COVID-19 Related Acute Respiratory Distress Syndrome: Not so Atypical

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A short running head: Severe COVID19: not atypical.

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To the editor,

Patients infected with the SARS-CoV2 virus frequently develop COVID-19 related acute respiratory distress syndrome (ARDS). It has been advocated that ARDS related to COVID-19 is not “typical” ARDS [1] because patients have a better compliance of the respiratory system (Crs) that is discrepant to the amount of shunt. Later it was specified that this relates specifically to “L” type ARDS with a low elastance, low lung weight and low V/Q [2]. Treatment recommendations that have been based on conceptional physiological models resulting from these observations go against long standing evidence based interventions such as low tidal volume ventilation and prone positioning [1, 2].

ARDS was first described over 50 years ago as a syndrome that presents with *“acute onset of tachypnea, hypoxemia, and loss of compliance after a variety of stimuli; the syndrome did not respond to usual and ordinary methods of respiratory therapy”*. This description is strikingly similar to the common presentation of patients with severe COVID-19 pneumonia. The mean compliance of the respiratory system (Crs) of intubated COVID19 patients ranged between 30-50 mL/cmH2O in two recent series [1, 3]. These values are actually comparable to those reported in LUNG-SAFE, the largest observational cohort study to date [4]. While patients with non-COVID-19 related ARDS do frequently <u>not</u> show signs of DAD on autopsy [5], the available autopsy reports of patients who died from COVID19 show DAD even in patients who never received mechanical ventilation [6]. The available data indicate that severe COVID-19 pneumonia is similar to the original description of the syndrome and fits within the current consensus definition.

In recent years, the pulmonary critical care community has come to realise that

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ARDS can be split into subphenotypes (figure 1) that might respond differently to interventions [7]. Heterogeneity can be observed in: (1) the etiology of lung injury, (2) physiological changes, (3) morphology of affected lung parenchyma and (4) biological response. Based on post-hoc analyses of randomized clinical trials, patients with systemic hyper-inflammation might respond different to higher end-expiratory pressure, restrictive fluid management or immunomodulation with simvastatin treatment while patients with a non-focal lung morphology benefit more from recruitment than prone positioning [8, 9]. However, no one is advocating for implementing these personalised approaches into clinical practice before they are validated in prospective clinical trials, despite a much stronger basis of evidence than is currently provided for COVID-19 related ARDS phenotypes.

Etiology is generally a minor determinant of the pathophysiological presentation of ARDS, meaning that many patients with a similar “hit” show different biological, physiological and morphological patterns. COVID19-related ARDS is an etiological subphenotype of ARDS with a particular set of characteristics: frequent DAD, (possibly) a higher than expected Crs, low PaO2/FiO2 values, frequent non-focal morphology and some suggestions of profound systemic inflammation (figure 1). But are patients with COVID-19 related ARDS inherently different from “typical ARDS”? With appreciation of the heterogeneity within ARDS we have come to realise that there is no “typical ARDS”.

Despite the described heterogeneity that is inherent to the syndromic definition of ARDS, low tidal volume ventilation was found to decrease mortality in an unselected population and prone positioning was effective in patients with persistent hypoxemia. Yet, these interventions are the ones that are now challenged for the supportive

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treatment of COVID-19 related ARDS [2]. Does subphenotyping of COVID-19 related ARDS require a different level of evidence before we adjust clinical practice? Or were we too strict in implementing subphenotype based interventions in the pre-COVID-19 era? I would argue that we should maintain the highest standard to adjust our clinical practice and resist the temptation to jump to conclusions and provide alternative treatments that might harm our patients.

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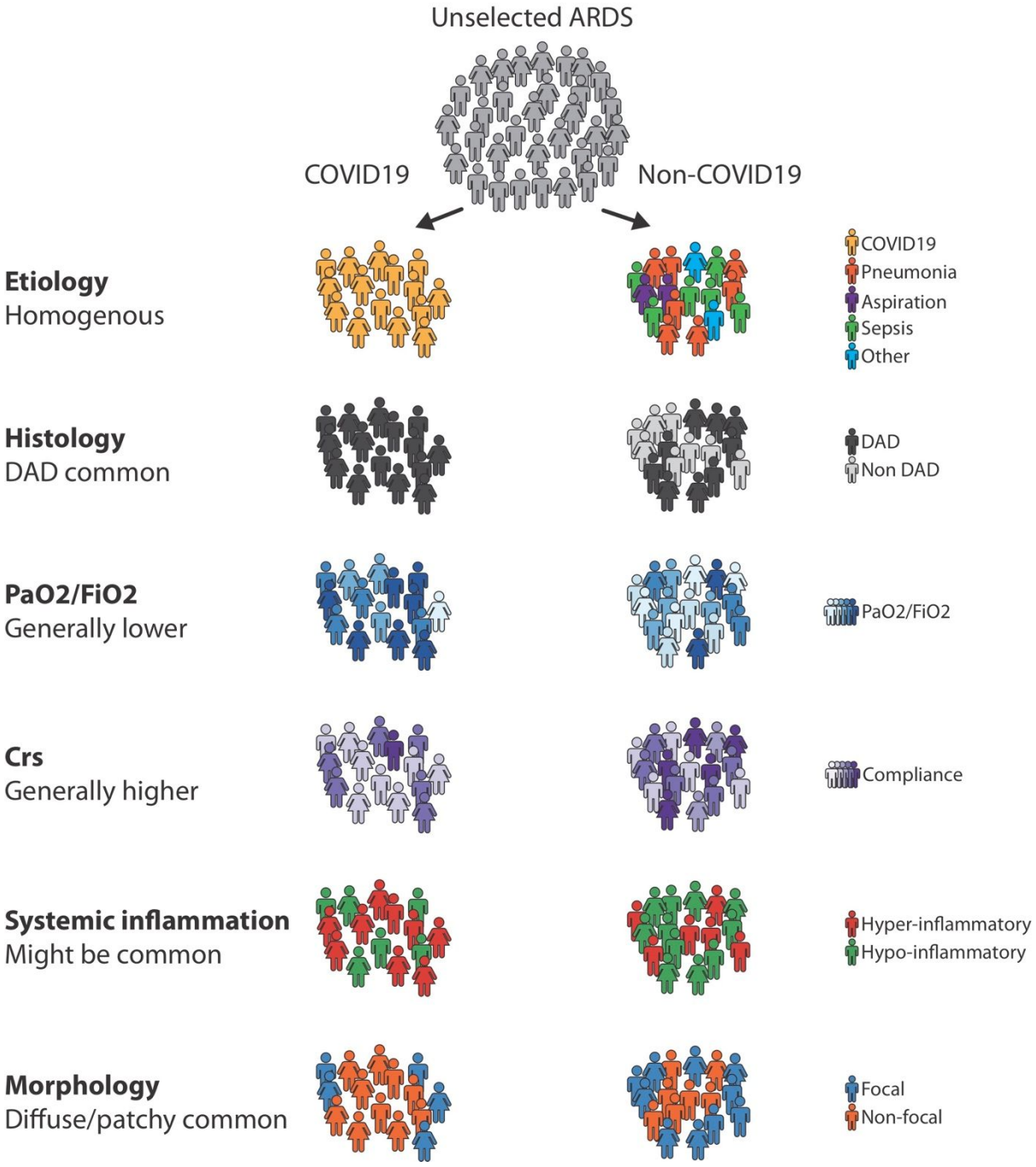
Figure 1: Subphenotypes of ARDS, stratified for the etiological subphenotype of COVID-19 related ARDS.



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