Biomarker Levels Concur with a Risk Stratification Criteria in Covid-19 Pneumonia, a Role for a Prognostic-Tool for Identification of Clinical Deteriorators

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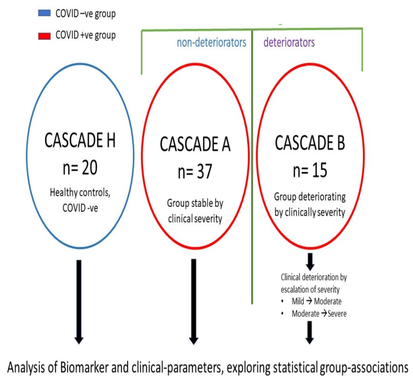
Abstract

Rationale: COVID-19 pneumonia patients present with respiratory symptoms that range in severity from mild, moderate to severe. Only a small group of patients require high-dependency/intensive care. They account for much of the COVID-19 pneumonia mortality. A reliable early prognostic for severe COVID-19 pneumonia is needed to improve outcomes. To address this unmet need, we tested a wide range of potentially important peripheral blood biomarkers in a group of clinically defined stratified COVID-19 patients in order to identify the most predictive of disease progression. **Methods:** Patients and healthy controls recruited are summarised in Figure 1. They were clinically stratified into mild, moderate and severe according to their degree of respiratory failure on admission. Biomarkers levels, taken on admission and repeated samples on the ward were analysed using ANOVA across severity groups. Spearman-correlation coefficients against pairs of average levels from each biomarker within severity-group and healthy controls at time 1 and 2 were assembled into a 76x76 matrix and agglomerative hierarchical clustering was applied to generate the final heatmaps. Linear-discriminant analysis (LDA) was carried out on a reduced optimised set of biomarkers to explore the boundaries between the clinical severity groups. **Results:** Degree of lymphopaenia, neutrophil levels, TNF-α, INR-levels, and pro-inflammatory cytokines; IL6, IL8, CXCL9 and D-dimers were significantly increased in COVD-19 patients compared to healthy controls ($p<0.05$, 95% C.I.). C3a and C5 was significantly elevated in all categories of severity compared to healthy controls ($p<0.05$), C5a levels were significantly different between "moderate" and "severe" categories ($p<0.01$). sC5b-9 was significantly elevated in both the "moderate" and "severe" category of patients compared to healthy controls ($p<0.001$).Heatmap analysis demonstrated distinct visual differences of biomarker profiles between the clinical severity groups. LDA on the deteriorators, non-deteriorators and healthy volunteers as a combined function of the predictor variables: C3, eosinophil-counts, granulocyte colony-stimulating factor (G-CSF), fractalkine, IL10, IL27, LTB4, lymphocyte count, MIG/CXCL9, M-CSF, platelet count and sC5b-9 showed clear separation between the groups based on biomarker/blood-count levels. **Conclusions:** Diagnostic and clinical assessments followed by robust statistical and machine learning approaches could identify peripheral blood biomarkers for prognostic stratification of patients with COVID-19 on arrival in hospital. The pattern of discriminating biomarkers between stable and deteriorating COVID-19 patients evolved with time. The biomarkers of those requiring increased support including IMV, showed dysregulation of the terminal complement pathway.

Methods

Figure 1. Schematic summary of the organisation of groups within the CASCADE study. CASCADE-H: recruited from hospital volunteers with stable medical conditions including diabetes and hypertension from non-clinical staff at Queen Alexandra Hospital, UK, 10 aged ≤50years and 10 >50years. CASCADE-A: 37 patients with stable clinical severity throughout hospital stay. CASCADE-B: 15 patients who deteriorated and required either IMV or died .



Results

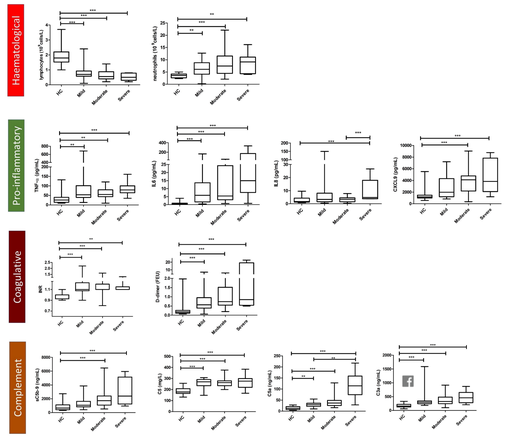


Figure 2. Clinical severity categories reveal underlying significant differences in biomarker profiles. Classes of biomarkers separated those COVID-19 pneumonia patients with mild, moderate and severe respiratory failure.

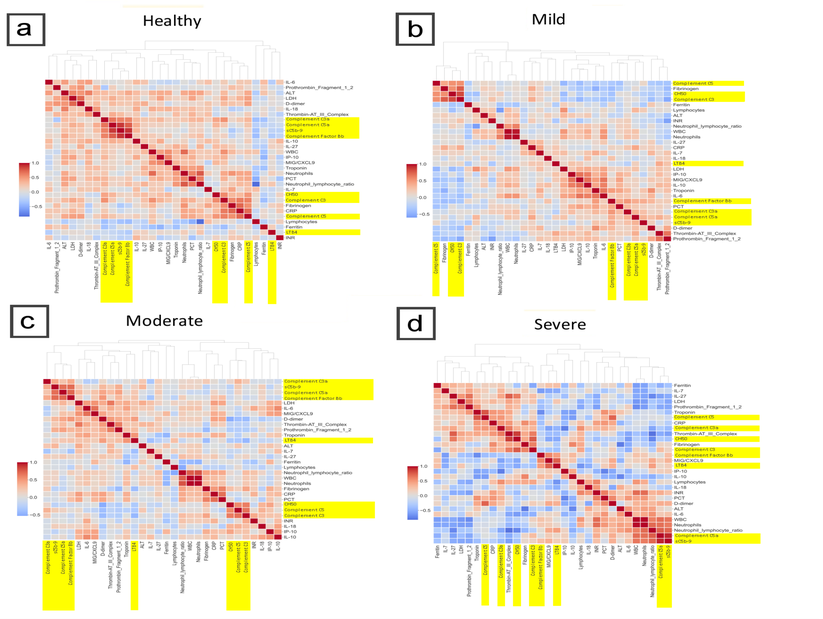


Figure 3. Differential Spearman-correlation coefficient relationships of biomarkers across COVID-19 disease severities. Red pixels indicate positive correlation (where biomarkers have an additive effect), blue pixels represent negative correlation (where biomarkers have an opposing effect to each other). Complement related biomarkers are highlighted in yellow. The amount of "blue" pixels indicating lower correlation increase with worsening of respiratory failure.

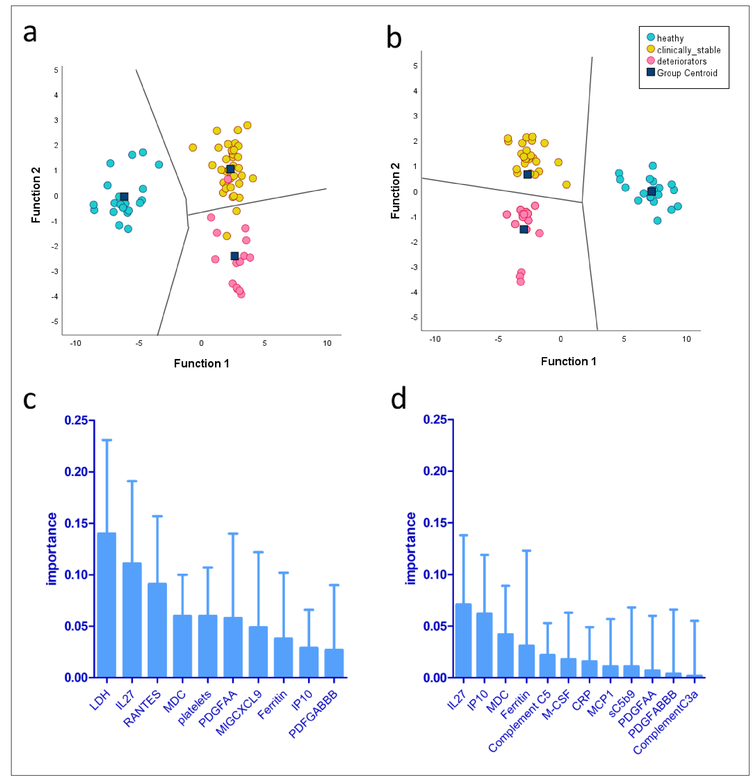


Figure 3. Machine-learning employing Linear Discriminant Analysis (LDA) prediction algorithm to identify patients with an increased risk of clinical deterioration. (a) LDA carried out on biomarker values at time-point 1 (admission to hospital) and (b) LDA at time-point 2 (day-1 of clinical deterioration). (c) Biomarkers in rank-order for LDA-model at time-point 1 (d) biomarkers pertinent to LDA-model time-point 2. Note the change in pattern of the biomarkers with time

Discussion

A total of 76 biomarkers were tested and the CASCADE study showed the levels of biomarkers correlated with "final" degree of severity of respiratory failure experienced by the patients. These patterns changed in time within each the severity groups. Our LDA-model was able to reduce the set of biomarkers and predicted which patients were at a higher risk of deterioration and death. What was interesting is that the pattern of biomarker changes in the set of later samples demonstrated that C5a, C3a and C5b-9 had become major discriminants, each of which has recognised pathological roles.

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