

# **A Case Report of COVID-19 Pneumonia With Severely Elevated Inflammatory Markers. A Narrative Review of Clinical and Laboratory Predictors of Severe Disease.**

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No conflicts of interest to report.

Financial Disclosures: None

Sources of Funding: None

**Abstract:****Introduction:**

In late December 2019, the coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China. It quickly spread and emerged as a global pandemic with far-reaching impacts on society. As clinical research on this novel virus emerges, there is a limited amount of data that review clinical and laboratory predictors of severe disease. We present a case of a patient with severely elevated inflammatory markers who remained clinically stable during his hospital course.

**Case discussion:**

A 53-year-old male presented to the emergency room with 11 days of persistent fevers and new-onset anterior chest tightness. He was admitted to the hospital due to a reported oxygen desaturation at home to 87% (taken by his spouse, a healthcare professional) and ambulatory oxygen desaturation down to 87%. He was noted to have severely elevated inflammatory markers, lymphopenia, and computed tomography pulmonary angiography findings consistent with COVID-19. He remained on room air and clinically stable throughout his 3 day hospital course. While his C-reactive protein levels improved, his ferritin and erythrocyte sedimentation rate continued to elevate. He was discharged home and was symptom-free within 4 days of hospital discharge.

**Discussion:**

COVID-19 has proven to be a viral disease with a high transmission rate, that has caused over 100,000 deaths in the United States, thus far. The decision to admit a patient must balance the risks of transmission with the benefit of being readily available to provide urgent supportive care should the patient develop complications. Thus, there is a significant benefit to being able to predict poor outcomes. We performed a targeted review of the literature, focusing on clinical and laboratory predictors of poor outcomes in COVID-19. Our case report and narrative review outlines these findings within the context of our case.

## A Case Report of COVID-19 Pneumonia with Severely Elevated Inflammatory markers. A Narrative Review of Clinical and Laboratory Predictors of Severe Disease.

### **Introduction:**

In late December 2019, a pneumonia caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, Hubei Province, China. This novel virus spread across the globe resulting in a pandemic and worldwide effects. The World Health Organization named the disease caused by SARS-CoV2, "COVID-19" (Coronavirus disease 2019). While studies have evaluated clinical and laboratory characteristics of COVID-19 fatalities and patients with severe disease, there is limited data in those with mild disease. This creates challenges predicting which patients will progress to severe disease. This report describes the case of a patient with severely elevated inflammatory markers and moderate lymphopenia, concerning for impending development of severe disease, who did not require supplemental oxygen and remained clinically stable through his hospital course.

### **Case Report:**

A 53-year-old male with a history of hypertension was admitted to the hospital with persistent fevers and a high clinical suspicion for COVID-19. He had no smoking history and was in good aerobic condition. His medication list included Flonase and Amlodipine-Benazepril 5-20mg once daily. The patient had a workplace exposure to a known COVID-19 case and subsequently developed subjective fevers, chills, and a mild headache. He presented to the "COVID clinic" on day 3 of symptoms. He was examined, determined to be low-risk, lacked any concerning clinical findings, tested for COVID-19, and dispositioned to home quarantine. His fevers and chills persisted into day 11 of illness. He also developed a decrease in appetite and anterior chest tightness. His wife (a healthcare professional) applied a home pulse oximeter, which measured an oxygen saturation of 87%. The patient returned to the emergency department for evaluation. He endorsed muscle aches and fatigue. He denied any shortness of breath, lightheadedness, nausea, vomiting, or diarrhea.

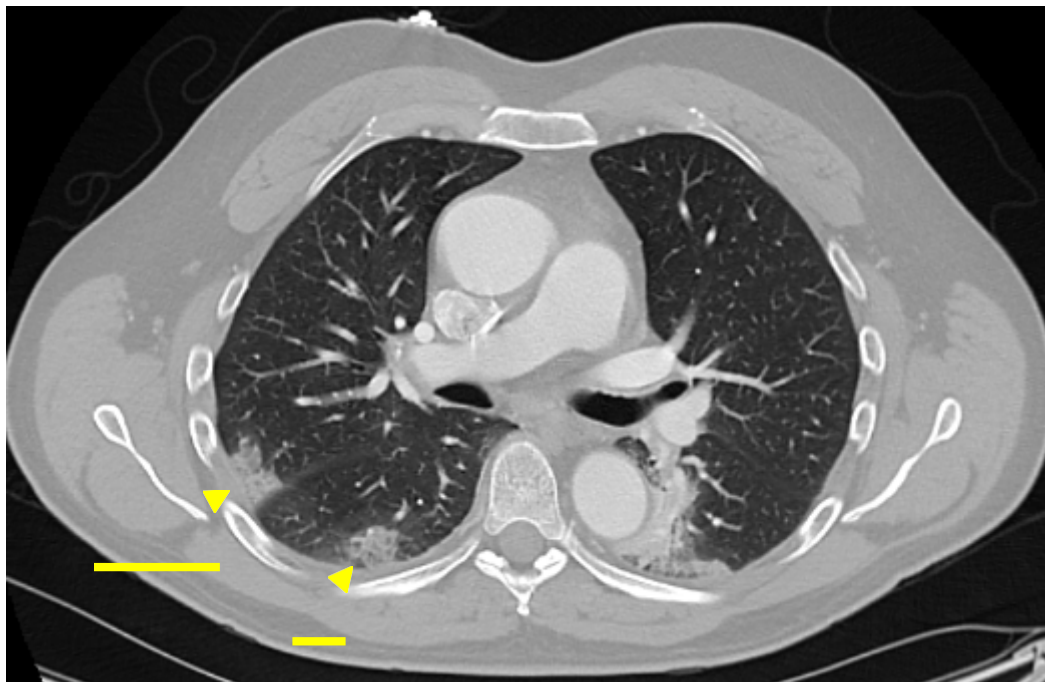
On exam, his temperature was 99.4 degrees Fahrenheit, pulse 100, blood pressure 127/78, respiratory rate 16, and oxygen saturation 97% on room air. His ambulatory oxygen saturation dropped to 87%. The patient was awake, alert, appropriate, and in no acute distress. His mucous membranes were moist. His heart exam revealed a regular rate and rhythm without murmurs. His pulmonary exam revealed bibasilar crackles and no wheezing, rales, or rhonchi. His abdominal exam was unremarkable. His extremities were warm and well-perfused.

His laboratory values revealed a white blood cell count of 5.5, a lymphocyte percentage of 15.1%, an

absolute lymphocyte count of 0.8, and a mild neutrophilia. His platelet count was slightly depressed at 127. His creatine kinase was normal. His high-sensitivity troponin was low risk at 6.4. His inflammatory markers were significant for an erythrocyte sedimentation rate of 55, C-reactive protein of 8.15, lactate dehydrogenase of 321, ferritin of 1698, and a D-dimer of 0.70. An interleukin-6 level was drawn on admission and resulted three days later at 55.6. A procalcitonin level was not drawn. A repeat COVID-19 test was drawn and resulted positive the next day. His initial COVID-19 test drawn in “COVID clinic” also returned positive.

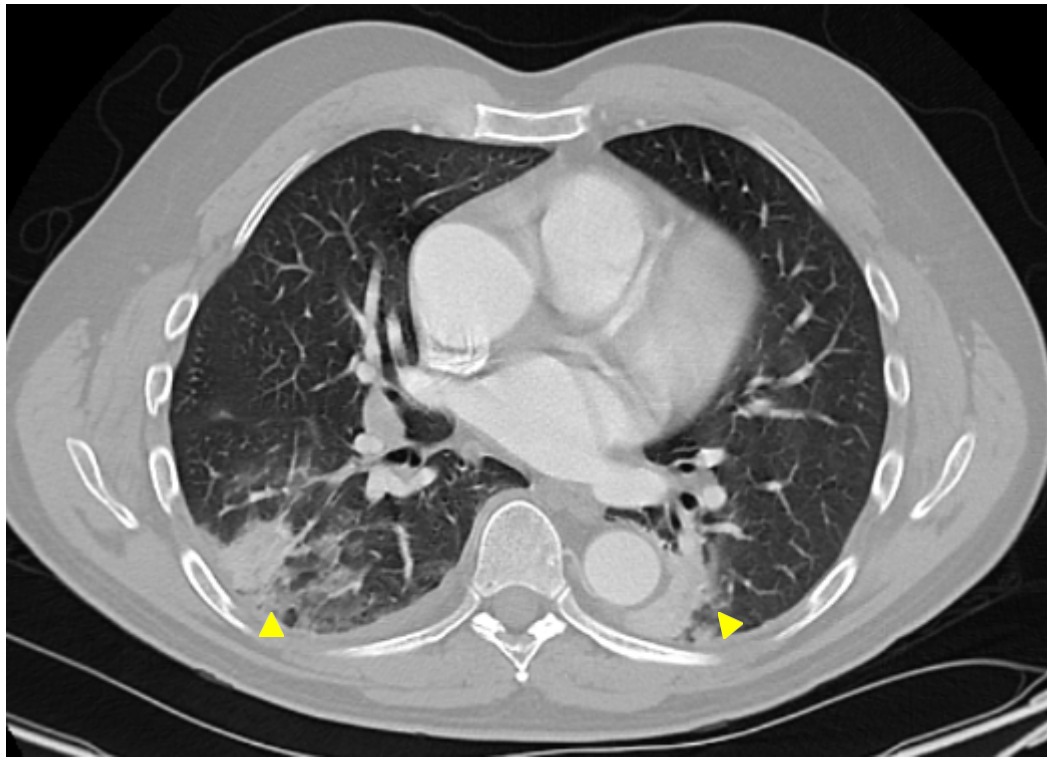
A portable chest x-ray revealed a non-specific patchy airspace opacity within the right lower lobe. A computed tomography pulmonary angiography [Figure 1] revealed multi-focal air-space opacities, which can be seen in multi-focal community-acquired pneumonia. Further discussion with radiology revealed that multi-focal peripheral ground glass opacities could be seen, which are commonly reported features of COVID-19. His EKG revealed a regular rate and rhythm with no ST changes or T-wave inversions.

Figure 1a:



*Multi-focal, peripheral, rounded ground glass opacities seen on the right upper and adjacent lower lobes (arrows) are commonly reported features of COVID-19*

Figure 1b:



*The multi-focal subsegmental consolidations, with ill-defined ground-glass opacities, of the posterior lower lobes (arrows), are non-specific.*

The patient was admitted to the hospital due to his ambulatory desaturation, report of chest tightness, duration of illness, and his universally severely-elevated inflammatory markers. He was placed on ceftriaxone 1g once daily and azithromycin 500mg once daily. He was placed in a negative pressure room with airborne isolation precautions. He was maintained on continuous pulse oximetry and telemetry. He remained on room-air during his three day hospital course and experienced no episodes of dyspnea. His chest tightness resolved. His lymphopenia and thrombocytopenia improved, while his inflammatory markers continued to elevate [Table 1]. His total white blood cell count, creatine kinase, and high-sensitivity troponin's all remained within normal limits. His appetite improved on day 3 of admission, and the patient began to feel more energy. His ambulatory oxygen saturation dropped to 87% on ambulation but promptly returned to 96%. Given his significant clinical improvement, the patient was discharged. He was given home isolation recommendations per Center for Disease Control and Prevention guidance and was told to contact the local public health department to receive additional instruction. A telephone follow-up two days post-discharge revealed significant clinical improvement. A follow-up phone call four days post-discharge revealed the patient had achieved complete symptom resolution.

Table 1:

Lab	Day 0	Day 1	Day 2	Day 3
WBC x 10 <sup>3</sup> /μL	5.5	5.2	5.5	4.4
Neutrophils abs x 10 <sup>3</sup> /μL	4.1	4.1	3.8	2.6
Neutrophil %	74.4	78.1	68.7	59.3
Lymphocyte abs x 10 <sup>3</sup> /μL	0.8	0.6	1.0	1.1
Lymphocyte %	15.1	11.6	18.7	25
Platelet x 10 <sup>3</sup> /μL	127	122	155	182
C-reactive protein mg/dL	8.15	9.01	5.05	
Erythrocyte sedimentation rate mm/hr		55	68	74
Ferritin ng/mL		1698	1723	1880
D-dimer μg/mL	0.70	1.11		
LDH U/L	321	321	316	
Albumin g/dL	4.1	4.1	3.6	3.8
Prothrombin time s	14.0			
Aspartate aminotransferase U/L	38	33	31	42
Alanine aminotransferase U/L	31	30	32	53
Creatine kinase U/L	46	50	51	49
Interleukin-6 pg/mL	55.6			
High-sensitivity troponin ng/L	6.4	6.8	6.1	

**Discussion:**

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We reviewed the literature for clinical and laboratory predictors of poor outcomes in COVID-19. We identified five retrospective studies and one prospective cohort study [Table 2, Table 3]. Four COVID-19 comparison groups were identified: severe versus non-severe disease, non-survivor versus survivor, refractory versus non-refractory COVID-19, and ARDS versus no ARDS groups. We will categorize the severe, non-survivor, refractory, and ARDS groups into a poor outcomes description in our discussion below. Of note, this review will not evaluate predictors of myocarditis in COVID-19, a known cause of disease mortality.

#### Clinical course:

Fever, cough, and fatigue are the most commonly reported symptoms of COVID-19 [1,2,3,4]. A recent COVID-19 meta-analysis substantiated this by reporting the most common disease-related symptoms as fever (82%, 95% CI 56-99%; n=4410), cough (61%, 95% CI 39-81%; n=3985), muscle aches and/or fatigue (36%, 95% CI 18-55%; n=3778), and dyspnea (26%, 95% CI 12-41%; n=3700) [10]. The duration of symptoms is also an important part of the clinical evaluation. There are two reported peaks of COVID-19. The first occurs at 14 days and the second occurs at 22 days [5]. One retrospective study reported median days to admission of 8 [7]. A second retrospective study reported median days to intubation of 14.5 [6]. Two additional retrospective studies reported mean days to death of 11 and 17.8 days [3,11].

#### Co-morbidities:

Older age and co-morbidities are well-accepted risk factors for poor outcomes. A meta-analysis revealed over twice the odds of developing severe disease for patients with hypertension (OR 2.36, 95% CI 1.46-3.83), cardiovascular disease (OR 3.42, 95% CI 1.88-6.22), and respiratory disease (OR 2.46, 1.76-3.44). However, high statistical heterogeneity was acknowledged [8]. Additional retrospective studies comparing the prevalence of co-morbidities in COVID-19 cases revealed similar, but inconsistent findings [Table 3].

#### Laboratory markers:

COVID-19 patients commonly have lymphopenia [2,7,21]. One study determined that lymphopenia could predict disease severity. At day 10-12, a lymphocyte percentage of less than 20% predicted “pre-severe” disease, while a percentage >20% predicted “moderate” disease that is curable. At day 17-19, a lymphocyte percentage <5% predicted severe illness requiring ICU level care, while a percentage >20% was more reassuring [9]. It is worth noting that lymphopenia can also be seen in autoimmune conditions, stress, acute infection, recent surgery, immunosuppressive drugs, and even as incidental findings in the elderly [12]. Leukocytosis is not consistently present, but is associated with poor outcomes. This is likely due to sepsis, a reported complication of COVID-19. Inflammatory markers are commonly elevated [Table 3]. The erythrocyte sedimentation rate is non-specific. Elevated lactate dehydrogenase, C-reactive protein, prothrombin time, and d-dimer are more commonly cited as predictors of severe disease [4,6,19,20,21,22]. Two retrospective studies cited 245 and 450 as cut-off values, respectively, for lactate dehydrogenase [4,6]. One retrospective study cited 5 as the cut-off value for C-reactive protein [4]. While ferritin is not consistently elevated, two retrospective studies cited 300 as a cut-off for predicting poor outcomes [4,6].

**Table 2 – Characteristics of included studies**

Study	Nation of origin	COVID-19 comparison groups	Study design	Sample size
Mo et al. [2]	China	Refractory vs. Non-refractory	Retrospective cohort	155
Wu et al. [4]	China	ARDS vs. No ARDS	Retrospective cohort	201
Zhou et al. [6]	China	Non-survivor vs. Survivor	Retrospective cohort	191
Zhang et al. [7]	China	Severe vs. Non-severe COVID-19	Retrospective cohort	140
Du et al. [19]	China	Non-survivor vs. Survivor	Prospective cohort	179
Li et al. [20]	China	Non-survivor vs. Survivor	Retrospective cohort	102



Co-morbidities and laboratory findings	Non-survivor vs. Survivor [6]	Refractory vs. Non-refractory disease [2]	ARDS vs. No ARDS [4]	Severe vs. Non-severe disease[7]	Non-survivor vs. Survivor [20]	Non-survivor vs. Survivor [19]
Hypertension	48% vs. 23%	No significant difference	27.4% vs. 13.7%	No significant difference	No significant difference	61.9% vs. 28.5%
Diabetes mellitus	31% vs. 14%	12% vs 3%	19% vs. 5.1%	No significant difference	No significant difference	No significant difference
Coronary artery or cardiovascular disease	24% vs. 1%	14% vs 0%	No significant difference	No significant difference	13% vs. 2%	57.1 vs 10.8%
Respiratory disease or COPD	7% vs 1%	NA	NA	No significant difference	No significant difference	NA
Leukocytes 10 <sup>9</sup> /L	9.8 vs. 5.2	No significant difference	8.32 vs. 5.02 10 <sup>9</sup> /mL**	5.3 vs. 4.5	9.1 vs. 5.5	8.9 vs. 5.1
Lymphocytes 10 <sup>9</sup> /L	0.6 vs. 1.1	No significant difference	0.67 vs. 1.08 10 <sup>9</sup> /mL**	0.7 vs. 0.8	0.5 vs. 0.9	0.7 vs. 0.8
Platelets 10 <sup>9</sup> /L	165.5 vs. 220	159 vs. 179 x	178 vs. 187 x 10 <sup>9</sup> /mL**	NA	113 vs. 206.5	NA
ESR	NA	No significant difference	No significant difference	NA	NA	NA
CRP mg/L	NA	46 vs. 23	83 vs. 234	47.6 vs. 28.7	78.7 vs. 25.4	86.4 vs. 36
LDH U/L	521 vs. 253.5	293 vs. 241	396 vs. 257	NA	569 vs. 272	NA
Ferritin	1435.3 vs. 503.2 µg/L	NA	1029 vs. 457 ng/mL	NA	NA	NA
D-dimer µg/mL	5.2 vs. 0.6	No significant difference	1.16 vs. 0.52	0.4 vs. 0.2	2.1 vs. 0.7	1.1 vs 0.5
PT seconds	12.1 vs. 11.4	NA	11.7 vs. 10.6	NA	14.9 vs. 14.1	No significant difference
Interleukin-6 pg/mL	11.0 vs. 6.3	NA	7.39 vs. 6.29	NA	48.4 vs. 4.2	NA
Procalcitonin ng/mL	0.1 vs. 0.1	No significant	No significant	0.1 vs 0.05	0.19 vs. 0.05	0.1 vs. 0.1

		difference	difference			
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**Table 3 – COVID-19 clinical and laboratory indices**

*Note: Clinical significance was defined by  $p < 0.05$ . Percentages are reported as prevalence of the co-morbidity within each respective group.*

*Laboratory findings were specified as values on admission for all five retrospective cohort studies.*

*Abbreviations: ARDS, acute respiratory distress syndrome; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase; PT, prothrombin time; NA, not addressed.*

*\*\*We believe 10<sup>9</sup>/mL units are reflected as an error and should reflect 10<sup>9</sup>/L. We have contacted the referenced journal to inquire.*

**Conclusion:**

The 2020 COVID-19 pandemic introduced a novel conundrum for the medical community. Hospital admission risks must be weighed against the benefit of intervening at the earliest sign of complications. A firm understanding of clinical and laboratory indices are a crucial part of this decision. We propose three basic steps to this decision: 1) consider co-morbidities, specifically hypertension, diabetes mellitus, cardiovascular disease, and respiratory disease, 2) consider duration of illness, with two peaks of illness occurring at 14 and 22 days, and 3) evaluate laboratory indices with a focus on lymphopenia, lactate dehydrogenase >245, C-reactive protein > 5.0, ferritin >300, and an elevated d-dimer. As an additional point, our case report and literature review demonstrates that while COVID-19 can cause significantly elevated inflammatory markers, it remains important to interpret these laboratory findings within the context of a comprehensive clinical evaluation. Future studies covering interleukin-6, procalcitonin, and other lab markers may provide additional value.

Limitations of this review include a lack of studies completed in the United States. Population and clinical practice habits may vary between the United States and China. Additional studies evaluating local populations would help provide additional clarity. Relatively small sample sizes, a wide range of lab results, and statistical heterogeneity detracts from the statistical power. Lastly, five of the six evaluated studies were performed retrospectively.

**Acknowledgments:**

We would like to thank Dr. Paul Clark for his consultation and review of the patient's chest CT scan findings.

**Disclosures:**

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**References:**

1. Singhal T. "A Review of Coronavirus Disease-2019." *The Indian Journal of Pediatrics*, April 2020, 87(4):281-286.
2. Mo P et al. "Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China." *Clinical Infectious Diseases*. 16Mar2020.
3. Leung C. "Clinical features of deaths in the novel coronavirus epidemic in China." *Rev Med Virol*. 2020; e2103.
4. Wu C et al. "Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China." *JAMA Internal Medicine*. 13Mar2020.
5. Ruan Q et al. "Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China." *Intensive Care Med*. 2020.
6. Zhou F et al. "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study." *The Lancet*. 28Mar2020;99:1054-1062.

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7. Zhang J et al. "Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China." *Epidemiology and Genetics*. 18Feb2020.
8. Yang J et al. "Prevalence of co-morbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis." *International Journal of Infectious Disease*. 5Mar2020.
9. Tan L, Wang Q et al. "Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study." *Signal Transduction and Targeted Therapy*. 27Mar2020.
10. Nascimento I et al. "Novel Coronavirus (COVID-19) Infection in Humans: A Scoping Review and Meta-Analysis." *J. Clin. Med* 2020, 9(4), 941.
11. Ruan S. "Likelihood of survival of coronavirus disease 2019." *Lancet Infectious Dis*. 30Mar2020.
12. Brass D, McKay P, Scott F. "Investigating an incidental finding of lymphopenia." *BMJ*. 3Mar2014.
13. Sarzi-Puttini P et al. "COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome?". *Clinical and Experimental Rheumatology*. 2020.
14. Singhal T. "A Review of Coronavirus Disease-2019." *The Indian Journal of Pediatrics*. 87(4):281-286. April 2020.
15. Wu Z, McGoogan J. "Characteristics of and Important Lessons From The Coronavirus Disease 2019 (COVID-19) Outbreak in China. Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention." *JAMA*. 24Feb2020.
16. Lake M. "What we know so far: COVID-19 current clinical knowledge and research." *Clinical Medicine*. Vol 20, No 2: 124-7. 2020.
17. Galli C, Plebani M. "Clinical laboratory and SARS-CoV-2 infection: where do we stand?" *Clin Chem Lab Med*. 24Mar2020. (*accepted*)
18. Lippi G, Plebani M. "Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis." *Clinica Chimica Acta*. 3Mar2020. (*accepted*)
19. Du R-H, Liang L-R, Yang C-Q, et al. "Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study." *Eur Respir J* 2020; 55:2000524.
20. Li K, et al. "Predictors of fatality including radiographic findings in adults with COVID-19." *Respiratory Research*. 21:146. 2020.
21. Yan et al. "An interpretable mortality prediction model for COVID-19 patients." *Nature Machine Intelligence*. Vol. 2: 283-88. May2020.
22. Poggiali et al. "Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in CoVID-19 patients." *Clinica Chimica Acta*. 135-138. Jun2020.

