Torino, 30.3.2022

Update on clinical and epidemiological aspects of COVID-19

Pierluigi Viale

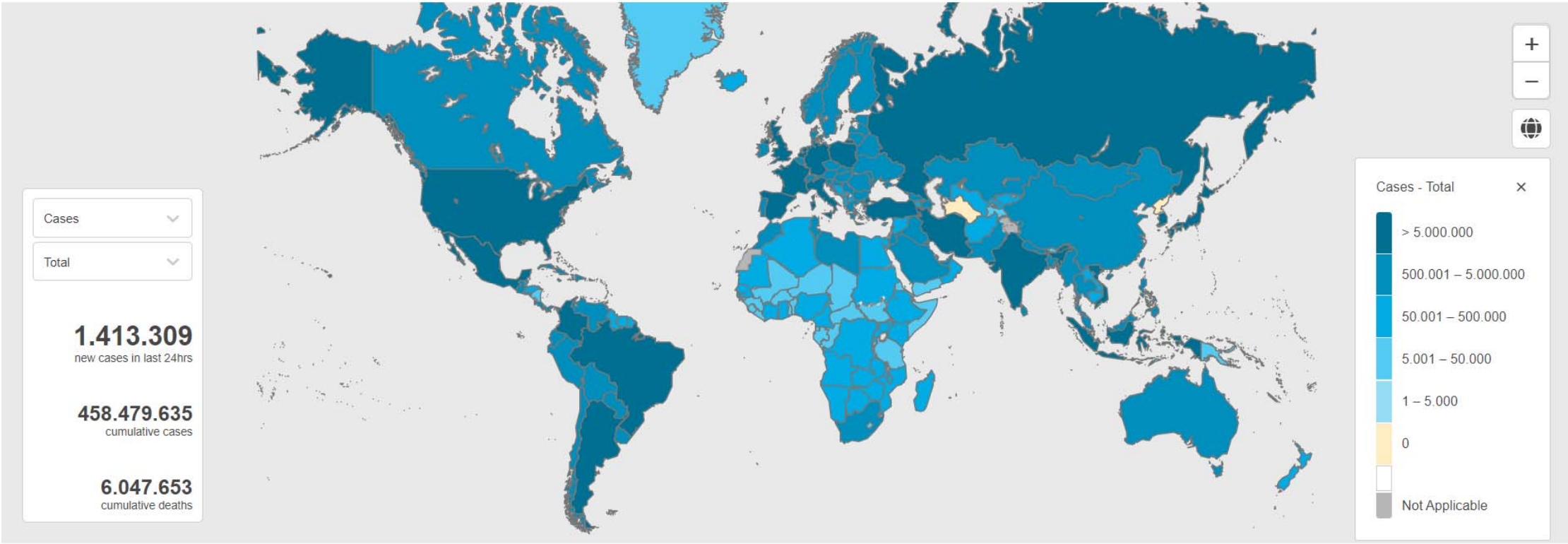
Dipartimento Interaziendale per la Gestione Integrata del Rischio Infettivo

IRCCS Policlinico S. Orsola – AUSL Bologna – IRCCS Istituti Ortopedici Rizzoli Bologna –AUSL Imola

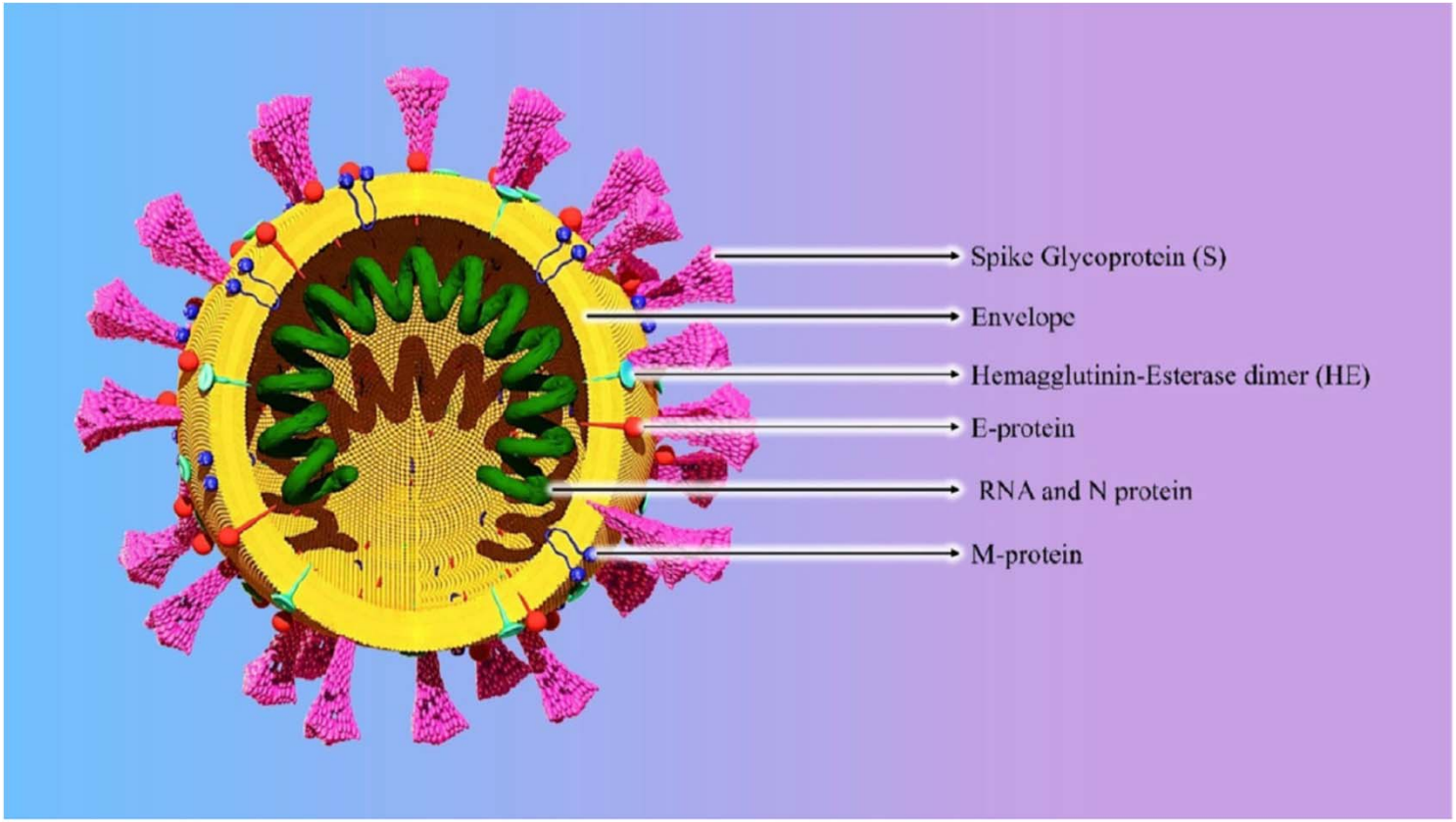
World Health Organization

WHO Coronavirus (COVID-19) Dashboard

Overview Measures Data Table Explore



Globally, as of **5:56pm CET, 15 March 2022**, there have been **458.479.635 confirmed cases** of COVID-19, including **6.047.653 deaths**, reported to WHO. As of **13 March 2022**, a total of **10.712.423.741 vaccine doses**

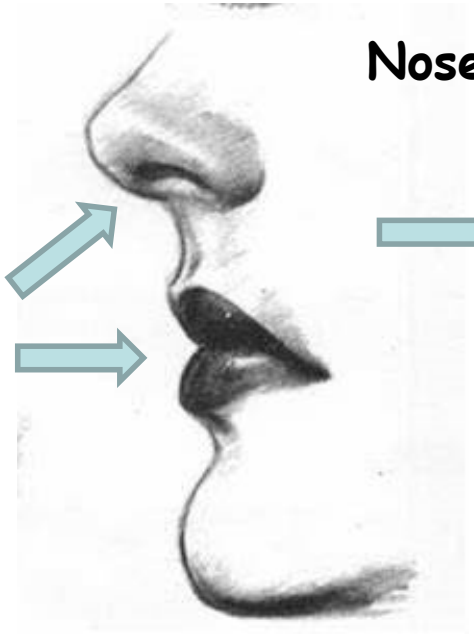


After the fusion, replication of viral RNA occurs in the host cytoplasm by a unique mechanism in which RNA polymerase binds to a leader sequence and then detaches and reattaches at multiple locations, allowing for the production of a nested set of mRNA molecules with common 3' ends.

Lung alveoli

Heart blood vessels lining

Nose epithelial



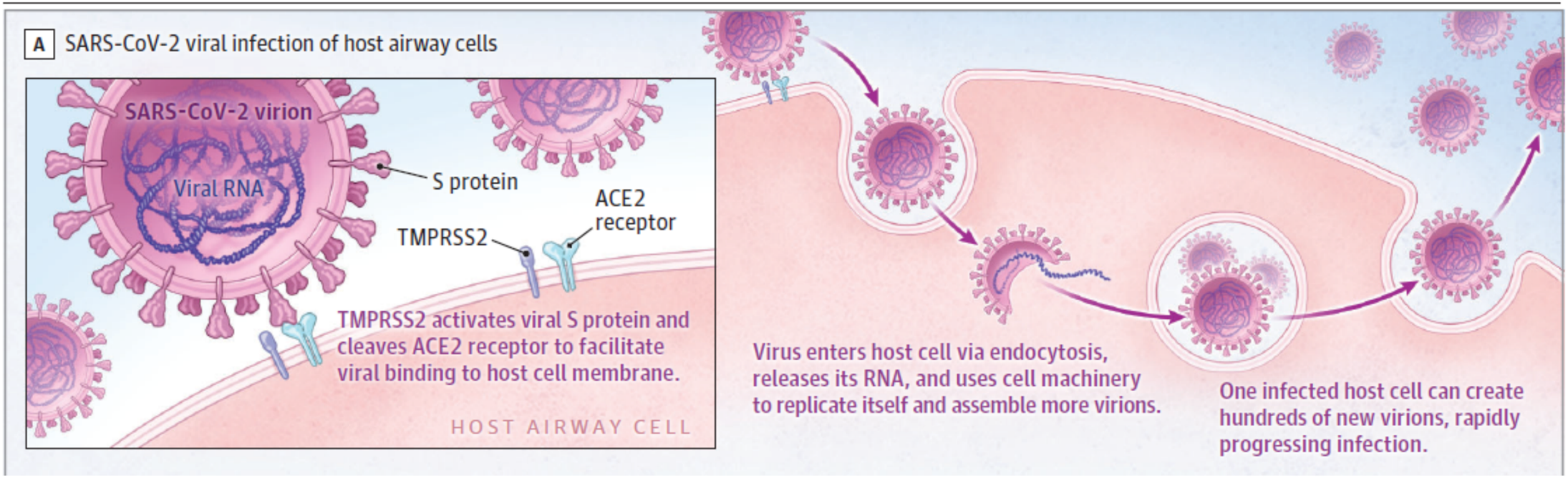
Every cell rich in a cell-surface receptor
the angiotensin-converting enzyme 2

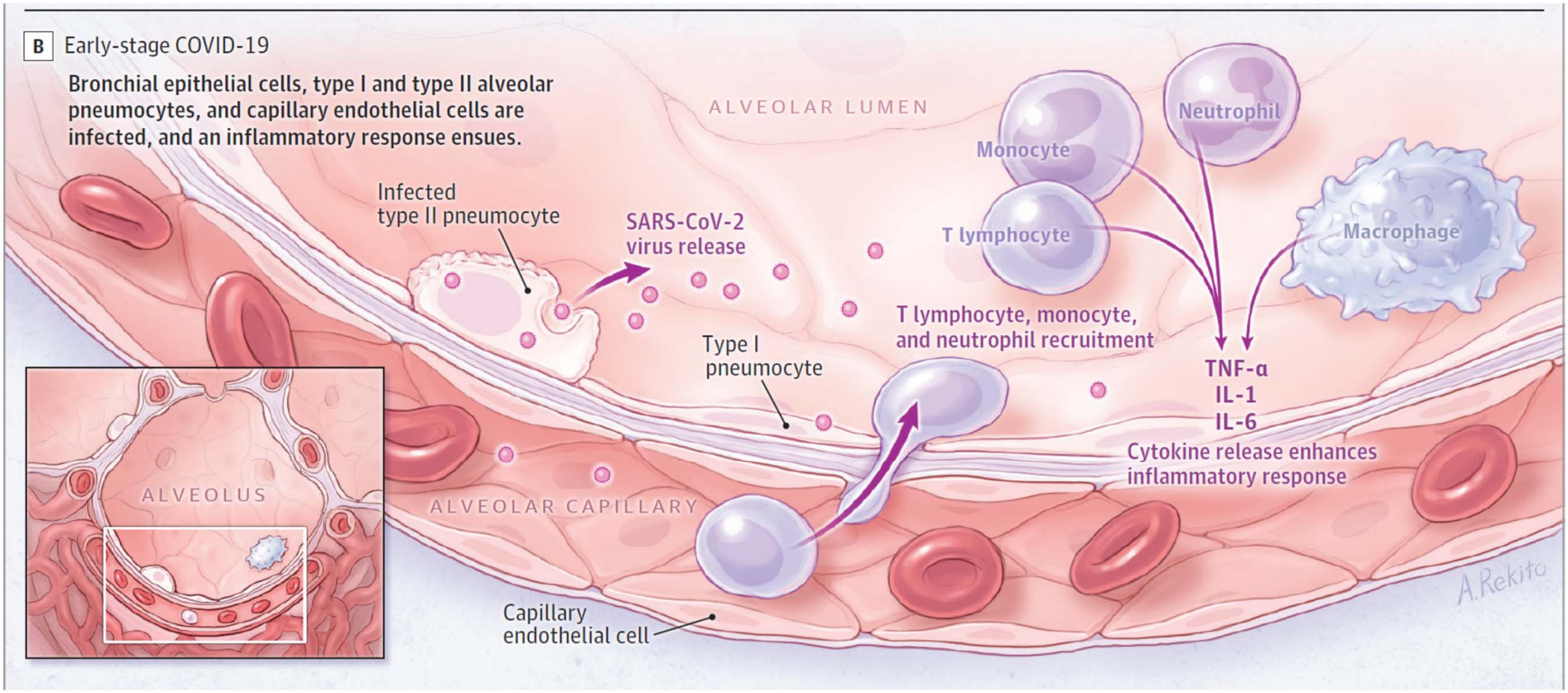
Blood vessels lining

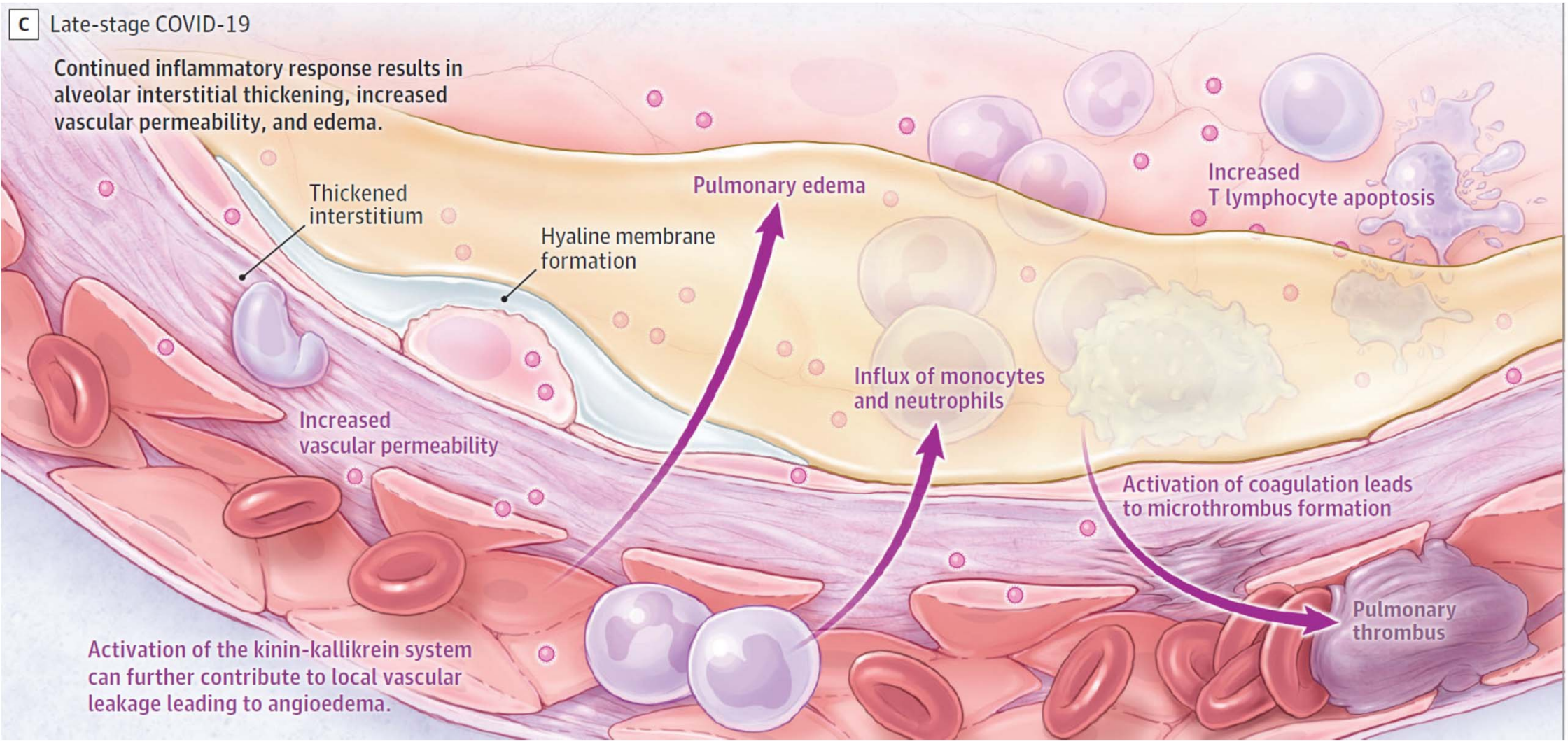
Lower digestive tract

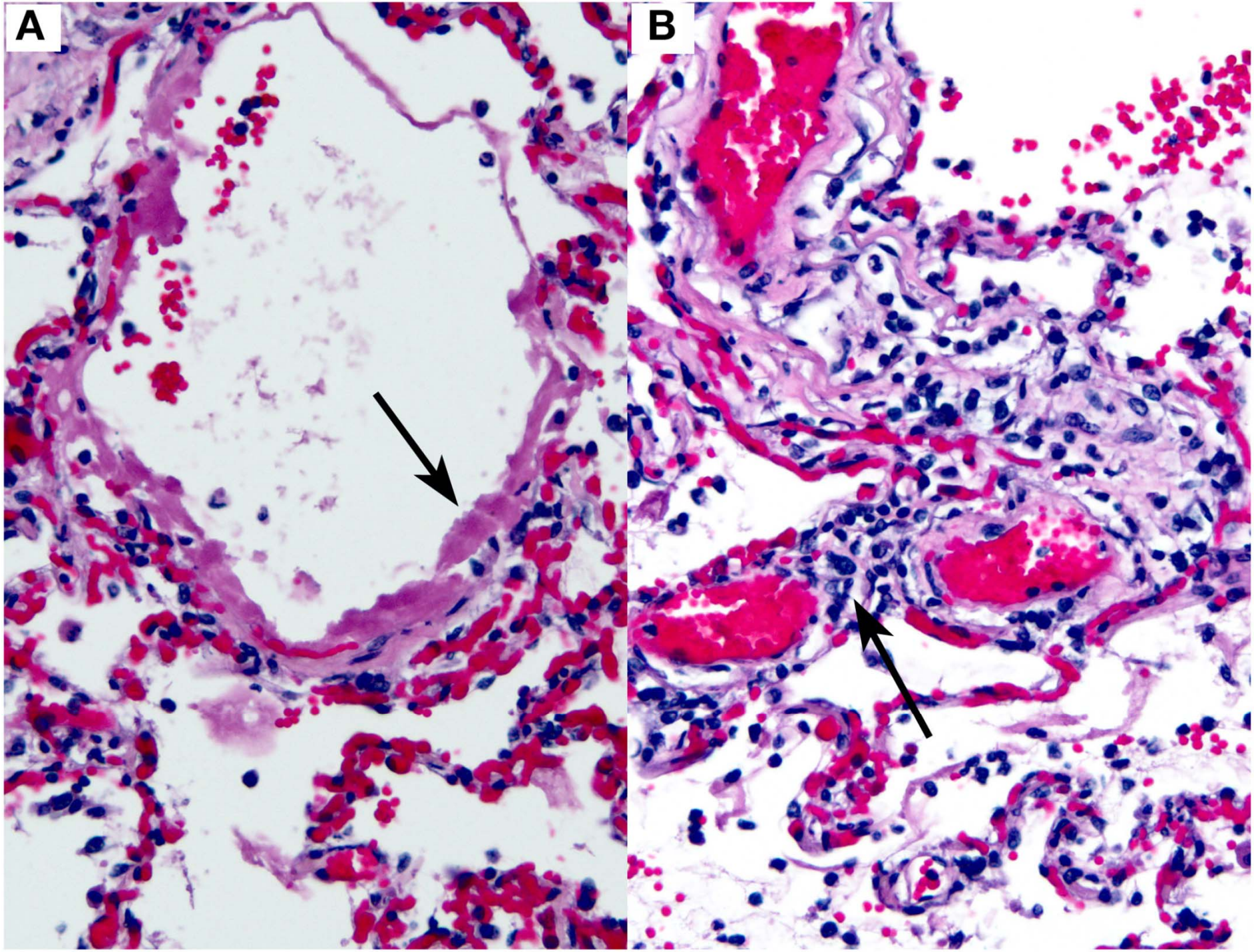
Kidney cells

Neural cortex and brain stem


A SARS-CoV-2 viral infection of host airway cells
SARS-CoV-2 virion
Viral RNA
S protein
ACE2 receptor
TMPRSS2
TMPRSS2 activates viral S protein and cleaves ACE2 receptor to facilitate viral binding to host cell membrane.
HOST AIRWAY CELL
Virus enters host cell via endocytosis, releases its RNA, and uses cell machinery to replicate itself and assemble more virions.
One infected host cell can create hundreds of new virions, rapidly progressing infection.


B Early-stage COVID-19
Bronchial epithelial cells, type I and type II alveolar pneumocytes, and capillary endothelial cells are infected, and an inflammatory response ensues.
ALVEOLAR LUMEN
Neutrophil
Monocyte
T lymphocyte
Macrophage
Infected type II pneumocyte
SARS-CoV-2 virus release
T lymphocyte, monocyte, and neutrophil recruitment
Type I pneumocyte
TNF-α
IL-1
IL-6
Cytokine release enhances inflammatory response
ALVEOLUS
ALVEOLAR CAPILLARY
Capillary endothelial cell
A.Rekito

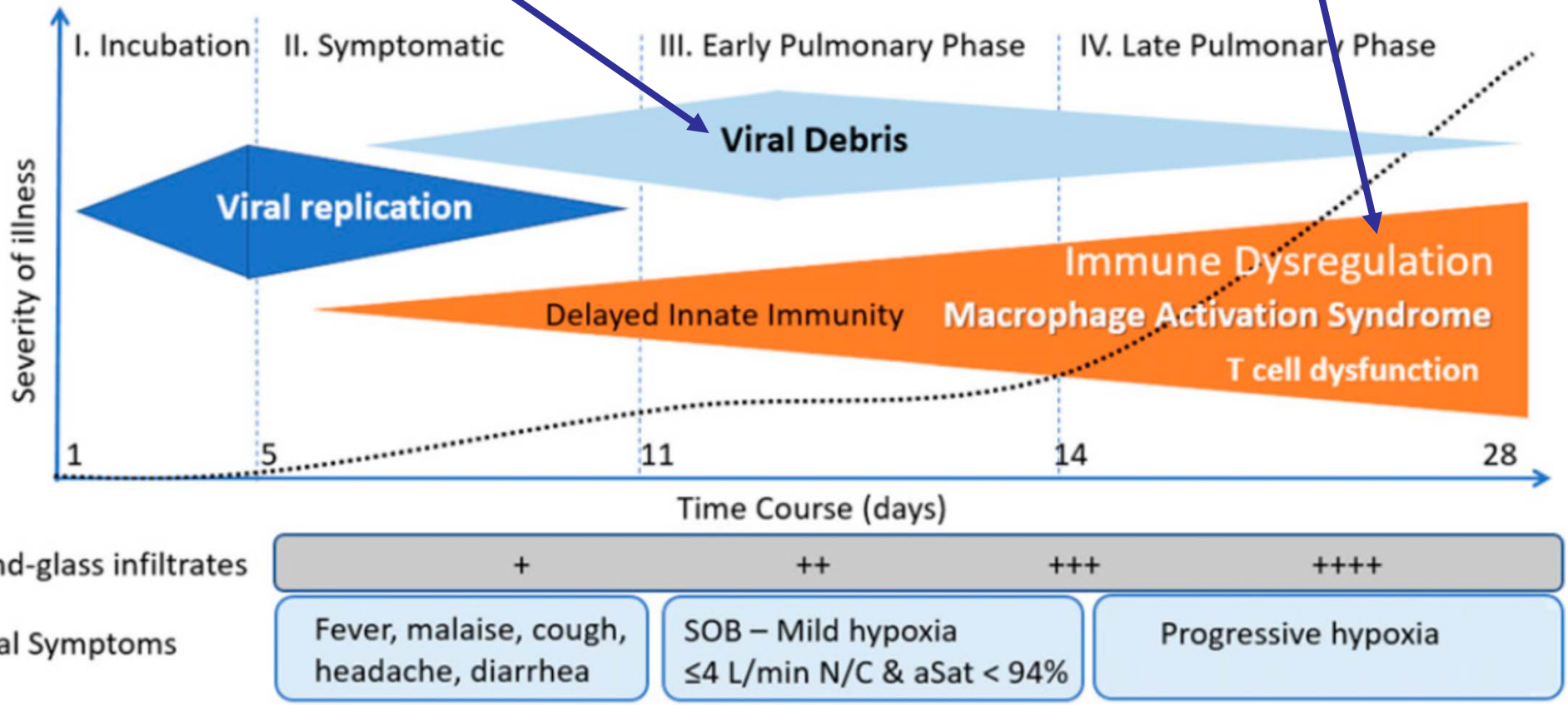

C Late-stage COVID-19
Continued inflammatory response results in alveolar interstitial thickening, increased vascular permeability, and edema.
Thickened interstitium
Hyaline membrane formation
Pulmonary edema
Increased T lymphocyte apoptosis
Influx of monocytes and neutrophils
Increased vascular permeability
Activation of coagulation leads to microthrombus formation
Pulmonary thrombus
Activation of the kinin-kallikrein system can further contribute to local vascular leakage leading to angioedema.

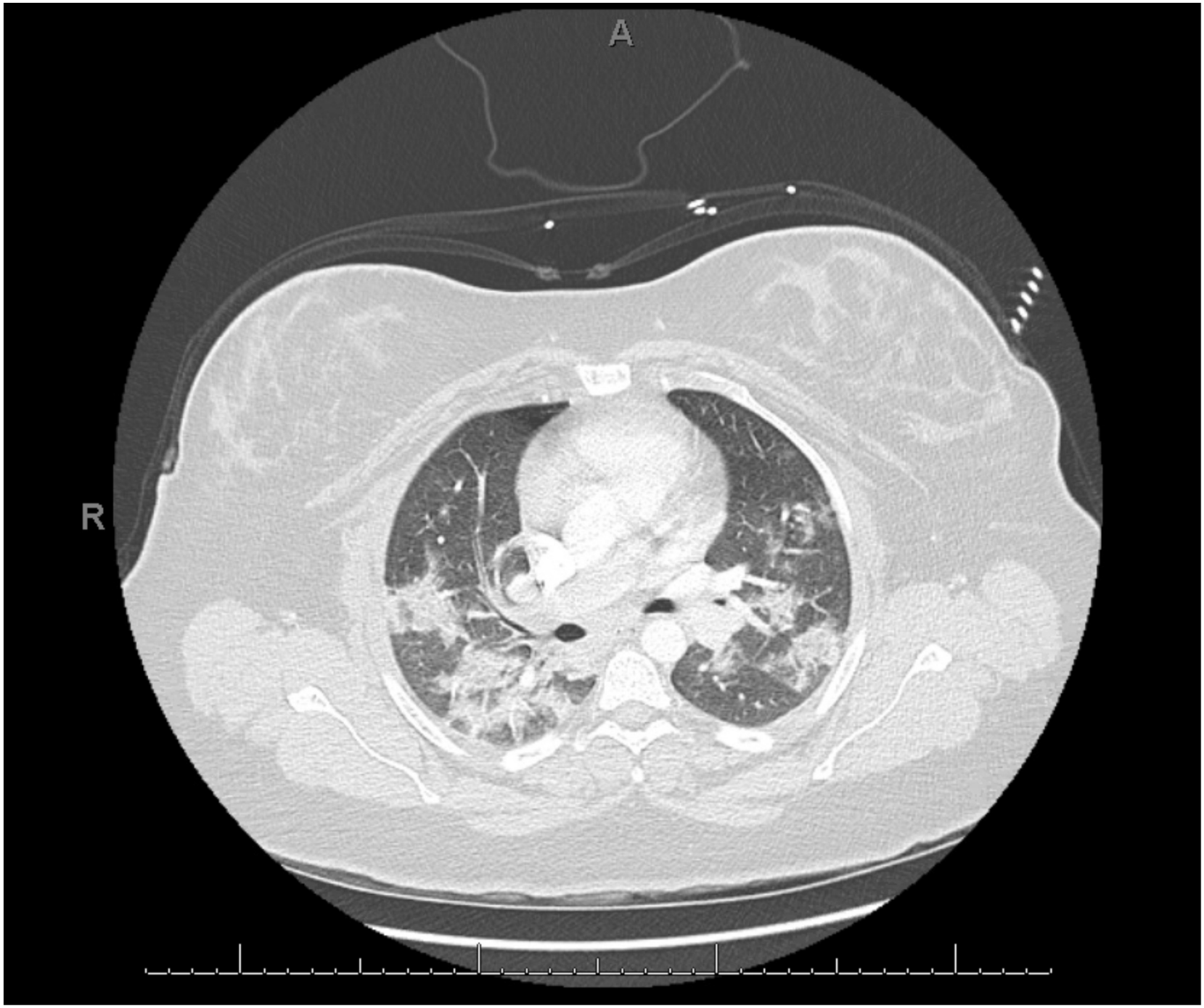

A
B

CLINICAL STAGES of COVID-19

An high viral load leads to a high concentration of viral RNA fragments mantaining a powerful immunostimulatory activity

Ongoing macrophage activation with the production of pro-inflammatory mediators despite viral clearance is responsible for the progressive pulmonary phase in patients with severe infection



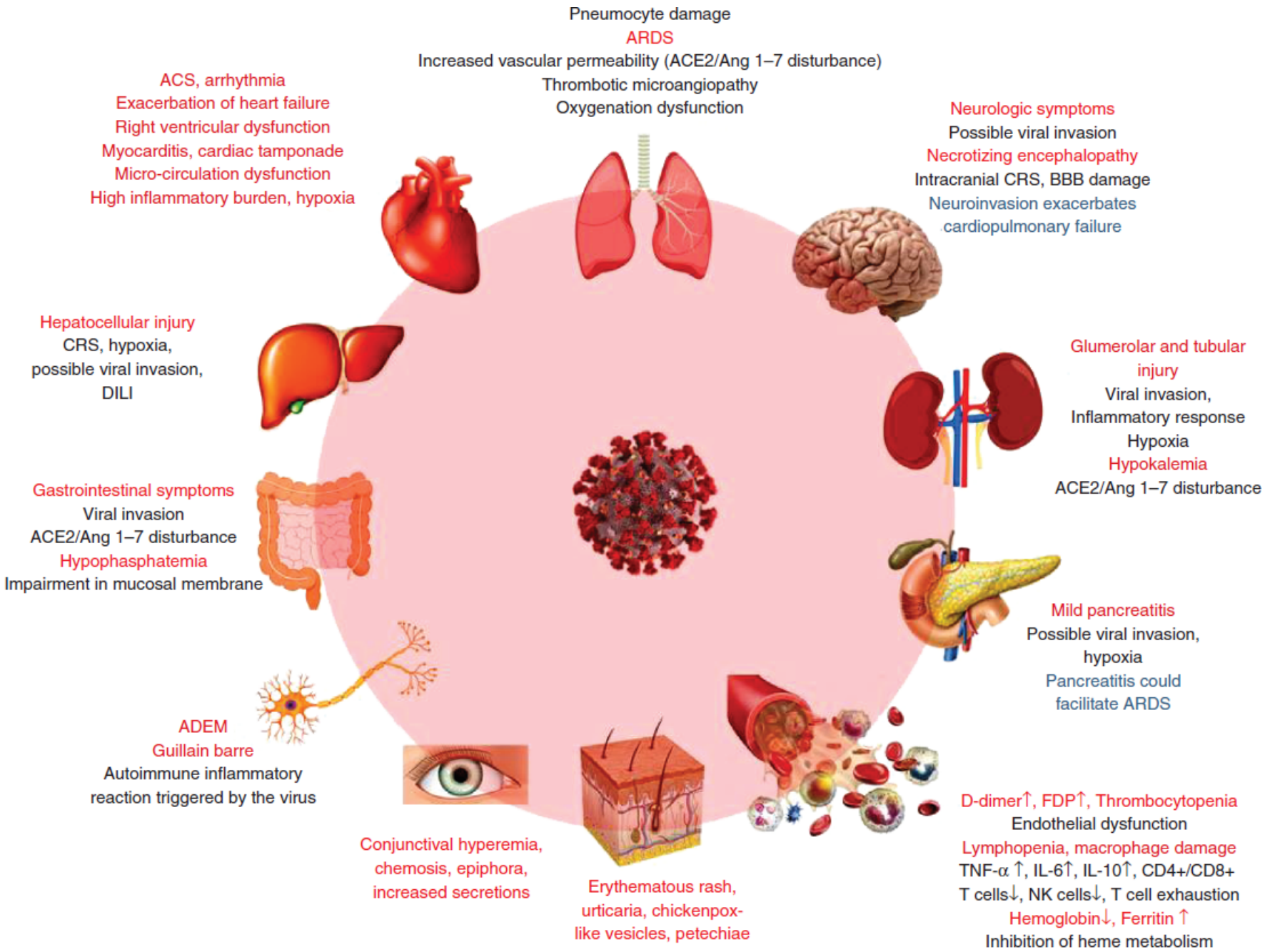

A
R

Clinical characteristics of coronavirus disease 2019 in China.

Guan WJ, et al. N Engl J Med. 2020; 382:1708–20.

A list of the most common clinical symptoms of SARS-CoV-2 infection based on a 1,099 patient study in China.

Symptoms Percentage	(%)
Fever	88.7
Cough	67.8
Fatigue	38.1
Sputum production	33.7
Shortness of breath	18.7
Myalgia or arthralgia	14.9
Sore throat	13.9
Headache	13.6
Chills	11.5
Nausea or vomiting	5
Nasal congestion	4.8
Diarrhea	3.8


Pneumocyte damage
ARDS
Increased vascular permeability (ACE2/Ang 1–7 disturbance)
Thrombotic microangiopathy
Oxygenation dysfunction
ACS, arrhythmia
Exacerbation of heart failure
Right ventricular dysfunction
Myocarditis, cardiac tamponade
Micro-circulation dysfunction
High inflammatory burden, hypoxia
Neurologic symptoms
Possible viral invasion
Necrotizing encephalopathy
Intracranial CRS, BBB damage
Neuroinvasion exacerbates cardiopulmonary failure
Hepatocellular injury
CRS, hypoxia, possible viral invasion, DILI
Glumerolar and tubular injury
Viral invasion,
Inflammatory response
Hypoxia
Hypokalemia
ACE2/Ang 1–7 disturbance
Gastrointestinal symptoms
Viral invasion
ACE2/Ang 1–7 disturbance
Hypophasphatemia
Impairment in mucosal membrane
Mild pancreatitis
Possible viral invasion, hypoxia
Pancreatitis could facilitate ARDS
ADEM
Guillain barre
Autoimmune inflammatory reaction triggered by the virus
Conjunctival hyperemia, chemosis, epiphora, increased secretions
Erythematous rash, urticaria, chickenpox-like vesicles, petechiae
D-dimer↑, FDP↑, Thrombocytopenia
Endothelial dysfunction
Lymphopenia, macrophage damage
TNF-α ↑, IL-6↑, IL-10↑, CD4+/CD8+ T cells↓, NK cells↓, T cell exhaustion
Hemoglobin↓, Ferritin ↑
Inhibition of heme metabolism

Cardiovascular Implications of Fatal Outcomes of Patient With Coronavirus Disease

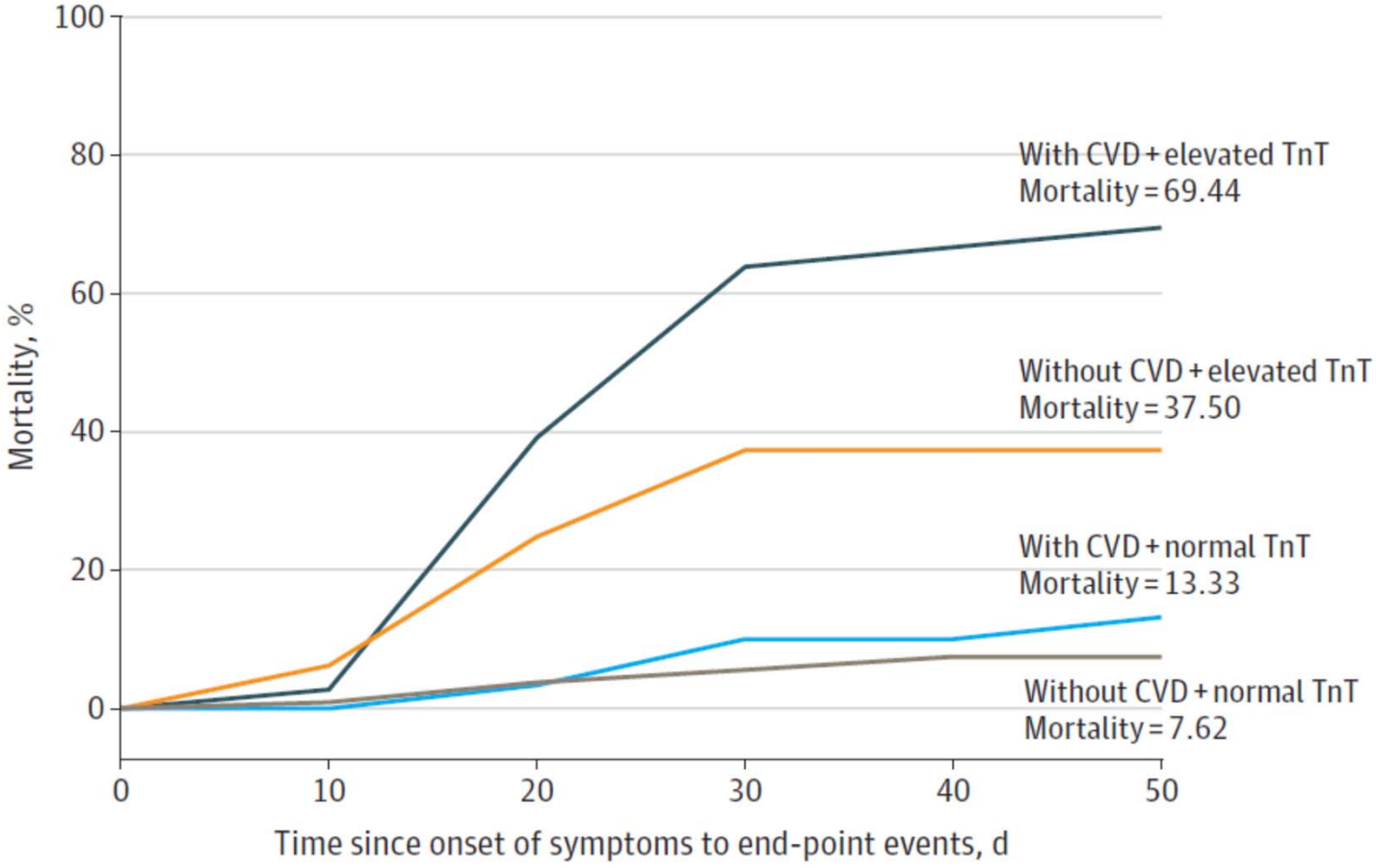
GuoT et al, JAMA Cardiol. 2020;5(7):811-818

Retrospective study aimed to evaluate the association of underlying cardiovascular disease and myocardial injury with fatal outcomes in patients with COVID-19.

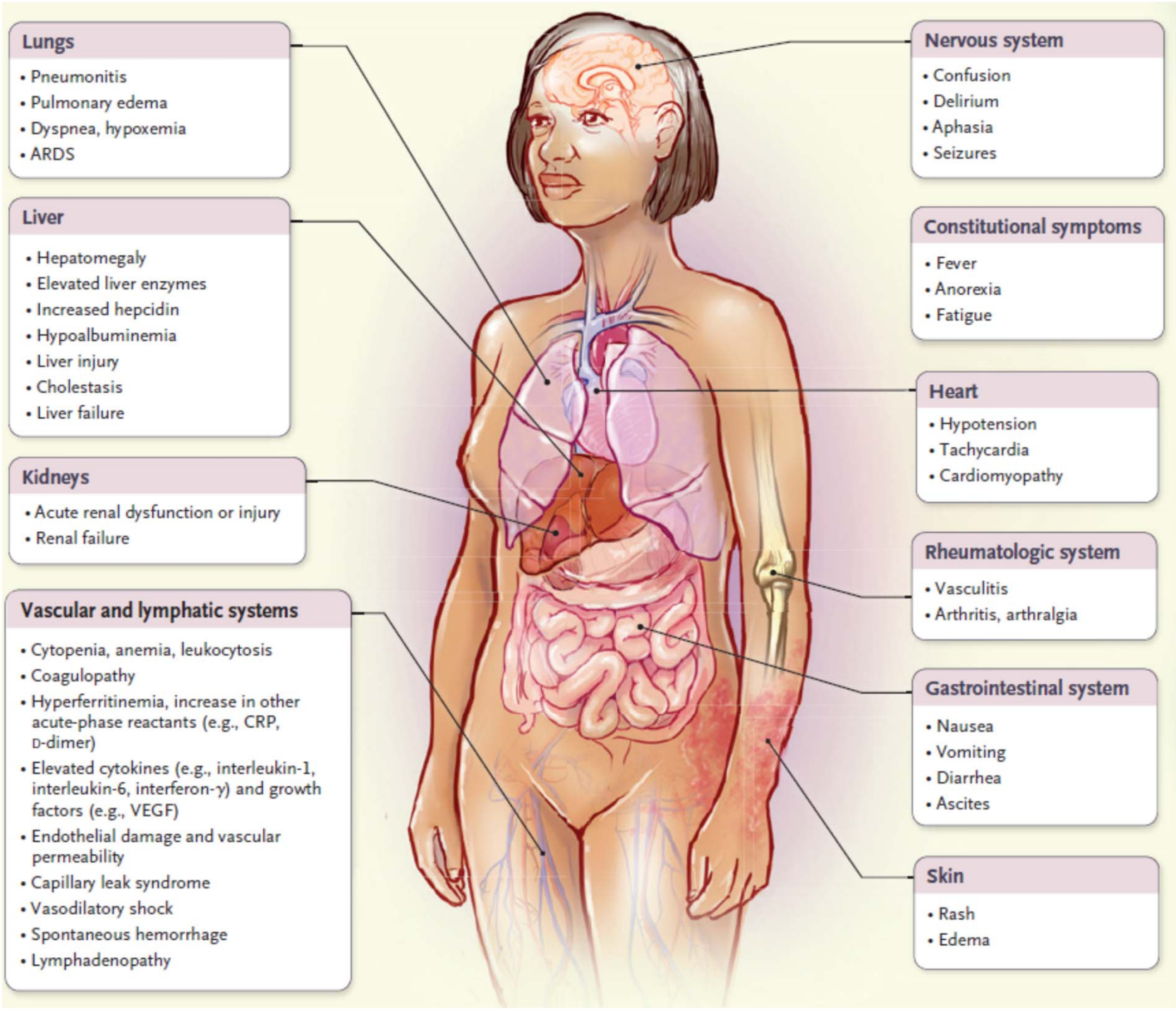
Mortality of Patients With COVID-19 With/Without Cardiovascular Disease and With/Without Elevated Troponin T Levels

187 enrolled patients.

Overall, 35.3% had underlying CVD including hypertension, coronary heart disease, and cardiomyopathy, and 52 (27.8%) exhibited myocardial injury as indicated by elevated TnT levels.



Cytokine Storm
Clinical features



N Engl J Med 2020;383:2255-73.

Definizione malattia COVID-19

La gravità della malattia COVID-19 viene definita secondo i seguenti criteri:

- **Lieve: pazienti con sintomi di lieve entità e imaging torace negativo**

- **Moderata: pazienti con febbre, sintomi respiratori ed imaging compatibile con diagnosi di polmonite**

- **Grave: febbre, sintomi respiratori, segni radiografici di polmonite più almeno uno dei seguenti: i) RR >30 atti/min, ii) SatO2 <93% in aa, iii) PaO2/FiO2 <300 mmHg**

- **Critica: in presenza di uno dei tre: i) insufficienza respiratoria grave da richiedere ventilazione meccanica, ii) shock settico, iii) insufficienza multiorgano**

Zhejiang University School of Medicine, Apr 2020

WHO Eight-category ordinal scale.

1. not hospitalized, no limitations of activities;
2. not hospitalized, limitation of activities, NO home oxygen requirement, or both;
3. hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons);
4. hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19– related or other medical conditions);
5. hospitalized, requiring any supplemental oxygen;
6. hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices;
7. hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
8. death

Development and validation of a prediction model for severe respiratory failure in hospitalized patients with SARS-CoV-2 infection: a multicentre cohort study (PREDI-CO study). *Bartoletti M et al, Clin Microbiol Infect 2020 Aug 8*

derivation cohort

739 hospitalized patients with COVID-19

Excluded patients:
- 28 Hospital discharge within 24 hours
- 67 Respiratory failure within 24 hours from admission

644 Patients included in the analysis

validation cohort

526 hospitalized patients with COVID-19

Excluded patients:
- 13 Hospital discharge within 24 hours
- 44 Respiratory failure within 24 hours from admission

469 Patients included in the analysis

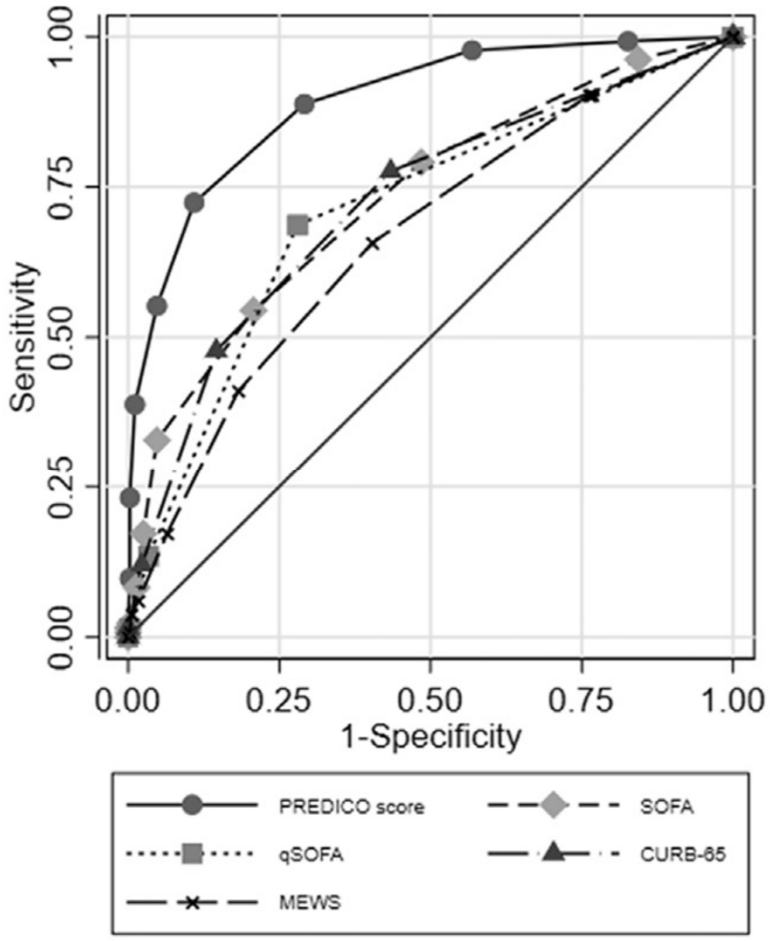
Development and validation of a prediction model for severe respiratory failure in hospitalized patients with SARS-CoV-2 infection: a multicentre cohort study (PREDI-CO study). *Bartoletti M et al, Clin Microbiol Infect 2020 Aug 8*

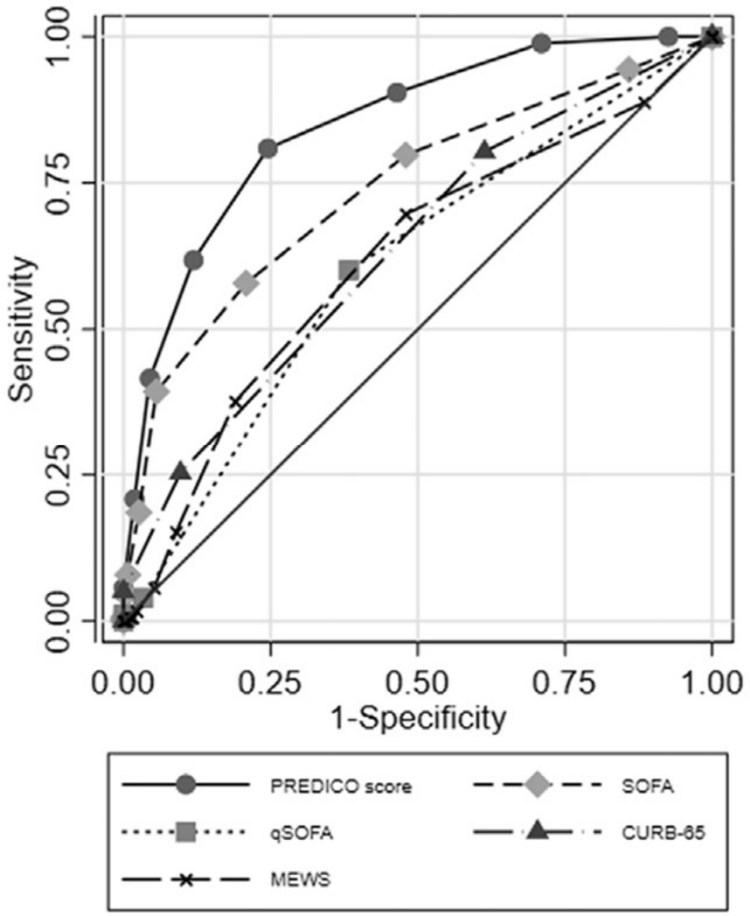
Multivariate analysis of risk factors for respiratory failure in derivation and validation cohort

	Derivation cohort				Validation cohort		
	OR	95% CI	p	β-coefficient	OR	95% CI	p
Age ≥70 years	2.74	1.66–4.50	<0.001	1.01	2.25	1.45–3.49	<0.001
Obesity	4.62	2.78–7.70	<0.001	1.53	1.07	0.72–1.60	0.73
Fever ≥38°C at hospitalization	1.73	1.30–2.29	<0.001	0.55	1.87	0.99–3.52	0.05
RR ≥ 22 breaths/min	3.75	2.01–7.01	<0.001	1.32	2.44	1.41–4.21	0.001
Lymphocytes ≤0.9 × 10^9/L	2.69	1.60–4.51	<0.001	0.99	1.94	1.15–3.27	0.01
CRP ≥10 mg/dL	5.91	4.88–7.17	<0.001	1.78	8.44	4.72–15.07	<0.001
LDH ≥350 IU/L	2.39	1.11–5.11	0.025	0.87	3.34	2.51–4.44	<0.001
Creatinine ≥1 mg/dL	2.38	1.59.–3.56	<0.001	0.87	1.35	1.16–1.57	<0.001

Development and validation of a prediction model for severe respiratory failure in hospitalized patients with SARS-CoV-2 infection: a multicentre cohort study (PREDI-CO study). *Bartoletti M et al, Clin Microbiol Infect 2020 Aug 8*

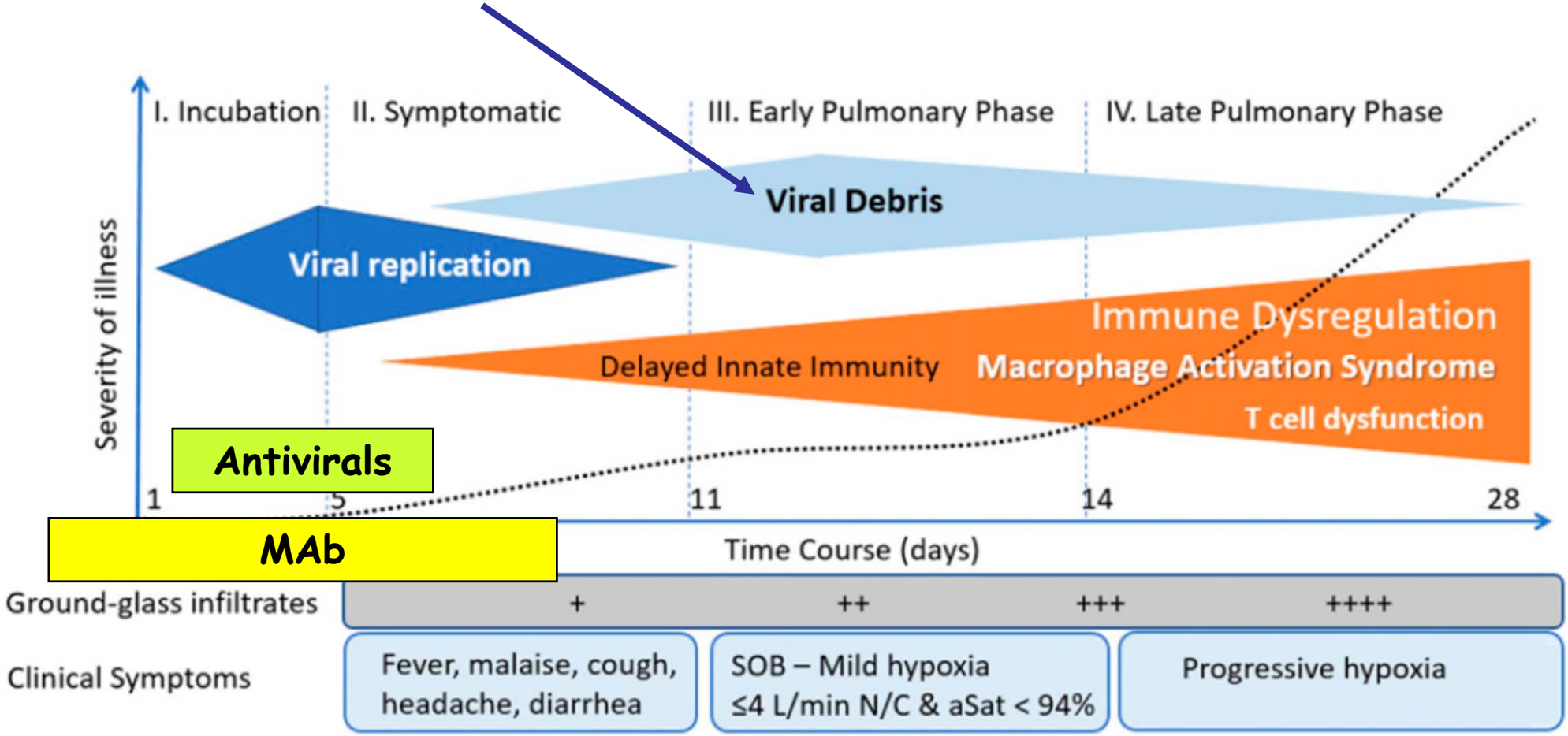
Comparison of prediction ability for severe respiratory failure in hospitalized individuals with a diagnosis of COVID-19 of the PREDICO score with qSOFA, SOFA, CURB-65 and MEWS scores





CLINICAL STAGES of COVID-19

An high viral load leads to a high concentration of viral RNA fragments mantaining a powerful immunostimulatory activity



The US Institute for Health Metrics and Evaluation models suggest that on around Jan 17, 2022 there were 125 million omicron infections a day in the world, which is more than ten times the peak of the delta wave in April, 2021.

The omicron wave is inexorably reaching every continent with only a few countries in eastern Europe, North Africa, southeast Asia, and Oceania yet to start their wave of this SARS-CoV-2 variant.

The unprecedented level of infection suggests that more than 50% of the world will have been infected with omicron between the end of November, 2021 and the end of March, 2022.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Population Immunity and Covid-19 Severity with Omicron Variant in South Africa

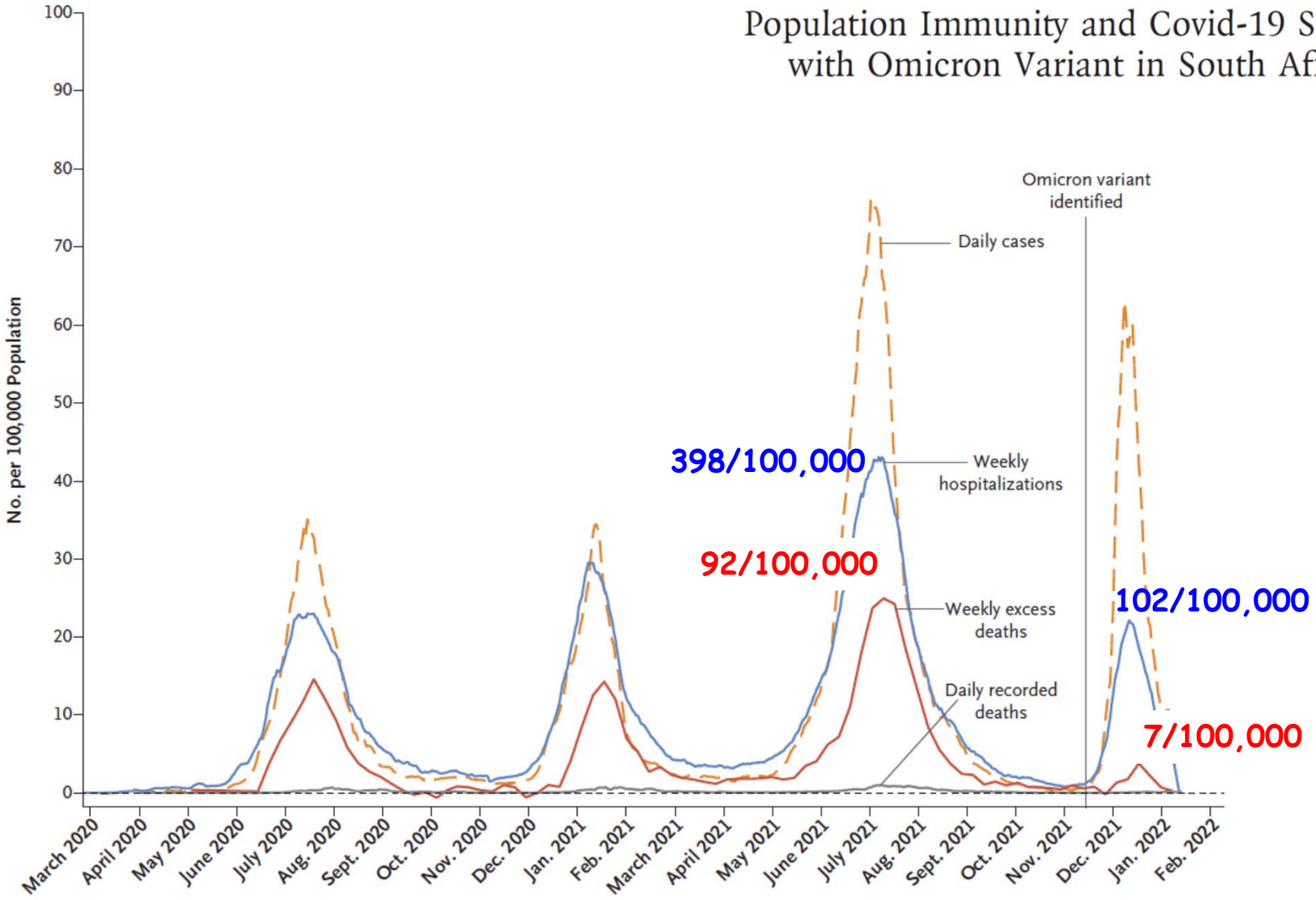
Shabir A. Madhi, Ph.D., Gaurav Kwatra, Ph.D., Jonathan E. Myers, M.D., Waasila Jassat, M.Med., Nisha Dhar, Ph.D., Christian K. Mukendi, M.Sc., Amit J. Nana, B.Sc., Lucille Blumberg, M.Med., Richard Welch, B.Sc., Nicoletta Ngorima-Mabhena, M.B., Ch.B., and Portia C. Mutevedzi, Ph.D.

This article was published on February 23, 2022, at NEJM.org.

7010 participants, of whom 1319 (18.8%) had received a Covid-19 vaccine. The seroprevalence of SARS-CoV-2 IgG ranged from 56.2% (95% confidence interval [CI], 52.6 to 59.7) among children younger than 12 years of age to 79.7% (95% CI, 77.6 to 81.5) among adults older than 50 years of age.

ORIGINAL ARTICLE

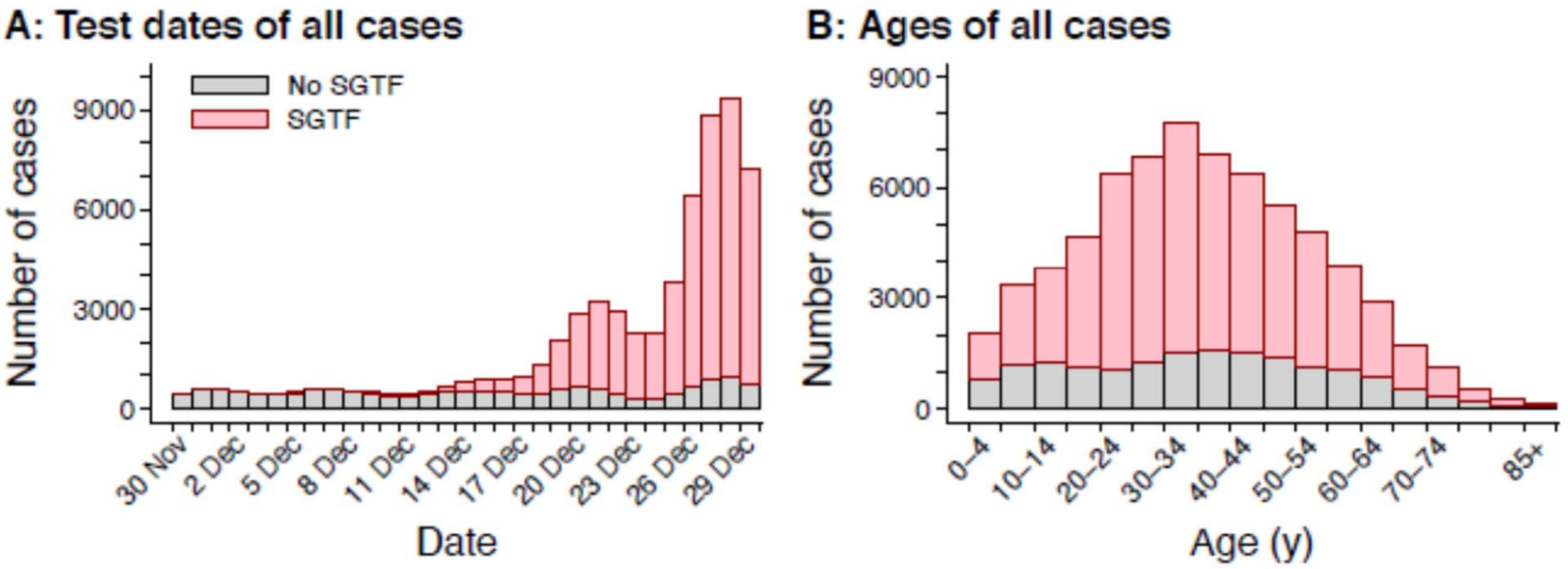
Population Immunity and Covid-19 Severity with Omicron Variant in South Africa



Clinical outcomes among patients infected with Omicron (B.1.1.529) SARS-CoV-2 variant in southern California. *Lewnard JA et al, medRxiv preprint posted January 11, 2022.*

The analyses included 52,297 cases with SGTF (Omicron) and 16,982 cases with non-SGTF (Delta [B.1.617.2]) infections, respectively.

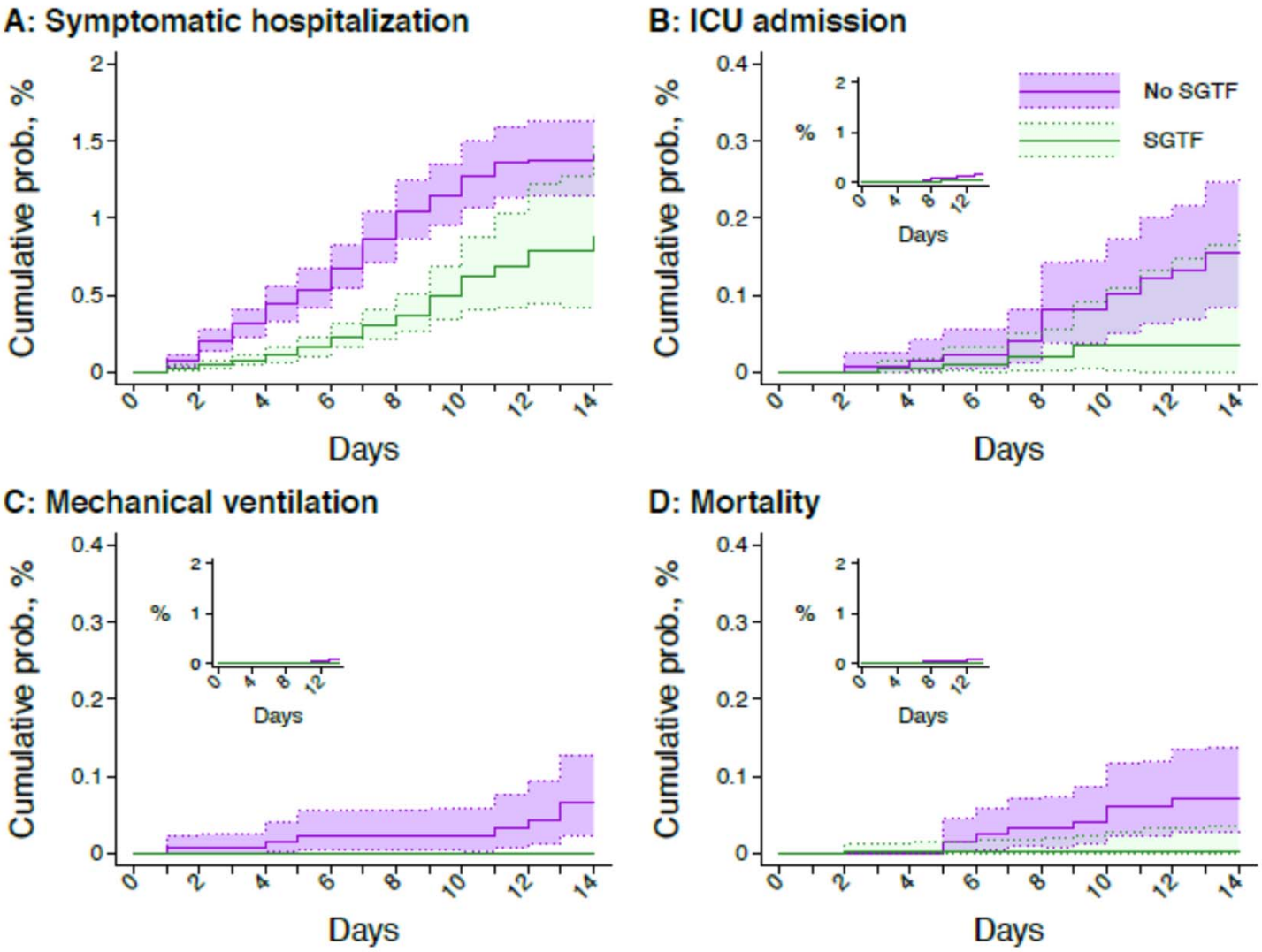
Attributes of cases with SGTF and non-SGTF samples detected



Clinical outcomes among patients infected with Omicron (B.1.1.529) SARS-CoV-2 variant in southern California.

Lewnard JA et al, medRxiv preprint posted January 11, 2022.

Times to severe outcomes



Median duration of hospital stay was 3.4 (2.8-4.1) days shorter for hospitalized cases with Omicron variant infections as compared to hospitalizedpatients with Delta variant infections, reflecting a 69.6% (64.0-74.5%) reduction in hospital length of stay.

For some weeks or months, the world should expect low levels of virus transmission

However …

New SARS-CoV-2 variants will surely emerge and some may be more severe than omicron. Immunity, whether infection or vaccination derived, will wane, creating opportunities for continued SARS-CoV-2 transmission. Given seasonality, countries should expect increased potential transmission in winter months.

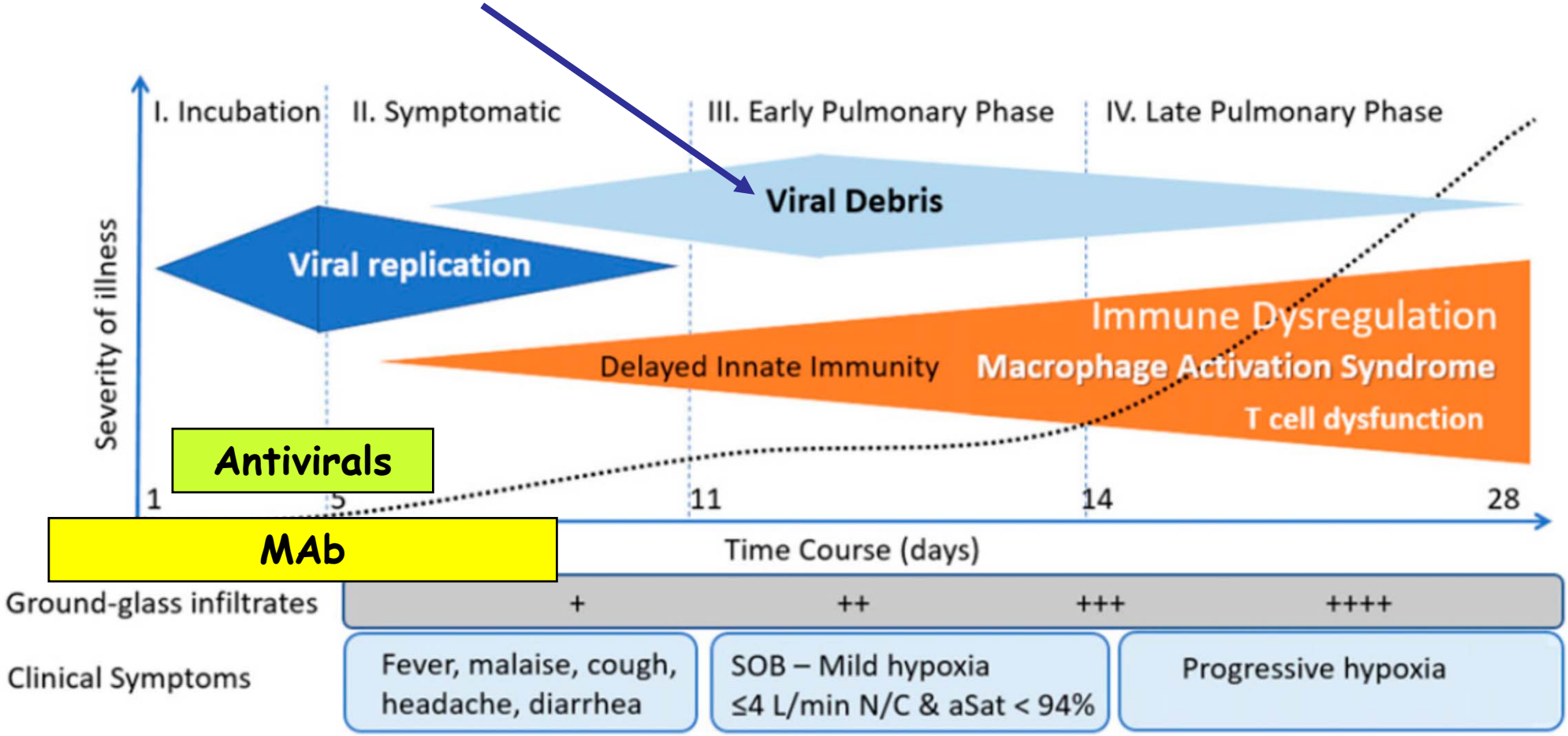
However …

The impacts of future SARS-CoV-2 transmission on health will be less because of broad previous exposure to the virus, regularly adapted vaccines to new antigens or variants, the advent of antivirals, and the knowledge that the vulnerables can protect themselves during future waves by using high-quality masks and physical distancing.

COVID-19 will become another recurrent disease that health systems and societies will have to manage.

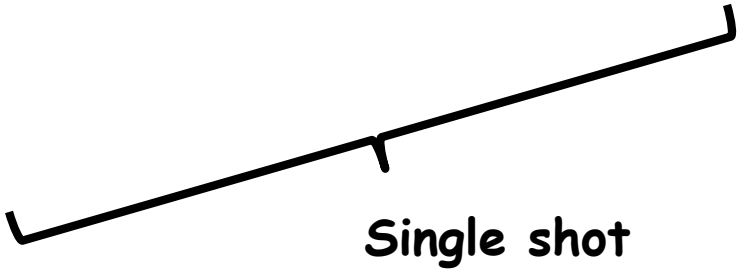
CLINICAL STAGES of COVID-19

An high viral load leads to a high concentration of viral RNA fragments mantaining a powerful immunostimulatory activity



Risorse disponibili

ANTIVIRALI	REMDESIVIR 200 mg LD poi 100 mg qd ev per 3 giorni
	MOLNUPIRAVIR 800 mg bid x 5 giorni
	NIRMATRELVIR/RITONAVIR 250/100 mg bid x 5 giorni
ANTICORPI MONOCLONALI	SOTROVIMAB (500 mg)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*

This article was published on December 16, 2021, at NEJM.org.

A phase 3, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of treatment with molnupiravir started within 5 days after the onset of signs or symptoms in nonhospitalized, unvaccinated adults with mild-to-moderate, laboratory-confirmed Covid-19 and at least one risk factor for severe Covid-19 illness. Participants in the trial were randomly assigned to receive 800 mg of molnupiravir or placebo twice daily for 5 days. The primary efficacy end point was the incidence hospitalization or death at day 29.

total of 1433 participants underwent randomization; 716 were assigned to receive molnupiravir and 717 to receive placebo. With the exception of an imbalance in sex, baseline characteristics were similar in the two groups. A planned interim analysis was performed when 50% of 1550 participants had been followed through day 29.A

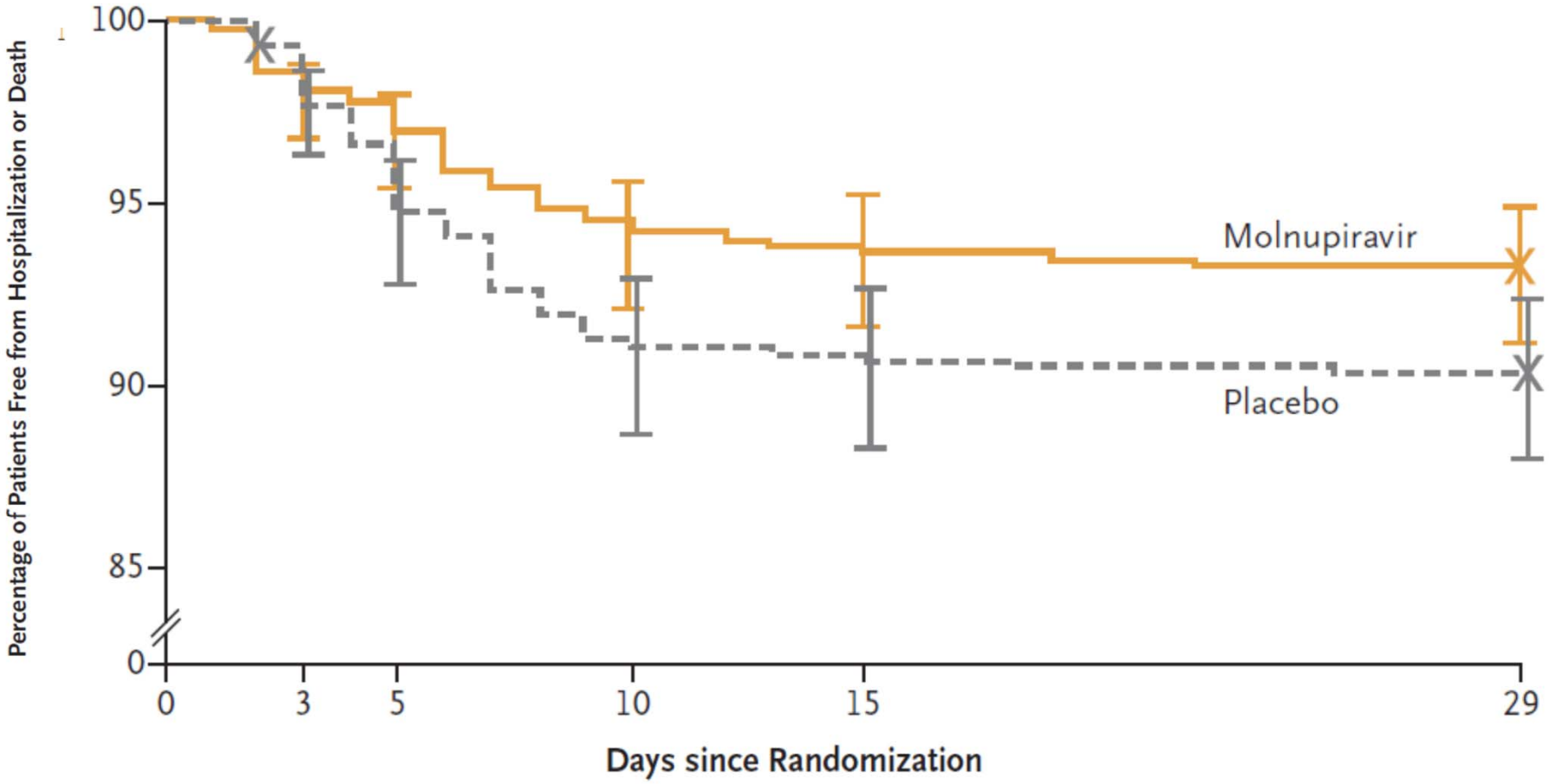
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*

The risk of hospitalization for any cause or death through day 29 was lower with molnupiravir (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%]) (difference, −6.8 percentage points; 95% confidence interval, −11.3 to −2.4; P = 0.001).



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*

Table 2. Incidence of Adverse Events in the Safety Population.

Adverse Events and Discontinuation	Molnupiravir (N=710)	Placebo (N=701)	Estimated Difference (95% CI)*
	number (percent)		*percentage points*
Participants with adverse events			
≥1 Adverse event	216 (30.4)	231 (33.0)	−2.5 (−7.4 to 2.3)
≥1 Adverse event related to the assigned regimen†	57 (8.0)	59 (8.4)	−0.4 (−3.3 to 2.5)
≥1 Serious adverse event	49 (6.9)	67 (9.6)	−2.7 (−5.6 to 0.2)
≥1 Serious adverse event related to the assigned regimen†	0	1 (0.1)	−0.1 (−0.8 to 0.4)
Death	2 (0.3)	12 (1.7)	−1.4 (−2.7 to −0.5)
Participants who discontinued the assigned regimen because of an adverse event			
Adverse event	10 (1.4)	20 (2.9)	−1.4 (−3.1 to 0.1)
Adverse event related to the assigned regimen†	4 (0.6)	3 (0.4)	0.1 (−0.8 to 1.1)
Serious adverse event	5 (0.7)	13 (1.9)	−1.2 (−2.5 to 0.0)
Serious adverse event related to the assigned regimen†	0	0	0.0 (−0.5 to 0.5)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†

This article was published on December 22, 2021, at NEJM.org.

A randomized, double-blind, placebo-controlled trial involving non hospitalized patients with Covid-19 who had symptom onset within the previous 7 days and who had at least one risk factor for disease progression (age ≥60 years, obesity, or certain coexisting medical conditions). Patients were randomly assigned to receive intravenous remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) or placebo. The primary efficacy end point was a composite of Covid-19–related hospitalization or death from any cause by day 28.

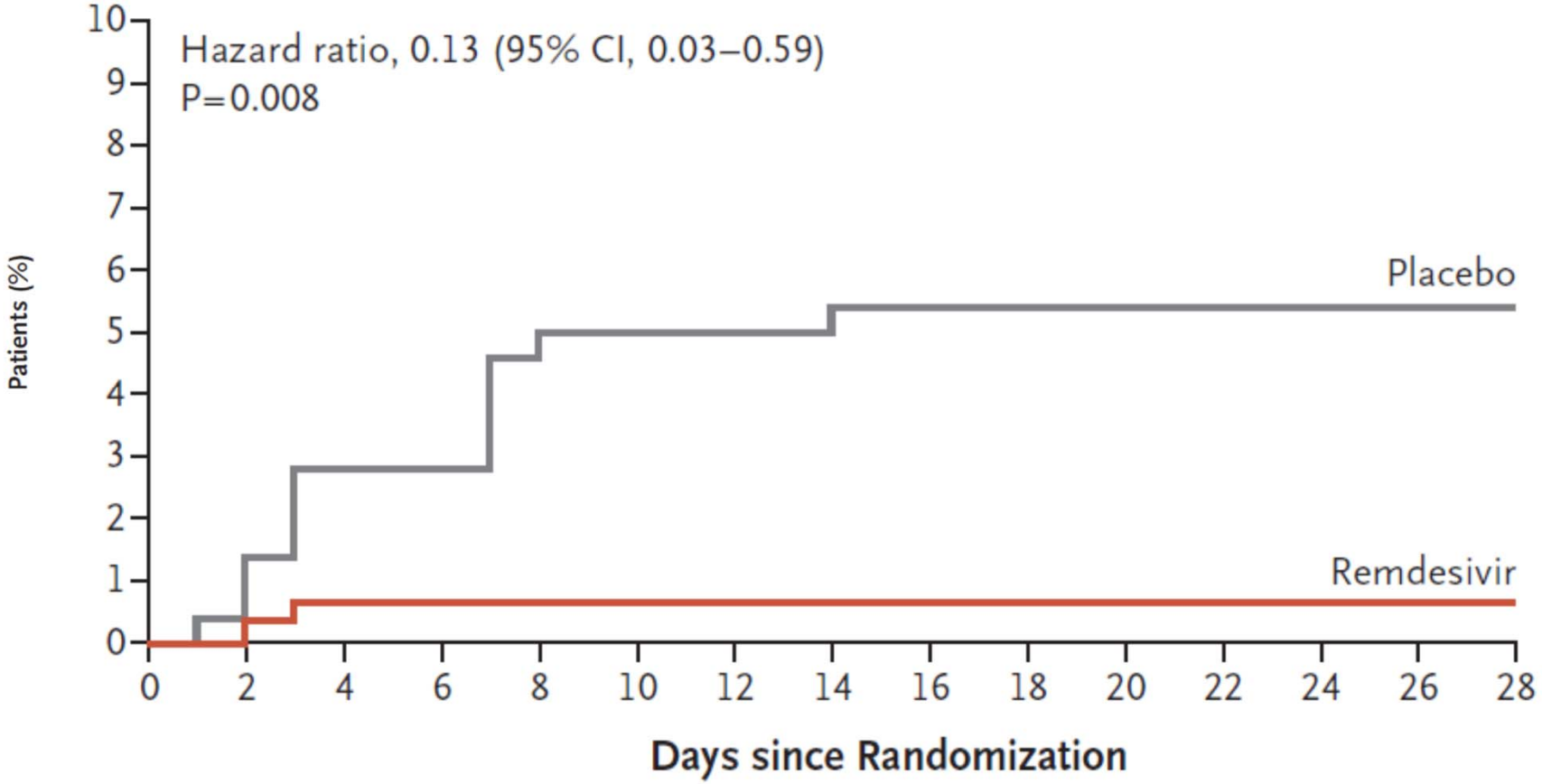
A total of 562 patients who underwent randomization and received at least one dose of remdesivir or placebo were included in the analyses: 279 pts in the remdesivir arm and 283 in the placebo arm.

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†

Covid-19–related hospitalization or death from any cause occurred in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group (hazard ratio, 0.13; 95% confidence interval [CI], 0.03 to 0.59; P = 0.008).

Covid-19–Related Hospitalization or Death from Any Cause

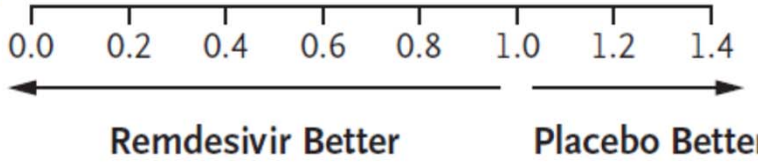


Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†

Covid-19–Related Hospitalization or Death from Any Cause at Day 28, According to Demographic and Clinical Characteristics at Baseline.

Subgroup	Remdesivir	Placebo	Hazard Ratio (95% CI)
	no./total no. of patients (%)		
Residence in the United States	2/264 (0.8)	12/267 (4.5)	0.17 (0.04–0.76)
Age ≥60 yr	1/83 (1.2)	9/87 (10.3)	0.11 (0.01–0.86)
Male sex	1/148 (0.7)	9/145 (6.2)	0.11 (0.01–0.84)
Diabetes mellitus	2/173 (1.2)	14/173 (8.1)	0.14 (0.03–0.63)
Obesity	1/154 (0.6)	9/156 (5.8)	0.11 (0.01–0.88)
Hypertension	2/138 (1.4)	10/130 (7.7)	0.17 (0.04–0.76)
Ethnic group			
Not Hispanic or Latinx	2/146 (1.4)	8/158 (5.1)	0.26 (0.06–1.22)
Hispanic or Latinx	0/123	6/112 (5.4)	—
Chronic lung disease	0/67	4/68 (5.9)	—
Cardiovascular or cerebrovascular disease	0/20	2/24 (8.3)	—
Current cancer	0/12	2/18 (11.1)	—



Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†

Table 3. Adverse Events.*

Event	Remdesivir (N = 279)	Placebo (N = 283)
	no. of patients (%)	
Primary safety end point: any adverse event	118 (42.3)	131 (46.3)
Adverse events		
Nausea	30 (10.8)	21 (7.4)
Headache	16 (5.7)	17 (6.0)
Cough	10 (3.6)	18 (6.4)
Diarrhea	11 (3.9)	11 (3.9)
Dyspnea	7 (2.5)	15 (5.3)
Fatigue	10 (3.6)	11 (3.9)
Ageusia	8 (2.9)	7 (2.5)
Anosmia	9 (3.2)	6 (2.1)
Dizziness	5 (1.8)	10 (3.5)
Chills	6 (2.2)	8 (2.8)
Pyrexia	1 (0.4)	11 (3.9)
Covid-19 pneumonia	2 (0.7)	8 (2.8)
Adverse event related to trial regimen	34 (12.2)	25 (8.8)
Serious adverse event†	5 (1.8)	19 (6.7)
Adverse event leading to discontinuation of trial regimen	2 (0.7)	5 (1.8)
Death	0	0

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

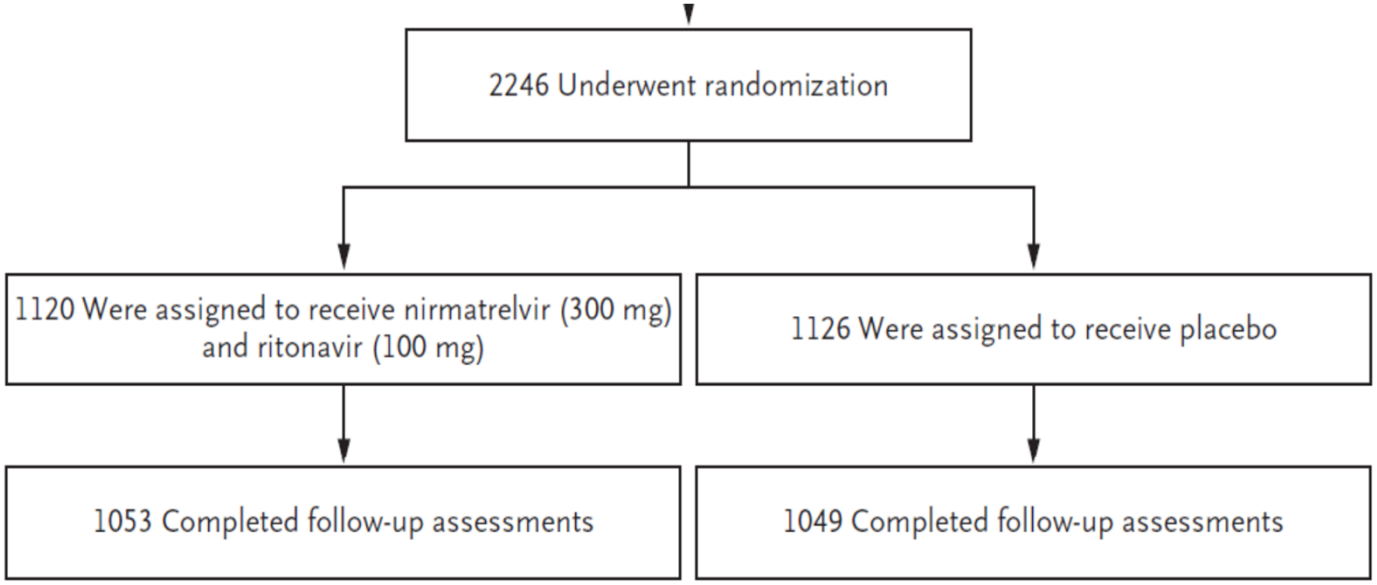
Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Jennifer Hammond, Ph.D., Heidi Leister-Tebbe, B.S.N., Annie Gardner, M.P.H., M.S.P.T., Paula Abreu, Ph.D., Weihang Bao, Ph.D., Wayne Wisemandle, M.A., MaryLynn Baniecki, Ph.D., Victoria M. Hendrick, B.Sc., Bharat Damle, Ph.D., Abraham Simón-Campos, M.D., Rienk Pypstra, M.D., and James M. Rusnak, M.D., Ph.D., for the EPIC-HR Investigators*

This article was published on February 16, 2022, at NEJM.org.

A phase 2–3 double-blind, randomized, controlled trial in which symptomatic, unvaccinated, nonhospitalized adults at high risk for progression to severe coronavirus disease 2019 were assigned in a 1:1 ratio to receive either 300 mg of nirmatrelvir plus 100 mg of ritonavir (or placebo every 12 hours for 5 days.

Covid-19–related hospitalization or death from any cause through day 28, viral load, and safety were evaluated

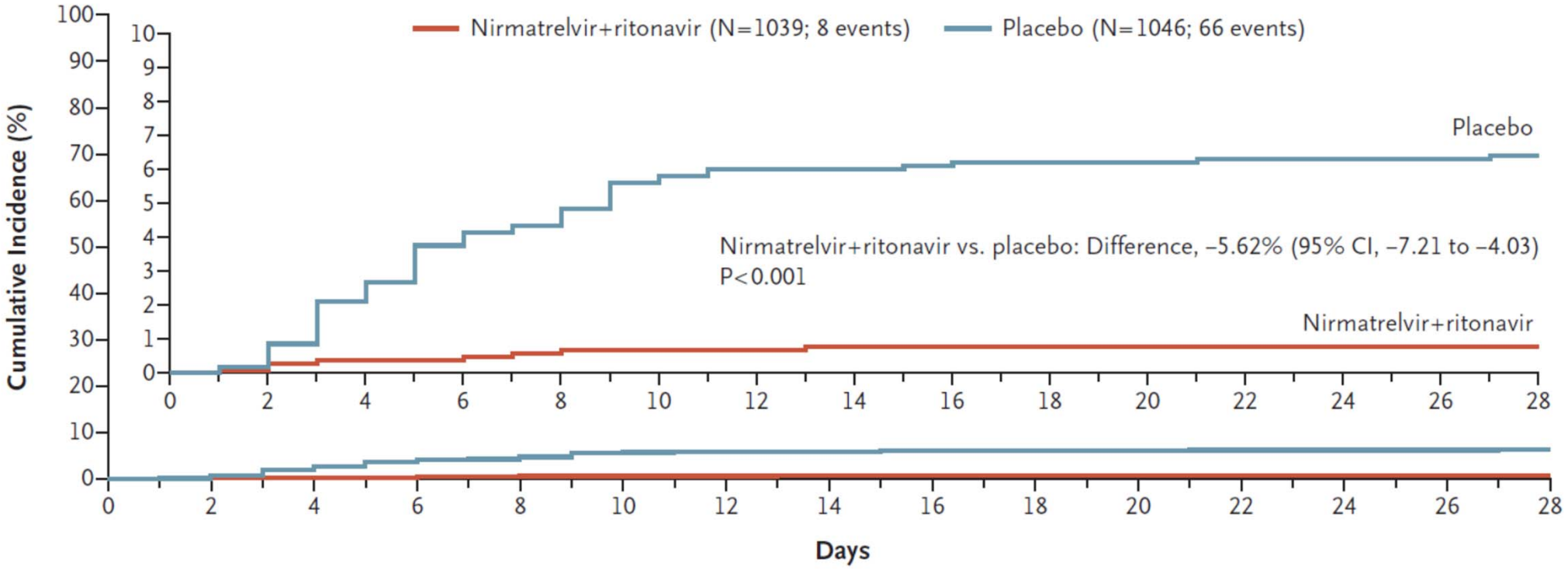


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Covid-19–Related Hospitalization or Death from Any Cause through Day 28 among Patients Treated ≤5 Days after Symptom Onset



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Outcomes According to Time Since Onset of Covid-19 Symptoms

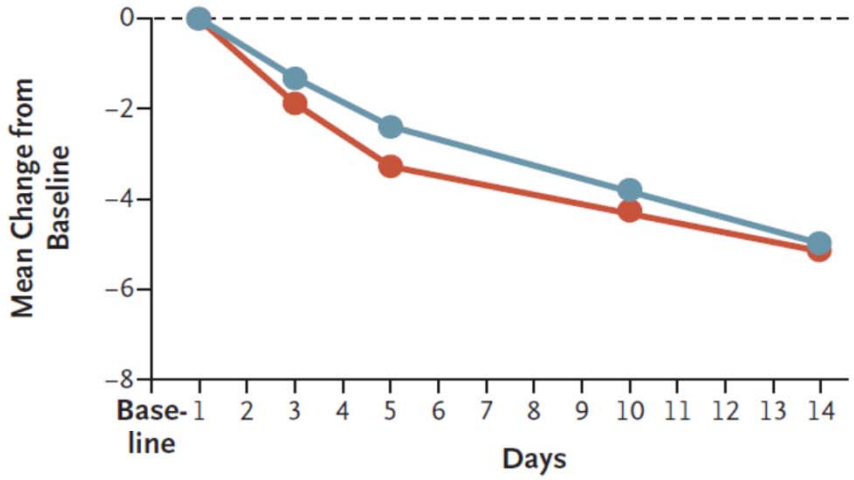
	Treated ≤3 Days after Onset of Symptoms (modified intention-to-treat population)		Treated ≤5 Days after Onset of Symptoms	
	Nirmatrelvir+ritonavir (N=697)	Placebo (N=682)	Nirmatrelvir+ritonavir (N=1039)	Placebo (N=1046)
Patients with event — no. (%)	5 (0.72)	44 (6.45)	8 (0.77)	66 (6.31)
Hospitalization for Covid-19	5 (0.72)	44 (6.45)	8 (0.77)	65 (6.21)
Death from any cause	0	9 (1.32)	0	12 (1.15)
Average time at risk for event — days	27.29	26.19	27.05	25.97
Average follow-up — days	27.45	27.25	27.20	27.05
Estimated percentage with event (95% CI) — %	0.72 (0.30 to 1.73)	6.53 (4.90 to 8.68)	0.78 (0.39 to 1.56)	6.40 (5.06 to 8.08)
Difference (±SE) from placebo — percentage points	−5.81±1.01		−5.62±0.81	
95% CI of difference	−7.78 to −3.84		−7.21 to −4.03	
P value	<0.001		<0.001	

ORIGINAL ARTICLE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Nirmatrelvir+ritonavir (NMV-r) Placebo

A Overall Population

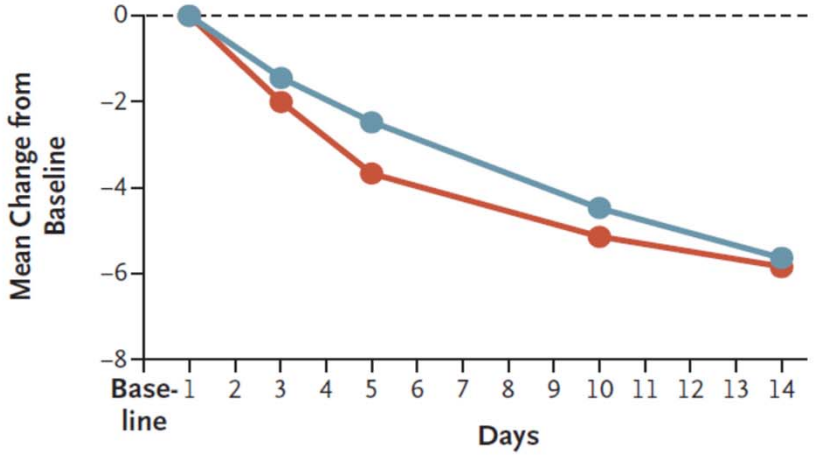


No. at Risk					
NMV-r	552	529	508	502	507
Placebo	553	525	507	475	500
Mean (±SE) Change from Baseline vs. Placebo		−0.55 ±0.11	−0.8 ±0.10	−0.44 ±0.10	−0.16 ±0.08
P Value		<0.001	<0.001	<0.001	<0.045

ORIGINAL ARTICLE

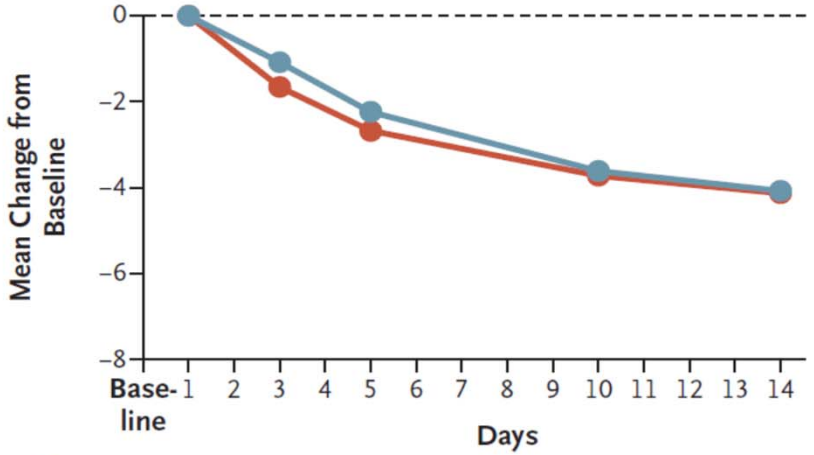
Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

B Seronegative



No. at Risk					
NMV-r	318	304	297	296	293
Placebo	312	294	284	267	273
Mean (±SE) Change from Baseline vs. Placebo		−0.56 ±0.14	−1.20 ±0.13	−0.67 ±0.14	−0.21 ±0.12
P Value		<0.001	<0.001	<0.001	0.07

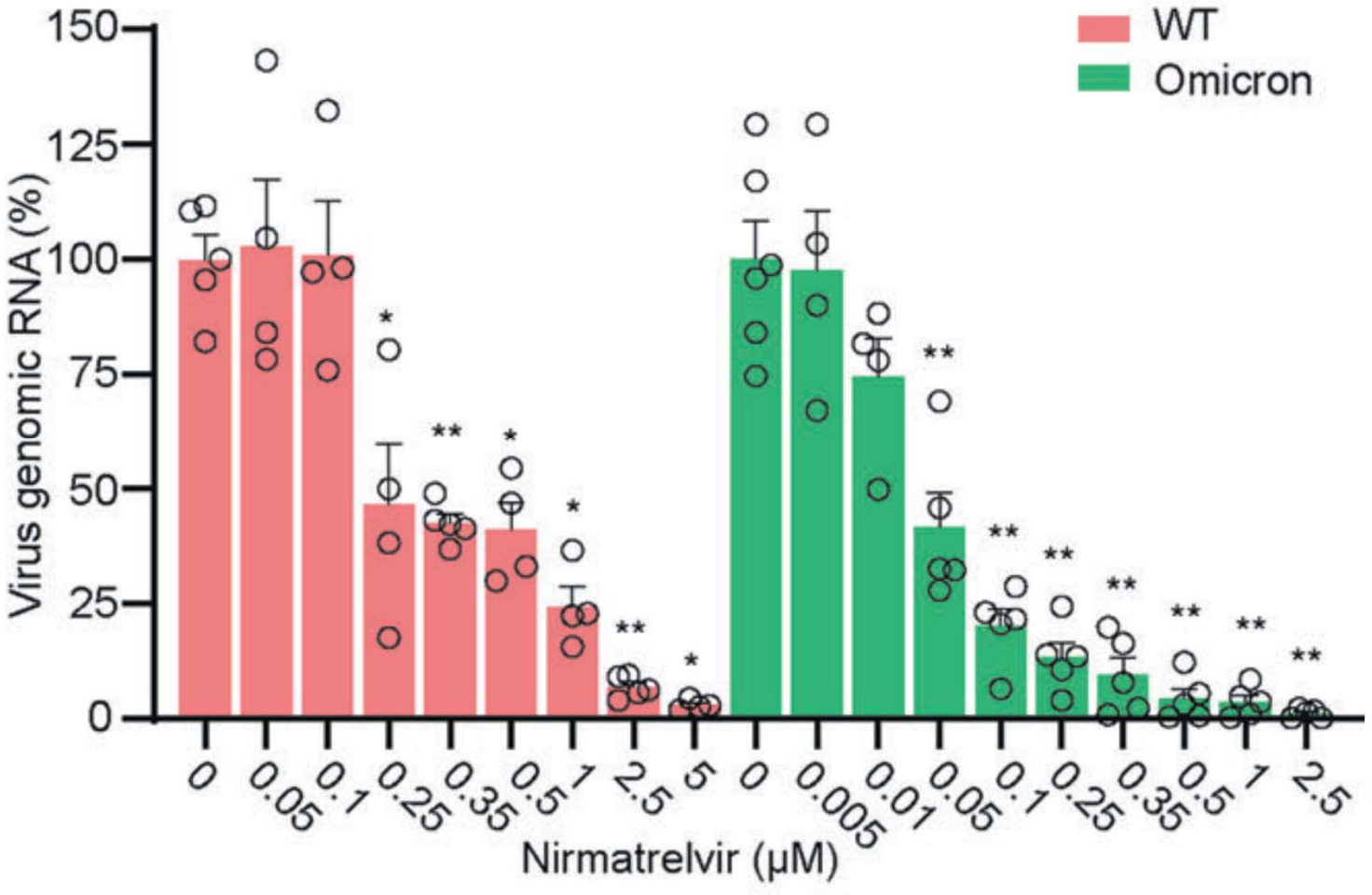
C Seropositive



No. at Risk					
NMV-r	231	222	208	203	211
Placebo	233	223	215	200	219
Mean (±SE) Change from Baseline vs. Placebo		−0.58 ±0.18	−0.44 ±0.16	−0.11 ±0.12	−0.06 ±0.11
P Value		0.001	0.01	0.37	0.60

SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination

Pi L et al Cell Research 2022 0:1–3; https://doi.org/10.1038/s41422-022-00618-w



COVID-19 CLINICAL UNMET NEEDS

Morbidity and survival After Hospital Discharge (Long COVID)

The COVID19 -related disease in immunocompromised people

The PIMS-TS/MIS(-C) mystery

The on-off syndrome in long term ICU patients

Patterns of Long COVID Symptoms: A Multi-Center Cross Sectional Study.

Yelin D, on Behalf of The LongCOV Res. Group. J Clin Med. 2022;11:898.

Symptomatic patients were recruited from four countries. Data were collected regarding demographics, comorbidities, acute disease and persistent symptoms. Factor analysis was performed to elucidate symptom patterns. Associations of the patterns with patients' characteristics, features of acute disease and effect on daily life were sought.

Overall 1027 symptomatic post-COVID individuals were included in the analysis.
The majority of participants were graded as having a non-severe acute COVID-19 (N = 763, 74.3%).
Six patterns of symptoms were identified :

- **Cognitive**
- **Pain-syndrome**
- **Pulmonary**
- **Cardiac**
- **Anosmia-dysgeusia**
- **Headache**

The cognitive was the major symptoms pattern, explaining 26.2% of the variance. The cognitive pattern was higher in patients who were outpatients during the acute disease. The pain-syndrome pattern was associated with acute disease severity, higher in women and increased with age.
The pulmonary pattern was associated with prior lung disease and severe acute disease.
Only two of the patterns (cognitive and cardiac) were associated with failure to return to pre-COVID occupational and physical activity status.

ESCMID rapid guidelines for assessment and management of long COVID

Yelin D et a, Clin Microbiol Inf Feb 6,2022

Prevalence of symptoms by time from acute diseases

Symptom	4-12 weeks	6-12 months
Fever/feverish	1-51%	0,7%
Fatigue	5-83%	4-35,8%
Headache	4-36%	1,5-5%
Chest pain/tightness	3-35%	3-7%
Joint pain/arthralgia	10-48%	0,6-32,5%
Myalgia	1-32%	0,6-9,2%
Dyspnea	2-64%	1,9-40,8%
Cough	5-45%	3,2%
So		
Ag		
An		
Loss of appetite	1-9%	0,3-3%
Confusion / 'brain fog'	9-14%	0,6%
Depression		
Sleep disorder	10-69%	1,5-43,3%
Palpitations	2-11%	0,6-9%
Rash	8-15%	4%

Future progression to pulmonary fibrosis is raising as one of the major concerns

1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study.

Huang L, et al. Lancet 2021;398:747–58.

An ambi-directional cohort study of COVID-19 survivors who had been discharged from Jin Yin-tan Hospital (Wuhan) between Jan 7 and May 29, 2020. At 6-month and 12-month follow-up visit, survivors were interviewed with questionnaires on symptoms and health-related quality of life, and received a physical examination, a 6-min walking test, and laboratory tests.

1276 COVID-19 survivors completed both visits

The proportion of patients with at least one sequelae symptom decreased from 68% at 6 months to 49% at 12 months (p<0·0001).

The proportion of patients with dyspnoea, slightly increased from 26% to 30% at 12-month visit (p=0·014).

Additionally, 26% patients had anxiety or depression at 12-month visit.

Work status before COVID-19	
Retired	658/1252 (53%)
Full-time or part-time job	479/1252 (38%)
Jobless	70/1252 (6%)
Homemaker	41/1252 (3%)
Full-time student	4/1252 (0%)
Work status at 12-month follow-up	
Returned to original work	422/479 (88%)
Returned to pre-COVID-19 level of work	321/422 (76%)
Not returned to pre-COVID-19 level of work	101/422 (24%)
Not returned to original work	57/479 (12%)
Due to decreased physical function	18/57 (32%)
Unwilling to return to original work	14/57 (25%)
Unemployment	10/57 (18%)
Others	15/57 (26%)

Long COVID 12 months after discharge: persistent symptoms in patients hospitalised due to COVID-19 and patients hospitalised due to other causes—a multicentre cohort study

Rivera-Izquierdo M et al, BMC Medicine 2022; 20:92

Prospective cohort study, conducted in Spain. The sample was composed of 906 adult patients; 453 patients hospitalised due to COVID-19 and 453 hospitalised due to other causes from Mar to Apr 2020, and discharged alive. The main outcomes were (1) the prevalence of SPS at 12 months after discharge and (2) the incidence of SPS after discharge. Outcome data at 12 months were compared between the exposed and non-exposed cohorts.

Logistic regression models comparing the prevalence of sequelae and persistent symptoms (SPS) in patients hospitalized due to COVID-19 compared with patients hospitalized due to other causes.

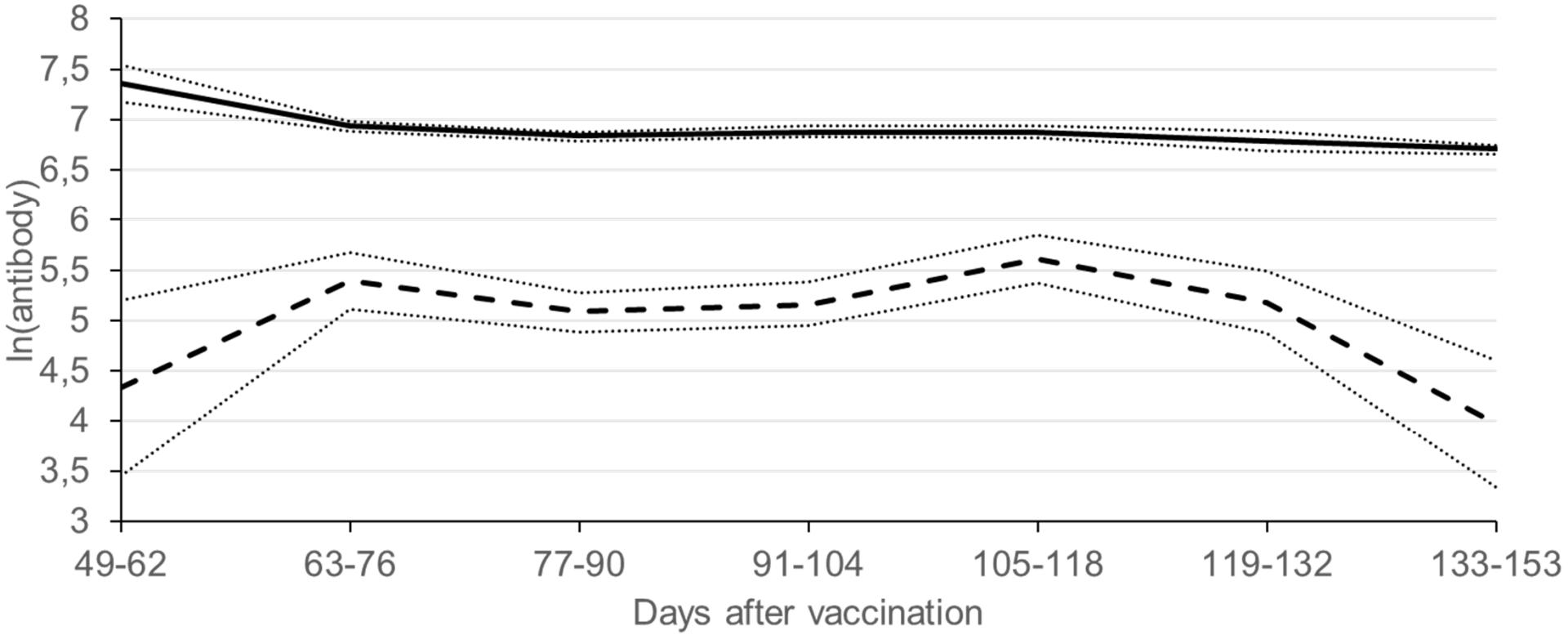
Multivariate models included sex, age, ICU admission and comorbidities ascovariates

SPS[1]	OR	95%CI
Any SPS	1.13	0.85 to 1.51
General/systemic SPS	0.82	0.56 to 1.19
Fatigue	0.57	0.36 to 0.90
Muscle or joint pain	0.82	0.52 to 1.30
Respiratory SPS	1.47	1.00 to 2.16
Dyspnoea	1.13	0.76 to 1.68
Neurological SPS	2.20	1.21 to 3.96
Headache	1.28	0.52 to 3.13
Sensitivity disorders	0.82	0.31 to 2.17
Confusion, memory loss	1.83	0.74 to 4.81
Mental health SPS	1.21	0.75 to 2.27
Depressive symptoms	1.08	0.89 to1.28
Anxiety symptoms	1.56	1.08 to 2.04
Sleep disturbances	1.11	0.88 to 1.48
Dermatological SPS	0.44	0.19 to 1.00
Digestive SPS	0.28	0.13 to 0.62

COVID-19 CLINICAL UNMET NEEDS

- Morbidity and survival After Hospital Discharge (Long COVID)
- ➡ The COVID19 -related disease in immunocompromised people
- The PIMS-TS/MIS(-C) mystery
- The on-off syndrome in long term ICU patients

Mean ln(RBD) and 95% confidence limits in HCW (continuous line) and SOT recipients (broken line) between 49 and 153 days after vaccination, adjusted for sex and age



1062 SOT pts / 1560 HCWs

ORCHESTRA

CONNECTING EUROPEAN COHORTS TO INCREASE COMMON AND EFFECTIVE RESPONSE TO SARS-COV-2 PANDEMIC: **ORCHESTRA**

Clinical outcome in solid organ tx recipients affected by COVID-19 compared to general population: a systematic review and meta-analysis

Gatti M et al, on behalf of ORCHESTRA study group , CMI accepted

Prospective or retrospective observational studies comparing clinical outcome in SOT recipients affected by COVID-19 versus general population were included. Studies were excluded if no comparator group was provided, or quantitative target outcome results were lacking.

Overall, 590,375 enrolled patients were included (5,759 SOT recipients vs. 584,616 general populations). According to the study periods, no vaccinated patients were included among SOT recipients or general populations due to lack of COVID-19 vaccine availability.

Clinical outcome in solid organ tx recipients affected by COVID-19 compared to general population: a systematic review and meta-analysis *Gatti M et al, on behalf of ORCHESTRA study group , CMI accepted*

Results of meta-analysis for primary and secondary outcomes

Primary outcome

Outcome	Studies	No. of patients (Tx vs.comparators)	No. of events tx group	No. of events comparators	Odds ratio (95% CI)	Heterogeneity (I^2; p value)	Publication bias (p value Egger's test)
30-day mortality rate	17	3,752 vs. 159,745	407/3,752	23,634/159,745	1.13 (0.94-1.35) p=0.20	33.9% p=0.09	0.69

Clinical outcome in solid organ tx recipients affected by COVID-19 compared to general population: a systematic review and meta-analysis *Gatti M et al, on behalf of ORCHESTRA study group , CMI accepted*

Secondary outcome

Outcome	Studies	No. of patients (Tx vs.comparators)	Odds ratio (95% CI)	Heterogeneity (I^2; p value)	Publication bias (p value Egger's test)
Severe respiratory failure	6	667 vs. 5,304	1.35 (0.89-2.04) p=0.15	73.2% p=0.002	0.22
Mechanical ventilation	12	3,376 vs. 12,637	1.38 (0.91-2.09) p=0.13	85.8% p<0.001	0.14
Hospitalization	15	1,352 vs. 10,766	0.99 (0.57-1.70) p=0.96	25.7% p=0.17	<0.001
ICU admission	9	2,989 vs. 8,132	1.56 (1.03-2.36) p=0.03	79.1% p<0.001	0.69
AKI occurrence	10	3,073 vs. 11,376	2.50 (1.81-3.45) p<0.001	72.6% p<0.001	0.47
Superinfections	6	499 vs. 1,051	1.12 (0.35-3.52) p=0.85	93.4% p<0.001	0.04

A Portrait of SARS-CoV-2 Infection in Patients Undergoing Hematopoietic Cell Transplantation: A Systematic Review of the Literature

Bailey AJM et al, Curr. Oncol. 2022, 29: 337–349.

A total of 1285 adult HCT recipients were described in 11 studies. The age range was 18–82 years. In 18 studies that reported on 54 pediatric HCT recipients, the age range was 0.6–17 years.

On average, the patients were 18.9 months post-HCT (range 0.9 to 293 months) before their diagnosis with COVID-19. A total of 521 patients (40.5%) were recipients of autologous HCT, 758 (59.0%) were recipients of allogeneic HCT, and 6 (0.5%) received CAR T-cell therapy.

Overall, the mortality rates were high, with 21% of adults and 6% of pediatric HCT recipients succumbing to COVID-19.

The factors reported to be associated with increased mortality included

age	**HR = 1.21, 95% CI 1.03–1.43, p = 0.02**
ICU admission	**HR = 4.42, 95% CI 2.25–8.65, p < 0.001 for allogeneic HCT recipients**
	HR = 2.26, 95% CI 1.22–4.20, p = 0.01 for autologous HCT recipients),
low platelet count	**OR = 21.37, 95% CI 1.71–267.11, p = 0.01 for platelets count > 80.000 / mmc**

Performance status was associated with decreased mortality HR = 0.83, 95% CI 0.74–0.93, p = 0.001).

COVID-19 CLINICAL UNMET NEEDS

Morbidity and survival After Hospital Discharge (Long COVID)

The COVID19 -related disease in immunocompromised people

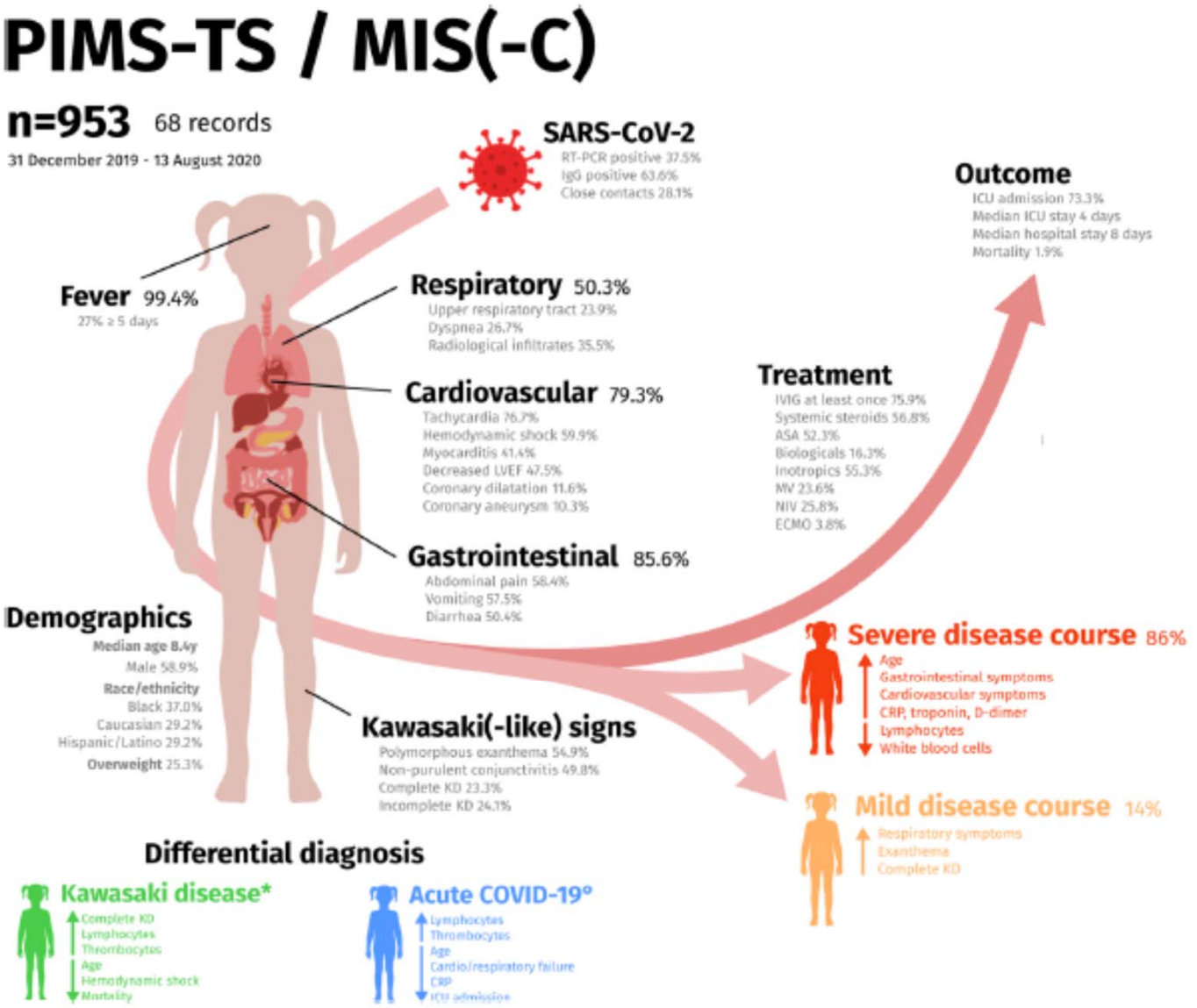
➡ **The PIMS-TS/MIS(-C) mystery**

The on-off syndrome in long term ICU patients

Multisystem inflammatory syndrome in children related to COVID-19: a systematic review

Hoste L et al Eur J Pediatrics 2021; 180:2019–2034

In total, 953 patients with PIMS-TS/MIS(-C) were reported, with individual patient information (single-case data) available for 138 patients (14.5%).



Multisystem inflammatory syndrome in children related to COVID-19: a systematic review

Hoste L et al Eur J Pediatrics 2021; 180:2019–2034

CLINICAL FINDINGS	RATE
FEVER (during at least 5 days)	**96%**
GE SYMPTOMS	**86%**
abdominal pain	58%
diarrhoea	57%
vomiting	50%
CARDIOVASCULAR	**79%**
Tachycardia	76.7%
hypotension	59.9%
myocarditis	41.4%
LVEF <55%	40.4%
PERICARDIAL EFFUSION	**22.3%**
RESPIRATORY SYMPTOMS	**50.4%**
THROMBOSIS	**2%**
EXANTHEMA	**54.9%**
CONJUNCTIVITIS	**49.8%**

- substantially higher inflammation compared to historical KD [non-PIMS-TS/MIS(-C) cohorts was reported
- coagulation markers were substantially upregulated
- myocardial injury markers were often elevated
- hyponatremia was frequent

ICU admission was common (73.3%)
A majority of cases (86%) experienced severe course.

Eighteen deaths were described (1.9%)

Residual cardiac dysfunction was present in 7.3% of cases.
Two patients showed persistent neurological damage after PIMS-TS/MIS(-C).
No other residual morbidity was reported