Early Inflammatory Profiles Predict Maximal Disease Severity in COVID-19

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Results

Between March 2020 and April 2021, we included 312 individuals for analysis

PCA and cluster analysis demonstrated 4 distinct clusters. Demographics of the cohort and the 4 clusters are shown in Table 1

Table 1. Participant Demographics

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Non-Caucasian ethnicity (%)</th>
<th>Smokers (%)</th>
<th>Ever drank (%)</th>
<th>Diabetes (%)</th>
<th>Hypertension (%)</th>
<th>Severe disease (%)</th>
<th>Immunosuppressed (%)</th>
<th>vWF (%)</th>
<th>IL18 (%)</th>
<th>IL17A (%)</th>
<th>IL15 (%)</th>
<th>IL12p70 (%)</th>
<th>TNF alpha (%)</th>
<th>ICAM 1 (%)</th>
<th>Eselectin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47 (37-56)</td>
<td>59 (50-68)</td>
<td>25 (20-30)</td>
<td>10 (12%)</td>
<td>32 (34-36)</td>
<td>10 (13%)</td>
<td>36 (34-38)</td>
<td>27 (25-29)</td>
<td>10 (14%)</td>
<td>30 (30)</td>
<td>27 (28)</td>
<td>44 (41)</td>
<td>27 (28)</td>
<td>10 (12)</td>
<td>27 (26)</td>
<td>26 (23)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>2</td>
<td>52 (45-59)</td>
<td>62 (59-65)</td>
<td>20 (21-23)</td>
<td>4 (4-6%)</td>
<td>32 (30-34)</td>
<td>13 (13%)</td>
<td>31 (29-34)</td>
<td>25 (23-27)</td>
<td>13 (12%)</td>
<td>30 (30)</td>
<td>27 (28)</td>
<td>42 (40)</td>
<td>27 (28)</td>
<td>10 (12)</td>
<td>27 (26)</td>
<td>26 (23)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>3</td>
<td>50 (43-56)</td>
<td>62 (59-65)</td>
<td>25 (20-30)</td>
<td>25 (23-27)</td>
<td>30 (28-32)</td>
<td>13 (13%)</td>
<td>31 (29-34)</td>
<td>25 (23-27)</td>
<td>13 (12%)</td>
<td>30 (30)</td>
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<td>18 (17)</td>
</tr>
</tbody>
</table>

<Heatmap demonstrating the differences in biomarkers between clusters>

Clustering and progression to moderate or severe disease

Cluster 1 – Less inflamed. This cluster was characterized by low levels of inflammation

Cluster 2 – Tissue repair. Compared to cluster 1, this cluster had upregulation of growth factors (EGF, VEGF, PDGF, TGFβs) and endothelial activation (e-selectin, p-selectin)

Cluster 3 – Tissue injury. This cluster had the highest levels of markers of early alveolar epithelial injury (RAGE, ST2). Levels of innate immune activation (IL-6, procalcitonin, CRP, TNFα) and coagulation (d-dimer, TPO) were higher than between clusters 1 and 2, but lower than cluster 4, and compared to cluster 4 this cluster had relative downregulation of growth factors, markers of endothelial activation and immune regulation (IL-10, PDL1)

Cluster 4 – Systemic inflammation. This cluster had the highest levels of markers of innate immune activation, coagulation and microbial translocation (f-FABP, Beta-2-glucan)

Association between cluster membership and increasing maximal disease severity

In univariate analysis, compared to cluster 1, while all clusters had a higher odds of increased disease severity, cluster 3 (tissue injury) had the strongest association with more severe disease

In multivariate analysis, adjusting for demographic variables associated with increased risk of severe COVID-19, membership in cluster 3 remained most strongly associated with more severe disease

Conclusions

Distinct early inflammatory profiles predicted maximal disease severity independent of known risk factors for severe COVID-19

A cluster with relative downregulation of growth factor and endothelial markers, and early evidence of alveolar epithelial injury, was associated with highest risk of disease progression

Whether this inflammatory pattern reflects a dysregulated inflammatory response to SARS-CoV-2 that could improve targeted treatment requires further study

References & Acknowledgements


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