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MORNING BRIEF

Scientific Review

22 July 2020

The purpose of the Morning Brief is to summarize and present key information, research articles and other relevant publications pertaining to critical care and COVID-19.

Stellenbosch University Research Response Team

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Content

T and B cell receptor sequencing

Please cite this article in press as: Schultheiß et al., Next-Generation Sequencing of T and B Cell Receptor Repertoires from COVID-19 Patients Showed Signatures Associated with Severity of Disease, Immunity (2020), https://doi.org/10.1016/j.immuni.2020.06.024

Immunity

CellPress

Article

Next-Generation Sequencing of T and B Cell Receptor Repertoires from COVID-19 Patients Showed Signatures Associated with Severity of Disease

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Likely that ability to mount protective adaptive immune response plays role in control or progression to severe disease

Likely that anti-viral and promotion of adaptive immunity most promising early in disease, while suppression of inflammation necessary in late disease.

Aimed to describe the adaptive immune response in hospitalised and mild to moderate recovered cases – immunosequencing, serology, cytokines and flow cytometry

Hypothesis: early recovery patients would have persistent immune receptor signatures in post-infection blood

20 samples from 19 recovered patients
- Mild to moderate disease, outpatients
- Median age 34, majority no comorbidities

50 samples from 20 active hospitalised patients
- Median age 67, 18/20 with comorbidities, 12/20 critically ill on mech ventilation or ECMO

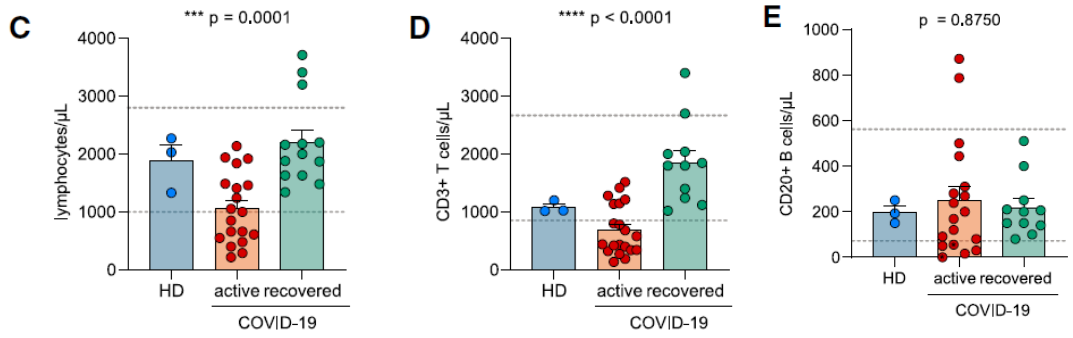
39 healthy SARS-CoV-2 antibody negative controls, age-matched

32 of 37 patients evaluable were positive for antibodies by ELISA at least at one time point

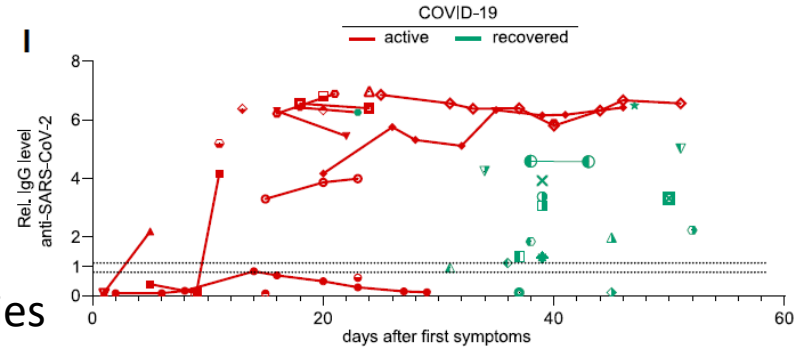
35 of 37 positive by neutralisation assay at least at one time point

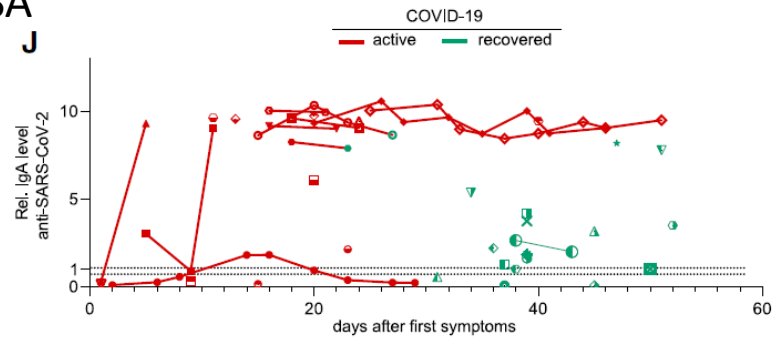
Active cases generally higher titres than recovered patients

Variability in titres among the recovered patients

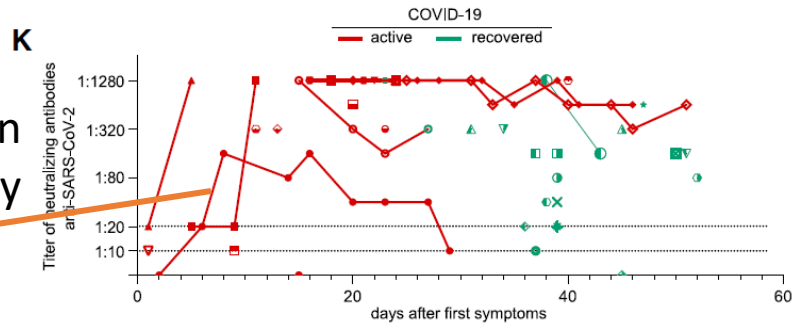


Antibodies by ELISA





Neutralisation assay



Haematological malignancy, stem cell transplant 7 months before, on immunosuppressive therapy for graft-versus-host disease

Cytokine and flow cytometry analysis

- Not discussed in detail
- Interesting finding – several cytokines remain elevated in recovered asymptomatic patients

B and T cell receptor background
Antigen-binding region varies between cells = variable region
Two variable regions from two chains of the receptor
Each consists of 3 hypervariable regions
Repertoire = total collection of unique antigen-binding regions, ++ variation which ensures that virtually any structure of an antigen can be recognised and bound
Humans at least 10^11 unique specificities
Binding of antigen to a specific B-cell receptor, activates cell and leads to clonal expansion
Lymphocyte expresses several exact copies of only 1 type of antigen binding region

Mechanism for diversity of naïve B and T cells – the variable region of the antigen binding site is not encoded by a single gene segment, but by several different segments which are rearranged and recombined during lymphocyte development

Activated B-cells further diversified by somatic hypermutation – "fine-tuning" of binding affinity by point mutations during clonal expansion – positive selection of antigen-binding regions with better binding affinity

Next generation sequencing of T and B cell receptors – DNA sequences, qualitative information presence or absence of sequences, diversity of the repertoire
Created T and B cell receptor sequence repository (online, public)
37 patients, 69 time points
overall >6.2 million BCR
>8.3 million TCR sequences

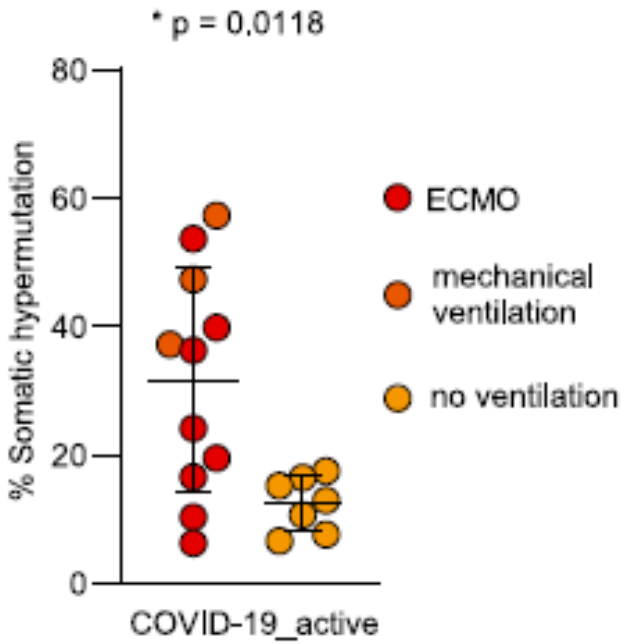
Aimed to investigate nature of protective versus detrimental B and T cell responses, specifically whether there were differences in the receptor repertoire between these groups

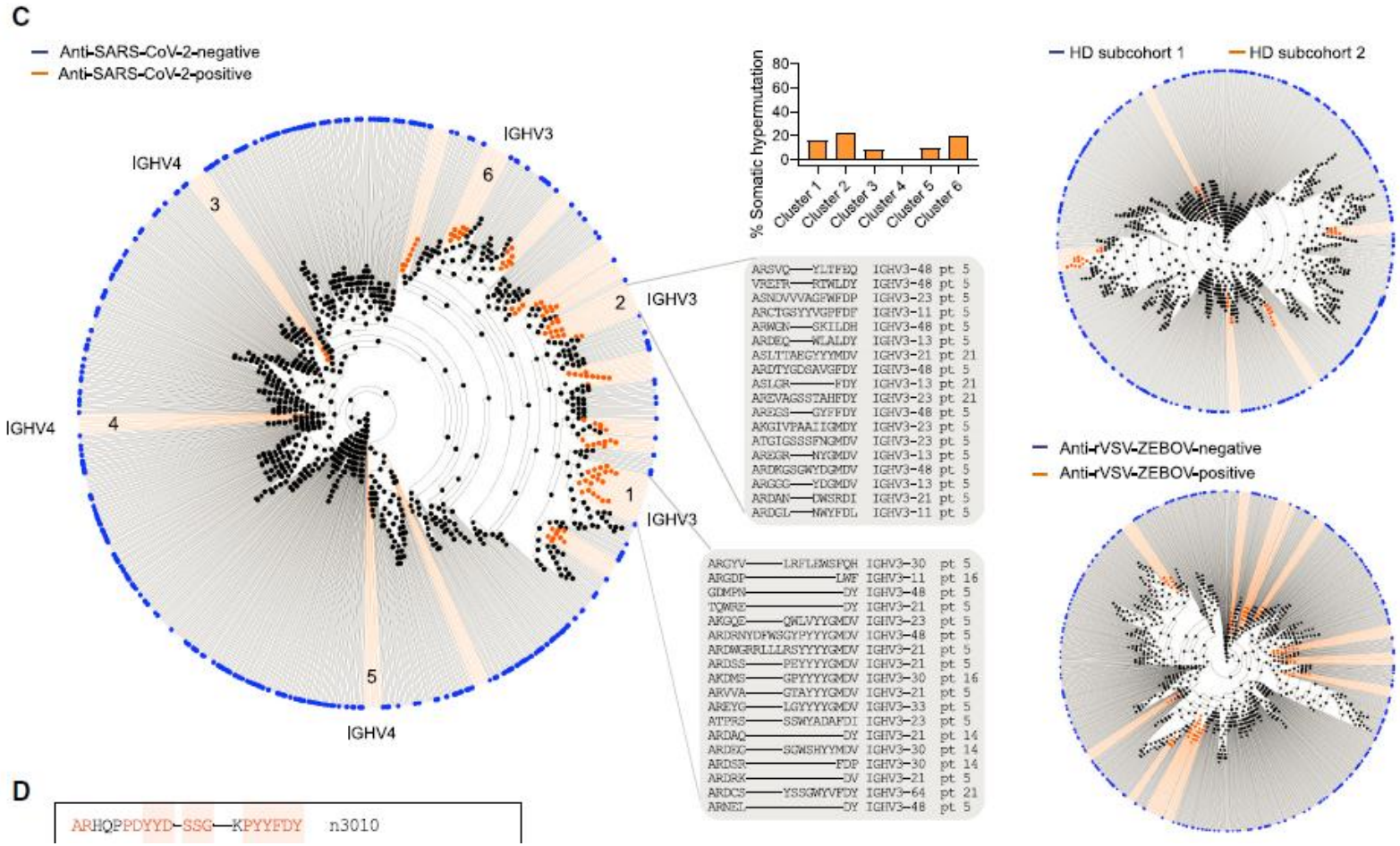
- Diversity
- % somatic hypermutation in B cells
- Identifying specific sequences that likely originate from SARS-CoV-2 specific T and B cells
- Comparison of "public" and "private" clonotypes

Did not quite have the study design and data to answer their question – discussed in their limitation section

More somatic hypermutation in patients on ventilation / ECMO vs not

- Indication of low % of naive B-cells
- Broad range across individuals
- BCRs with high somatic hypermutation did not show greater clonal expansion than those without





Looked for convergent BCR sequences across COVID-19 patients, to identify potential antibodies specific to SARS-CoV-2

Compared

- 13 Covid-19 repertoires
  - Aligned to 6 SARS-CoV-2 antibody negative healthy person repertoires
- 13 rVZV-EBOV Ebola vaccine vaccinated immunogenic healthy persons
  - Aligned to 5 rVZV-EBOV vaccinated non-immunogenic healthy persons
- 13 and 6 healthy controls

Show preferential usage of Ig heavy chain variable region 3 (IGHV3) subfamily genes, mostly rearranged with Ig heavy chain joining region 4 (IGHJ4) or IGHJ6 gene segments

Low levels of somatic hypermutation – may suggest that the diversity of the naive B-cell repertoire is important in effective immune response – speculative

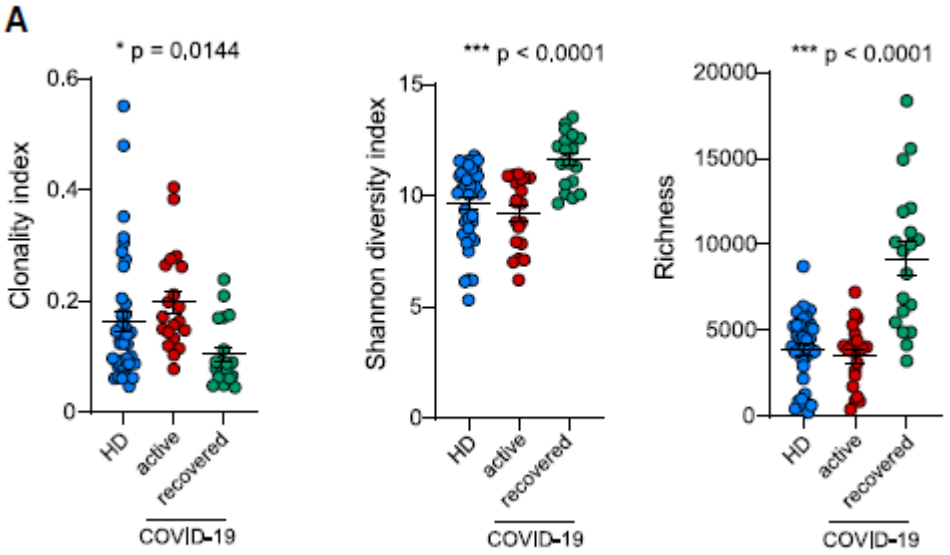
No single dominant clone emerged in response to SARS-CoV-2

T cell findings

- Increased diversity and richness in recovered patients compared to healthy patients – diversification may be important for effective immune response

“Public” T-cell clonotypes shared by > 60% of population
“Private” clonotypes not widely shared – if present in several individuals exposed to same infectious agent, can be assumed to be specific to that agent, measured with pGen index

- Clusters exclusively present in severe cases (vs mild cases) were predominantly public clonotypes
- Several clusters exclusively present in recovered cases and shared by several individuals, were private, possibly representative of specific SARS-CoV-2 T-cells



Limitations

- Few samples, few early samples, no comparison of symptomatic mild vs symptomatic severe disease

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This summary was prepared by Dr E Maasdorp as part of the daily brief to the TBH ICU team.