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Prognostic Factors Associated with High-Risk for Fatal ARDS in COVID-19 and Potential Role for Precision Medicines as Part of COVID-19 Supportive Care Algorithms

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Approximately 20-30% of patients infected with the new coronavirus, SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), develop viral pneumonia that causes an acute lung injury (ALI) capable of rapid progression to viral sepsis and acute respiratory distress syndrome (ARDS) [1]. A systemic inflammatory response syndrome, also referred to as cytokine storm or cytokine release syndrome [CRS], is generally thought to be the driving force behind the ARDS and often irreversible multi-organ dysfunction associated with the severe-critical forms of COVID-19 [1]. There have been conflicting reports about the prognostic value of co-morbidities as well as clinical and laboratory parameters that are associated with a high risk for the development of respiratory failure, ARDS, and multi-organ dysfunction in COVID-19. This report summarizes our current knowledge regarding the patient characteristics, co-morbidities, and laboratory parameters associated with disease progression and development of ARDS in COVID-19.

Wu et al. reported that among 201 COVID-19 patients, ~42% developed ARDS, and of these patients with ARDS ~52% died [2]. Risk factors associated with the development of ARDS included older age as well as higher lactate dehydrogenase (LDH) and D-dimer (a fibrin degradation product and marker of coagulation system dysfunction or disseminated intravascular coagulopathy [DIC]) values [2]. Notably, patients ≥65 years of age had a ~3.3-fold increased risk of developing ARDS than patients <65 years of age (95% CI: 2.1-5.1, P<0.001). Importantly, they also observed that once patients with ≥65 years of age develop ARDS, their risk of death is 6.2-fold higher (95% CI: 3.3-11.7, P<0.001) than the risk of younger patients. Similar findings were reported by Lian et al., who compared the risk of ARDS for patients ≥60 years of age vs. that for patients <60 years of age and found that the older patient population had a 3.1-fold higher risk of developing ARDS [3]. Lian et al. also showed that older patients had a significantly higher CRP level than younger patients (19.9 mg/L [5.6-44.7 mg/L] vs. 6.8 mg/L [2.0-16.9 mg/L], P<0.001) [3]. Zhou et al. reported on the clinical course and mortality-associated risk factors in COVID-19 patients. Whereas the median age for non-survivors was 69 years, the median age for survivors was 52 years (P<0.0001) [4]. Thirty-two of 191 patients (16.8%) developed ARDS at a median

of 14.5 days (IQR: 12.0-19.0 days), and 31 of these patients requiring mechanical ventilation (MV) died (~97%). The median time from illness onset to ARDS was twelve days for non-survivors and ten days for survivors. Older age, diabetes, as well as higher levels of serum D-dimer, LDH, and Ferritin were associated with a higher risk of death [4]. Serum LDH>245 U/L, D-dimer >1,000 ng/mL, and Ferritin >300 μg/L had univariable odds ratio (OR) values of 45.4 (95% CI: 6.1-338.4), 20.0 (95% CI: 6.5-61.6), and 9.10 (95% CI: 2.0-40.6), respectively [4].

A recent review of 17 clinical studies by Carver and Jones also confirmed that older age, diabetes, higher serum levels of inflammation markers (LDH, C-reactive protein [CRP]), and coagulopathy with higher D-dimer levels in the serum are associated with a higher risk for ARDS [5]. A meta-analysis of 13 studies by Zheng et al. including a total of 3,027 COVID-19 patients identified age ≥65 years (OR = 6.1, 95% CI: 4.0-9.2, P<0.00001), diabetes (OR = 3.7, 95% CI: 2.7-5.0, P<0.00001), hypertension (OR = 2.7, 95% CI: 1.6-4.6, P=0.0002), LDH >245 U/L (OR = 43.2, 95% CI: 9.9-188.5, P<0.00001), D-dimer >500 ng/mL (OR = 43.2, 95%CI: 9.9-188.5, P<0.00001) as significant risk factors for disease progression [6]. The prognostic significance of CRP, Ferritin, D-dimer, and LDH was further confirmed by Terpos et al. [7].

Disease progression from mild-moderate to severe-critical was systematically analyzed by Bi et al. [8]. Among the 417 patients who were classified as mild or moderate at the time of initial assessment, 21.6% (90/417) progressed to the severe stage. Those who progressed to the severe stage progressed within on average 9.5 days (95% CI: 8.7-10.3) after symptom onset. They developed ARDS on average 11.0 days (95% CI: 9.7-12.3) after symptom onset. Patients with certain co-morbidities such as diabetes and hypertension at baseline and/or laboratory parameters such as high concentration of CRP, LDH, and high concentration of D-dimer formed a higher risk subgroup with a higher likelihood of progression to ARDS. In this high-risk group, Bi et al. estimated that 43% (95%CI: 35-52%) cases (i.e., twice as many as the 21.6% for the total population of mild-moderate patients) became severe and 9% (95%CI: 4%-14%) required ICU admission within 14 days from symptom onset [8]. Notably, older patients had a 3.6-fold (95% CI: 1.8-6.9) higher risk of progression to ARDS. Almost half (46.3%, 50/108) of the patients at ≥60 years of age progressed to the severe or critical stage [8].

More information has recently become available regarding the patient characteristics, disease progression, and clinical outcomes for the COVID-19 patient population in the U.S. Gold et al reported the results on 305 patients hospitalized in Georgia in the month of March 2020 [9]. 37.6% of the 117 patients in the high risk age category ≥65 years required high-flow oxygen, or noninvasive ventilation (NIV), whereas 41.0% developed ARDS and required MV. By comparison, 25.6% of the total population required high-flow oxygen or NIV, and 30.6% developed ARDS. The ARDS rates requiring MV were 23.9% for the 50-64 years age group, and 18.2% for the 18-49 years age group [9]. Richardson et al. reported the data on 5700 COVID-19 patients who were hospitalized in the New York City area between March 1 and April 4, 2020. 1151 patients (20.2%) developed ARDS and required MV [10]. Two hundred eighty-two of these patients (24.5%) died. The mortality rate was highest for the ≥65 years of age subgroup (97.2%). Of the 2634 patients who either died or were discharged alive, 12.2% had developed ARDS requiring MV. For the >65 years age group, this percentage was 25.4%.

In summary, approximately 20% of COVID-19 patients with mild-moderate disease progress to severe-critical disease and this percentage is ~40% for the high-risk subgroup ≥65 years of age with co-morbidities or laboratory parameters indicative of systemic inflammation such as high levels of CRP, LDH, and Ferritin or a dysfunction of the coagulation system as evidenced by elevated D-dimer levels. High-risk patients not only have a higher incidence of ARDS, but they also progress faster and have a significantly higher mortality rate. Treatments capable of preventing the disease progression and/or reducing the case mortality rate in the high-risk COVID-19 patients are urgently needed.

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In this context, precision medicines we [11-18] and others [19] have developed as anti-inflammatory drug candidates could be repurposed as adjuncts of the supportive care algorithms in an effort aimed reducing the case mortality rate which remains an unmet and urgent medical challenge for high-risk patients.

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