Deux contributions à BELVIR 2025 — Études transcriptomiques sur le Long COVID

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Synthèse par Marc Jamoulle

Deux travaux majeurs ont été présentés au 13e symposium annuel BELVIR, illustrant la manière dont la transcriptomique sanguine, l'analyse des biomarqueurs et les approches de modélisation avancées permettent d'éclairer les mécanismes du Long COVID et leur retentissement clinique. Ces études combinent données moléculaires, indicateurs fonctionnels, imagerie et variables thérapeutiques afin d'obtenir une vision intégrée de la persistance virale et de ses conséquences sur la santé globale des patients.

Auteurs

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1. **Étude 1 — Analyse du réseau de biomarqueurs du Long COVID**
   (Poster par Daniel Sanson, abstract ci-dessous)

Cette étude repose sur deux approches complémentaires : une sélection supervisée de variables par algorithme Boruta et un modèle de réseau corrélationnel. Elle montre que le Long COVID est un syndrome caractérisé par un enchevêtrement de signaux inflammatoires, immunitaires, plaquettaires et viraux, révélant des marqueurs centraux tels que IL-18, PTGS2, HDAC5, ainsi que des corrélations significatives avec les traitements.

2. **Étude 2 — Anticorps neutralisants et persistance virale**
   (Présentation orale par Mss Chenyu voir ci-dessous)

Cette étude démontre que les patients Long COVID conservent une réponse vaccinale normale, mais que la large neutralisation observée est paradoxalement associée à la persistance virale, notamment via ORF3a. Elle met en évidence un profil immunitaire particulier pour le variant Delta, dominé par une réponse IgE atypique.

3. Le rôle central de l’indicateur fonctionnel COOP–WONCA

Les COOP–WONCA Charts ont été utilisés comme instrument d’évaluation globale de l’état de santé. Les analyses montrent des corrélations importantes entre les scores COOP et des biomarqueurs tels que IL-18, PTGS2 et HDAC5, permettant de relier la signature transcriptomique à l’impact fonctionnel.

4. ORF1ab et Mpro : marqueurs de persistance virale et clefs thérapeutiques

ORF1ab est un indicateur direct de réplication virale résiduelle. Mpro, protéase principale du SARS-CoV-2, est essentielle à la réplication virale. La détection d’ORF1ab implique la présence de Mpro. Paxlovid, inhibiteur de Mpro, est associé à une amélioration clinique et à une réduction de l’inflammation.

5. Synthèse clinique globale

Le Long COVID apparaît comme un syndrome objectivable caractérisé par une persistance virale, une activation immunitaire chronique et une altération de la santé fonctionnelle. Les COOP–WONCA constituent un outil essentiel pour relier biologie moléculaire et réalité clinique, tandis que les biomarqueurs identifiés ouvrent la voie à une médecine personnalisée du Long COVID.

POSTER 10

Abstract 10 | Desentangling the Long Covid biomarker network: Insights into viral persistence and therapeutic response using random forest feature selection

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Long COVID, also referred to as post-acute sequelae of SARS-CoV-2 infection (PASC), is a complex multisystem syndrome characterized by persistent symptoms across diverse biological systems. Accumulating evidence indicates SARS-CoV-2 viral persistence and subsequent inflammation, coagulation defects, auto-antibody development, and tissue damage as root causes. Our groups and others have demonstrated viral RNA and protein persistence (SIMOA) up to 2 years after acute COVID. To identify biomarkers predictive of clinical outcome, Boruta, a supervised feature selection algorithm based on random forest classification, was utilized to objectively identify demographic, clinical (patient-reported COOP score, clinician-reported Long COVID grade), and molecular (nCounter digital transcriptomics) predictors from 78 patients with long-term follow-up. In addition to the variables selected by Boruta, age, sex, vaccination status, COVID episodes, viral RNA load (VL), and SARS-CoV-2 ORF1ab (protease target of Paxlovid) transcripts were added based on prior biological relevance. A Gaussian graphical model was then established, applying a correlation-based approach to visualize and examine the interdependencies among selected variables. The resulting correlation network revealed prominent clusters and interconnected modules involving immunological markers (e.g., *IL18* with COOP Feeling, $r = 0.32$, $p = 0.0075$; *HDAC5* with COOP Change, $r = 0.39$, $p = 0.00094$), clinical scores and patient-reported outcomes, and therapeutic interventions (e.g., antiplatelet therapy with Long COVID grade, $r = -0.43$, $p = 0.00044$; antiviral therapy (Paxlovid) with Long COVID grade, $r = -0.27$, $p = 0.026$). The variable Delta COOP, representing temporal changes in patient-reported general health status, exhibited significant correlations with specific RNAs including *PTGS2* ($r = 0.41$, $p = 0.0081$), *DDX50* ($r = -0.31$, $p = 0.045$), and *NCF2* ($r = 0.41$, $p = 0.0083$), indicating its relevance in assessing disease progression, identifying central nodes with high connectivity. VL was inversely correlated with *PTGS2* ($r = -0.36$, $p = 0.0012$), and positively correlated with *HDAC5* ($r = 0.31$, $p = 0.0061$). Of note, both are promising therapeutic targets since *PTGS2*, which encodes COX-2, is inhibited by well-known anti-inflammatory drugs such as aspirin and ibuprofen, while the *HDAC5* gene can be targeted by FDA-approved histone deacetylase inhibitors including Vorinostat, Panobinostat, and Belinostat. Moreover, Paxlovid use also showed a negative correlation with *IL18* ($r = -0.25$, $p = 0.028$). The analysis underscored complex interplay between immune mediators, platelet-related markers (*IL12A/HDAC5*), and symptom domains, further identifying time after acute COVID as a key factor of *TLR7* ($r = 0.42$, $p = 0.0002$), Long COVID grade ($r = 0.43$, $p = 0.0003$) and viral load ($r = -0.39$, $p = 0.0006$).
In conclusion, combining supervised Boruta selection and network correlation analysis provides a comprehensive framework for characterizing the intricate biology of Long COVID and prioritizing candidate viral (VL) and/or immune biomarkers (IL18) or therapeutic targets (PTGS2/HDAC5).

SHORT TALK

Abstract 12 | Broadly neutralizing antibodies to SARS-CoV-2 in Long COVID are associated with viral persistence and clinical outcome

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Long COVID (also known as post-acute sequelae of SARS-CoV-2, PASC) is a chronic condition in which symptoms persist months or years after the acute infection. Neutralizing antibody responses induced by infection and/or vaccination are a surrogate marker for protection against COVID-19. However, their potential role in Long COVID patients is currently unclear. Herein, we performed pseudoneutralization assays (MSD) of 10 different SARS-CoV-2 variants and whole blood digital transcriptomics (nCounter, Nanostring) in a real-world, perspective Long Covid cohort (n=49 paired samples), examining possible correlations with clinical (brain imaging (SPECT-CT), severity, COOP chart scores) and demographic data. Across all variants, the number of vaccine doses was significantly correlated with broad neutralization activity ($P<0.001$, $R>0.4$ for WT, Alpha, Beta, Gamma, Delta), indicating vaccine response is not defective in Long COVID patients. Moreover, broad neutralization activity was positively correlated with SARS-CoV-2 ORF3a RNA ($P= 0.0085$, $R = 0.37$), consistent with previous findings of viral persistence in Long COVID, while inflammatory chemokines CCL2 and CXCL10 ($P=0.016$, $R=-0.346$) were negatively correlated with broad neutralizing antibodies. Interestingly, for the Delta variant, a unique transcriptomic profile was observed compared to all other variants, with negative correlations to IgE heavy chain RNA (*IGHE* $P=0.00085$, $R=-0.37$) and cell cycle-related transcript *CDC20* ($P=0.00085$, $R=-0.37$). This points at an IgE-dominated humoral response to the Delta variant, which may help explain both its higher virulence and immune escape from neutralizing antibodies. Although middle-aged women are more frequently affected by Long COVID, age and sex were not significantly associated with neutralizing antibodies to any variant. From a clinical standpoint, broadly neutralizating antibodies were unexpectedly associated with worse clinical outcome, quantified by COOP score changes from baseline (higher values indicate worsening, $P= 0.0048$, $p = 0.42$). In conclusion, our data suggest the presence of a viral reservoir in Long COVID that continuously stimulates neutralizing antibody production, which is however associated with worse clinical outcome. Humoral immune response to the Delta variant is skewed to IgE dominance in Long COVID patients, in keeping with its higher virulence.