What are clinically relevant study endpoints for COVID-19 and Influenza?

Considerations for the Immunocompromised Host

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Conflict of Interest

Research support: AstraZeneka, Moderna, Asun Biopharma, Pulmotect, Pfizer, Merck

Consulting: AstraZeneka, Moderna, Merck, Invivyd

Outline

- How to run studies in immunocompromised patients?
- What are appropriate study populations and endpoints?
- Can studies in immunocompromised patients during peacetime be used for initial approval?

How to run studies in immunocompromised patients?

- Experience with RSV, influenza and parainfluenza virus
- Large multicenter consortia
  - Ad hoc
  - Future: networks

  - ImmunOptimize Network

Learn More

What are appropriate study populations and endpoints?

Target populations

- HCT
- Hematologic malignancies
- Solid organ transplants

Combination therapy

- Improved clinical outcomes and shorter duration of shedding

Enrichment

- Risk scores

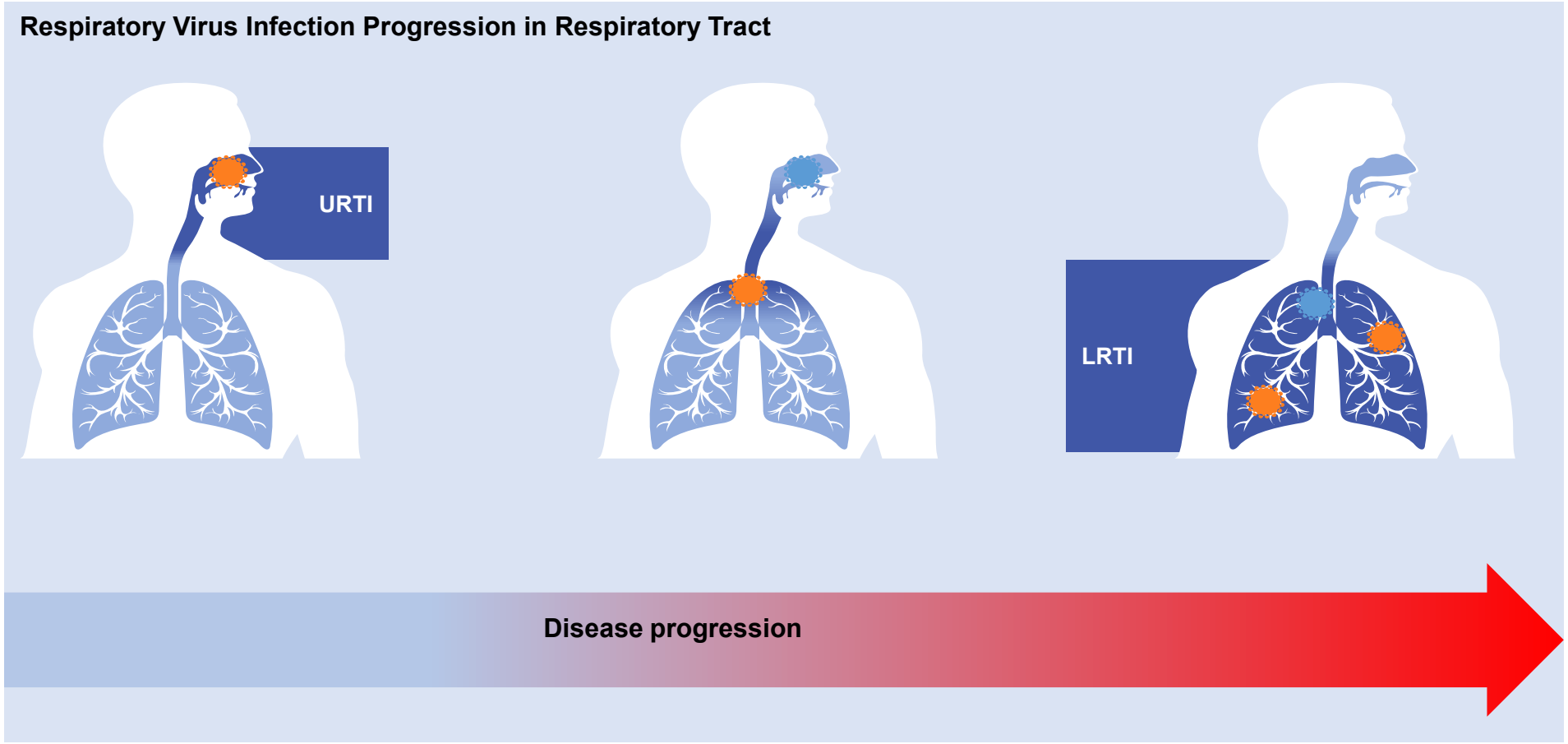
Drug

- Dose
- Duration
- Timing

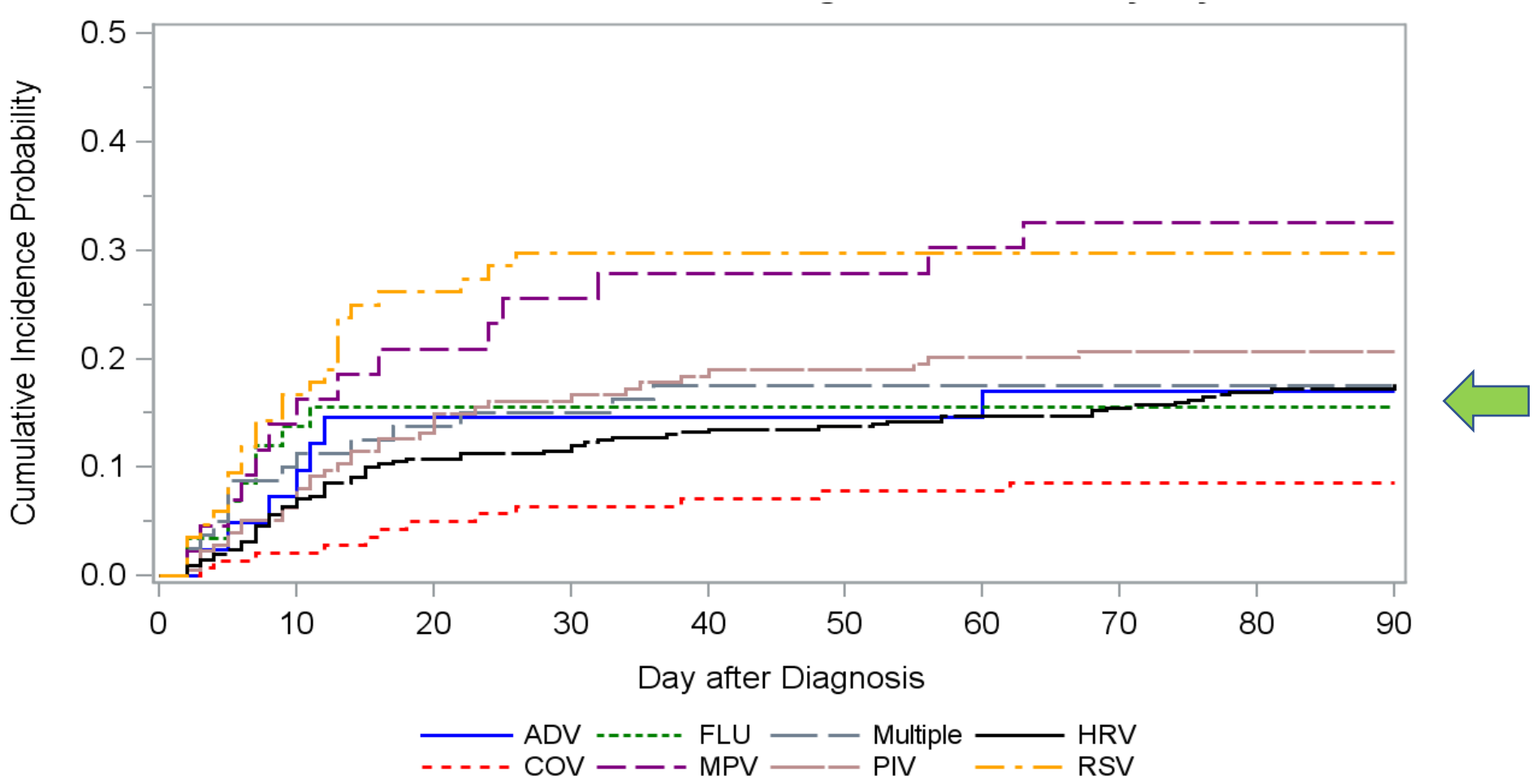
Endpoints

- Clinical
- Viral load (transmission)

Upper to Lower Tract Disease

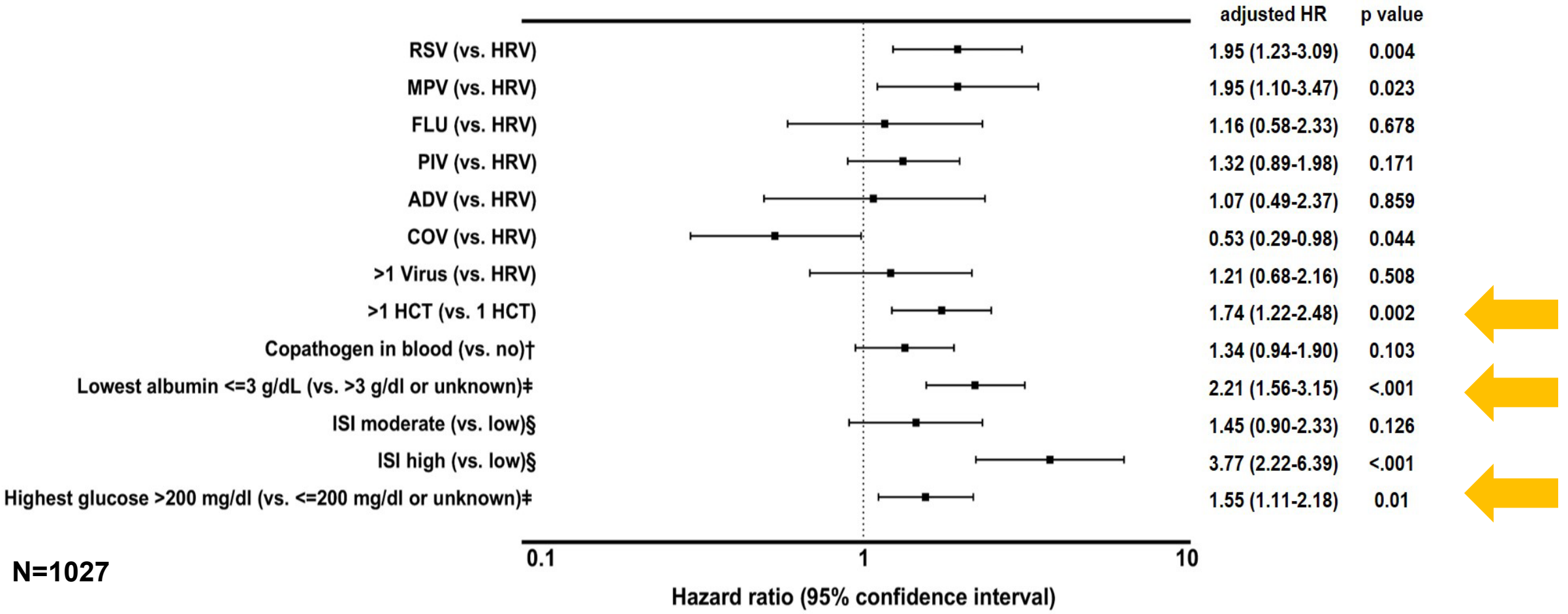


Progression LRTD in the PCR Era



N=1027, Ogimi et al. BMT 2022

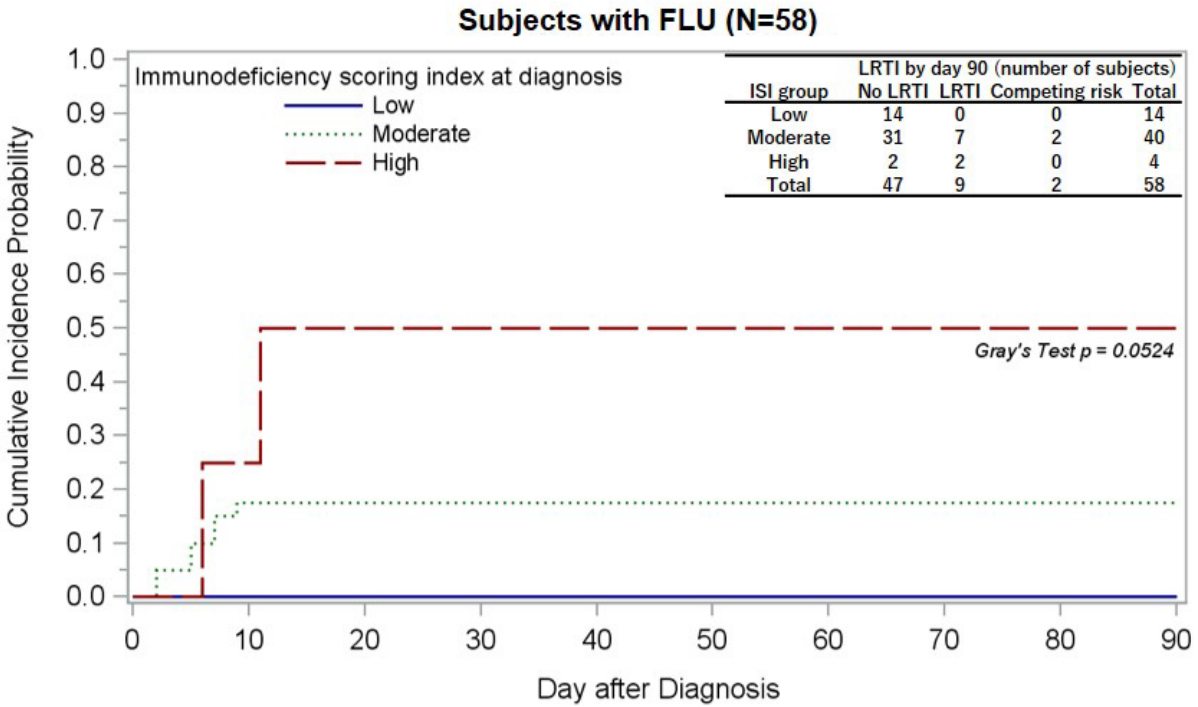
Progression to LRD: Risk Factors



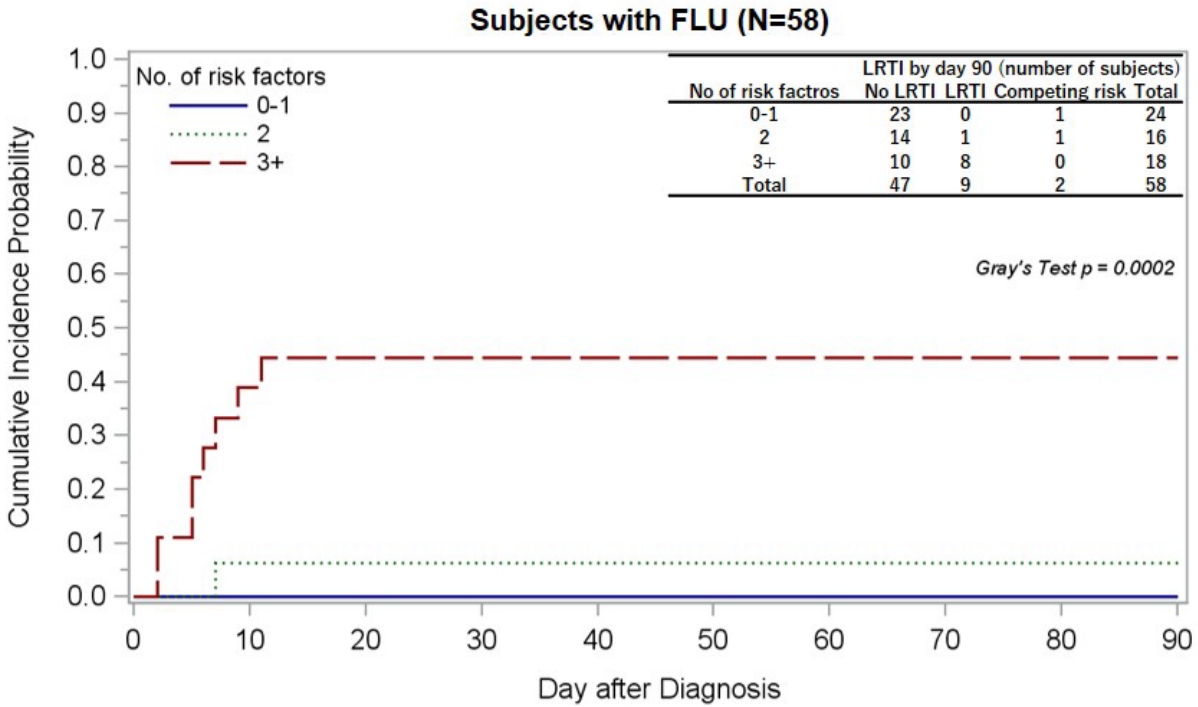
N=1027

Ogimi et al. BMT 2022

Risk Prediction: Immunodeficiency score vs. Number of Risk Factors: Influenza



ISI group	LRTI by day 90 (number of subjects) No LRTI	LRTI	Competing risk	Total
Low	14	0	0	14
Moderate	31	7	2	40
High	2	2	0	4
Total	47	9	2	58

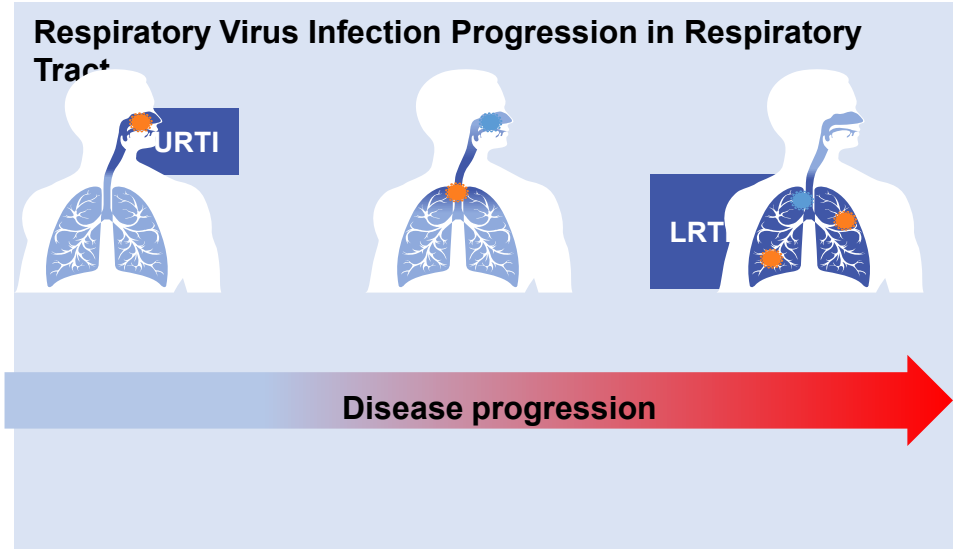


No of risk factros	LRTI by day 90 (number of subjects) No LRTI	LRTI	Competing risk	Total
0-1	23	0	1	24
2	14	1	1	16
3+	10	8	0	18
Total	47	9	2	58

Ogimi et al. BMT 2022

Other Clinical Endpoints for Studies of URI

- Death
  - Any case versus pulmonary death
- Emergency room visit
  - Often related to progression
  - Often results in admission in IC hosts
  - Alternative causes more common
- Hospital admission
  - Often Related to progression
  - Alternative causes more common
- URI can occur in patients hospitalized for other reasons



Viral Load as Predictor for Clinical Progression

SARS-CoV-2 Viral Load and Outcome

Data mostly from immunocompetent individuals

Temporal changes in SARS-CoV-2 clearance kinetics and the optimal design of antiviral pharmacodynamic studies: an individual patient data meta-analysis of a randomised, controlled, adaptive platform study (PLATCOV)

Phrutsamon Wongnak, William H K Schilling, Podjanee Jittamala, Simon Boyd, Viravarn Luvira, Tanaya Siripoon, Thundon Ngamprasertchai, Elizabeth M Batty, Shivani Singh, Jindarat Kouhathong, Watcharee Pagornrat, Patpannee Khanthagan, Borimas Hanboonkunupakarn, Kittiyod Poovorawan, Mayfong Mayxay, Kesinee Chotivanich, Mallika Imwong, Sasithon Pukrittayakamee, Elizabeth A Ashley, Arjen M Dondorp, Nicholas P J Day, Mauro M Teixeira, Watcharapong Piyaphanee, Weerapong Phumratanaprapin, Nicholas J White, James A Watson*, on behalf of* †

Lancet Infect Dis 2024; 24: 953–63

J Antimicrob Chemother 2024; **79**: 935–945
https://doi.org/10.1093/jac/dkae045 Advance Access publication 22 February 2024

Journal of Antimicrobial Chemotherapy

The relationship between viral clearance rates and disease progression in early symptomatic COVID-19: a systematic review and meta-regression analysis

Shivani Singh [1], Simon Boyd [1,2]*, William H. K. Schilling[1,2], James A. Watson[2,3], Mavuto Mukaka[1,2] and Nicholas J. White[1,2]

Viral clearance as a surrogate of clinical efficacy for COVID-19 therapies in outpatients: a systematic review and meta-analysis

Karen M Elias, Shanchita R Khan, Eva Stadler, Timothy E Schlub, Deborah Cromer, Mark N Polizzotto, Stephen J Kent, Tari Turner, Miles P Davenport, David S Khoury

Lancet Microbe 2024; 5: e459–67

Possible viral load endpoints

- **Slope – early decline**
- **Area under the curve**
- **Persistence**

Viral Load Decline predicts hospitalization

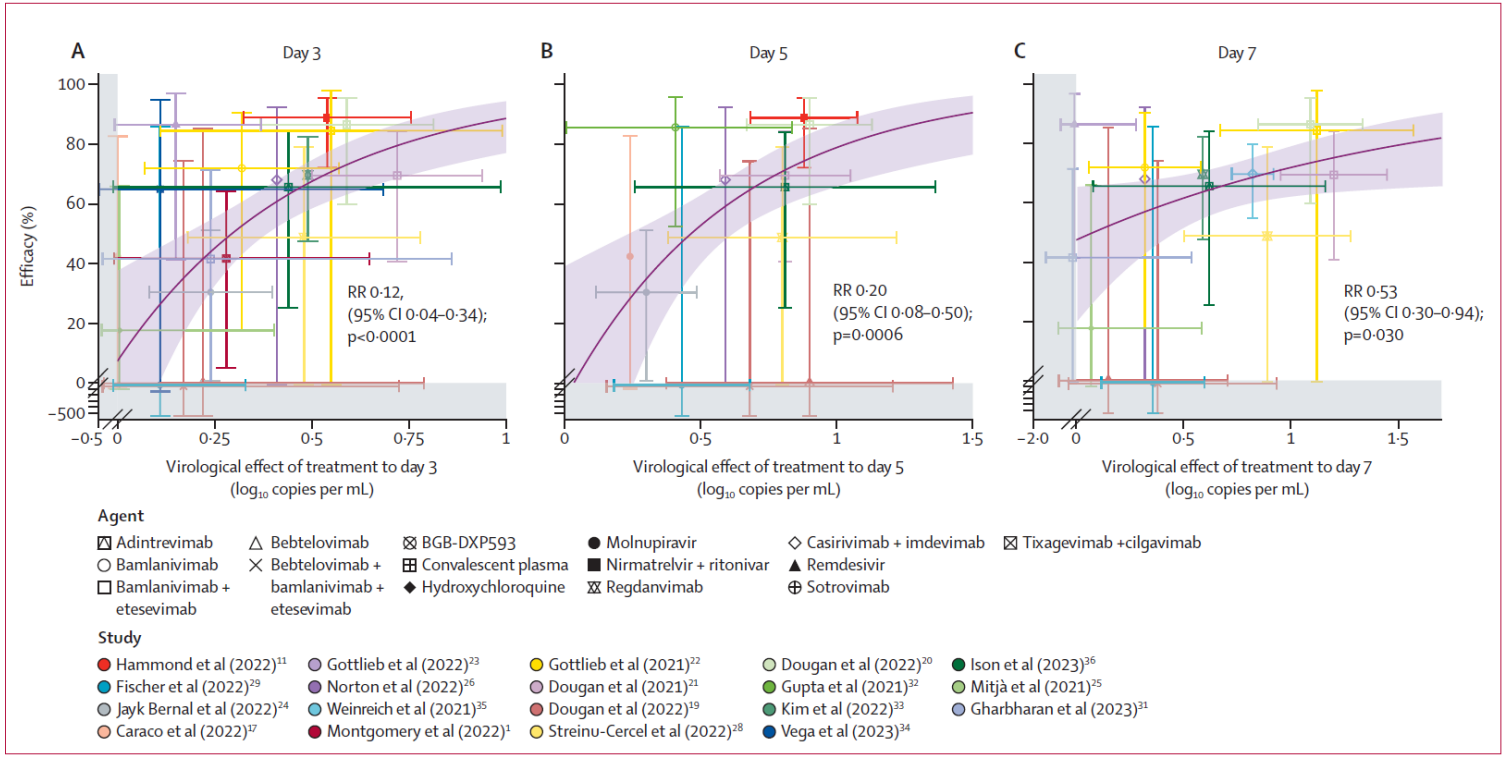


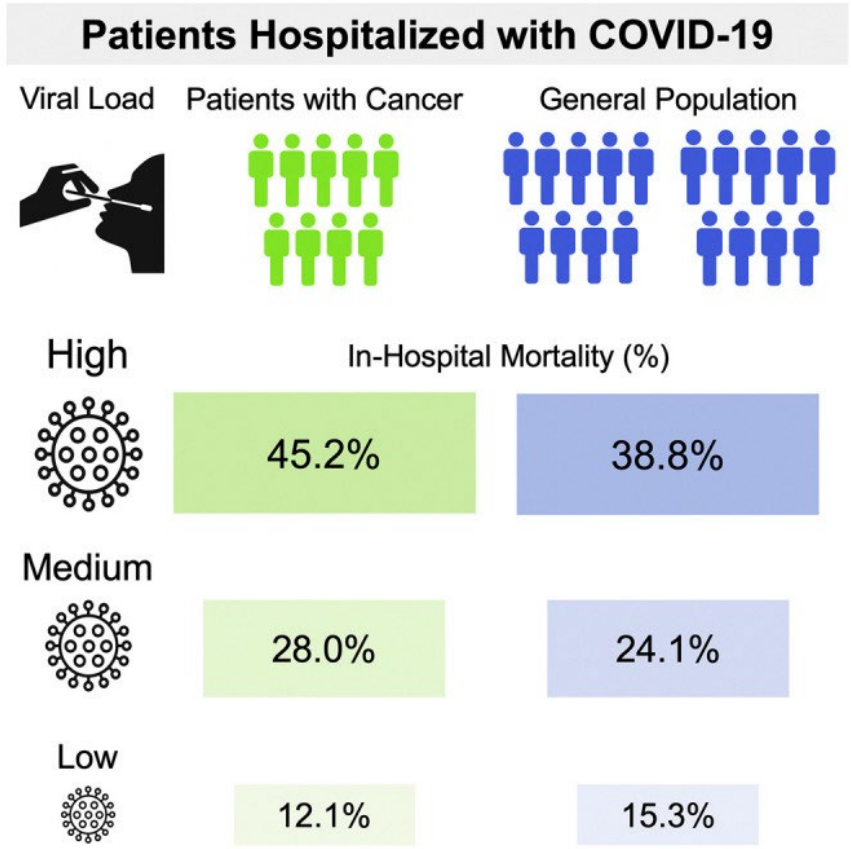
Figure 4: Correlation between virological effect and clinical efficacy in primarily unvaccinated outpatients with COVID-19 treated with small molecule antivirals, convalescent plasma, or monoclonal antibodies

Virological effect of treatment was the change in viral load from baseline to day 3 (A), day 5 (B), and day 7 (C). Clinical efficacy was 1 minus the relative risk of hospitalisation or death within 28 days with versus without treatment, converted to a percentage. Error bars of each datapoint indicate 95% CI. Points without horizontal error bars are studies for which it was not possible to calculate a 95% CI from the published data on the spread of virological treatment effect. The solid lines indicate the fitted regression models with 95% confidence regions indicated by shading. Grey shaded regions highlight a change in the scale of the axes. RR=relative risk.

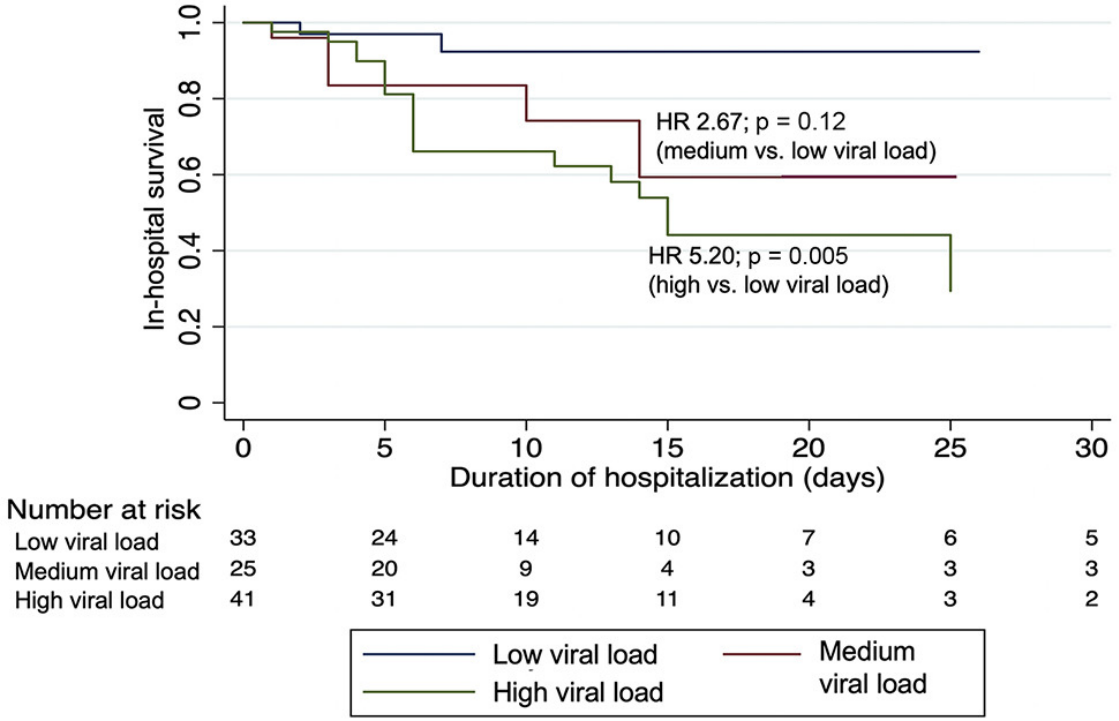
Elias KM et al. Lancet Microbe 2024

Viral load and Outcome in IC Hosts

Limited Data



SARS-CoV-2 - Cancer



Westblade, Cancer Cell 2020

Prolonged Shedding in IC Hosts and Viral Evolution

The NEW ENGLAND JOURNAL of MEDICINE

SARS-CoV-2 Variants in Patients with Immunosuppression

Lawrence Corey, M.D., Chris Beyrer, M.D., M.P.H., Myron S. Cohen, M.D., Nelson L. Michael, M.D., Ph.D., Trevor Bedford, Ph.D., and Morgane Rolland, Ph.D.

The Journal of Infectious Diseases

BRIEF REPORT

Prolonged Severe Acute Respiratory Syndrome Coronavirus 2 Replication in an Immunocompromised Patient

Ji Hoon Baang,[1] Christopher Smith,[2] Carmen Mirabelli,[3] Andrew L. Valesano,[1,3] David M. Manthei,[4] Michael A. Bachman,[4] Christiane E. Wobus,[3] Michael Adams,[2] Laraine Washer,[1] Emily T. Martin,[5] and Adam S. Lauring[1,3]

Article

SARS-CoV-2 evolution during treatment of chronic infection

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Check for updates

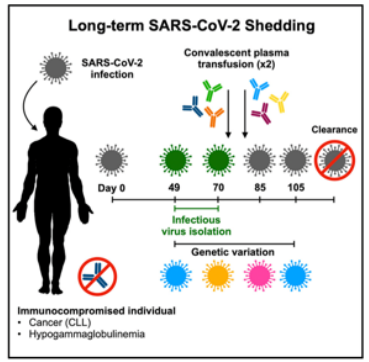
Steven A. Kemp[1,148], Dami A. Collier[1,2,3,148], Rawlings P. Datir[2,3,148], Isabella A. T. M. Ferreira[3,5], Salma Gayed[4], Aminu Jahun[3], Myra Hosmillo[3], Chloe Rees-Spear[3], Petra Mlcochova[3,7], Ines Ushiro Lumb[8], David J. Roberts[9], Anita Chandra[2,3], Nigel Temperton[7], The CITIID-NIHR BioResource COVID-19 Collaboration*, The COVID-19 Genomics UK (COG-UK) Consortium*, Katherine Sharrocks[4], Elizabeth Blane[3], Yorgo Modis[2,3,8], Kendra E. Leigh[2,3,8], John A. G. Briggs[8], Marit J. van Gils[9], Kenneth G. C. Smith[2,3], John R. Bradley[2,10], Chris Smith[11], Rainer Doffinger[12], Lourdes Ceron-Gutierrez[12], Gabriela Barcenas-Morales[12,13], David D. Pollock[14], Richard A. Goldstein[1], Anna Smielewska[4,15], Jordan P. Skittrall[4,15,16], Theodore Gouliouris[4], Ian G. Goodfellow[3], Effrossyni Gkrania-Klotsas[4], Christopher J. R. Illingworth[15,17], Laura E. McCoy[7] & Ravindra K. Gupta[2,3,18]✉

Cell

Article

Case Study: Prolonged Infectious SARS-CoV-2 Shedding from an Asymptomatic Immunocompromised Individual with Cancer

Graphical Abstract



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Highlights

- Persistent SARS-CoV-2 infection and shedding in immunocompromised individual

In Brief

This case study describes a female immunocompromised individual with chronic lymphocytic leukemia and acquired hypogammaglobulinemia who became persistently infected with SARS-CoV-2. Although asymptomatic throughout the course of infection, she demonstrated prolonged shedding of infectious SARS-CoV-2 virus and RNA. This study demonstrates that certain individuals may remain infectious for prolonged periods of time and highlights the need for further studies to understand risk factors for prolonged infectious SARS-CoV-2 shedding.

Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA hivma

The Longest Persistence of Viable SARS-CoV-2 With Recurrence of Viremia and Relapsing Symptomatic COVID-19 in an Immunocompromised Patient—A Case Study

Chiara Sepulcri,[1,2,✉] Chiara Dentone,[1,2,✉] Malgorzata Mikulska,[1,2,✉] Bianca Bruzzone,[1,2] Alessia Lai,[1,2] Daniela Fenoglio,[1,2,✉] Federica Bazzano,[1,2] Annalisa Bergna,[1,2] Alessia Parodi,[1,2] Siziana Altosole,[1] Emanuele Delfino,[1,2] Giulia Bartalucci,[1] Andrea Orsi,[1,2,✉] Antonio Di Biagio,[1,2,✉] Giampaglielmo Zehender,[1,2] Filippo Balletrisi,[1,2] Stefano Bonora,[1,2] Alessandro Sette,[3,4] Raffaele De Palma,[1,2,✉] Guido Silvestri,[1,2,4,✉] Andrea De Maria,[1,2,✉] and Matteo Bassetti[1,2,✉]

ARTICLE

Check for updates

https://doi.org/10.1038/s41467-021-26602-3 OPEN

Within-host evolution of SARS-CoV-2 in an immunosuppressed COVID-19 patient as a source of immune escape variants

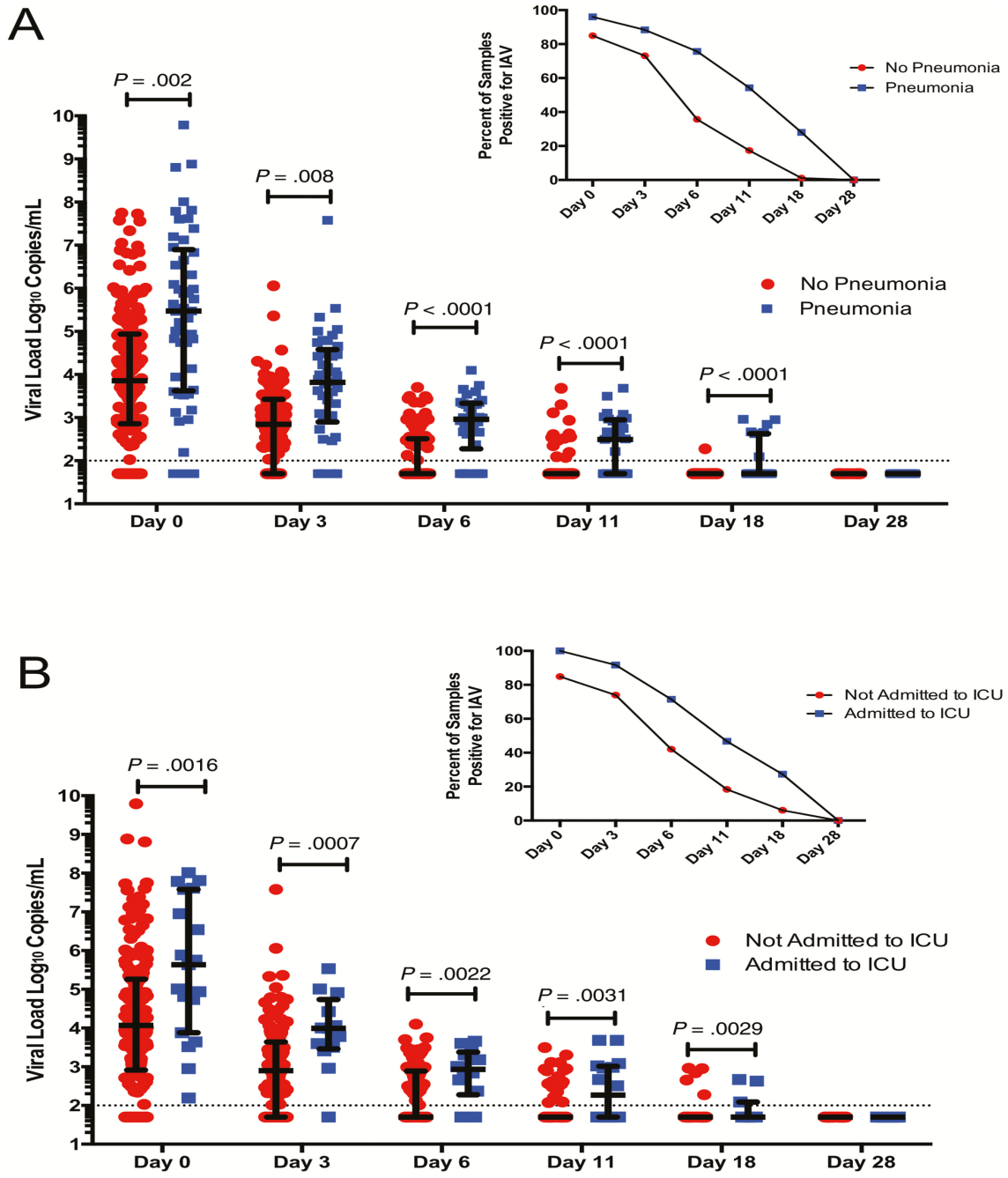
Sebastian Weigang[1,7], Jonas Fuchs[1,7], Gert Zimmer[2], Daniel Schnepf[1], Lisa Kern[1], Julius Beer[1],

Article

Increased viral variants in children and young adults with impaired humoral immunity and persistent SARS-CoV-2 infection: A consecutive case series

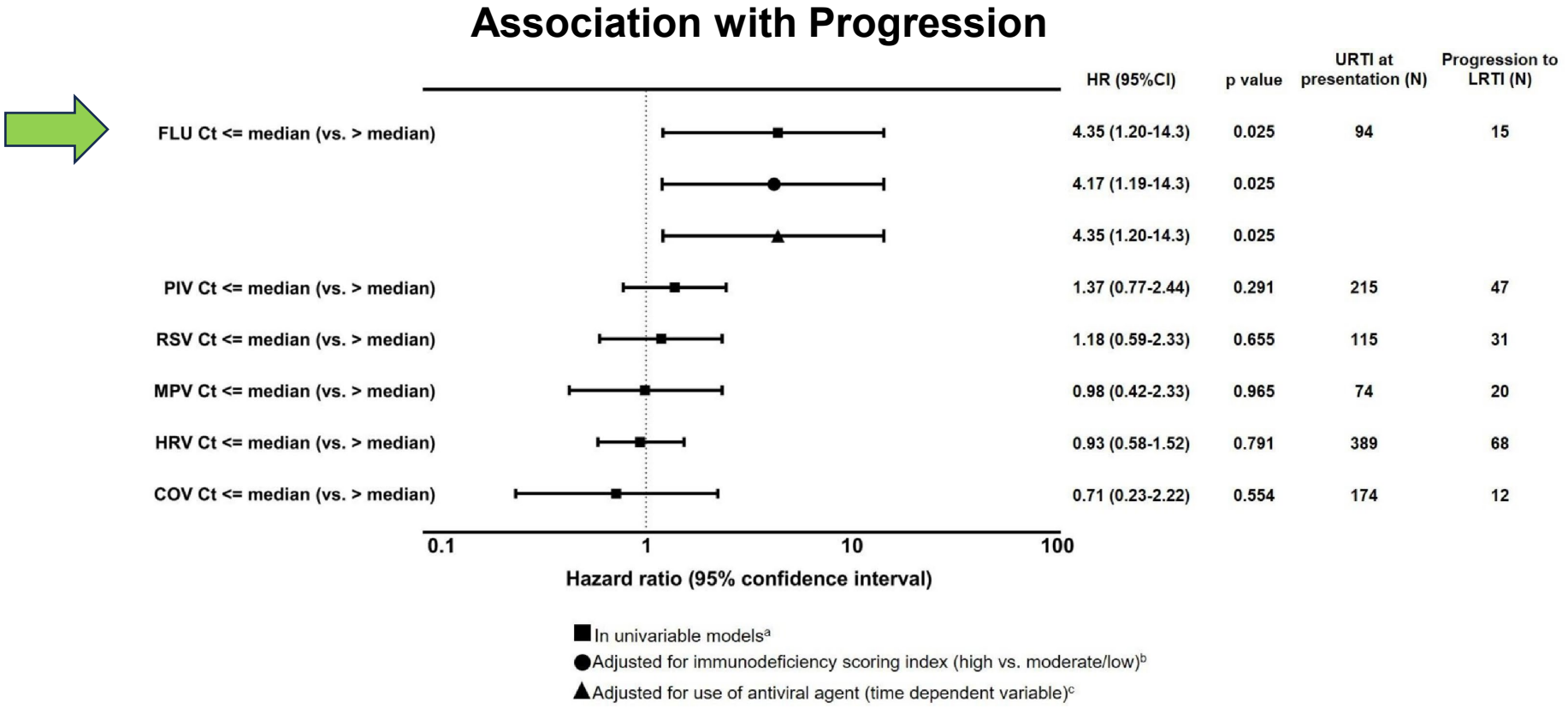
Thao T. Truong[a], Alex Ryutov[a], Utsav Pandey[b], Rebecca Yee[a], Lior Goldberg[c,d],

Influenza Viral Load after Transplantation



Kumar D *Clin Infect Dis*. 2018;67: 1322-1329

Initial Influenza Viral Load In Upper Respiratory Samples Predicts Progression to LRD



Ogimi C et al. J Clin Virol 2022

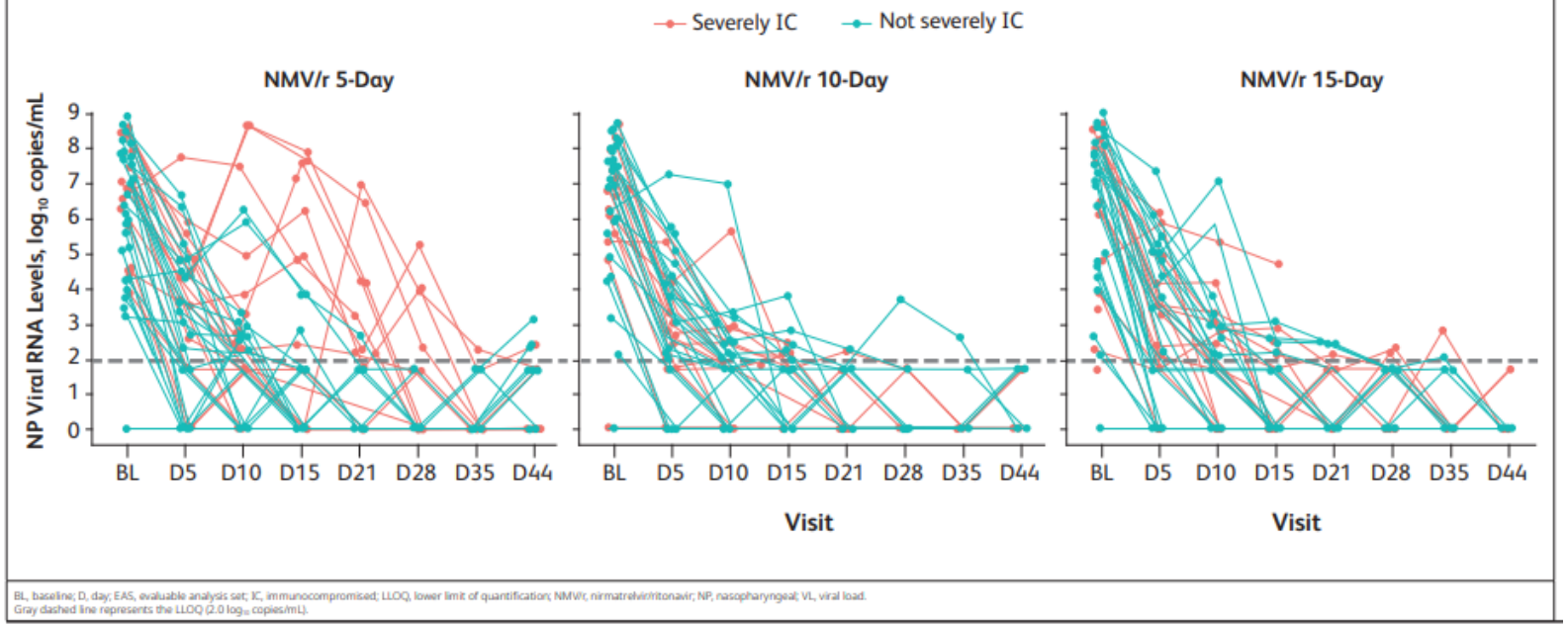
Duration of Treatment

Longer Duration needed in severely IC hosts

00658 Extended Nirmatrelvir/Ritonavir Treatment Durations for Immunocompromised Patients With COVID-19

Edward Weinstein,[1]* Annie Gardner,[1] Mary Almas,[1] Mary Lynn Baniecki,[2] Shunjie Guan,[2] Elena Tudone,[3] Simone Antonucci,[3] Kevin Gregg,[4] Roger Paredes,[5] Carolina Garcia-Vidal,[6] Adrian Camacho,[7] Wayne Wisemandle,[1] Steven G. Terra,[1] Jennifer Hammond,[1] James Rusnak[8]

Figure 3. Log_{10}-Nasopharyngeal SARS-CoV-2 RNA Levels Over Time by NMV/r Treatment Duration (EAS)



BL, baseline; D, day; EAS, evaluable analysis set; IC, immunocompromised; LLOQ, lower limit of quantification; NMV/r, nirmatrelvir/ritonavir; NP, nasopharyngeal; VL, viral load.
Gray dashed line represents the LLOQ (2.0 log_{10} copies/mL).

Presented at the Conference on Retroviruses and Opportunistic Infections; March 3–6, 2024; Denver, CO, USA

Can studies in immunocompromised patients during peacetime be used for initial approval?

- Post-pandemic epidemiology
- Site experience exists
- Composite endpoints that include viral load kinetics
  - Increase feasibility
  - Reduce transmission
  - Impact of variance development and resistance
- Applicability for less vulnerable populations?

Summary

- Viral load correlates with clinical endpoints in IC hosts
  - Sars-CoV-2
  - Influenza
- Persistent shedding
  - Common, especially in severely IC persons
  - Viral evolution - SARS-CoV-2
  - Resistance – Influenza
- Duration of treatment
  - Longer duration needed
  - Higher doses may prevent development of resistance
- Endpoints
  - Clinical progression: radiographic, oxygen dependency, need for additional management, death
  - Viral load kinetics: slope most predictive of clinical outcome
    - Remaining data gap in IC hosts
    - Optimal VL variable
- Trials in peacetime are possible: continued burden of disease
  - Monotherapy vs. combination therapy

Thank You