

**Title:** Statistical power boost for broadly applicable host immune response-based tools

**Background:** COVID-19 is a diversely manifested and potentially deadly disease. This is challenging for patient management and development of evidence-based tools, especially considering SARS-CoV-2 evolution and variable pandemic mitigation strategies. Early detection of COVID-19 progression aids in resource allocation and enables timely escalation of care. MeMed has developed a severity prediction test based on an algorithm combining measurements of three immune proteins, creating a technology-human biology synergy that leverages the immune response. Establishing health system comparability is essential when combining data from multiple COVID-19 sub-cohorts, which separately provide low statistical power. To address this, a framework was constructed assessing two dimensions of poolability: respiratory status and therapeutic management.

**Methods:** To derive the severity algorithm, 518 patients were recruited (March – Nov 2020) from IL (Hasharon, Beilinson, Hillel Yaffe, Shaare Zedek), DE (Saarland University) and US (Maimonides). Recruitment is ongoing (December 2020-today) for a validation study, with 548 patients recruited from US and IL. To establish sub-cohort comparability regarding respiratory status, the objective parameter SpO<sub>2</sub>/FiO<sub>2</sub> was selected, as the lowest value during the patient's hospitalization course is indicative of worst respiratory performance. Additionally, to establish the equivalence of therapeutic management, adherence to NIH treatment guidelines was scored.

**Results:** SpO<sub>2</sub>/FiO<sub>2</sub> median (interquartile range, IQR) values for US versus IL patients intubated with mechanical ventilation (IMV) are 91.0 (6.8) and 90.5 (9.0), respectively (p=0.98). Median (IQR) values for non-IMV US versus IL patients are 373.0 (205.0) and 328.0 (194.0), respectively (p=0.12). The adherence rates to NIH treatment guidelines per treatment class are also not significantly different (p=0.113 to p=1.000)

**Conclusion:** SpO<sub>2</sub>/FiO<sub>2</sub> values for IL and US are comparable, supporting that the respiratory status and healthcare of COVID-19 patients is not significantly different across geographies. Similarly, NIH guideline adherence rates are comparable. Together, the objective respiratory parameter and treatment scoring, indicate that patients can be pooled from these sub-cohorts.