers.
    - Considerable resource allocation (requires N95 respirators, physicians, respiratory therapists) – all resources which will be in slim supply during an epidemic.
- Benefits of bronchoscopy:
    - Benefit of diagnosing COVID-19 is dubious at this point (given that treatment is primarily supportive).
- Bottom line on bronchoscopy?
    - Bronchoscopy might be considered in situations where it would otherwise be performed (e.g. patient with immunosuppression with concerns for Pneumocystis pneumonia or fungal pneumonia).
    - **Bronchoscopy should *not* be done for the purpose of ruling COVID-19 in or out (as this entails risk with no definite benefits)(Bouadma et al.).**

Anti-Viral Therapy

Caveats on anti-viral therapy

- No anti-viral therapy has been proven to work for COVID-19 in humans. Multiple RCTs are ongoing; hopefully they will bring us further information soon.
    - *Whenever possible, patients should be enrolled in RCTs*.
- Information is provided below about some of the more popular agents which are being used by some practitioners.
    - Inclusion in this chapter is *not* a recommendation to use one or more of these medications. This information is simply provided as a background to help us understand these therapies.
    - A focus is placed on lopinavir/ritonavir and chloroquine since these agents are currently available.
    - Practitioners are encouraged to review available evidence and reach their own conclusions regarding whether to use these medications.
    - If you have experience or new evidence or opinions on anti-viral therapy, please share it on the COVID-19 discussion page here.

Single vs. Multi-drug regimens

- Another unknown is whether a *single* drug could work, or whether a combination of multiple anti-viral agents is needed.
- Analogous to HIV, it's possible that two or three anti-virals working in synergy might be needed. Combinations of agents could increase *toxicity* however (especially cardiotoxicity).

indications for antiviral therapy

- When
    - Retrospective data from SARS suggests that earlier treatment (e.g. within 1-2 days of admission) may be more effective than reserving therapy until severe organ failures occur (Chan 2003). This is consistent with data from influenza that suggests a finite treatment window occurring relatively early in the disease course.

- Who
  - The vast majority of patients will do fine without any therapy, so in most cases there's no need for antiviral therapy.
  - However, *waiting* until patients are severely ill before initiating therapy could cause us to miss an early treatment window, during which the disease course is more modifiable.
  - Predictors of adverse outcome might be useful in predicting who will do poorly and thus who might benefit most from early anti-viral therapy? (see section below on prognosis).

Remdesivir

- Remdesivir might be an excellent antiviral, based on a study involving *in vitro* and animal data with MERS (e.g. Sheahan 2020).
- Unfortunately, remdesivir is not commercially available. Remdesivir was used on the basis of "compassionate use" for one of the first patients with COVID-19 in the United States (Holshue 2020).
- Remdesivir is being used in one trial in the United States being sponsored by NIAID. Enrollment in this trial is the most desirable approach to antiviral therapy (if feasible).

Lopinavir/ritonavir (Kaletra)

General description

- This is a combination of antiviral agents used in treatment of HIV (including post-exposure prophylaxis following needle-stick injury).
- Compared to remdesivir, lopinavir/ritonavir has the advantage that it's widely available and has an established toxicity profile (it does have known side-effects and drug interactions, but these are generally tolerable).
- Lopinavir/ritonavir appears to work synergistically with ribavirin. Available human data on SARS and MERS have *combined* these three agents together. It's possible that a cocktail of all three drugs is required for efficacy (potentially explaining failures of any of these agents in isolation). A recent very small study on lopinavir/ritonavir alone wasn't particularly impressive, suggesting that triple therapy with lopinavir/ritonavir/ribavirin might be necessary (Young 3/3/20).

Mechanism of action

- Lopinavir and ritonavir are protease inhibitors, which block viral replication.
- Lopinavir seems to be the agent which actually acts on the virus. Ritonavir is a CYP3A inhibitor which functions primarily to reduce metabolism of lopinavir, thereby boosting lopinavir levels.

In vitro data

- Lopinavir showed *in vitro* antiviral activity against SARS at concentration of 4 ug/ml. However, when combined with ribavirin, lopinavir appears considerably more effective (with an inhibitory concentration of 1 ug/mL (Chu et al. 2004).
- For reference, the peak and trough serum concentrations of lopinavir are 10 and 5.5 ug/ml (Chu et al. 2004).

Animal data

- Lopinavir/ritonavir was effective against MERS-CoV in a primate animal model (Chan 2015).

Human data

Effect of Lopinavir/Ritonavir on viral load in patients with SARS

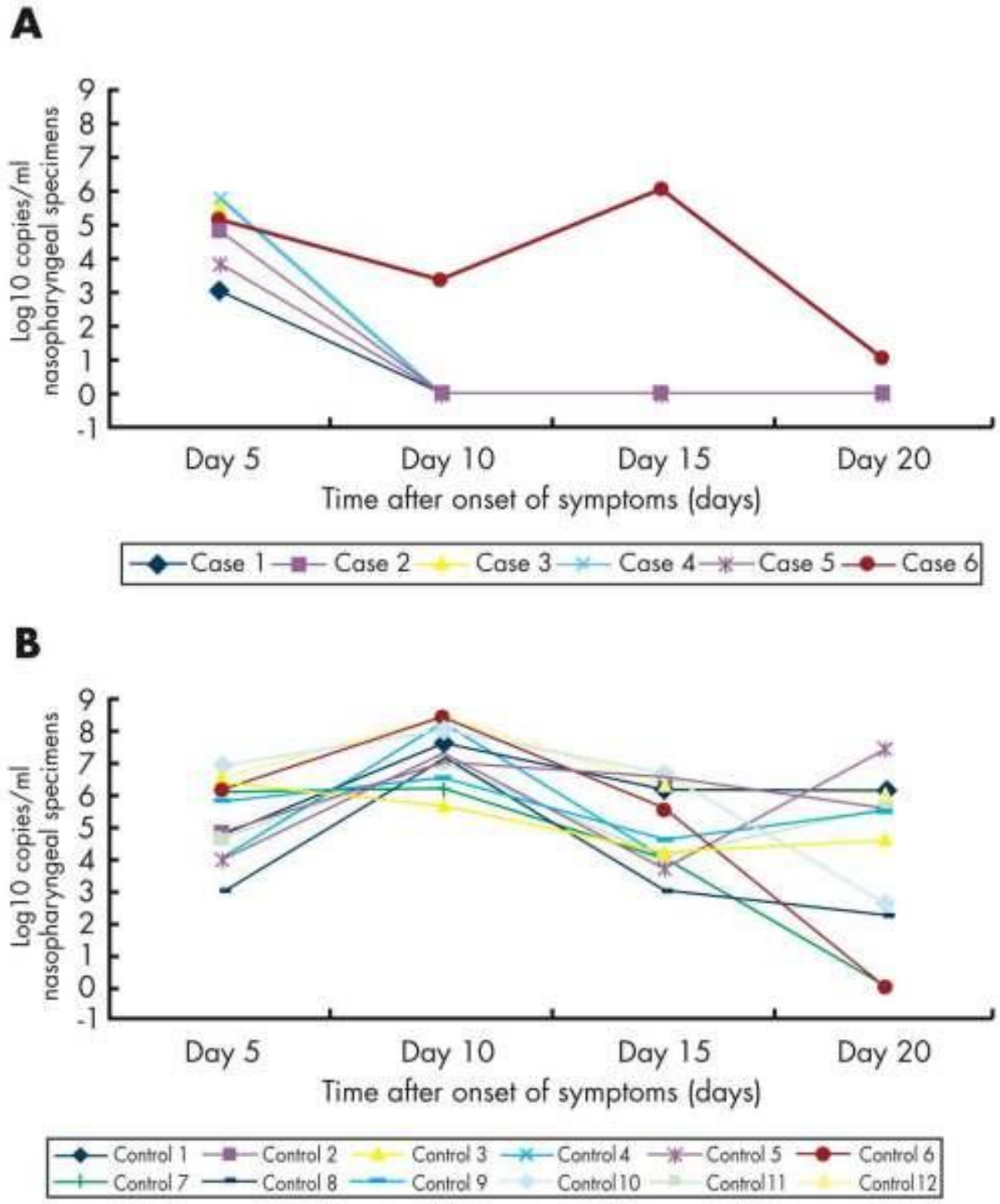


Figure 2 (A) Change in viral load by sequential quantitative RT-PCR for SARS associated coronavirus in nasopharyngeal swabs of six patients in the initial treatment subgroup. Note that case 6 was given pulse methylprednisolone on day 7. (B) Change in viral load by sequential quantitative RT-PCR for SARS associated coronavirus in nasopharyngeal swabs of 12 patients in the historical control group.

- Chu et al. 2004: Open-label before/after study on SARS.
  - 41 patients treated with lopinavir/ritonavir plus ribavirin were compared to 111 historical control patients treated with ribavirin alone. Baseline imbalances did exist between groups (patients treated with lopinavir/ritonavir had lower initial lactate dehydrogenase (LDH) levels – so they weren't as sick).

    - Poor clinical outcomes (ARDS or death) were lower in treatment group (2.4% vs. 29%). These differences persisted in multivariable models, which attempted to correct for baseline imbalances between the groups.
    - Use of lopinavir/ritonavir use correlated with a dramatic reduction in viral load (figure above).
    - All patients received concomitant ribavirin. The dose was 4 grams oral loading dose followed by 1.2 grams PO q8hr (or 8 mg/kg IV q8hr) for 14 days.
- Chan et al. 2003: Retrospective matched multi-center cohort study on SARS
    - 75 patients treated with lopinavir/ritonavir were compared with controls (matched on the basis of sex, age, comorbidities, lactate dehydrogenase level, and use of pulse-dose steroid).
    - Up-front treatment with lopinavir/ritonavir combined with ribavirin correlated with reduced mortality (2.3% versus 16%). However, rescue therapy with lopinavir/ritonavir (often *without* concomitant ribavirin) didn't seem to make any difference. The ribavirin dose was 2.4 grams loading dose, followed by 1.2 grams PO q8hr (or 8 mg/kg IV q8hr) for 10-14 days.
- Park et al. 2019: Retrospective cohort study on post-exposure prophylaxis against MERS
    - This is a retrospective cohort study involving 22 patients with high-risk exposure to a single MERS patient (table below). As a control group, four hospitals with outbreaks of MERS were selected.
    - Post-exposure prophylaxis consisted of a combination of lopinavir/ritonavir (400 mg / 100 mg BID for 11-13 days) plus ribavirin (2000 mg loading dose, then 1200 mg q8hr for four days, then 600 mg q8hr for 6-8 days).
    - MERS infections didn't occur in anyone treated with post-exposure prophylaxis (table below). However, the manner in which the control group was selected (retrospectively selecting hospitals with MERS outbreaks) likely biased the study in favor of showing a benefit of post-exposure prophylaxis.
    - Post-exposure therapy was generally well tolerated, although most patients reported some side-effects (most commonly nausea, diarrhea, stomatitis, or fever). Laboratory evaluation shows frequent occurrence of anemia (45%), leukopenia (40%), and hyperbilirubinemia (100%).
- Young et al. 3/3/2020
    - Cohort study describing 16 COVID-19 patients in Singapore. Among six patients with hypoxemia, five were treated with lopinavir/ritonavir (200 mg/100 mg BID, which is half of the usual dose of lopinavir).
    - Among the five patients, two patients deteriorated and had persistent nasopharyngeal virus carriage.
    - Possible reasons for these underwhelming results might include: statistical underpowering, low dose of lopinavir/ritonavir, lack of synergistic ribavirin, and/or late initiation of therapy. For further discussion see PulmCrit blog on this study here.
- Other evidence of lower quality:
    - Lopinavir/ritonavir has been used to treat one patient with COVID-19 (Kim 2020).
    - Lopinavir/ritonavir was reported to be effective in some case reports of MERS (Momattin 2019).
- Lopinavir/ritonavir is currently under investigation within multiple RCTs in China (but none in the United States).

Table I
Clinical and demographic characteristics of healthcare workers in the prophylaxis and non-prophylaxis groups

Characteristics	Total ($N = 43$)	PEP group ($N = 22$)	Non-PEP group ($N = 21$)	*P*-value
Age (years), median (IQR)	29.0 (24–33)	27.5 (24–33)	31 (28–43)	0.031
Female	28 (65.1)	15 (62.2)	13 (61.9)	0.666
Occupation				0.658
Doctor	19 (44.2)	9 (40.9)	10 (47.6)	
Nurse	24 (55.8)	13 (59.1)	11 (52.4)	
Protective equipment use				
Surgical mask	2 (4.7)	0	2 (9.5)	0.233
Gloves	3 (7.0)	0	3 (14.3)	0.108
Types of exposure situation*				
Direct care without aerosol-generating procedure	39 (90.7)	22 (100.0)	17 (81.0)	0.048
Airway suction	17 (39.5)	16 (72.7)	1 (4.8)	<0.001
Nebulizer treatment	15 (34.9)	15 (68.2)	0	<0.001
Intubation	6 (14.0)	5 (22.7)	1 (4.8)	0.185
Manual ventilation	3 (7.0)	2 (9.1)	1 (4.8)	>0.999
Cardiopulmonary resuscitation	2 (4.7)	0	2 (9.5)	0.233
Bronchoscopy	2 (4.7)	0	2 (9.5)	0.233
MERS-CoV infection	6 (14.0)	0	6 (28.6)	0.009

PEP, post-exposure prophylaxis; IQR, interquartile range; MERS-CoV, Middle East respiratory syndrome coronavirus.
Values are no. (%) unless otherwise indicated.
* Several healthcare workers had more than one type of exposure, and duplicated exposures were recorded.

Dosing

- (1) Lopinavir/Ritonavir (Monograph from MedScape)
  - Standard dose (and dose used against coronaviruses) is 400 mg / 100 mg PO BID.
  - Generally no adjustment is made in renal dysfunction.
  - Crushing and administering tablets via a gastric tube may decrease absorption by ~50%. Increased doses might be considered in this situation (Best et al. 2011).
- (2) Ribavirin (Monograph from MedScape)
  - Unknown whether synergistic ribavirin is useful.
  - The best validated regimen is probably Chu et al. 2004: 4 grams oral loading dose followed by 1.2 grams PO q8hr (or 8 mg/kg IV q8hr) for 14 days.

Contraindications/cautions regarding Lopinavir/Ritonavir:

- Serious adverse effects may include:
  - Hypersensitivity reaction, angioedema
  - Stevens-Johnson syndrome / Toxic epidermal necrolysis / Erythema multiforme
  - QT prolongation & Torsade de Pointes
  - AV block, PR prolongation
  - Hyperglycemia, hypertriglyceridemia
  - Renal failure
  - Anemia, leukopenia, neutropenia
  - Pancreatitis
  - Hepatotoxicity
- Common adverse reactions:
  - Nausea/vomiting, diarrhea
  - Insomnia, anxiety
- Contraindicated in:
  - Cardiac disease (ischemic heart disease, cardiomyopathy, structural heart disease, QT prolongation)
  - Liver disease
- Monitoring: Transaminase levels
- Overall tolerability?
  - In Chu et al. 2004, 41 patients with SARS tolerated lopinavir/ritonavir reasonably well (one patient needed to discontinue due to doubling of transaminase levels).
  - In Chan 2003, 75 patients with SARS were treated with lopinavir/ritonavir without reports of severe adverse effects.

Further information

- PulmCrit blog 3/4 discussing the Young study and double vs. triple therapy.
- Further information on this is available in a recent review by Yao TT et al.

Chloroquine

General description

- Chloroquine is generally used for treatment of malaria and amebiasis. It has anti-viral activity in vitro, but no established track record in treatment of viral disease.
- The toxicity profile seems to be acceptable (e.g. its widely used as malaria prophylaxis — albeit at a much lower dose than is currently being considered for COVID-19).

Mechanism of action

- Chloroquine appears to work via multiple mechanisms, including:
  - Interference with with the cellular receptor ACE2 (potentially making it particularly effective against SARS and COVID-19).
  - Impairment of acidification of endosomes, which interferes with virus trafficking within cells.
- Chloroquine also has immunosuppressive activities. It's unknown whether such immunosuppressive action could be *beneficial* or *harmful* (analogous to steroid therapy).

In vitro data

- *In vitro* data using cell lines shows that chloroquine can inhibit COVID-19 with an 50% inhibitory concentration of 1 uM, implying that therapeutic levels could be achieved in humans (Wang 2020). The 50% inhibitory concentration of chloroquine for SARS is closer to 9 uM, suggesting that chloroquine could be more effective against COVID-19 than SARS (Al-Bari 2017).

Animal data

- Chloroquine failed to work in mice infected with SARS (Bernard 2006).

Human data

- Emerging reports from China suggests that chloroquine has been studied with favorable results, but data is currently not available (Gao 2020). An expert consensus group in China is recommending a treatment regimen of 500 mg PO twice daily for patients without contraindications (Zhi 2020). Hopefully, clinical data with chloroquine will be published shortly.

Dosing (Monograph from MedScape)

- 500 mg chloroquine *phosphate* contains 300 mg of chlorquine itself (a.k.a. chloroquine base).
- 500 mg PO twice daily for 10 days is the regimen recommended by a group in China for patients without contraindications (Zhi 2020).
- May require dose adjustment in renal or hepatic dysfunction.

Contraindications/cautions

- Serious adverse effects may include:
  - QT prolongation & Torsades de Pointes
  - Reduction in seizure threshold
  - Anaphylaxis or anaphylactoid reaction

    - Neuromuscular impairment
    - Neuropsychiatric disorders (potential to increase delirium)
    - Pancytopenia, neutropenia, thrombocytopenia, aplastic anemia
    - Hepatitis
- Common adverse reactions:
    - Nausea/vomiting, diarrhea, abdominal pain
    - Visual disturbance, headache
    - Extrapyramidal symptoms
- Monitoring: Serial complete blood count, QT interval
- Contraindicated in: Porphyria, G6PD deficiency, epilepsy, heart failure, recent myocardial infarction.

Comments

- Mixed messages from China regarding how widely this is being used or recommended.
    - Many articles don't mention chloroquine at all.
    - A few articles strongly recommend this (Zhi 2020, Gao 2020)
- Chikungunya Virus Caveat: Chloroquine was effective for chikungunya virus *in vitro,* but subsequently failed to work in primate model (in fact, immunosuppressive effects of chloroquine actually *increased* viral levels)(Roques et al 2018). This underscores the fact that *in vitro* effects on cell lines may not necessarily translate into beneficial clinical effects (especially given complex immunomodulatory effects of chloroquine).
- Hopefully additional data will be forthcoming shortly.

Oseltamavir & other neuraminidase inhibitors

- Neuraminidase inhibitors *don't* seem to work against COVID-19 (Tan et al 2004).
- Initial empiric therapy with neuraminidase inhibitors could be reasonable during influenza season in critically ill patients, if there is concern that the patient might have influenza pneumonia.
    - Currently, in many locations, patients presenting with viral pneumonia are much more likely to have influenza than COVID-19.

Anti-bacterial therapy

Initial empiric antibiotics

- COVID-19 itself is not an indication for antibiotics.
- Initially, there may be concerns regarding the possibility of a superimposed bacterial pneumonia. When in doubt, it may be sensible to obtain bacterial cultures and procalcitonin, prior to initiation of empiric antibiotic therapy. Based on culture and procalcitonin results, antibiotics might be discontinued in <48 hours if there isn't evidence of a bacterial infection (this is exactly the same as management of influenza pneumonia).

Delayed bacterial superinfection

- Bacterial pneumonia can emerge during the hospital course (especially ventilator-associated pneumonia in patients who are intubated).
    - Among patients who died from COVID-19, one series found that 11/68 (16%) had secondary infections (Ruan 3/3/20).
- This may be investigated and treated similarly to other ventilator-associated pneumonias, or hospital-acquired pneumonias.

Steroid

- Steroid should *not* generally be used. Steroid hasn't demonstrated benefit in prior SARS or MERS epidemics. Steroid may increase viral shedding (Lee 2004).
- Nearly all articles recommend against the use of steroid.

Ascorbic acid

- Ascorbic acid did appear to improve mortality in the multi-center CITRIS-ALI trial. However, interpretation of this trial remains hopelessly contentious due to nearly unsolvable issues with survival-ship bias (discussed here).
- Extremely limited evidence suggests that ascorbic acid could be beneficial in animal models of coronavirus (Atherton 1978).
- Administration of a moderate dose of IV vitamin C could be considered (e.g. 1.5 grams IV q6 ascorbic acid plus 200 mg thiamine IV q12). This dose seems to be safe. However, *there is no high-quality evidence to support ascorbic acid in viral pneumonia.*

Haemodynamic support

Avoid fluid resuscitation

- Patients *rarely* are shocked on admission (even among critically ill patients, admission blood pressure is generally normal and lactate elevations are mild-moderate)(Yang et al 2/21).
    - Overall, the rate of reported "sepsis" is generally low (<5%). The virus doesn't seem to generally cause a septic shock picture (but of course, patients may always suffer from superimposed bacterial septic shock).
- The cause of death from COVID-19 is nearly always ARDS – which may be *exacerbated* by fluid administration.
- Gentle fluid administration could be considered for patients with evidence of hypoperfusion and a history suggestive of total body hypovolemia (e.g. prolonged nausea/vomiting and diarrhea).

Cardiomyopathy

- COVID-19 does commonly cause troponin elevations (which generally will *not* represent type-I myocardial infarctions).
- Ruan 3/3/20 reported that ~7% of patients die of fulminant myocarditis. This may also be a contributing factor in ~33% of deaths.
- Wang 2/7 reported that arrhythmia was a cause of ICU transfer in 12% of patients.
- Troponin elevation seems to be a strong prognostic indicator for mortality (see prognosis section below). It's unclear to what extent this represents cardiac involvement *causing* death versus troponin merely being an indicator of severe global illness placing stress on the heart. Elevated troponin levels correlate with mortality across a *variety* of critical illnesses.

Invasive Mechanical Ventilation

Ventilator settings

- Tidal volumes should be targeted to a lung-protective range (4-6 ml/kg ideal body weight).
- Informal reports coming out of Italy and Singapore suggest that:
    - i) Driving pressures required *aren't* very high.
    - ii) Patients require lots of PEEP and also respond well to prone ventilation.
- This suggests that a primary problem may be small airway closure and *atelectasis* (rather than reduced lung compliance). That's a good thing, because these issues are generally manageable, as follows:
    - i) If conventional ventilation is used, PEEPs should be utilized as per the ARDSnet PEEP ladder. An ARDSnet table is shown below. This table doesn't need to be followed exactly, but it may be useful as a general guide.

- ii) Consider that *early* APRV could be very useful for some patients . APRV is essentially an aggressive recruitment strategy which can help sort out how much recruitable lung the patient has.
- Iii)Early Prone ventilation

- Permissive hypercapnia will likely be extremely important when ventilating these patients in a safe fashion. The safe extent of permissive hypercapnia is unknown, but as long as hemodynamics are adequate a pH of >7.1 or >7.15 may be tolerable (hypercapnia is preferred over lung-injurious ventilation).

High & Low PEEP tables from ARDSnet

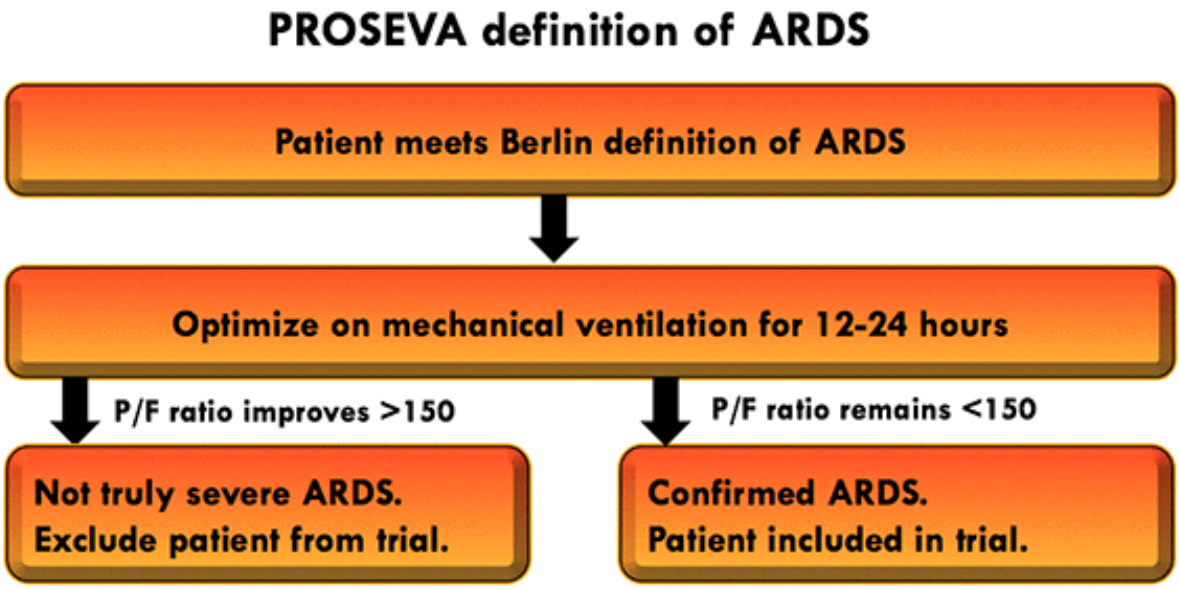
FiO2	Low PEEP	High PEEP
0.3	5	5-14
0.4	5-8	14-16
0.5	8-10	16-20
0.6	10	20
0.7	10-14	20
0.8	14	20-22
0.9	14-18	22
1.0	18-24	22-24

PEEP tables don't need to be followed precisely, but can be useful as a general guide. The WHO recommends using a high-PEEP strategy, which seems consistent with available experience thus far with COVID-19. If high PEEPs are used, make sure to keep tidal volumes low to prevent excessively high plateau pressures. APRV is an alternative strategy which would likewise provide high mean airway pressures.

-The Internet Book of Critical Care, @PulmCrit

Proning

- **Prior to consideration of proning, optimization on the ventilator for 12hrs is generally preferable**
- For failure to respond to initial ventilator optimization (e.g. with persistent PaO2/FiO2 below 150), prone ventilation may be considered. However, there are some reasons that prone ventilation might *not* be desirable here:
  - Prone ventilation is very labour-intensive. This would require exposing numerous healthcare providers to the patient, multiple times per day.
- Nevertheless, prone ventilation does seem to be a useful intervention for profound or refractory hypoxemia.



ECMO

- Patients with COVID-19 are often relatively young and suffering from single-organ failure due to a reversible aetiology, so many would be excellent candidates for ECMO (probably mostly VV ECMO).
- Indications and timing are unclear.
- In an epidemic, ECMO capabilities would probably rapidly become saturated.
- Discuss with ECMO referral service early

Renal failure

- Renal failure requiring dialysis is reported in a subset of patients admitted to ICU.
- The exact mechanism is unclear at this point, but some conjectures may be reached based on SARS (Chu et al. 2005).
    - SARS causes renal failure in ~7% of patients. The pathology shows acute tubular necrosis, which appears to be a reflection of generalized multi-organ failure. In some cases rhabdomyolysis may have contributed as well. Renal failure correlates with a poor overall prognosis (92% mortality with renal failure versus 9% without). In multivariable analysis, renal failure was the strongest predictor of mortality (more-so even than ARDS).

Prognosis

General prognosis

- (1) It remains unclear what fraction of patients are hospitalized.
    - There may be lots of patients with mild illness who don't present to medical attention and aren't counted.
    - The vast majority of infected patients (e.g. >80%) *don't* get significantly ill and *don't* require hospitalization.
- (2) Among *hospitalized* patients (Guan et al 2/28)
    - ~10-20% of patients are admitted to ICU.
    - ~3-10% require intubation.
    - ~2-5% die.
- (3) Longer term outcomes: Prolonged ventilator dependency ?

    - Patients who survive the initial phases of the illness may still require prolonged ventilator support (possibly developing some radiographic elements of fibrosis)(Zhang 2020).
    - As the epidemic progresses, an issue which may arise is a large volume of patients unable to wean from mechanical ventilation.
- (*Caveat*: There are *numerous* sets of numbers published and they vary *a lot*. However, from the clinician's standpoint the precise numbers don't really matter.)

Epidemiological risk factors

- Risk factors
    - Older age
    - Male sex
    - Medical comorbidities
        - Chronic pulmonary disease
        - Cardiovascular disease (including hypertension and coronary artery disease)
        - Cerebrovascular disease
        - Diabetes
- The largest series of mortality data comes from the Chinese CDC (table below). The *absolute* numbers may vary depending on whether some cases were missed, but the *relative* impact of various risk factors is probably accurate.

TABLE 1. Patients, deaths, and case fatality rates, as well as observed time and mortality for n=44,672 confirmed COVID-19 cases in Mainland China as of February 11, 2020.

Baseline characteristics	Confirmed cases, N (%)	Deaths, N (%)	Case fatality rate, %	Observed time, PD	Mortality, per 10 PD
Overall	44,672	1,023	2.3	661,609	0.015
Age, years					
0–9	416 (0.9)	–	–	4,383	–
10–19	549 (1.2)	1 (0.1)	0.2	6,625	0.002
20–29	3,619 (8.1)	7 (0.7)	0.2	53,953	0.001
30–39	7,600 (17.0)	18 (1.8)	0.2	114,550	0.002
40–49	8,571 (19.2)	38 (3.7)	0.4	128,448	0.003
50–59	10,008 (22.4)	130 (12.7)	1.3	151,059	0.009
60–69	8,583 (19.2)	309 (30.2)	3.6	128,088	0.024
70–79	3,918 (8.8)	312 (30.5)	8.0	55,832	0.056
≥80	1,408 (3.2)	208 (20.3)	14.8	18,671	0.111
Sex					
Male	22,981 (51.4)	653 (63.8)	2.8	342,063	0.019
Female	21,691 (48.6)	370 (36.2)	1.7	319,546	0.012
Occupation					
Service industry	3,449 (7.7)	23 (2.2)	0.7	54,484	0.004
Farmer/laborer	9,811 (22.0)	139 (13.6)	1.4	137,992	0.010
Health worker	1,716 (3.8)	5 (0.5)	0.3	28,069	0.002
Retiree	9,193 (20.6)	472 (46.1)	5.1	137,118	0.034
Other/none	20,503 (45.9)	384 (37.5)	1.9	303,946	0.013
Province					
Hubei	33,367 (74.7)	979 (95.7)	2.9	496,523	0.020
Other	11,305 (25.3)	44 (4.3)	0.4	165,086	0.003
Wuhan-related exposure*					
Yes	31,974 (85.8)	853 (92.8)	2.7	486,612	0.018
No	5,295 (14.2)	66 (7.2)	1.2	71,201	0.009
Missing	7,403	104	2.8	103,796	0.010
Comorbid condition†					
Hypertension	2,683 (12.8)	161 (39.7)	6.0	42,603	0.038
Diabetes	1,102 (5.3)	80 (19.7)	7.3	17,940	0.045
Cardiovascular disease	873 (4.2)	92 (22.7)	10.5	13,533	0.068
Chronic respiratory disease	511 (2.4)	32 (7.9)	6.3	8,083	0.040
Cancer (any)	107 (0.5)	6 (1.5)	5.6	1,690	0.036
None	15,536 (74.0)	133 (32.8)	0.9	242,948	0.005
Missing	23,690 (53.0)	617 (60.3)	2.6	331,843	0.019
Case severity‡					
Mild	36,160 (80.9)	–	–	–	–
Severe	6,168 (13.8)	–	–	–	–
Critical	2,087 (4.7)	1,023 (100)	49.0	31,456	0.325
Missing	257 (0.6)	–	–	–	–

Laboratory risk stratification

- Blood cell count abnormalities
  - *Lymphopenia* and its trends over time (prolonged or worsening lymphopenia portends poor outcome)(Chu et al. 2004)
  - Neutrophil/lymphocyte ratio (NLR) appears to be a superior prognosticator when compared to either lymphopenia or C-reactive protein (Liu et al. pre-print). As shown in

the second figure below, neutrophil/lymphocyte ratios >3 could suggest a worse prognosis.

- Higher levels of C-reactive protein.
- Higher levels of troponin (this may be very strong prognostic factor, but it's difficult comparing values obtained across different laboratories.)
- (References: Ruan 3/3/20, Xie et al. 2020, Wang et al. 2/7/20.)

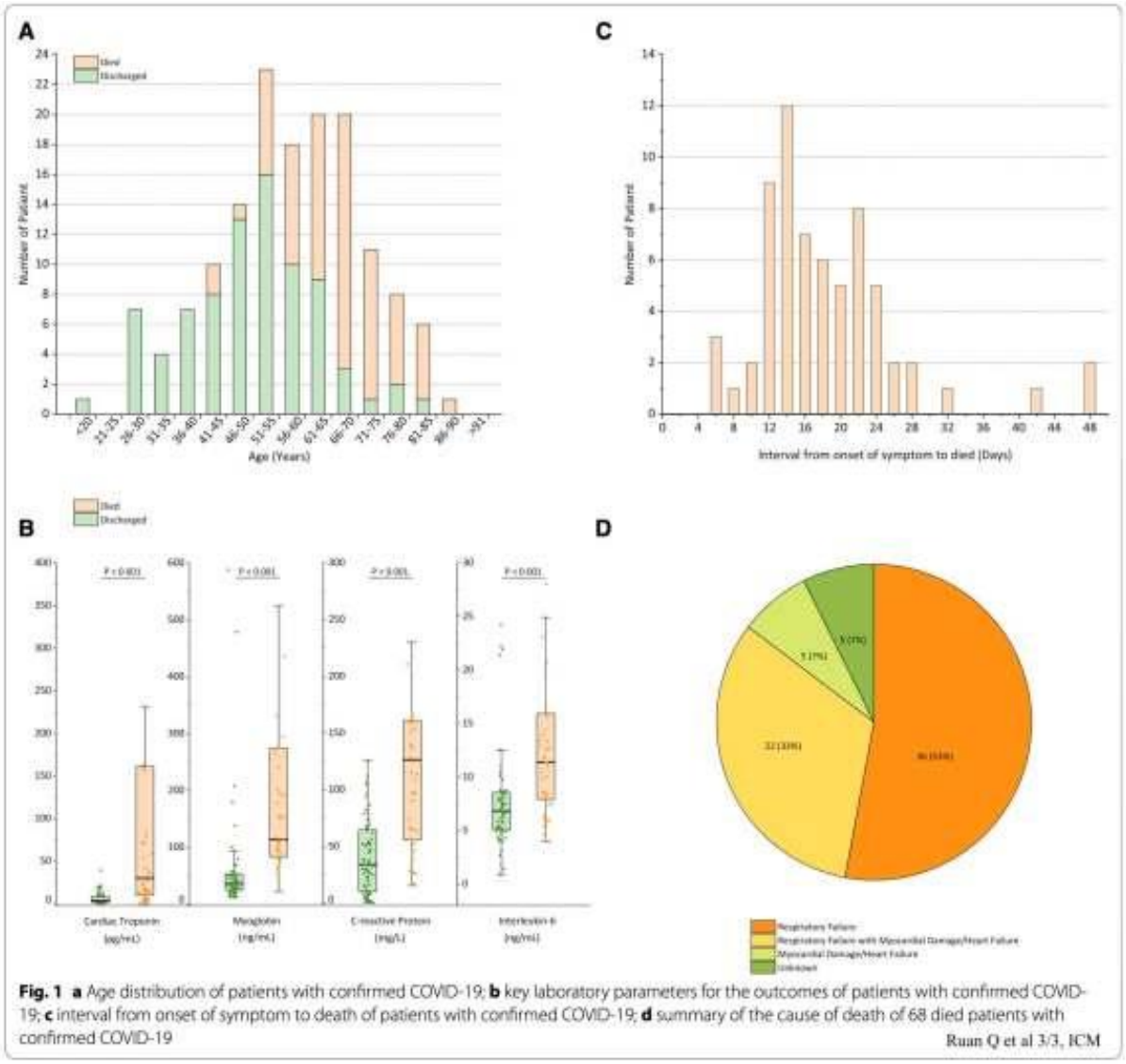


Fig. 1 **a** Age distribution of patients with confirmed COVID-19; **b** key laboratory parameters for the outcomes of patients with confirmed COVID-19; **c** interval from onset of symptom to death of patients with confirmed COVID-19; **d** summary of the cause of death of 68 died patients with confirmed COVID-19

Ruan Q et al 3/3, ICM

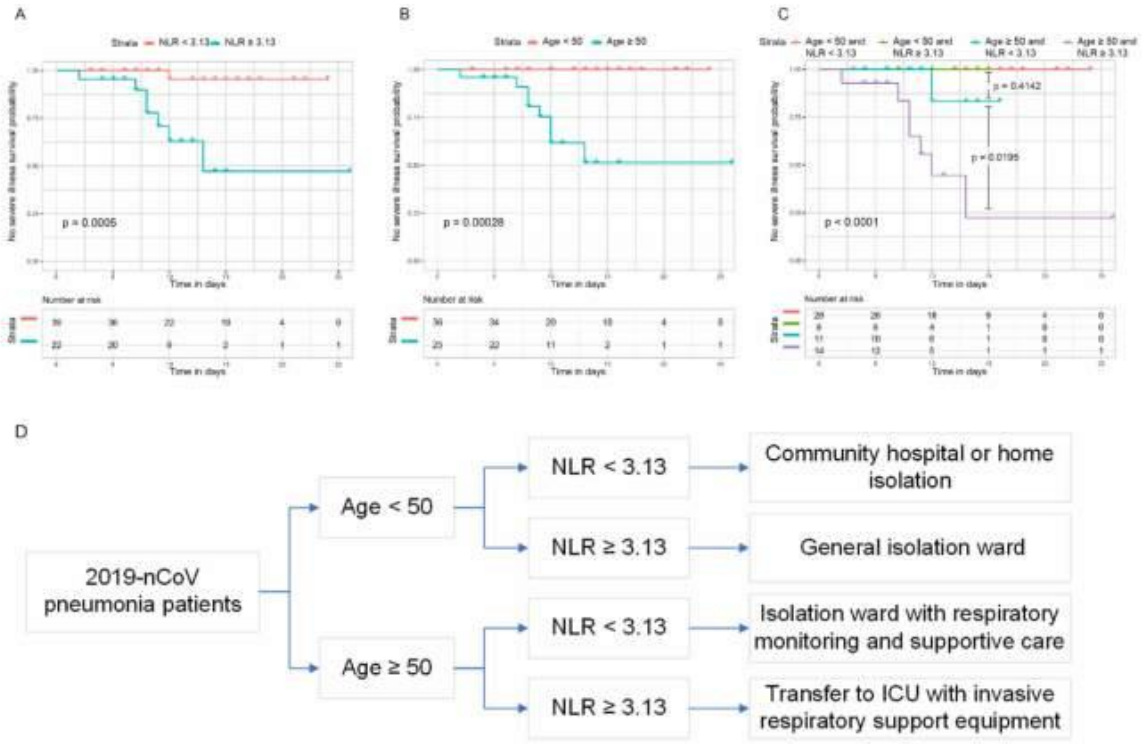
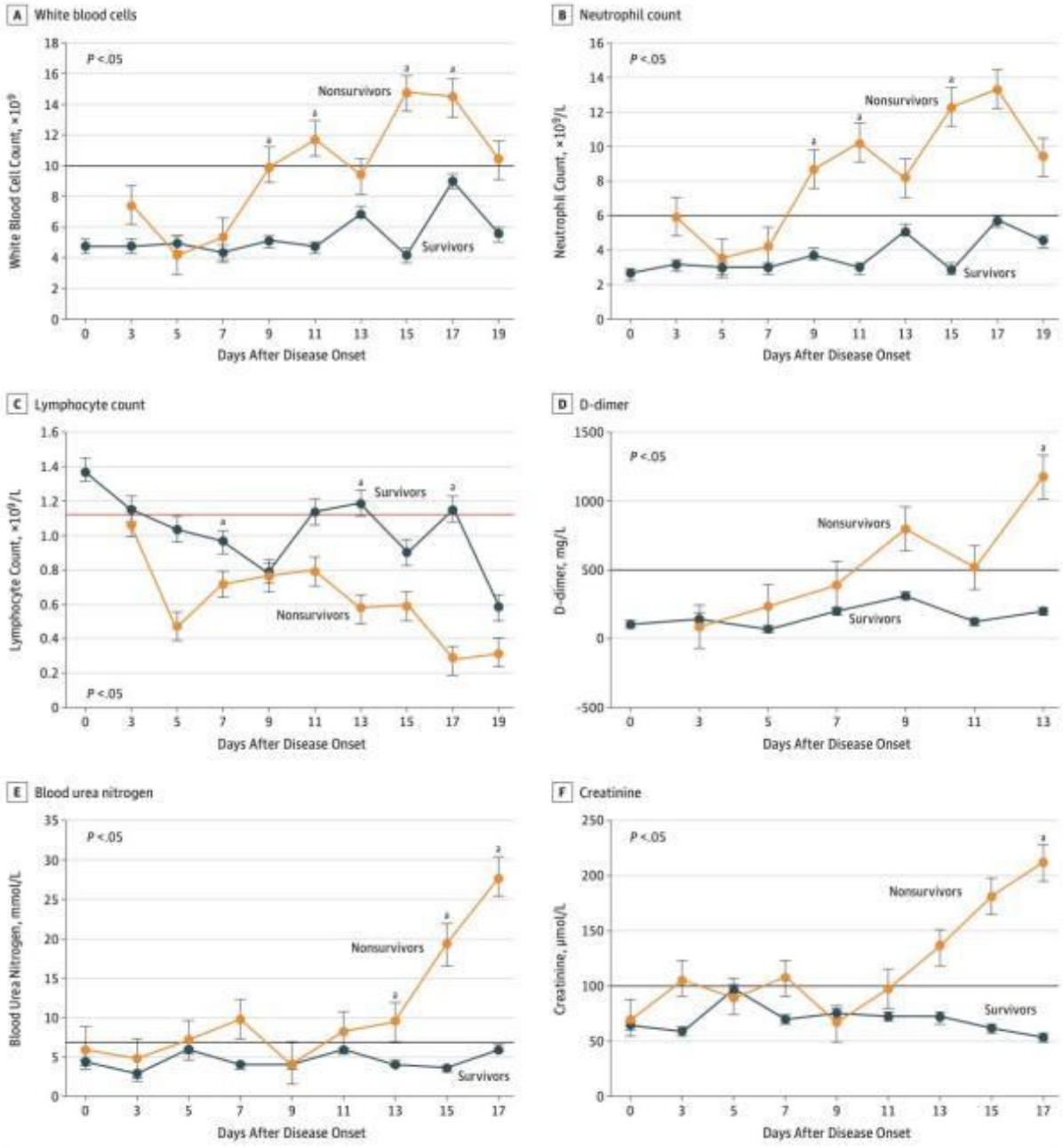


Figure 3. Kaplan–Meier curves of risk group stratification for no severe illness in 2019-nCoV cohorts. (A) The range of NLR for each risk group were as follows: low risk: <3.13, and high risk: ≥ 3.13. (B) Risk group stratification with age and (C) NLR with age. (D) 2019-nCoV pneumonia management process.

Liu J et al. Pre-print: NLR ratio predicts severe illness patients with 2019 Novel Coronavirus in the Early Stage

Figure 2. Dynamic Profile of Laboratory Parameters in 33 Patients With Novel Coronavirus–Infected Pneumonia (NCIP)



Timeline charts illustrate the laboratory parameters in 33 patients with NCIP (5 nonsurvivors and 28 survivors) every other day based on the days after the onset of illness. The solid lines in black show the upper normal limit of each parameter, and the solid line in red shows the lower normal limit of lymphocyte count.

[a] $P < .05$ for nonsurvivors vs survivors.

Wang D et al 2/7/20 PMID 32031570

Disposition

Avoidance of unnecessary emergency department or clinic visits

- Health systems should ideally be put in place to dissuade patients from presenting to the clinic or emergency department for testing to see if they have COVID-19 (e.g. if they have mild constitutional symptoms and don't otherwise require medical attention).
- Korea has developed a system of drive-thru testing, which avoids exposure of other patients in the emergency department. Outdoor testing also ensures ongoing circulation of fresh air.

Home disposition

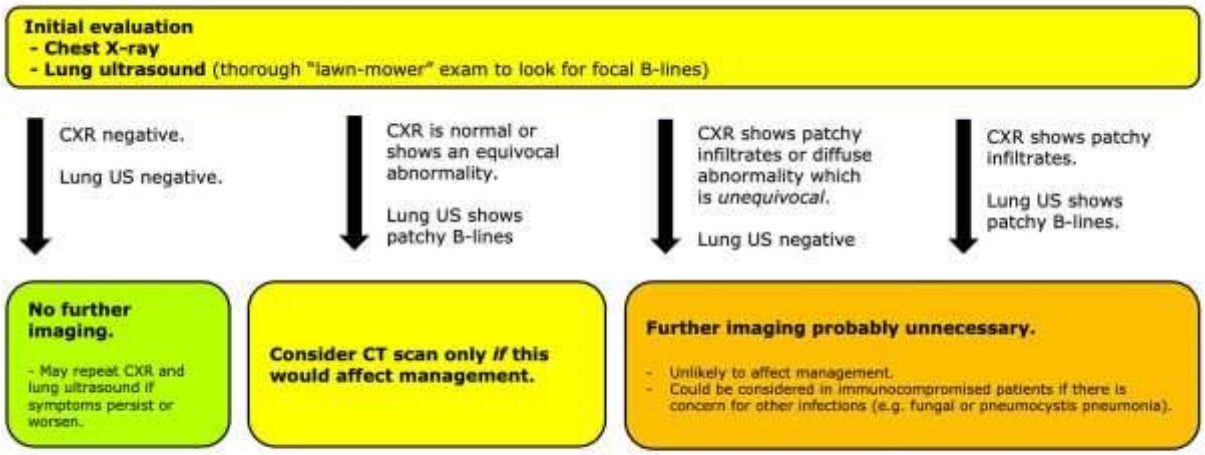
- The vast majority of patients with coronavirus will recover spontaneously, without requiring any medical attention (perhaps >80% of patients).
- Patients with mild symptoms can generally be discharged home, with instructions to isolate themselves. These decisions should be made in coordination with local health departments, who can assist in follow-up.
- Features favoring home discharge may include:
    - Ability to understand and comply with self-isolation (e.g. separate bedroom and bathroom).
    - Ability to call for assistance if they are deteriorating.
    - Having household members who aren't at increased risk of complications from COVID-19 (e.g. elderly, pregnant women, or people with significant medical comorbidities).
    - Lack of hypoxemia, marked chest infiltrates, or other features that would generally indicate admission.
- For more, see CDC interim guidance for disposition of patients with COVID-19 here and here.

Possible approach to respiratory failure & suspected COVID-19

- **Isolate & notify infection control**
  - ❑ Masks on patient & staff immediately (if not already in negative pressure room).
- **History**
  - ❑ Travel history.
  - ❑ ROS (focus on constitutional symptoms, upper & lower respiratory symptoms & GI system).
- **Labs**
  - ❑ Basic (e.g. electrolytes, coagulation studies).
  - ❑ CBC *with differential cell count.*
  - ❑ Nasopharyngeal swab for influenza and other endemic respiratory viruses (RSV etc.).
  - ❑ Nasopharyngeal swab for COVID-19 if possible.
  - ❑ Blood cultures & urine for pneumococcal/legionella antigens if concern for systemic bacterial infection.
  - ❑ C-Reactive Protein (CRP) & Procalcitonin if available.
- **Imaging**
  - ❑ Lung ultrasonography (thorough "lawn-mower" approach to look for focal infiltrates).
  - ❑ Chest X-ray.
  - ❑ May consider CT but only if it will truly affect management (schema below).
- **Treatment**
  - ❑ Empiric antibiotics for bacterial pneumonia if this is a concern.
  - ❑ Don't give steroid unless there is another indication (e.g. COPD).
  - ❑ Avoid fluid administration if possible (especially avoid using 30 cc/kg fluid bolus).

-The Internet Book of Critical Care, by @PulmCrit

Possible schema for imaging in patients with respiratory symptoms and suspected COVID-19



The optimal imaging strategy remains unknown. Chest X-ray and lung ultrasonography are a sensible place to start. CT scanning could have a role in some equivocal situations, but is generally unlikely to affect clinical management (since treatment for mild COVID-19 is supportive).

-The Internet Book of Critical Care, by @PulmCrit