

# Clinical risk stratification in COVID-19: the need for a revised approach?

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## Introduction

Accumulating evidence indicates a central role of vascular endothelial injury and immunothrombosis in the pathogenesis of severe COVID-19.<sup>1–3</sup> Pulmonary perfusion defects, representing micro- and macro-thromboses, are ubiquitous and extensive in those receiving intensive care.<sup>4,5</sup> The perfusion abnormalities are also present in those receiving ward-based care, occupying >20% of the lung volume.<sup>5</sup> While inflammatory and immunological drivers of COVID-19<sup>6</sup> remain highly relevant to disease severity and outcomes, occlusive pulmonary vasculopathy appears to play a key pathophysiological role in disease progression and respiratory failure. In this context, clinical risk stratification based on traditional models may be unsafe in COVID-19. This is consequent to the large reserve capacity of pulmonary perfusion, with respiratory failure occurring as a late and pre-terminal event in progressive perfusion loss.<sup>7</sup>

## Current approach to COVID-19 risk stratification

The current approach to clinical risk stratification in COVID-19 largely follows the model for a lower-respiratory illness and relies on symptoms and signs of respiratory failure (dyspnea and hypoxemia) to have a linear relationship with pathological progression. The World Health Organisation (WHO) defines mild COVID-19 as a limited upper respiratory infection with no radiological abnormalities. Patients with radiological changes with/without dyspnea, but no hypoxemia, have moderate disease, and those who develop hypoxemia ( $\text{SPO}_2 < 90\%$ ) have severe disease. Patients who develop acute respiratory distress syndrome (ARDS) are deemed critically ill. Mild and moderate disease are managed expectantly with an advisory to monitor for symptom progression. If symptoms worsen or hypoxemia occurs, hospitalization is advised, and

supplemental oxygen is provided along with therapeutic agents. Critical illness is managed based on established ARDS protocols. Venous thromboembolism prophylaxis is advised for hospitalized patients.

## Clinicopathological discordance in COVID-19 and flaws in the current approach

A striking feature of COVID-19 is the rapid deterioration seen in the second week of illness after days of smoldering infection.<sup>8</sup> Respiratory failure progresses abruptly from the onset of hypoxemia or dyspnea. As the clinical deterioration occurs around the time when adaptive immunity appears, it was initially postulated that the rapid deterioration, resulting in severe disease, occurs due to a dysregulated adaptive immune response. However, a fundamental assumption in this hypothesis is that clinical deterioration mirrors pathological deterioration, and that, this occurs concurrently in COVID-19. This assumption has several flaws. First, in several clinical conditions (e.g. coronary artery disease), pathology can progress significantly before signs or symptoms appear. Second, in COVID-19, the pathological progression is linear from symptom onset in those who develop severe disease. This is best demonstrated by radiological features of ground-glass opacities (GGO) that occur in the first week of illness, that progresses to consolidation, while new GGO appear.<sup>9</sup> A dissociation between pathological deterioration and progression of respiratory failure thus exists in COVID-19. This is atypical for pneumonia, but typical for disorders of the pulmonary vasculature,<sup>7</sup> where a large reserve exists, that has to be compromised before the failure of gas exchange can occur.

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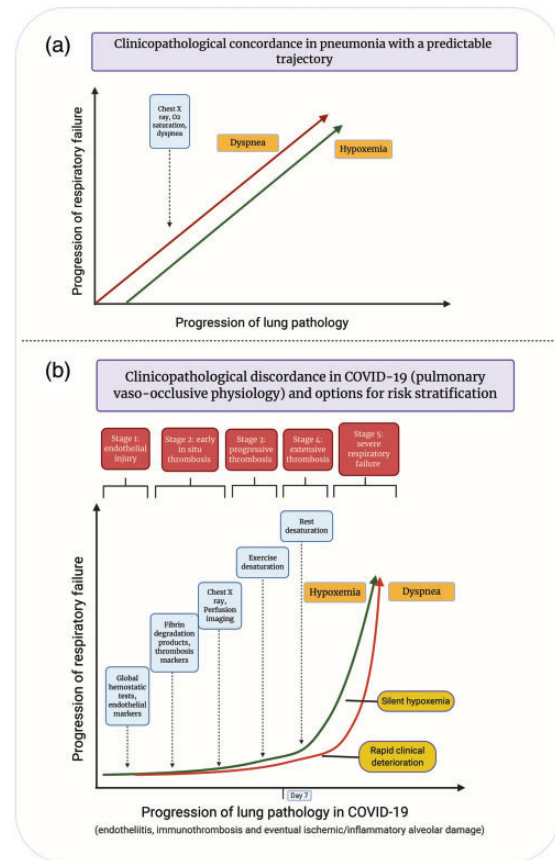


Additionally, while COVID-19 progresses from moderate to severe disease, it is observed that hypoxemia typically precedes dyspnea.<sup>10</sup> Significant hypoxemia may occur with the patient unaware, without increased work of breathing (“silent hypoxemia”). This is atypical for pneumonia, as for it to cause profound hypoxemia would require sufficient parenchymal involvement with alveolar exudate and increased extravascular lung water. Dyspnea would therefore accompany severe hypoxemia. This conundrum may be resolved by realizing that pulmonary vascular occlusion is the major determinant of COVID-19 progression.<sup>11</sup> In pulmonary vaso-occlusive disorders (except in post-capillary occlusion), lung parenchymal injury is not necessary for impaired gas exchange, and profound hypoxemia can occur without dyspnea.

Due to this observed dissociation between pathological progression, arterial oxygenation, and work of breathing, resulting from a dominant pathophysiological role of pulmonary vasculopathy, a risk stratification approach based on the “pneumonia model” can be unsafe in COVID-19. For instance, home management of moderate disease may fail to detect disease progression leading to hypoxemia, before the onset of dyspnea. Patients may therefore present late to the emergency department followed by rapid clinical deterioration. Furthermore, at the onset of hypoxemia and dyspnea, pathology would have progressed significantly with the exhaustion of physiological reserves, and adverse outcomes may ensue despite supportive interventions.

## Proposed approach to clinical risk stratification

The realization that thrombotic pulmonary vascular occlusion occurs early in susceptible individuals and progresses in a linear fashion, and that respiratory failure is a late feature suggesting extensive vaso-occlusion, should transform our approach to the disease. A new risk stratification model based on the stage of pathological progression may be more appropriate in this situation (Fig. 1). Stage 1 denotes endothelial injury without thrombosis, as indicated by elevated vascular injury markers or by abnormal global hemostatic assays that reveal a prothrombotic state, but with no radiological changes. Though endothelial injury is not unique to COVID-19, the extent and severity of endothelial damage, and evidence of viral cytopathic effect, distinguishes it from other viral illnesses.<sup>12</sup> Various endothelial injury markers that have been associated with poor outcomes in COVID-19 include thrombomodulin, P-selectin, and von Willebrand factor.<sup>13</sup> With the endothelial injury promoting a pro-thrombotic state, viscoelastic hemostatic assays such as thromboelastogram,<sup>14</sup> rotational thromboelastometry, and clot wave analysis<sup>15</sup> could be utilized to demonstrate hypercoagulability in COVID-19. If performed early in the disease course, these may identify patients who subsequently progress to diffuse thrombosis. Stage 2 of



**Fig. 1.** Clinicopathological discordance in COVID-19 and options for risk stratification at various stages of the disease progression. In pneumonia, there is concordance between pathological progression and symptoms/signs of respiratory failure, as the dominant pathology is alveolar exudate and the dominant mechanism of hypoxemia is alveolar hypoventilation/shunting and venous admixing. This facilitates early clinical risk stratification based on symptoms (dyspnea), arterial oxygen saturation, and radiological features. However, in COVID-19, due to the dominant pathophysiological role of pulmonary vascular occlusion in disease progression and abnormal gas exchange, there is discordance between the extent of pathology and respiratory failure severity. Distinct features include silent hypoxemia and rapidly progressing respiratory failure from the onset of hypoxemia and dyspnea. An alternate approach to risk stratification, that employs endothelial and thrombotic biomarkers, tests of global hemostasis, perfusion imaging, and dynamic measures of perfusion adequacy such as exercise oximetry may help identify pathological progression early and guide interventions. Early and appropriate antithrombotic strategy based on pathological severity may alter the natural history of the disease with improvement in outcomes.

early thrombosis is indicated by elevated markers of thrombosis/fibrinolysis such as d-dimer, or radiological findings of sub-pleural GGO with corresponding perfusion defects, indicating microthrombosis. These perfusion defects are best appreciated on dual-energy computerized tomography<sup>4</sup> that concurrently demonstrates parenchymal and vascular pathology, and is much superior to high resolution CT scan in this regard. Inflammatory markers such as C-reactive protein, interleukin-6, ferritin, and lactate dehydrogenase

show a linear rise at this stage and is able to predict patients who are at risk of progression to severe disease.<sup>16</sup> Stage 3 is progressive pulmonary thrombosis characterized by hypoxemia on exertion often without dyspnea. Some patients may not progress beyond this stage but continue to have exertional hypoxemia at hospital discharge despite otherwise being asymptomatic.<sup>17</sup> Stage 4 denotes extensive vascular occlusion with or without diffuse parenchymal injury and characterized by rest hypoxemia requiring oxygenation support, at risk of rapidly progressing respiratory failure. As initial parenchymal injury is often limited, lung mechanics are typically preserved during this stage of illness. Stage 5 is advanced respiratory failure requiring ventilatory support, associated with diffuse alveolar injury and fulfilling the clinical criteria for ARDS.

Identifying patients in stages 2 and 3, who may not have dyspnea but have progressive pulmonary vascular occlusion, is critical, as it is plausible that providing definitive antithrombotic treatment may prevent tissue infarction and mitigate lung injury. Importantly, hemorrhagic pulmonary infarction is more common with small than large vessel occlusion<sup>18</sup> and may explain peripheral wedge-shaped lung opacities of COVID-19. Additionally, for patients in stages 4 and 5, along with supportive care, early treatment of reversible pathology of pulmonary micro- and macrothromboses may be considered to improve gas exchange<sup>19,20</sup> and limit lung injury.

## Summary and conclusions

The current risk stratification approach that follows a pneumonia model may be inappropriate for COVID-19, where pulmonary vascular occlusion appears to be the major determinant of respiratory failure. Clinicopathological discordance in COVID-19 limits early clinical identification of pathological progression and necessitates a modified approach to risk stratification, informed by pulmonary perfusion physiology. If thrombosis is a major determinant of hypoxemia and disease progression in COVID-19, early antithrombotic measures could avert disordered gas exchange<sup>20</sup> and ischemic lung injury, with improvement in outcomes. To conclude, a proactive and pathophysiological approach to risk stratification, with an intent to alter the natural history of the disease, may be superior to a reactive approach in COVID-19.

## Conflict of interest

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