LEVERAGING THE IMMUNE RESPONSE TO IMPROVE OUTBREAK MANAGEMENT: DERIVATION OF A RAPIDLY MEASURABLE HOST-PROTEIN SIGNATURE FOR STRATIFYING SEVERITY OF COVID-19 PATIENTS

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Background:

In most SARS-CoV-2-positive patients, a localized, short-lasting immune response is sufficient to clear virus from the lungs. However, in up to 14% of patients, a dysregulated immune response ensues, triggering a hyperinflammatory state that can lead to acute lung injury, acute respiratory distress syndrome, organ failure, and death. Despite multiple evaluation tools, early and objective detection of progression to severe COVID-19 disease remains a major challenge. We describe derivation of a rapidly measurable immune-signature that indicates the likelihood of severe COVID-19 outcome based on TNF-related apoptosis-induced ligand (TRAIL), interferon gamma-induced protein-10 (IP-10), and C-reactive protein (CRP), host-immune proteins that change expression levels in response to infection severity.

Results:

Between March and November 2020, 518 COVID-19 patients were recruited. 394 were eligible for the derivation cohort; 113 (28%) patients met the composite severe outcome. In area under the receiver operating curve (AUC) analysis, COVID-19 severity score with AUC 0.86 (95% confidence interval, CI: 0.81-0.91) outperformed other biomarkers reported as candidate severity stratification tools, including IL-6 (n= 139; AUC 0.77 (95%CI: 0.67-0.87); p=0.03).

Additionally, the tool's performance was assessed by demonstrating a significant trend in likelihood ratio going from low to high score bins, showing that the likelihood of severe outcome significantly increases with increasing score ($p < 0.01$). This trend was significant ($p < 0.01$) also when only severe patients meeting outcome on day of/after blood sampling were included (n=339; 58 severe and 281 non-severe). The probability for 14-day mortality was assessed with Kaplan-Meier survival estimator. Survival distribution was significantly different across the bins ($p < 0.01$).

Conclusions:

The COVID-19 severity score has potential to serve as an accurate risk stratification tool, facilitating timely escalation of care across acute settings. A multinational multicenter validation study is ongoing. Capability to perform the test rapidly and easily using the newly developed analyzer can support better triage decisions, leading to improved patient outcomes and objective resource allocation, thereby relieving burden on the healthcare system.

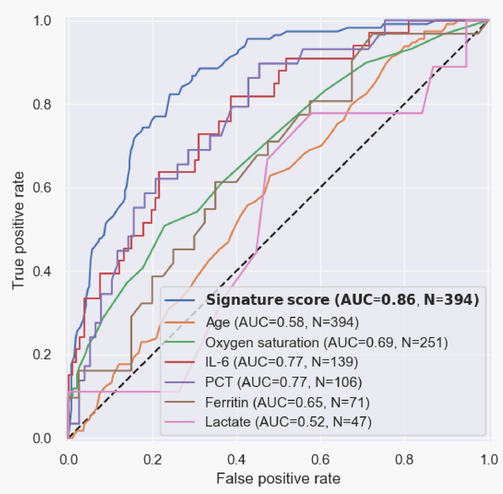
Methods:

SARS-CoV-2-positive hospital admitted adult patients were recruited in USA, Germany, and Israel. Severe outcome was defined as mortality or ICU-level care (i.e., ICU admission, high flow nasal cannula, continuous positive airway pressure, bi-level airway pressure, intubation with mechanical ventilation). TRAIL, IP-10 and CRP were measured using an analyzer that provides values from serum in 15 minutes.

To integrate TRAIL, IP-10 and CRP levels into a single score (ranging from 0-100) we chose regularized logistic regression due to its relative simplicity. The final model (MeMed COVID-19 Severity™) was trained on the entire derivation cohort and showed comparable results to 10-fold cross validation indicating it was not over-fitted.

To render the model clinically intuitive, four score bins were developed where each patient is assigned to a bin based on their score: bin 1, $0 \leq score \leq 20$, very low likelihood for severe outcome; bin 2, $20 < score < 40$, low likelihood for severe outcome; bin 3, $40 \leq score \leq 80$, moderate likelihood for severe outcome; and bin 4, $80 < score \leq 100$, high likelihood for severe outcome.

Host signature outperforms candidate severity biomarkers



Host signature is predictive of survival