The Daily COVID-19 Literature Surveillance Summary

March 10, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Epidemiology

- Can we open schools safely and limit the spread of SARS-CoV-2 infection? In a viewpoint article by the researchers of CDC, they present data that illustrates that in-person school attendance is not related to increased transmission or outbreaks in communities, with the significant exception to this being high school athletics. They state that overall, especially when proper prevention guidelines (facemasks, hand hygiene, postponing indoor and contact sports) is implemented, in-person school is safe for communities.

Transmission & Prevention

- Delayed large local reactions may occur with the mRNA-1273. In a letter to the editor of the New England Journal of Medicine, physicians describe a short 12-patient case series of delayed large local cutaneous reactions to the mRNA-1273 COVID-19 vaccination. The authors found that median time of onset of the reactions was on day 8 post-first dose, that all of the reactions appeared near the injection site, and resolution of symptoms occurred in a median of 6 days. The implication being that as more vaccinations occur en masse, clinicians need to have more information about these reactions to better help address patient concerns and management options when confronted with them.

- SARS-CoV-2 501Y.V2 variant escapes neutralization by South African COVID-19 donor plasma. A study conducted by researchers from South Africa investigated a SARS-CoV-2 pseudovirus expressing the South African variant lineage 501Y.V2 (B.1.351) and found it was able to effectively evade two major classes of neutralizing antibodies with dependence on the K417 residue. Samples of polyclonal plasma/sera from PCR-confirmed severe SARS-CoV-2 infection contained higher neutralizing antibody titers, however when assessed with the 501Y.V2 pseudovirus, 21/44 (48%) showed no detectable neutralization activity, signifying individuals with previous SARS-CoV-2 infection may have reduced antibody efficacy against the 501Y.V2 variant compared to previously identified variants. These findings suggest the need for rapidly adaptable vaccine design platforms and viral targets less susceptible to mutation for future immunogenicity.

R&D: Diagnosis & Treatments

- Early versus deferred timing of anti-SARS-CoV-2 convalescent plasma does not appear to differ in clinical impacts on COVID-19 patients. This controlled, open label phase II randomized clinical trial conducted by investigators at School of Medicine and Chilean Academic medical center in observed the outcomes of receiving early versus deferred convalescent plasma in 58 patients (1 patient withdrew consent) hospitalized with COVID-19 confirmed by RT-PCR. 28 participants received plasma on the day of enrollment and 30 patients received plasma between 3 days or greater than 7 days after enrollment based on development of respiratory failure or persistence of COVID-19 symptoms after 7 days of enrollment. There was no statistically different outcome between patients who received early or deferred convalescent plasma, suggesting clinical outcomes are not impacted by the timing of plasma initiation.

TABLE OF CONTENTS

EPIDEMIOLOGY

DATA AND POLICY TO GUIDE OPENING SCHOOLS SAFELY TO LIMIT THE SPREAD OF SARS-COV-2 INFECTION

Honein MA, Barrios LC, Brooks JT.. JAMA. 2021 Mar 2;325(9):823-824. doi: 10.1001/jama.2021.0374.
Level of Evidence: 5 - Review / Literature Review

BLUF

In a viewpoint article by the researchers of CDC in January of 2020, they present data that illustrates that in-person school attendance is not related to increased transmission or outbreaks in communities, with the significant exception to this being high school athletics. They state that overall, especially when proper prevention guidelines (facemasks, hand hygiene, postponing indoor and contact sports) is implemented, in-person school is safe for communities.

DELAYED LARGE LOCAL REACTIONS TO MRNA-1273 VACCINE AGAINST SARS-COV-2

Blumenthal KG, Freeman EE, Saff RR, Robinson LB, Wolfson AR, Foreman RK, Hashimoto D, Banerji A, Li L, Anvari S, Shenoy ES.. N Engl J Med. 2021 Mar 3. doi: 10.1056/NEJMc2102131. Online ahead of print.
Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

In a letter to the editor of the New England Journal of Medicine, physicians describe a short 12-patient case series of delayed large local cutaneous reactions (Table 1, Figure 1) to the mRNA-1273 COVID-19 vaccination. The authors found that median time of onset of the reactions was on day 8 post-first dose, that all of the reactions appeared near the injection site, and resolution of symptoms occurred in a median of 6 days. The implication being that as more vaccinations occur en masse, clinicians need to have more information about these reactions to better help address patient concerns and management options when confronted with them.

FIGURES

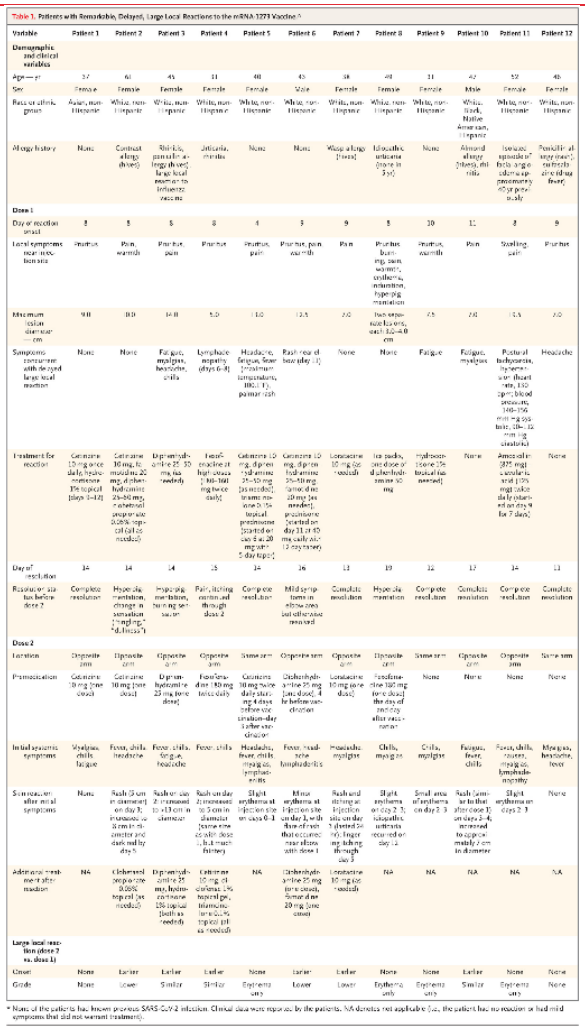

Table 1. Patients with Remarkable, Delayed, Large Local Reactions to the mRNA-1273 Vaccine.*

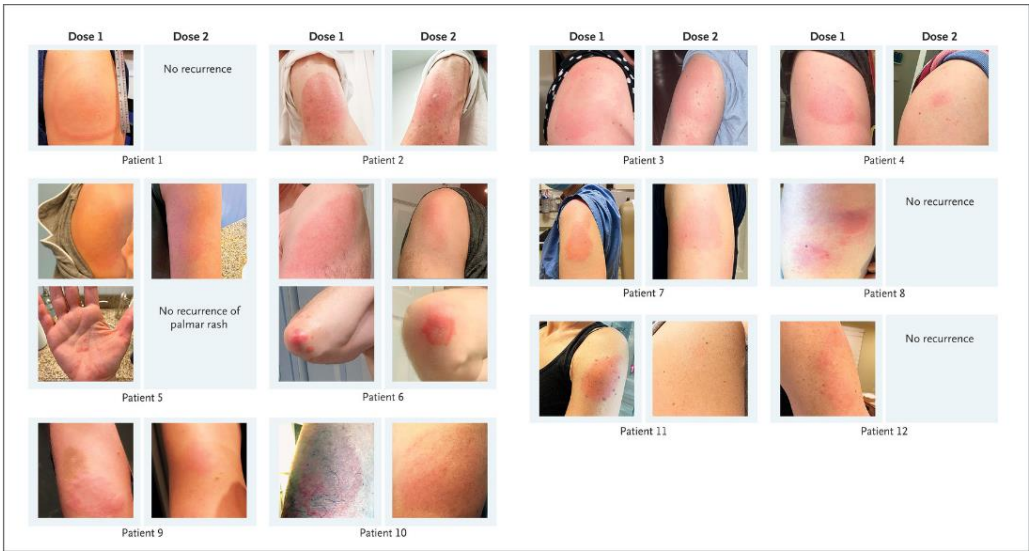

Figure 1. Delayed Cutaneous Reactions to mRNA-1273 Vaccine.

Shown are morphologic characteristics of delayed cutaneous reactions to mRNA-1273 vaccine, including annular plaques (in Patient 1), uniformly edematous plaques (in Patients 2, 6, and 11), and targetoid plaques (in Patient 3) near the site of vaccination. In several patients, there was considerable induration of the plaques (e.g., in Patients 8 and 9). In addition to a localized rash on the arm, two patients had other cutaneous symptoms, including papules on the palm and fingers (Patient 5) and urticarial plaques on the elbows (Patient 6). Patients 1, 5, 8, 9, 11, and 12 did not have a recurrence of large local reactions with the second dose, although some patients had minimal erythema. In Patients 2, 6, and 7, the reactions had an earlier onset and were lower grade after the second dose than after the first dose. In Patients 3, 4, and 10, the onset of the reactions after the second dose was earlier than after the first dose, but the reactions to the two doses were of a similar grade. Some photographs were taken by the patients using a mirror, so the images of the left and right arms may be transposed.

SARS-COV-2 501Y.V2 ESCAPES NEUTRALIZATION BY SOUTH AFRICAN COVID-19 DONOR PLASMA

Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, Lambson BE, de Oliveira T, Vermeulen M, van der Berg K, Rossouw T, Boswell M, Ueckermann V, Meiring S, von Gottberg A, Cohen C, Morris L, Bhiman JN, Moore PL.. Nat Med. 2021 Mar 2. doi: 10.1038/s41591-021-01285-x. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A study conducted by researchers from South Africa investigated a SARS-CoV-2 pseudovirus expressing the South African variant lineage 501Y.V2 (B.1.351) and found it was able to effectively evade two major classes of neutralizing antibodies with dependence on the K417 residue (See Figure 1). Samples of polyclonal plasma/sera from PCR-confirmed severe SARS-CoV-2 infection contained higher neutralizing antibody titers, however when assessed with the 501Y.V2 pseudovirus, 21/44 (48%) showed no detectable neutralization activity (See Figure 2), signifying individuals with previous SARS-CoV-2 infection may have reduced antibody efficacy against the 501Y.V2 variant compared to previously identified variants. These findings suggest the need for rapidly adaptable vaccine design platforms and viral targets less susceptible to mutation for future immunogenicity.

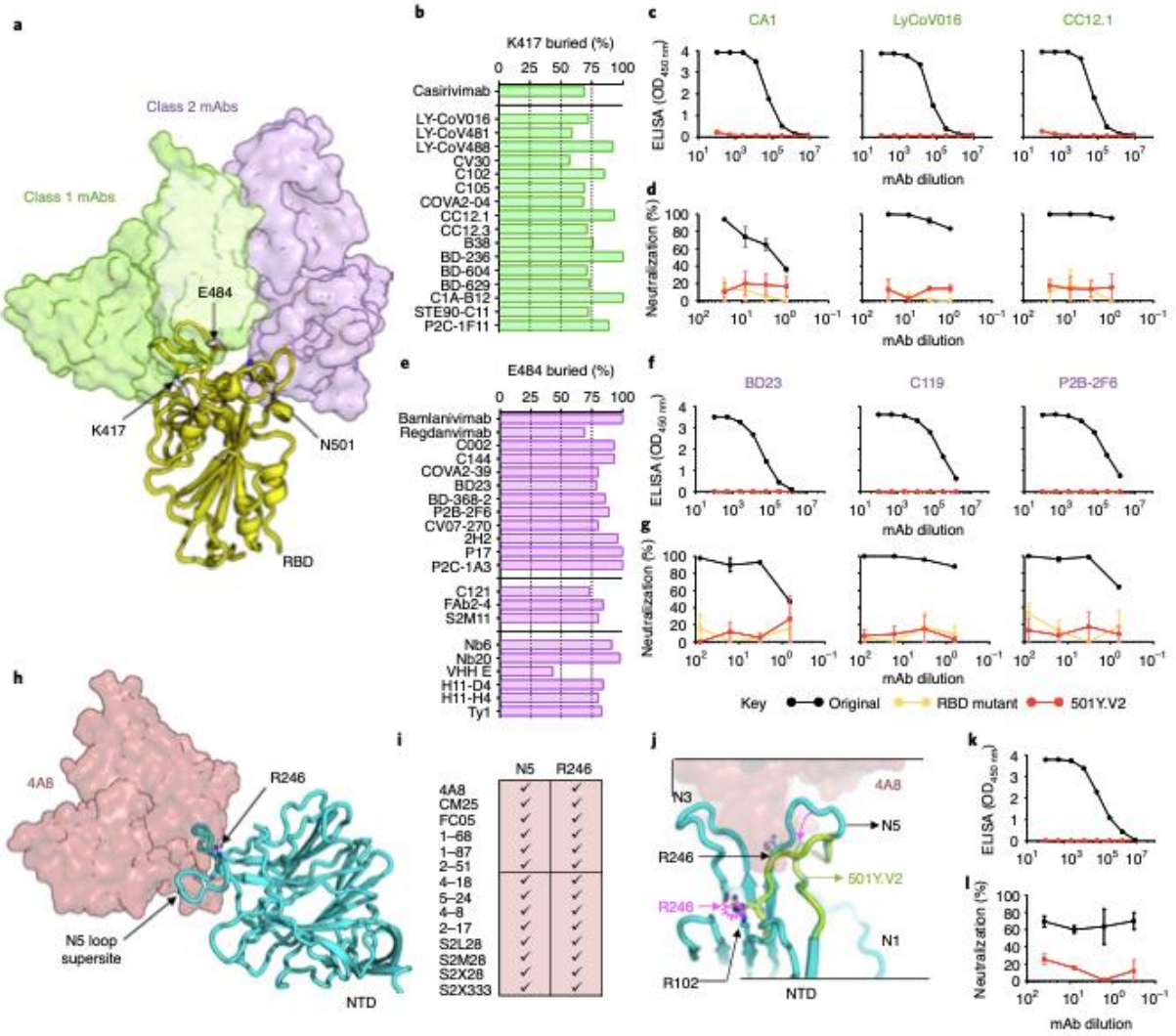

Fig. 1 | SARS-CoV-2 501Y.V2 is resistant to monoclonal antibodies.
a, Structure of SARS-CoV-2 RBD (yellow) modeled in complex with class 1 (translucent green) or class 2 (translucent purple) neutralizing antibodies. Side chains of residues K417, E484 and N501 are indicated. mAb, monoclonal antibody.
b, A plot showing percentage of K417 accessible surface area (x axis) buried (buried surface area) in class 1 antibody paratopes (listed on the y axis). VH3-53/66 antibodies are separated below the horizontal line.
c, ELISA binding for CA1, LyCoV016 and CC12.1 to the original (black) or the 501Y.V2 RBD (red).
d, Neutralization curves for the same antibodies shown in c, against the original pseudovirus (black), 501Y.V2 (red) or a chimeric construct that includes only
the RBD substitutions K417N, E484K and N501Y (orange).
e, Percentage of E484 accessible surface area buried in class 2 antibody paratopes (listed on y axis). VH1-2 antibodies (middle) or sy-/nanobodies (bottom) are separated with horizontal lines.
f, ELISA binding for BD23, C119 and P2B-2F6 to the original (black) or 501Y.V2 RBD (red).
g, Neutralization curves for the same antibodies shown in f, against original (black), 501Y.V2 (red) or RBD chimeric pseudoviruses (orange).
h, Structure of SARS-CoV-2 NTD (cyan) modeled in complex with VH1-24 neutralizing antibody (translucent maroon). The N5-loop supersite and residue R246 are indicated.
i, Contribution of N5 loop and R246 to NTD-directed neutralizing antibodies is indicated.
j, Modeling of the Δ242-244 deletion (lime green). NTD loops N1, N3 and N5 are shown and the position of R246 in the original NTD and 501Y.V2 NTD is labeled with black and pink, respectively. The minimum displacement for 501Y.V2 loop N5 and the accompanying clash with R102 are indicated with pink arrows.
k, ELISA binding for 4A8 to original (black) or 501Y.V2 NTD (red).
l, Neutralization curves for 4A8 against the original (black) or 501Y.V2 (red) pseudovirus. All experiments were performed in duplicate.

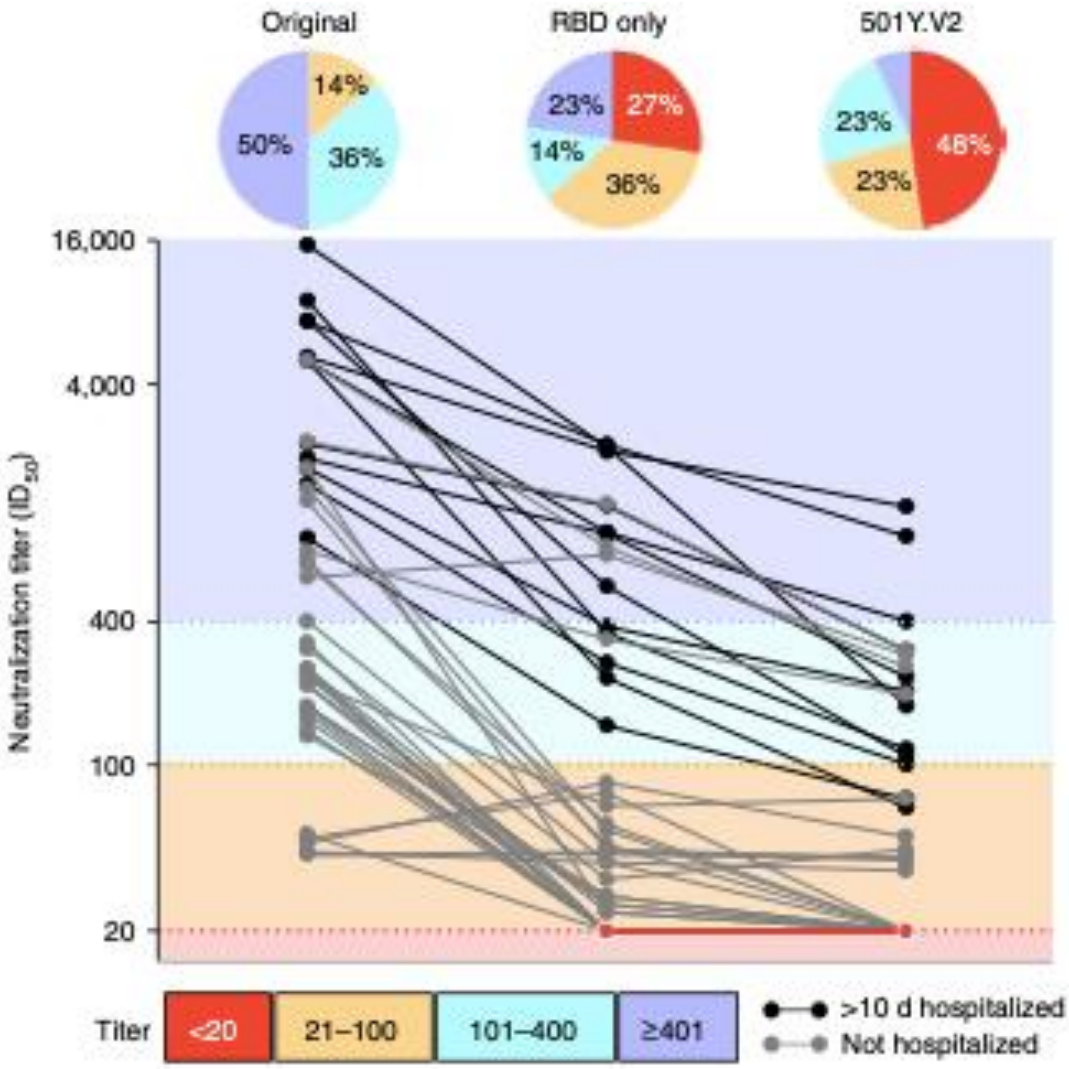

Fig. 2 | SARS-CoV-2 501Y.V2 increased resistance to neutralization by convalescent plasma/serum. Plasma/serum collected from individuals infected with SARS-CoV-2 was assessed for neutralization to the original lineage (Wuhan-1 D614G, left), an RBD chimeric mutant containing K417N, E484K and N501Y substitutions only (middle) or the 501Y.V2 lineage pseudovirus. Twelve of the samples were collected from donors hospitalized for >10 d with COVID-19 (black). The graph is colored according to the magnitude of neutralization titer, with ID50 greater or lesser than 1:400 colored dark or light blue, respectively and titer <100 colored orange. The limit of detection (knockout) was an ID50 < 20 (red). Pie charts above each set of data points summarize the proportion of samples in each titer group.

DYSREGULATED INNATE AND ADAPTIVE IMMUNE RESPONSES DISCRIMINATE DISEASE SEVERITY IN COVID-19

Janssen NAF, Grondman I, de Nooijer AH, Boahen CK, Koeken VACM, Matzaraki V, Kumar V, He X, Kox M, Koenen HJPM, Smeets RL, Joosten I, Brüggemann RJM, Kouijzer IJE, van der Hoeven HG, Schouten JA, Frenzel T, Reijers M, Hoefsloot W, Dofferhoff ASM, van Apeldoorn MJ, Blaauw MJT, Veerman K, Maas C, Schoneveld AH, Hoefer IE, Derde LPG, van Deuren M, van der Meer JWM, van Crevel R, Giamarellos-Bourboulis EJ, Joosten LAB, van den Heuvel MM, Hoogerwerf J, de Mast Q, Pickkers P, Netea MG, van de Veerdonk FL.. J Infect Dis. 2021 Feb 1:jiab065. doi: 10.1093/infdis/jiab065. Online ahead of print.

Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

Researchers from Radboud University Medical Center, The Netherlands measured plasma cytokines and analyzed proteomics in 147 COVID-19 patients, separated into ICU patients (n=38) with critical infections and non-ICU patients (n=109) with severe infections, comparing findings with healthy controls. They found that hepatocyte growth factor was significantly elevated (p=1.19 x 10^-6), and stem cell factor was significantly down-regulated (p=3.14x10^-7) in ICU patients compared to non-ICU patients (Figure 2b), suggesting these are potential biomarkers for development of severe COVID-19 infection.

ABSTRACT

The clinical spectrum of COVID-19 varies and the differences in host response characterizing this variation have not been fully elucidated. COVID-19 disease severity correlates with an excessive pro-inflammatory immune response and profound lymphopenia. Inflammatory responses according to disease severity were explored by plasma cytokine measurements and proteomics analysis in 147 COVID-19 patients. Furthermore, peripheral blood mononuclear cell cytokine production assays and whole blood flow cytometry were performed. Results confirm a hyperinflammatory innate immune state, while highlighting hepatocyte growth factor and stem cell factor as potential biomarkers for disease severity. Clustering analysis reveals no specific inflammatory endotypes in COVID-19 patients. Functional assays reveal abrogated adaptive cytokine production (interferon-gamma, interleukin-17 and interleukin-22) and prominent T cell exhaustion in critically ill patients, whereas innate immune responses were intact or hyperresponsive. Collectively, this extensive analysis provides a comprehensive insight into the pathobiology of severe to critical COVID-19 and highlight potential biomarkers of disease severity.

Figure 2b

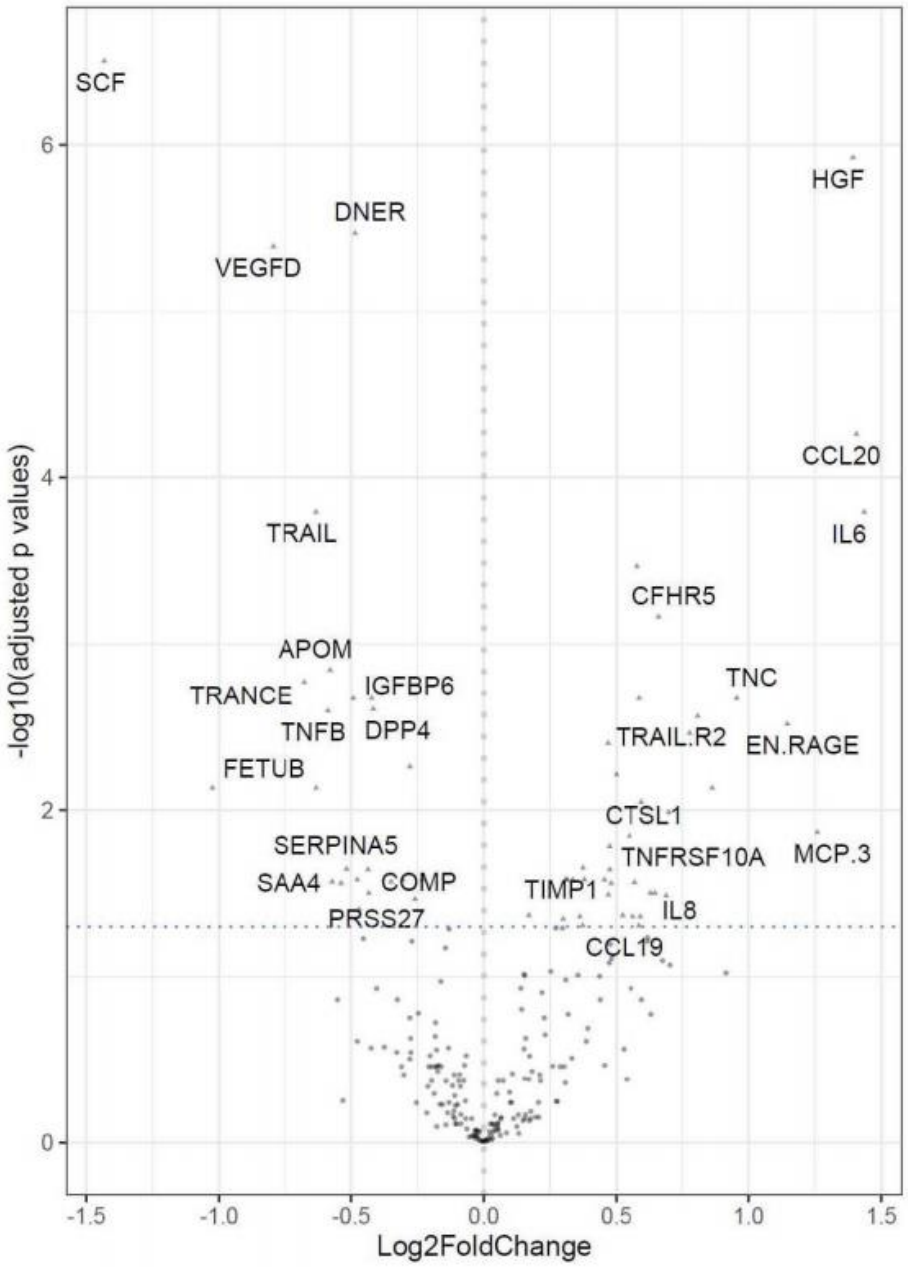

Figure 2. Proximity extension assay demonstrates differential protein expression in plasma according to COVID-19 disease severity. (B) After overlap analysis of differential protein expression in both the discovery and validation cohorts, 27 proteins were significantly up- or downregulated in ICU patients, as compared to non-ICU patients with adjusted P-values < 0.05 after correction for multiple testing. Most significantly upregulated proteins are HGF, CCL20 and IL-6; most significantly downregulated proteins are SCF, DNER, VEGFD and TRAIL. ICU, intensive care unit. HGF, hepatocyte growth factor. CCL20, chemokine (C-C motif) ligand 20. IL-6, interleukin-6. SCF, stem cell factor. DNER, delta and notch-like epidermal growth factor-related receptor. VEGFD, vascular endothelial growth factor D. TRAIL, tumour necrosis factor-related apoptosis-inducing ligand.

EARLY VERSUS DEFERRED ANTI-SARS-COV-2 CONVALESCENT PLASMA IN PATIENTS ADMITTED FOR COVID-19: A RANDOMIZED PHASE II CLINICAL TRIAL

Balcells ME, Rojas L, Le Corre N, Martínez-Valdebenito C, Ceballos ME, Ferrés M, Chang M, Vizcaya C, Mondaca S, Huete Á, Castro R, Sarmiento M, Villarroel L, Pizarro A, Ross P, Santander J, Lara B, Ferrada M, Vargas-Salas S, Beltrán-Pavez C, Soto-Rifo R, Valiente-Echeverría F, Caglevic C, Mahave M, Selman C, Gazitúa R, Briones JL, Villarroel-Espindola F, Balmaceda C, Espinoza MA, Pereira J, Nervi B.. PLoS Med. 2021 Mar 3;18(3):e1003415. doi: 10.1371/journal.pmed.1003415. eCollection 2021 Mar.

Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

This controlled, open label phase II randomized clinical trial conducted by investigators at School of Medicine and Chilean Academic medical center in observed the outcomes of receiving early versus deferred convalescent plasma in 58 patients (1 patient withdrew consent) hospitalized with COVID-19 confirmed by RT-PCR. 28 participants received plasma on the day of enrollment and 30 patients received plasma between 3 days or greater than 7 days after enrollment based on development of respiratory failure or persistence of COVID-19 symptoms after 7 days of enrollment. There was no statistically different outcome between patients who received early or deferred convalescent plasma, suggesting clinical outcomes are not impacted by the timing of plasma initiation (Table 2).

FIGURES

Table 2. Primary and secondary clinical outcomes.

Outcome	Early plasma group (n = 28)	Deferred plasma group (n = 30)	p-Value[a]	Crude effect estimate (95% CI)	Adjusted effect estimate (95% CI)
Primary clinical outcomes					
Composite outcome (death, mechanical ventilation, and/or hospital stay > 14 days), number/total (%)	9/28 (32.1)	10/30 (33.3)	>0.999	OR 0.95 (0.32–2.84)	OR 0.67 (0.14–3.31)
Mechanical ventilation, number/total (%)	5/28 (17.9)	2/30 (6.7)	0.246	OR 3.04 (0.54–17.2)	OR 2.98 (0.41–21.57)
Death, number/total (%)	5/28 (17.9)	2/30 (6.7)	0.246	OR 3.04 (0.54–17.2)	OR 4.22 (0.33–53.57)
Hospitalization > 14 days, number/total (%)	6/28 (21.4)	9/30 (30.0)	0.554	OR 0.64 (0.19–2.1)	OR 0.51 (0.13–2.05)
Secondary clinical outcomes					
30-day mortality, number/total (%)	5/28 (17.9)	2/30 (6.7)	0.246	OR 3.04 (0.54–17.2)	OR 4.22 (0.33–53.57)
Progression into respiratory failure[b], number/total (%)	13/28 (46.4)	12/30 (40.0)	0.791	OR 1.30 (0.46–3.68)	OR 1.46 (0.43–4.66)
Total days of mechanical ventilation requirement, median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.234	IRR 1.68 (0.30–9.42)	IRR 4.78 (2.20–10.40)
Total days of HFNC requirement, median (IQR)	0.0 (0.0–2.5)	0.0 (0.0–2.0)	0.751	IRR 0.70 (0.35–1.43)	IRR 0.65 (0.35–1.30)
Total days of oxygen requirement, median (IQR)	6.0 (3.0–12.0)	7.0 (2.0–16.0)	0.950	IRR 0.90 (0.53–1.53)	IRR 1.07 (0.64–1.78)
Total days of intensive and/or intermediate care requirement, median (IQR)	2.5 (0.0–8.25)	0.0 (0.0–8.5)	0.438	IRR 0.69 (0.37–1.31)	IRR 0.68 (0.36–1.26)
Total days of hospital stay, median (IQR)	9.0 (5.0–12.0)	8.0 (5.5–23.0)	0.806	IRR 0.78 (0.50–1.22)	IRR 0.86 (0.57–1.29)
SOFA score day 3, median (IQR)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	0.728	IRR 1.18 (0.78–1.79)	IRR 1.12 (0.84–1.48)
SOFA score day 7, median (IQR)	2.0 (2.0–4.0)	3.0 (1.0–4.0)	0.565	IRR 1.29 (0.74–2.22)	IRR 0.98 (0.65–1.48)

Adjusted ORs were estimated from a logistic regression model, and IRRs were estimated using a zero-inflated negative binomial model. Estimates were adjusted by age and SOFA score at enrollment.

[a]p-Value was calculated by Wilcoxon rank-sum test or Fisher's exact test.

[b]Respiratory failure defined as $PaO_2/FiO_2 < 200$.

HFNC, high-flow nasal cannula; IRR, incidence rate ratio; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

The primary and secondary clinical outcomes for patients in the early and deferred convalescent plasma groups was compared and there was no statistical significance based on p value.

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