IMMUNE RESPONSE TO SARS-CoV-2

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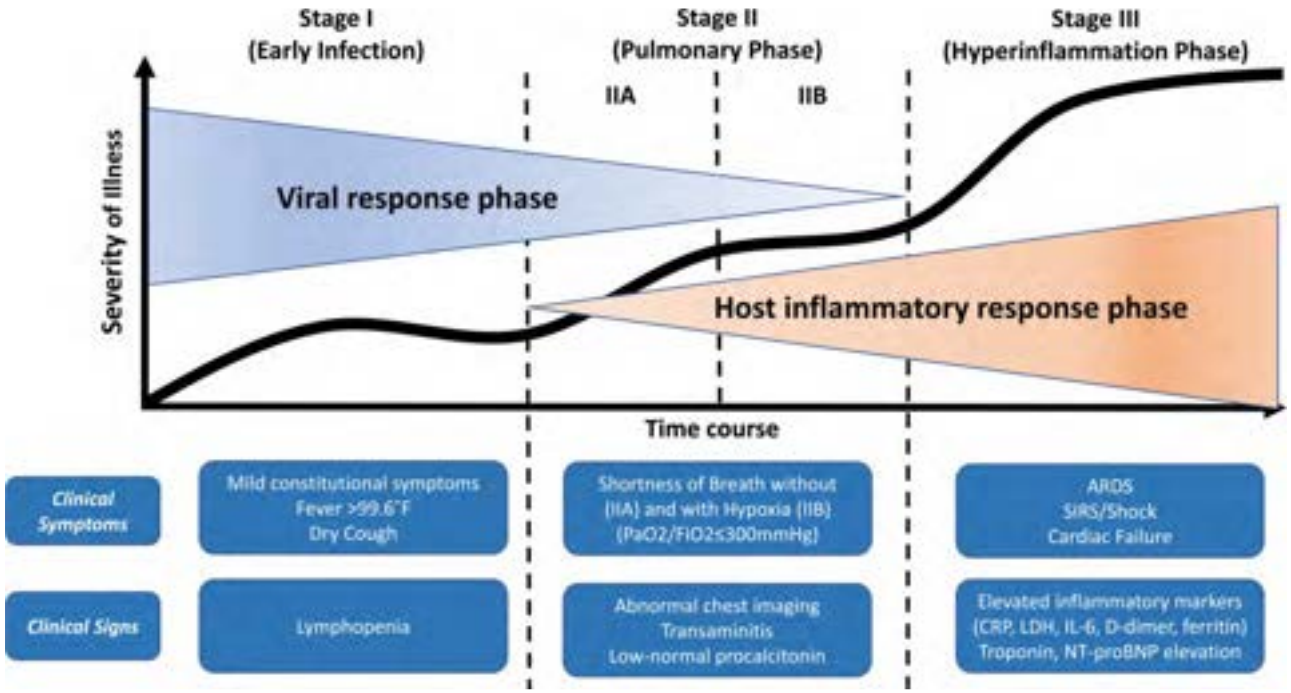
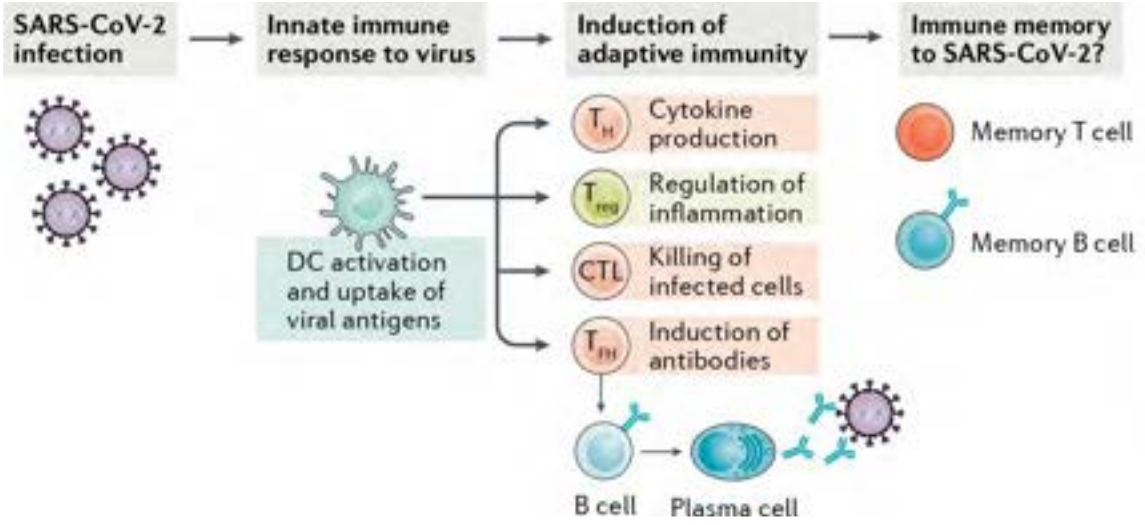
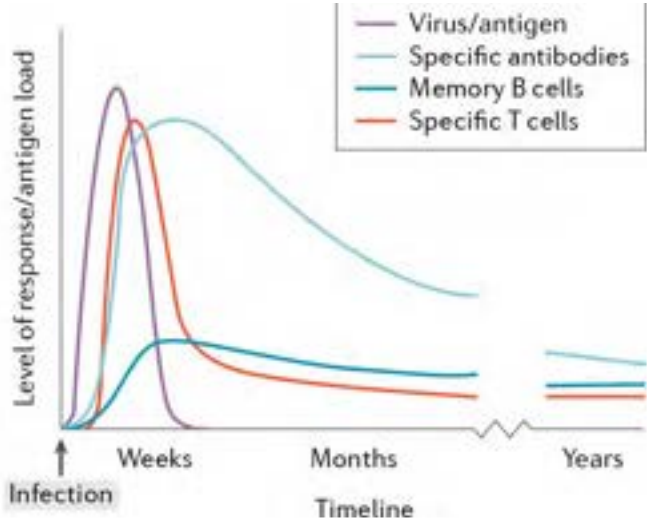
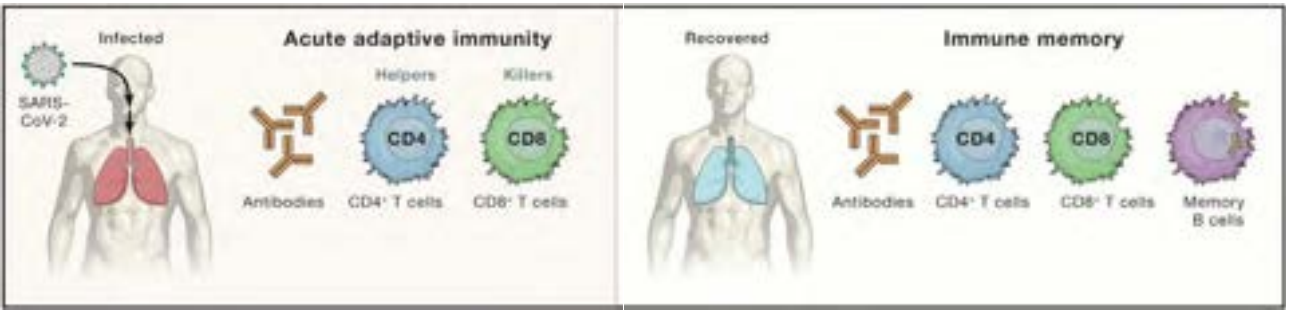
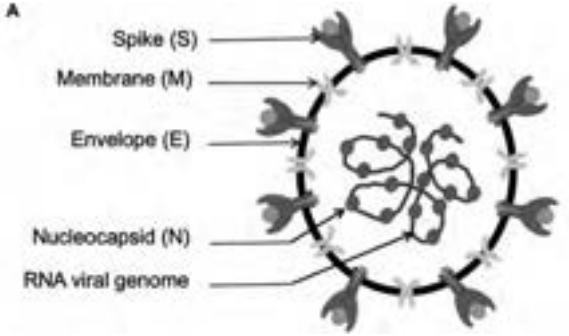


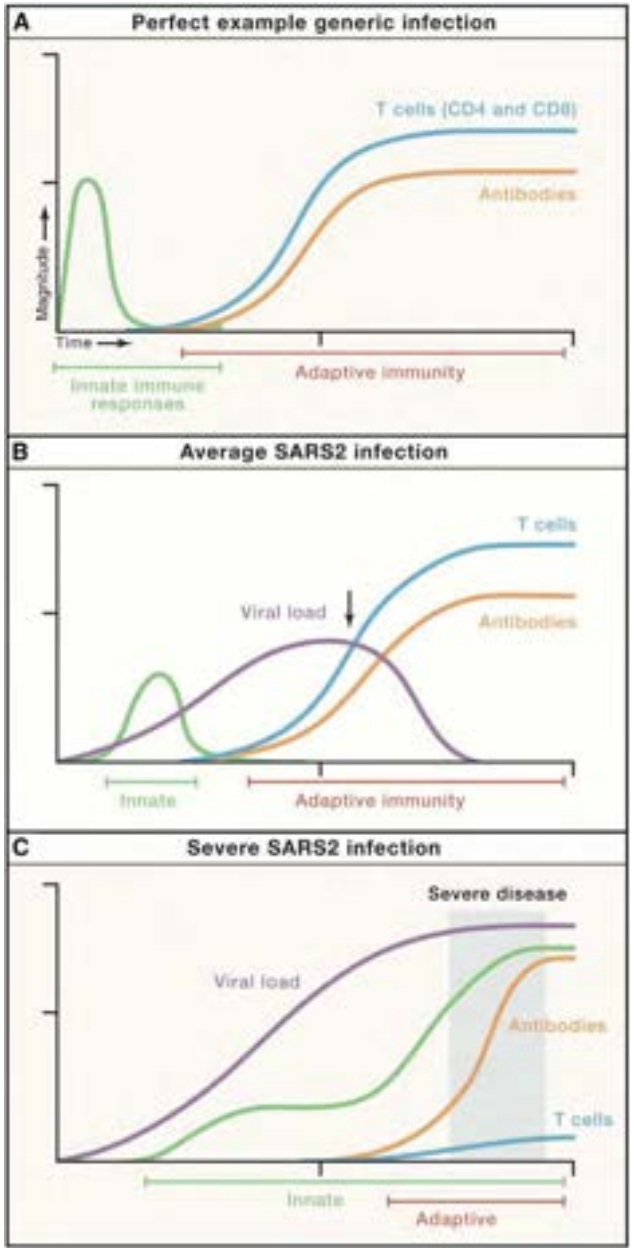
Hasan K. Siddiqi and Mandeep R. Mehra, MD
J of Heart and Lung Transpl 2020, 39:405

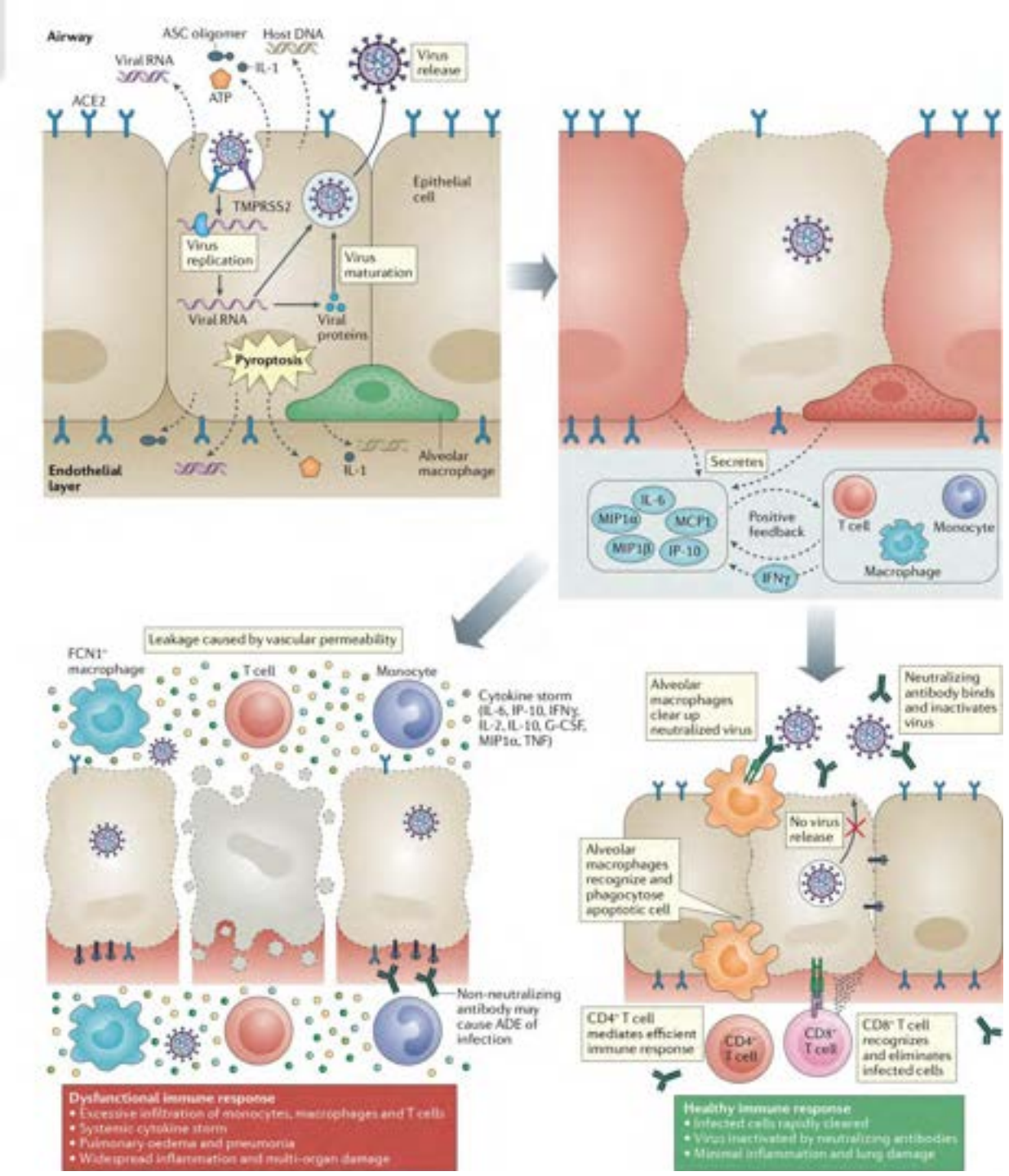

SARS-CoV-2 infection
Innate immune response to virus
Induction of adaptive immunity
Immune memory to SARS-CoV-2?
DC activation and uptake of viral antigens
T_H Cytokine production
T_{reg} Regulation of inflammation
CTL Killing of infected cells
T_{FH} Induction of antibodies
Memory T cell
Memory B cell
B cell
Plasma cell


Virus/antigen
Specific antibodies
Memory B cells
Specific T cells
Level of response/antigen load
Infection
Weeks
Months
Years
Timeline


Infected
SARS-CoV-2
Acute adaptive immunity
Helpers
Killers
CD4
CD8
Antibodies
CD4+ T cells
CD8+ T cells
Recovered
Immune memory
Antibodies
CD4+ T cells
CD8+ T cells
Memory B cells


A
Spike (S)
Membrane (M)
Envelope (E)
Nucleocapsid (N)
RNA viral genome


A
Perfect example generic infection
T cells (CD4 and CD8)
Antibodies
Magnitude
Time
Innate immune responses
Adaptive immunity
B
Average SARS2 infection
T cells
Viral load
Antibodies
Innate
Adaptive immunity
C
Severe SARS2 infection
Severe disease
Viral load
Antibodies
T cells
Innate
Adaptive



Tay et al.
Nature
Reviews 2020

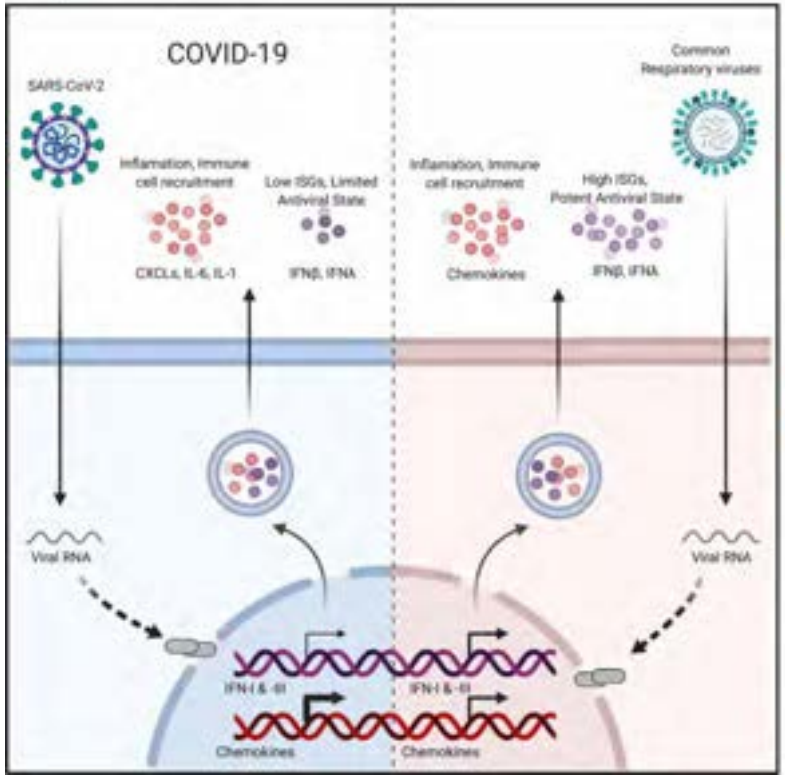
Cell

Blanco-Melo et al., 2020, Cell *181*, 1–10
May 28, 2020 © 2020 Elsevier Inc.
https://doi.org/10.1016/j.cell.2020.04.026

Article

Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19

Graphical Abstract



Authors

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In Brief

In comparison to other respiratory viruses, SARS-CoV-2 infection drives a lower antiviral transcriptional response that is marked by low IFN-I and IFN-III levels and elevated chemokine expression, which could explain the pro-inflammatory disease state associated with COVID-19.

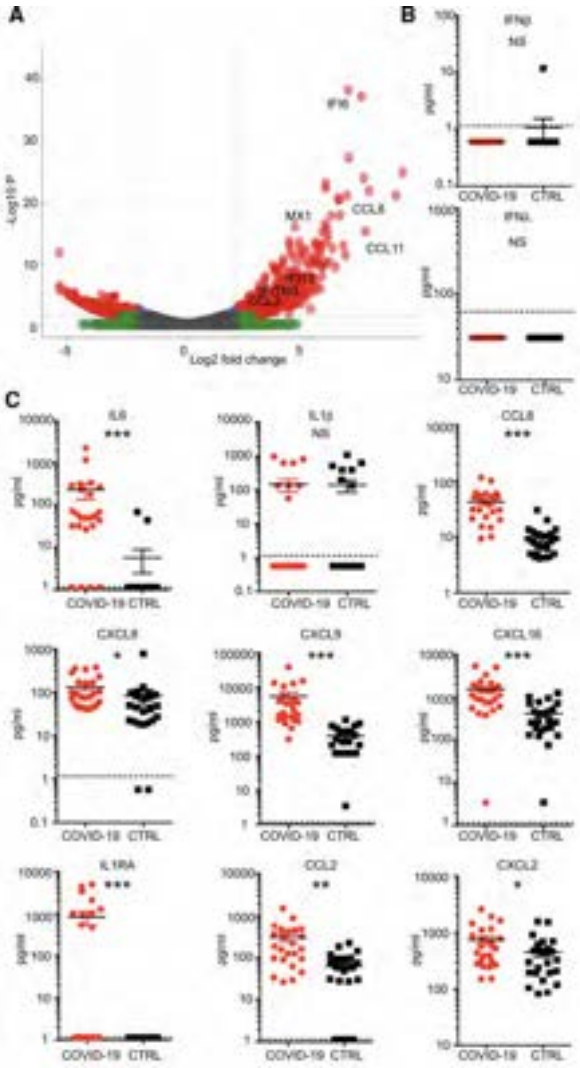


Figure 4. Transcriptional and Serological Profile of Clinical COVID-19 Patients

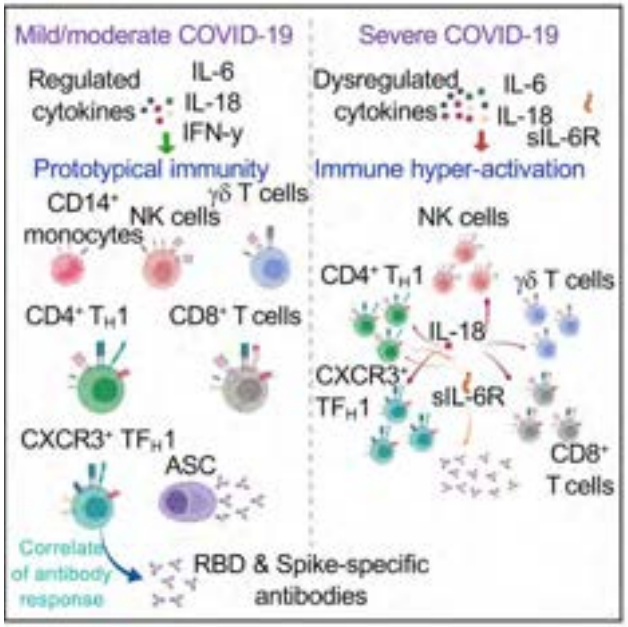
(A) Volcano plot depicting DEGs in post-mortem lung samples of two COVID-19 patients compared with healthy lung biopsies. DEGs (p-adjusted < 0.05) with a $|\log_2(\text{fold change})|$ of more than 2 are indicated in red. Non-significant DEGs with a $|\log_2(\text{fold change})|$ of more than 2 are indicated in green.

(B and C) Cytokine profiles of COVID-19 patients. Sera of 24 COVID-19 patients and 24 SARS-CoV-2-negative controls were analyzed by ELISA for the protein levels of (B) IFN-I and IFN-III or (C) a broad panel of cytokines. The dotted line depicts the limit of detection. Statistical significance was calculated by Mann-Whitney non-parametric t test. NS, non-significant; $^*p < 0.05$, $^{**}p < 0.005$, $^{***}p < 0.0001$.

Cell Reports
Medicine

Integrated immune dynamics define correlates of COVID-19 severity and antibody responses

Graphical Abstract



Highlights

- Analyses of 184 immune features define kinetics of immune responses to SARS-CoV-2
- Circulating $T_{FH}1$ cells in acute COVID-19 correlate with antibodies
- sIL-6R levels are elevated in severe COVID-19 but do not correlate with IL-6
- Elevated IL-6 and IL-18 correlate with immune cell hyperactivation

Authors

Marios Koutsakos, Louise C. Rowntree, Luca Hensen, ..., Thi H.O. Nguyen, Allen C. Cheng, Katherine Kedzierska

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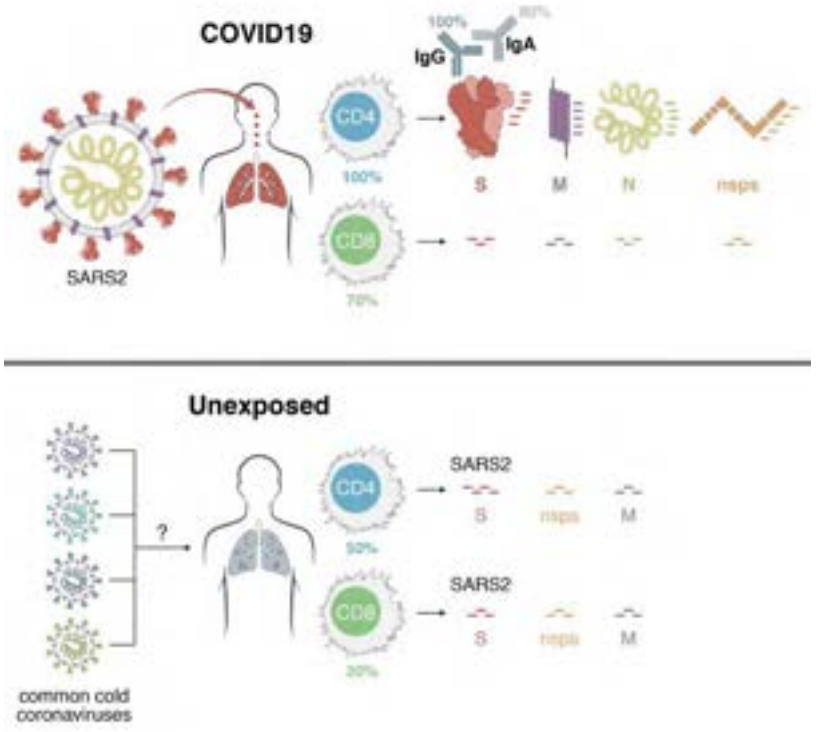
In brief

Koutsakos et al. perform a broad analysis of 184 immune features using blood samples from 85 COVID-19 cases across time and severity groups. The study defines circulating $T_{FH}1$ cells as a correlate of antibody responses and sIL-6R, IL-6, and IL-18 as correlates of disease severity.

Koutsakos et al., 2021, Cell Reports Medicine 2, 100208
March 16, 2021
https://doi.org/10.1016/j.xcrm.2021.100208

Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals



Understanding adaptive immunity to SARS-CoV-2 is important for vaccine development, interpreting coronavirus disease 2019 (COVID-19) pathogenesis, and calibration of pandemic control measures. Using HLA class I and II predicted peptide 'megapools', circulating SARS-CoV-2–specific $CD8^+$ and $CD4^+$ T cells were identified in ~70% and 100% of COVID-19 convalescent patients, respectively. $CD4^+$ T cell responses to spike, the main target of most vaccine efforts, were robust and correlated with the magnitude of the anti-SARS-CoV-2 IgG and IgA titers. The M, spike and N proteins each accounted for 11-27% of the total $CD4^+$ response, with additional responses commonly targeting nsp3, nsp4, ORF3a and ORF8, among others. For $CD8^+$ T cells, spike and M were recognized, with at least eight SARS-CoV-2 ORFs targeted. Importantly, we detected SARS-CoV-2–reactive $CD4^+$ T cells in ~40-60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating 'common cold' coronaviruses and SARS-CoV-2.

Science

RESEARCH ARTICLES

Cite as: J. M. Dan *et al.*, *Science* 10.1126/science.abf4063 (2021).

Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection

Jennifer M. Dan[1,2]*, Jose Mateus[1]*, Yu Kato[1]*, Kathryn M. Hastie[3], Esther Dawen Yu[1], Caterina E. Faliti[1], Alba Grifoni[1], Sydney I. Ramirez[1,2], Sonya Haupt[1], April Frazier[1], Catherine Nakao[1], Vamseedhar Rayaprolu[1], Stephen A. Rawlings[2], Bjoern Peters[1,2], Florian Krammer[4], Viviana Simon[4,5,6], Erica Ollmann Saphire[1,3], Davey M. Smith[2], Daniela Weiskopf[1]†, Alessandro Sette[1,2]†, Shane Crotty[1,2]†

[1]Center for Infectious Disease and Vaccine Research, La Jolla Institute for Immunology (LJI), La Jolla, CA 92037, USA. [2]Department of Medicine, University of California, San Diego (UCSD), La Jolla, CA 92037, USA. [3]Department of Medicine, Division of Infectious Diseases and Global Public Health, University of California, San Diego (UCSD), La Jolla, CA 92037, USA. [4]Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. [5]Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. [6]The Global Health and Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

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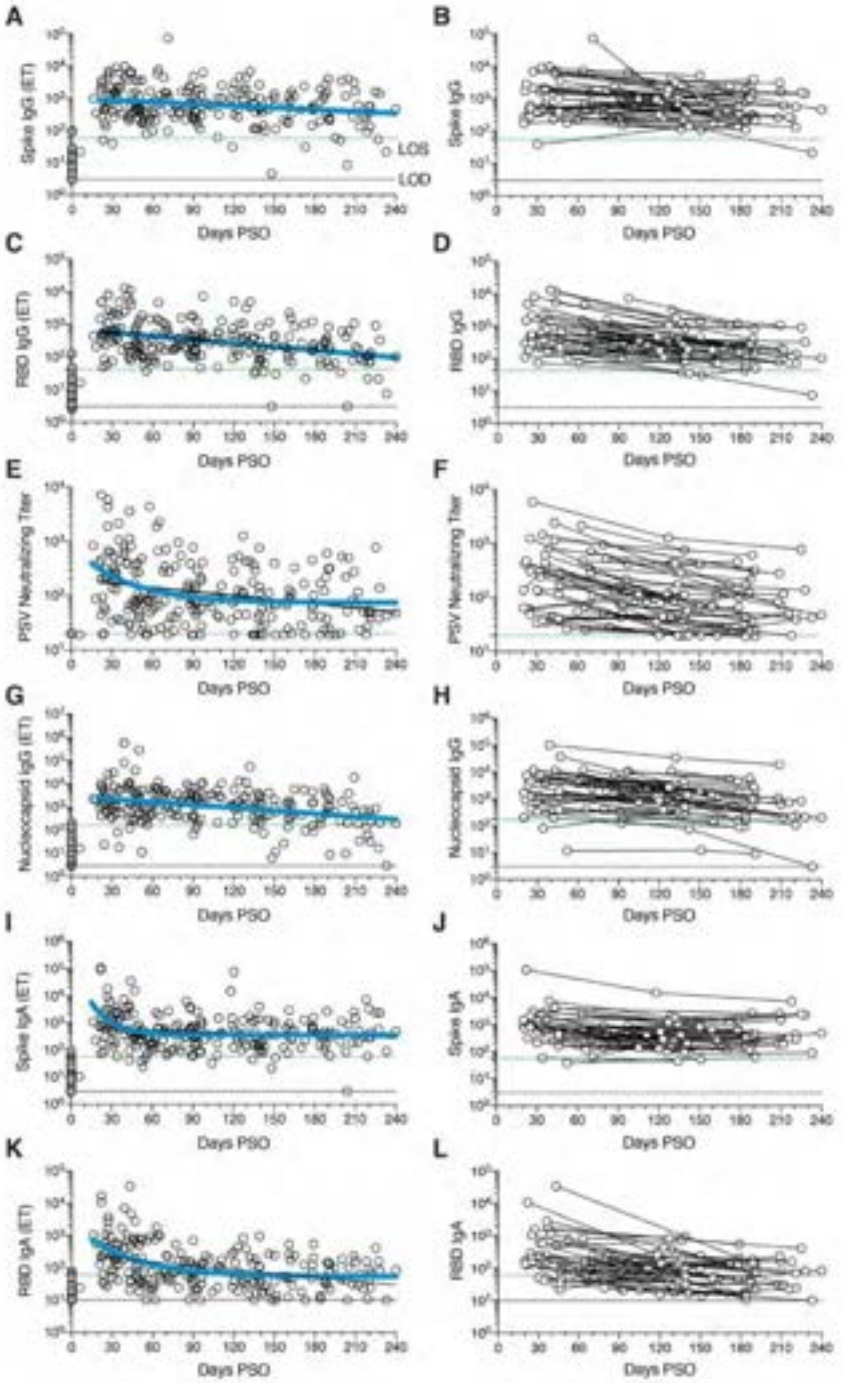
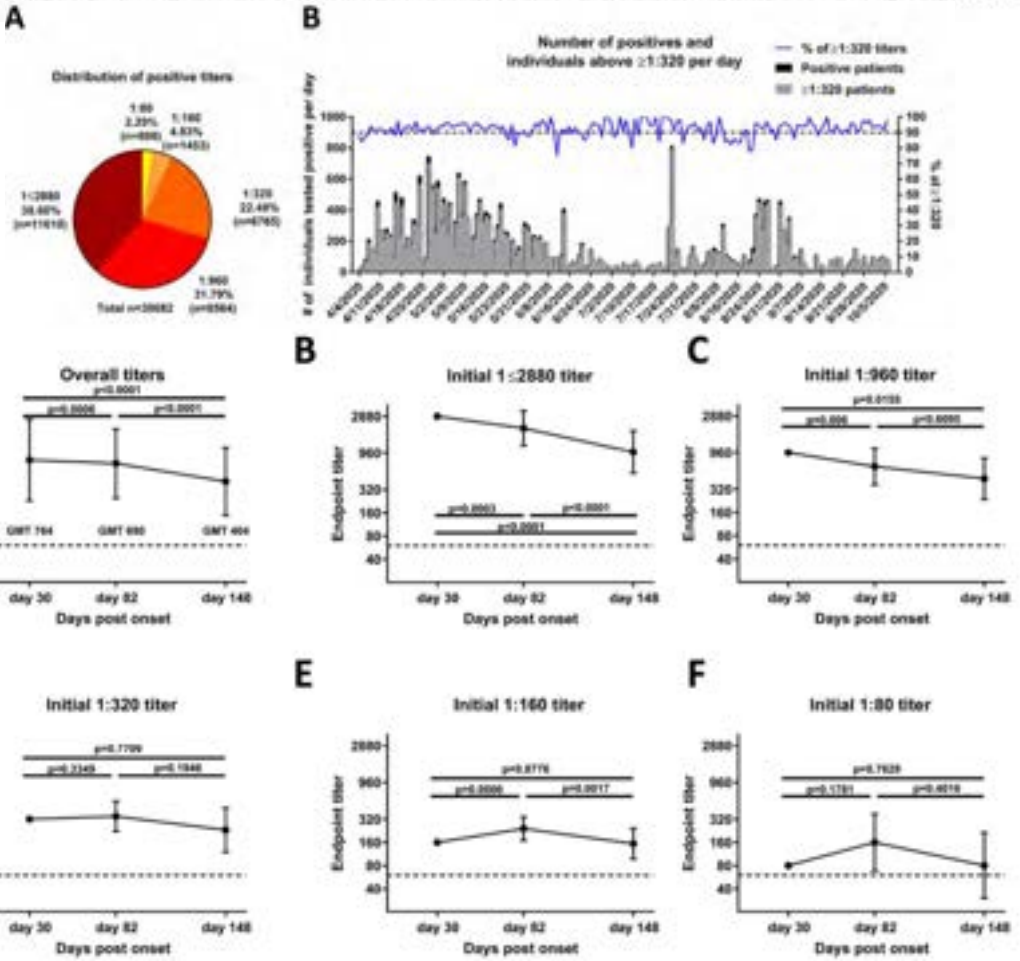
Understanding immune memory to SARS-CoV-2 is critical for improving diagnostics and vaccines, and for assessing the likely future course of the COVID-19 pandemic. We analyzed multiple compartments of circulating immune memory to SARS-CoV-2 in 254 samples from 188 COVID-19 cases, including 43 samples at ≥ 6 months post-infection. IgG to the Spike protein was relatively stable over 6+ months. Spike-specific memory B cells were more abundant at 6 months than at 1 month post symptom onset. SARS-CoV-2-specific CD4⁺ T cells and CD8⁺ T cells declined with a half-life of 3-5 months. By studying antibody, memory B cell, CD4⁺ T cell, and CD8⁺ T cell memory to SARS-CoV-2 in an integrated manner, we observed that each component of SARS-CoV-2 immune memory exhibited distinct kinetics.


A
Spike IgG (ET)
LOS
LOD
Days PSO
B
Spike IgG
Days PSO
C
RBD IgG (ET)
Days PSO
D
RBD IgG
Days PSO
E
PSV Neutralizing Titer
Days PSO
F
PSV Neutralizing Titer
Days PSO
G
Nucleocapsid IgG (ET)
Days PSO
H
Nucleocapsid IgG
Days PSO
I
Spike IgA (ET)
Days PSO
J
Spike IgA
Days PSO
K
RBD IgA (ET)
Days PSO
L
RBD IgA
Days PSO

Cite as: A. Wajnberg *et al.*, *Science* 10.1126/science.abd7728 (2020).

Robust neutralizing antibodies to SARS-CoV-2 infection persist for months

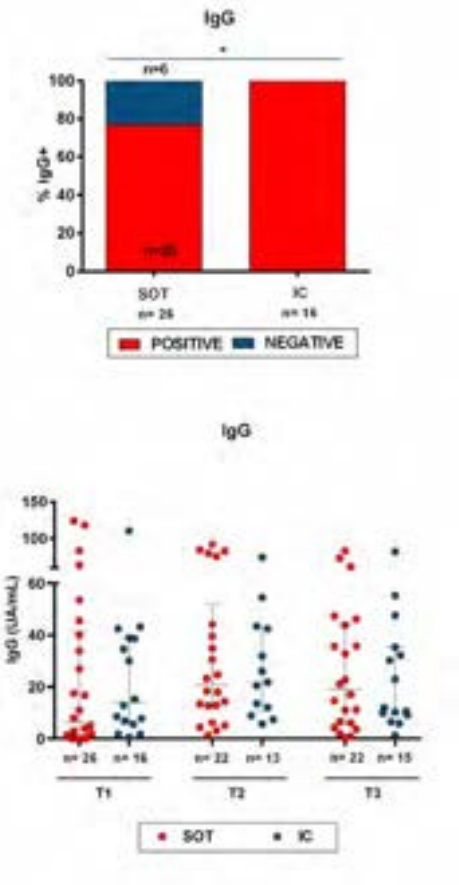
Ania Wajnberg[1]*, Fatima Amanat[2,3], Adolfo Firpo[4], Deena R. Altman[5], Mark J. Bailey[1], Mayce Mansour[1], Meagan McMahon[2], Philip Meade[2,3], Damodara Rao Mendu[4], Kimberly Muellers[1], Daniel Stadlbauer[2], Kimberly Stone[1], Shirin Strohmeier[2], Viviana Simon[2], Judith Aberg[5], David L. Reich[6], Florian Krammer[2]*, Carlos Cordon-Cardo[4]*

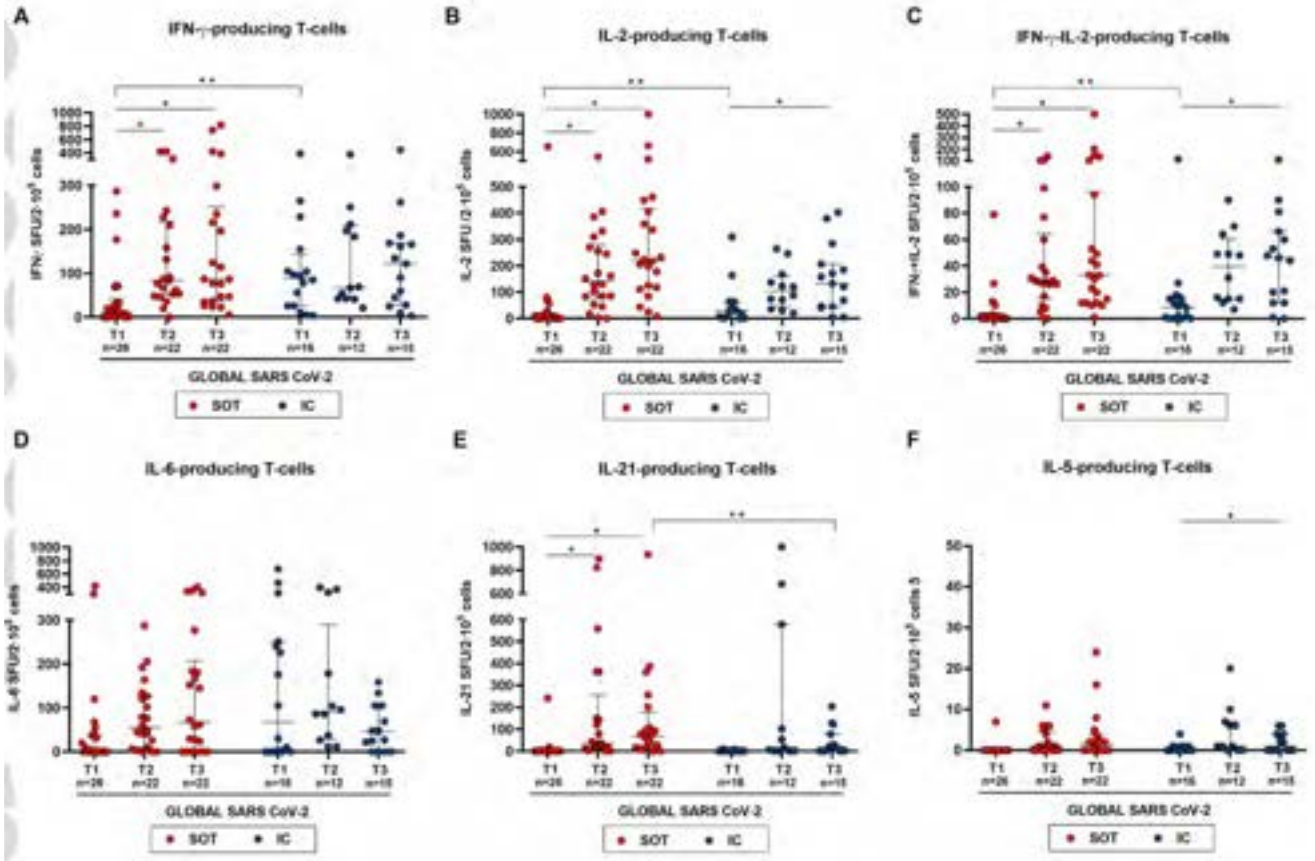


SARS-CoV-2-specific serological and functional T-cell Immune responses in solid organ transplant recipients

(Fava et al. AJT in press)

- 28 SOT recipients (18 kidney, 5 heart and 5 liver) and 16 immunocompetent (IC) patients with COVID-19 were analyzed during the acute phase of infection and at two convalescence periods
- Lymphopenia was more pronounced for SOT recipients(866±427 vs 1531±490 in IC; p<0.001)




A
IFN-γ-producing T-cells
IFN-γ SFU/2·10^5 cells
B
IL-2-producing T-cells
IL-2 SFU /2·10^5 cells
C
IFN-γ-IL-2-producing T-cells
IFN-γ-IL-2 SFU/2·10^5 cells
D
IL-6-producing T-cells
IL-6 SFU/2·10^5 cells
E
IL-21-producing T-cells
IL-21 SFU/2·10^5 cells
F
IL-5-producing T-cells
IL-5 SFU/2·10^5 cells
T1 n=26
T2 n=22
T3 n=22
T1 n=16
T2 n=12
T3 n=15
GLOBAL SARS CoV-2
SOT
IC

CORRESPONDENCE

Covid-19 and Kidney Transplantation

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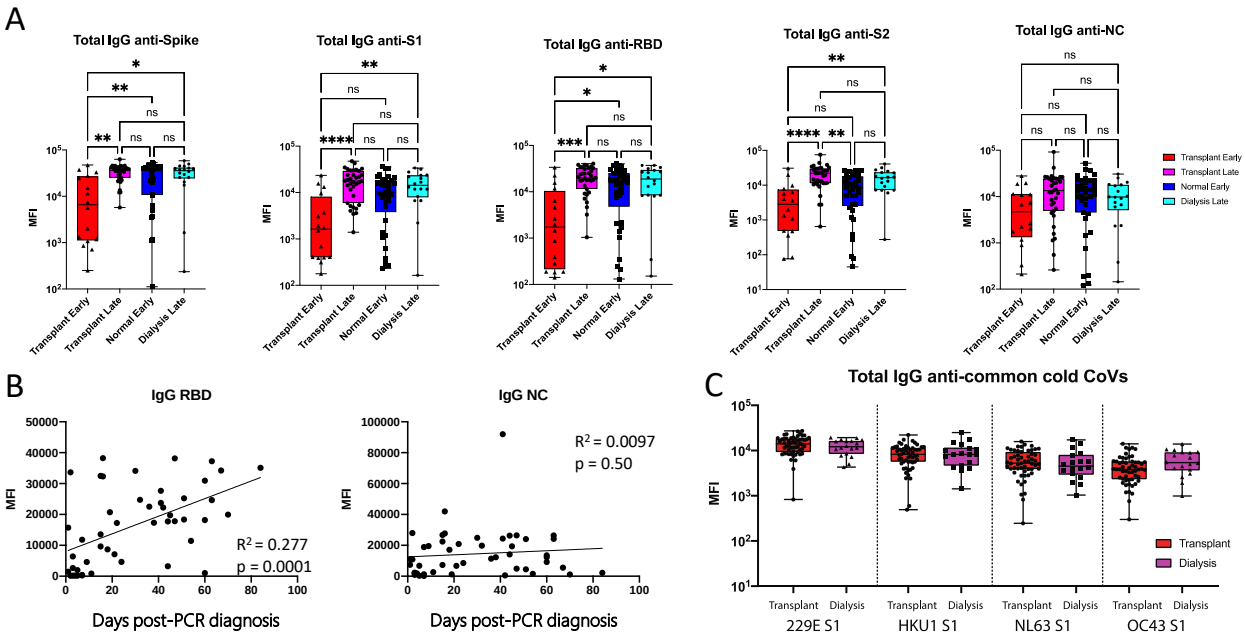
White-cell count	
Median (range) — per mm³	5300 (2100–14,700)
Patients with count <400 per mm³ — no./total no. (%)	6/28 (21)
Lymphocyte count	
Median (range) — per mm³	600 (100–1900)
Patients with count <1000 per mm³ — no./total no. (%)	22/28 (79)
Platelet count	
Median (range) — per mm³	146,000 (78,000–450,000)
Patients with count <150,000 per mm³ — no./total no. (%)	12/28 (43)
CD3 cell count	
Median (range) — per mm³	319 (34–1049)
Patients with count <706 per mm³ — no./total no. (%)	19/28 (68)
CD4 cell count	
Median (range) — per mm³	173 (6–507)
Patients with count <344 per mm³ — no./total no. (%)	20/28 (71)
CD8 cell count	
Median (range) — per mm³	132 (39–654)
Patients with count <104 per mm³ — no./total no. (%)	8/28 (29)

Delayed kinetics of IgG, but not IgA anti-Spike antibodies in transplant recipients following SARS-CoV-2 infection

Cravedi P,...Azzi Y, ...Akalin E, Maltzman J.

Generation of IgG anti-Spike but not anti-nucleocapsid is dependent on time after diagnosis

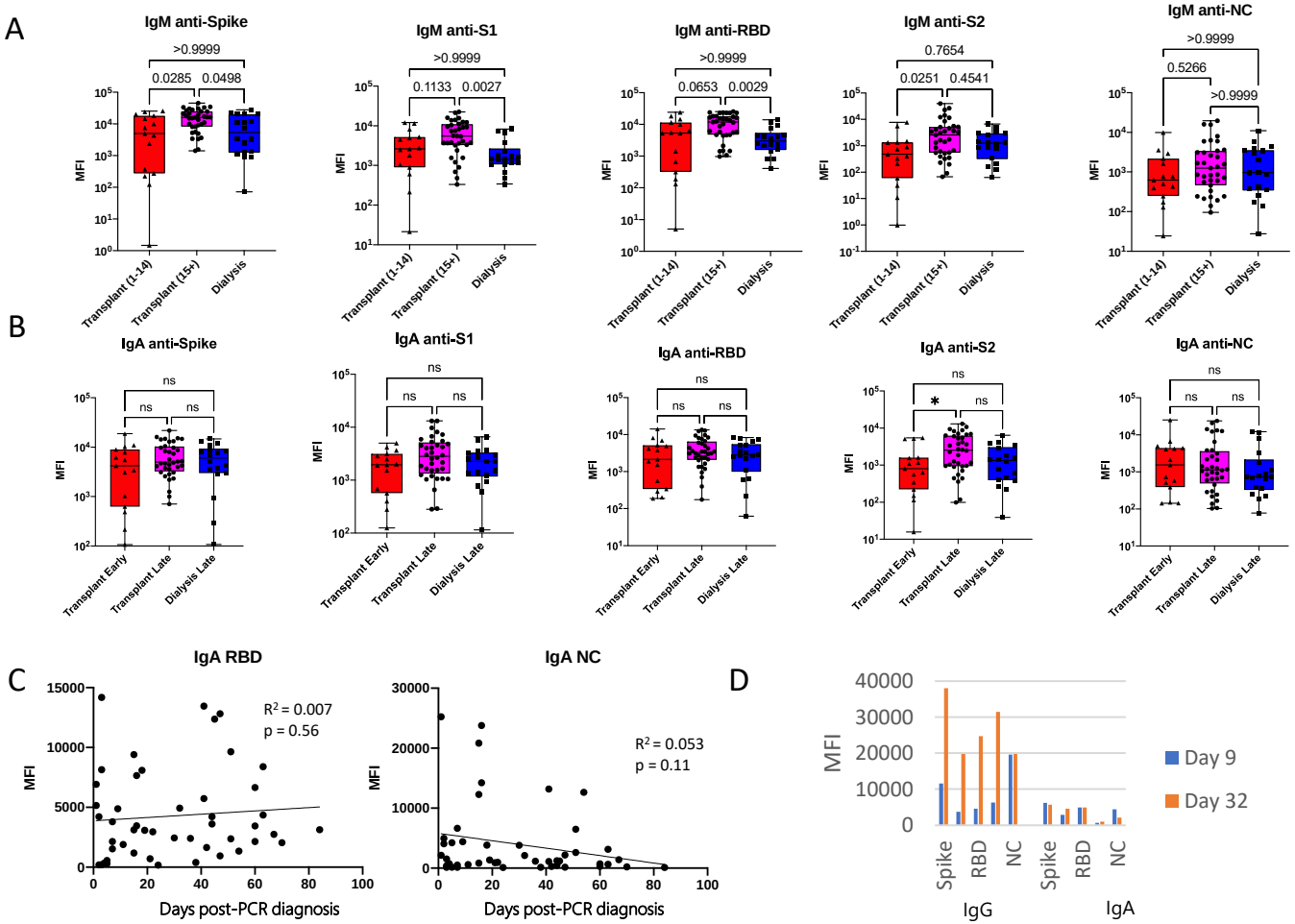


Notes: will change all numbers to * = <0.05, ** = <0.005, *** = <0.0005 and n.s. = > 0.05

Mann-Whitney for part C (unpaired, non-parametric data

Note that B does not include data from samples greater than 200 days post-diagnosis (that may start to see decreases from peak)

Generation of IgM and IgA anti-spike occur before 14 days after diagnosis

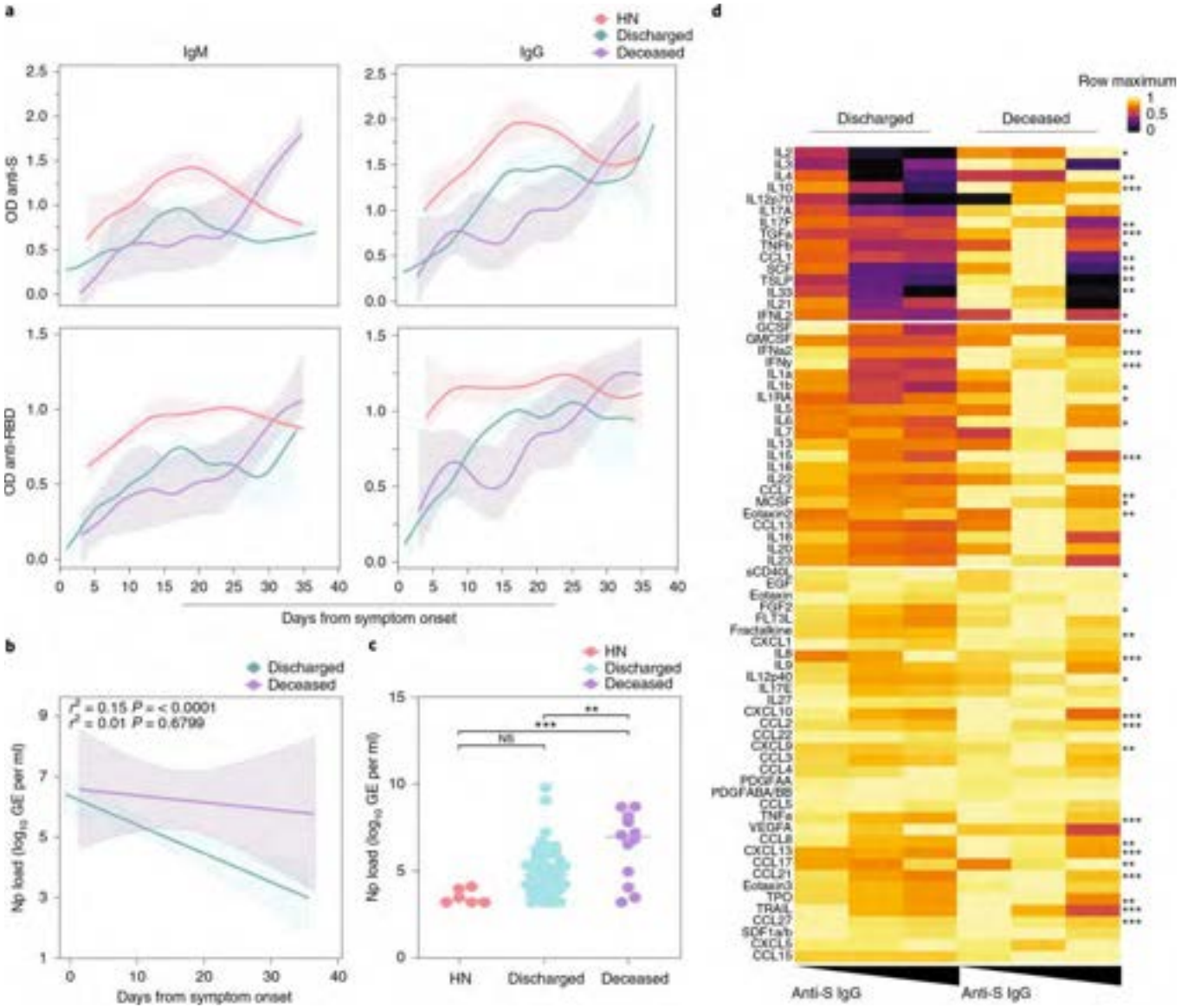


nature medicine

ARTICLES

Delayed production of neutralizing antibodies correlates with fatal COVID-19

Carolina Lucas[1,11], Jon Klein[1,11], Maria E. Sundaram[2,3], Feimei Liu[1], Patrick Wong[1], Julio Silva[1],



COVID-19 infection in kidney transplant recipients at the epicenter of pandemics

see commentary on page 1404

Yorg Azzi[1,2], Michael Parides[3], Omar Alani[2], Pablo Loarte-Campos[1,2], Rachel Bartash[4], Stefanie Forest[5], Adriana Colovai[2], Maria Ajaimy[1,2], Luz Liriano-Ward[1,2], Cindy Pynadath[1,2], Jay Graham[2,3], Marie Le[2,3], Stuart Greenstein[2,3], Juan Rocca[2,3], Milan Kinkhabwala[2,3] and Enver Akalin[1,2]

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Kidney International (2020) **98,** 1559–1567; https://doi.org/10.1016/j.kint.2020.10.004

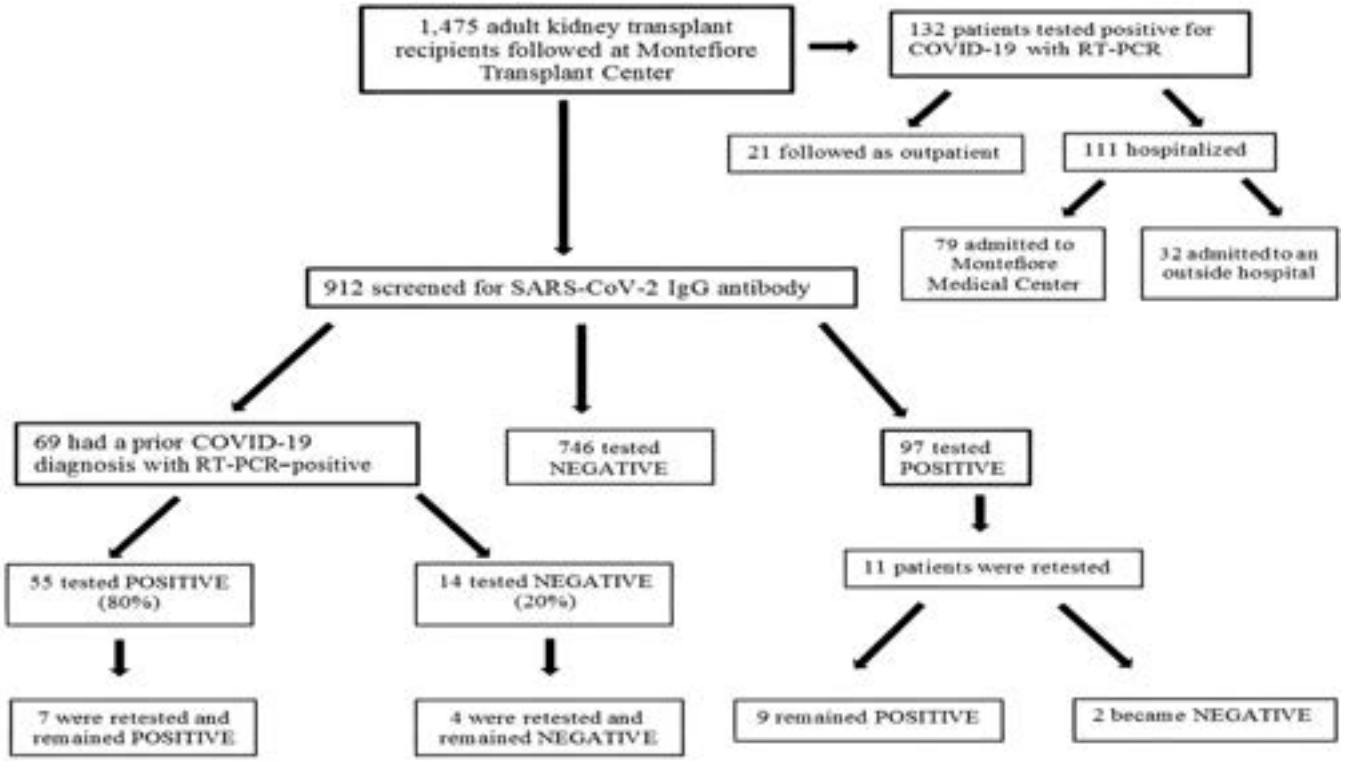

Figure 1 | Study design. COVID-19, coronavirus disease 2019; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

SUMMARY

- Severe COVID-19 pathogenesis is mediated through a dysregulated immune response
- There is an impaired interferon type 1 response and exacerbated NF-κB-driven inflammatory response with increased IL-6, sIL-6R, IL-18, IL-1Ra, CCL2, CCL8, CXCL2, CXCL8, CXCL9, and CXCL16 production in patients with COVID-19 infection leading to cytokine storm
- Circulating SARS-CoV-2-specific CD8+ and CD4+ T cells were identified in 70% and 100% of convalescent patients but declined with a half-life of 3-5 months
- Lymphopenia and low CD3, CD4, and CD8 cell counts are common in kidney transplant recipients with COVID-19
- 100% of immunocompetent patients develop antibodies to SARS-CoV-2 and it was stable up to 6-9 months
- 80% of kidney transplant recipients develop antibodies to SARS-CoV-2
- Anti-SARS-CoV-2 IgG production is delayed in transplant recipients
- Delayed seroconversion kinetics correlated with impaired viral control in deceased patients
- Despite an initial delay in T cell response, most transplant patients develop comparable functional immune response