Early View

Perspective

Clinical phenotypes of SARS-CoV-2: Implications for clinicians and researchers

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ABSTRACT

Patients with COVID19 present a broad spectrum of clinical presentation. Whereas hypoxemia is the marker of severity, different strategies of management should be customized to five specific individual phenotypes. Many intubated patients present with phenotype 4, characterized by pulmonary hypoxic vasoconstriction, being associated with severe hypoxemia with "normal" (>40 ml/cm H20) lung compliance and likely represents pulmonary microvascular thrombosis. Phenotype 5 is often associated with high plasma procalcitonin, and has low pulmonary compliance, being a result of co-infection or acute lung injury after non-invasive ventilation. Identifying these clinical phenotypes and applying a personalized approach would benefit in optimization of therapies and improving outcomes.

Tweeter feed:

SARS-CoV-2 infections present different specific individual phenotypes. Applying a personalized approach would benefit in optimization of therapies and outcomes improvement. @COVID19

The clinical spectrum of SARS-CoV-2 infection is broad, ranging from asymptomatic infection to flu-like illness (sometimes with digestive disturbances) to viral pneumonia. Patients with pneumonia may have only minor opacification with near normal Chest X-Rays but have a potential to develop an acute respiratory failure with severe hypoxemia of quick progression. Need for mechanical ventilation can be identified by increase in respiratory rates and requirement of high oxygen concentrations to maintain a venous oxygen saturation above 90%. However, due to the scenario of crisis with limited resources, many patients have been intubated with delay after failure trials of CPAP, non-invasive ventilation or high-flow nasal oxygen therapy. Thus, the estimation of risk factors for mechanical ventilation have not been well identified due to the lack of standardization of practices. This manuscript reports clinical experience from SARS-CoV-2 surge acquired in different hospitals from Italy and Spain (in march 27th, 2020) and it is supported by clinical observations, indeed. Further validation with stronger evidences would be required.

As with influenza, RT-PCR for SARS-CoV-2 is associated with frequent false negative results (1). Therefore, patients may be diagnosed by a characteristic CT scan. It is important to advise that high procalcitonin should not exclude the diagnosis, because it has been often reported in children and young adults and often suggests co-infection with a bacterial pathogen(2). Aging, hypertension and diabetes have been consistently reported as risk factors for death or severity, whereas pregnancy does not seem to be a risk factor like in influenza(3). Current reported information may have different profiles beyond China, affecting younger or obese subjects due to differences in prevalence and socialization. In China, SARS-CoV-2 has not shown a more severe disease in immunocompromised patients. That is in contrast with other respiratory viral agents, such as influenza, respiratory syncytial

virus, adenovirus, or rhinovirus, possibly because in coronavirus, the host innate immune response appears the main driver of lung tissue injury during viral infection(4). Caution should still be advised with immunocompromised patients as the total number of reported cases in this subgroup remains low.

Clinical and laboratory features are characteristic, with lymphocytopenia, elevation of lactate dehydrogenase, high plasma C-reactive protein and low procalcitonin(5). Many patients have hypercoagulability, increasing the risk of deep venous thrombosis, pulmonary artery micro-thrombosis, distal arterial micro-thrombosis affecting fingers, and cardiovascular events such as myocardial ischaemia, ischemic stroke, and pulmonary embolisms. In severe cases there can be dramatic elevation of D-Dimer values, reduced fibrinogen with a high INR and low platelet count, associated with the induction of tissue factor expression. Some ICU patients in China reported by Zhang et al (6) showed antiphospholipid autoimmune responses that led to thrombotic events, but lupus anticoagulant was not detected. Endothelial damage leading to inflammation and thrombosis plays a big role, indeed. Thus, all COVID19 hospitalized patients are tributary of benefit from prophylactic anticoagulation, unless they have severe thrombocytopenia or active bleeding. Long chain (unfractionated) heparin would theoretically be preferable because of their anti-inflammatory effects. Prescribing heparin to those patients with 6-fold levels of D-dimers above upper normal ranges has been associated with significantly reduced 28-day mortality rates (52% vs 32%, p=0.01) among 449 patients with severe SARS-CoV-2 infection in China (7). This scenario may suggest an alteration of the microvascular endothelium or a secondary micro-angiopathy activated by the virus or by an associated cytokine storm. Zhou et al (5) reported 54 non-survivors with median serum ferritine above

1400 ng/l. A few of these patients require bone marrow aspirate and may develop a hemophagocytic lymphohistiocytosis syndrome, requiring gamma-globulins and high-dose dexamethasone. As experience with endemic human coronavirus pneumonia is that it may double 12-month mortality(8), patients should be monitored after clinical cure to assess for persistent hyperinflammation or hypercoagulability and consideration for preventive interventions.

In an era of precision medicine, it is important to identify the main phenotypes in order to customize therapy in a personalized approach(9). A variety of proposed anti-viral, anti-inflammatory, anticoagulant and anti-fibrotic strategies may be beneficial or harmful depending on the state of disease. Recognition of different phenotypes of SARS-CoV-2 is therefore critical to clinicians and researchers for timely, effective and safe therapeutic interventions.

The most benign phenotype is the most common and only symptomatic therapy needs to be considered, being characterized by fever, headache or mild respiratory symptoms (like cough or sore throat) and malaise, but the chest X-ray is normal and hypoxemia is not present. A second phenotype represents 4/5 of hospitalizations and is characterized by the presence of hypoxemia or small chest-X ray opacities and these patients should be submitted to close respiratory monitorization, particularly respiratory rate and Sp02 because they are at risk of rapid deterioration progressing to death, if intubation is not timely instituted. These patients are typically hyper-inflamed and remain hypovolemic at hospital arrival. Thus, restriction of furosemide use should be considered, excepting if they have received a huge volume infusion.

Phenotype three represented 15% of hospitalizations in China(10) and present with greater hypoxemia and higher respiratory rates (to 30 breaths per minute or 25 bpm in healthy subjects under 55 years). Patients may present as phenotype 3 or progress from phenotype 2 because hypoxemia progress quickly. High IL-6 is a biomarker which may help to differentiate these two phenotypes. These phenotypes two and three are good candidates to randomized clinical trials to assess the efficacy of drugs with either anti-viral activity (to block replication very early), anti-inflammatory drugs or anti-fibrotic drugs. In our opinion, delaying intubation using non-invasive ventilation may induce acute lung injury. Given the good lung compliance and low work of breathing, these patients may avoid mechanical ventilation despite requirement for high FiO2, using prone position whereas they have spontaneous breathing. Pa02/Fi02 ratios should not be a criteria for intubation. Intubation should be clinically considered in presence of respiratory alkalosis with progressive hyperventilation when delivering high oxygen concentrations.

Phenotype 4 is characterized by severe hypoxemia requiring intubation, under strict measures to limit aerosolization. CT scans document edema in the lower lobes. Angio-CT in patients with multiple ground-glass opacities often disclose micro-embolic lesions. Lung ultrasonography is consistent with interstitial injury with B lines ("white lung") (11). In the presence of reduced sliding and multiple subpleural opacities, intubation should not be delayed, particularly when BB coalescent lines are present in all zones evaluated or in the majority (>3 fields explored). This phenotype is characterized by hypoxic vasoconstriction associated with severe hypoxemia. Nitric oxide or prostacyclin, when available, should be considered as potential rescue therapy. This phenotype has "normal" (>40 ml/cm H20) lung compliance and likely does not represents acute respiratory distress syndrome. The target

should be to maintain a Sav02 above 90%, avoiding ventilatory asynchronies. High PEEP in patients with normal compliance may have detrimental effects on hemodynamics (12). PEEP should be enough to be maintained at 8-10 cm H20, with higher levels compromising cardiovascular stability. Most patients had prior hyperinflammation, hyperpyrexia and are hypovolemic. Under these conditions, PEEP values above 10cm H20 may be harmful, being often associated with need of high dose vasopressors and acute kidney injury, complicating management. Respiratory rate should be lower than 20 bpm. Recruitment manoeuvres are not beneficial and are contraindicated. Prone positioning / supine cycles are of little benefit in this phenotype, contributing to increase risks of contamination and fatigue of healthcare workers. In this phenotype, high tidal volumes than 6ml/Kg are likely less harmful than in typical ARDS. Gattinoni et al (12) suggest that tidal volumes between 6-9 ml/Kg may be allowed to control hypercapnia because risk of ventilator-induced lung injury may be better tolerated if high lung compliances are maintained. These observations are consistent with a preliminary analyses of 16 patients (13).

Phenotype 5 is less common than phenotype 4 (see table 2) and it is an advanced stage with associated acute lung injury. Co-infection or acute lung injury is associated with increased plasma procalcitonin levels, which may help to distinguish it. This phenotype is rarely documented in patients who underwent rapid intubation, in our experience (table 1). It was typically present in patients with SARS-CoV-2 infection who were submitted to non-invasive ventilation (via helmet in Italy or facemask in China) but less common in patients started on ventilation promptly (14). Oxygenation should be assessed measuring the shunt fraction. Lung compliance show values under 40 ml/cm H20. This phenotype may benefit of high PEEP values and prone positioning, with a similar management strategy to ARDS. The

potential benefit of immunomodulatory agents at this stage may result in the emergence of severe adverse events, complicating management, such as systemic superinfections (viremia by cytomegalovirus and bacterial sepsis).

In summary, patients with COVID19 present a broad spectrum of clinical presentation . Whereas hypoxemia is the marker of severity, different strategies of management should be customized to the specific individual phenotypes (table 2). Applying a personalized approach would benefit in optimization of therapies and improving outcomes.

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Table 1 Clinical Data on 21 first patients requiring mechanical ventilation at the intensive care department in Hospital Hellin, Albacete, Spain*

Mean Age (range) years	61 (49-74)
Lung Compliance at onset of ventilation $\geq$ 40 ml/cm H_2O	14 (66.6%)
Lung Compliance at onset of ventilation < 30 ml/cm H_2O	7 (33.3%)
Deceased	2 (8.7%)
Successfully extubated	9 (34.8%)
Still intubated	12 (56.5%)

- Assessed at April 10th, 2020

Table 2. Clinical phenotypes of SARS-CoV-2 disease

Type	Proportion	Clinical features
1	80-85% of symptomatic patients	Fever, headache, mild respiratory symptoms, sore throat, no hypoxemia, normal CXR , excellent prognosis
2	~80% of hospitalised patients	Mild hypoxemka, minor, usually bilateral inflitrates on CXR, up to 15% may progress quickly to type 3
3	~15% of hospitalised patients	Moderate to severe hypoxemia and tachypnoea, high IL6 and other inflammatory markers. May progress to types 4 or 5.
4	~2/3 of patients needing mechanical ventilation	Severe hypoxemia requiring mechanical ventilation, normal lung compliance, good response to NO. Prone position of little benefit. TV > 6ml/Kg allowed. RR < 20 bpm. PEEP < 10cm H20.
5	~1/3 of patients needing mechanical ventilation	High procalcitonin, may be increased if mechanical ventilation is delayed in severely hypoxic patients, more in keeping with classical ARDS. Protective ventilatory strategy

		and prone position indicated.