Tractament personalitzat de la COVID

Carolina Garcia-Vidal

Servicio de Enfermedades Infecciosas

Hospital Clínic, Barcelona

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BARCELONA
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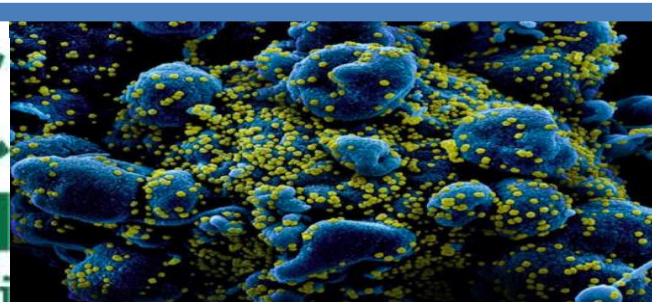
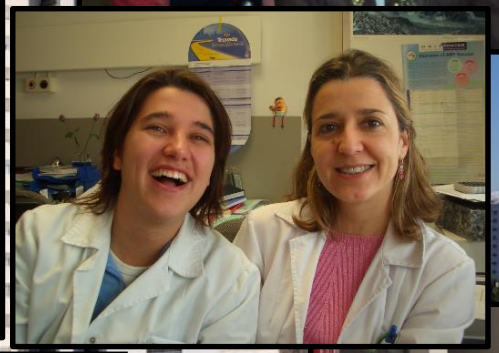
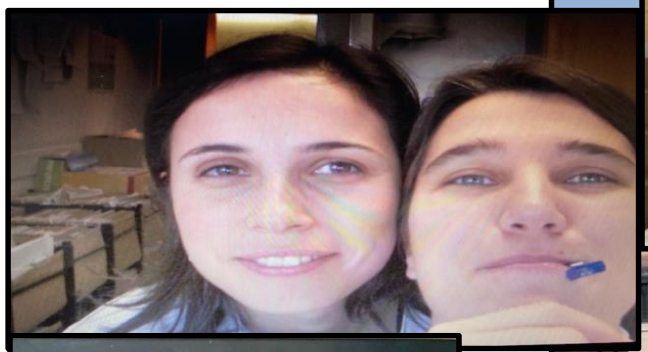
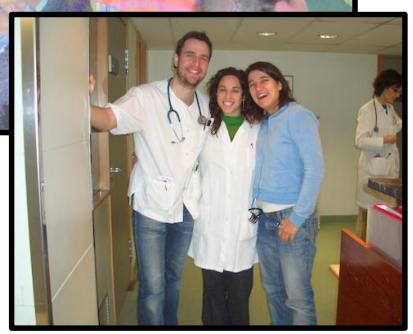






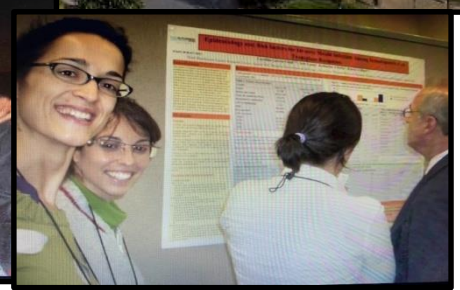




- Quiroderma





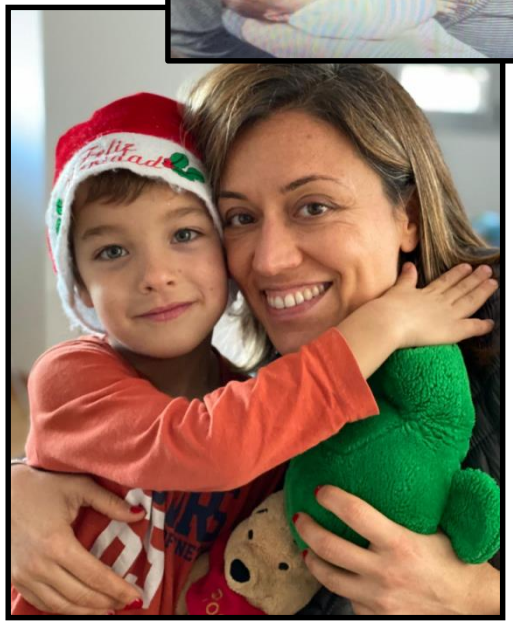


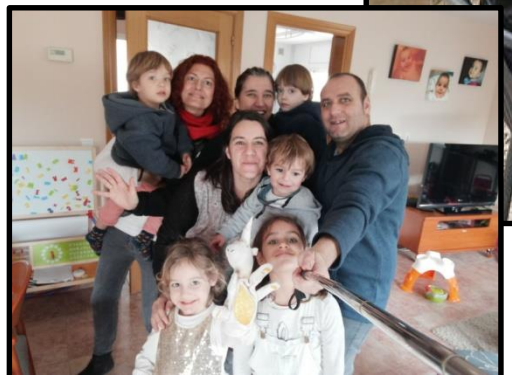










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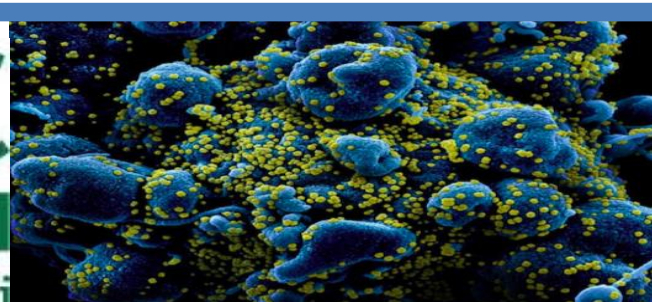
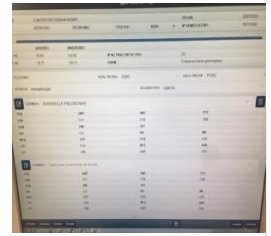
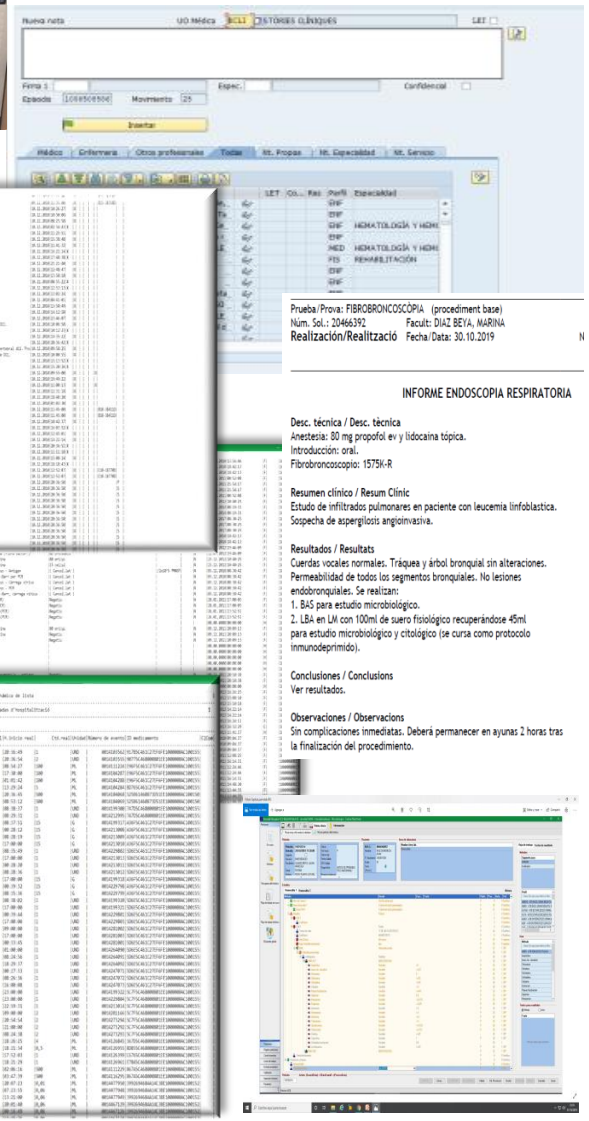


Innovation against COVID19

6 de maig!

Searching for solutions





Prueba/Prova: FIBROBRONCOSCÒPIA (procediment base)
Núm. Sol.: 20466392 Facult: DIAZ BEYA, MARINA
Realización/Realització Fecha/Data: 30.10.2019

INFORME ENDOSCOPIA RESPIRATORIA

Desc. técnica / Desc. tècnica
Anestesia: 80 mg propofol ev y lidocaina tópica.
Introducción: oral.
Fibrobroncoscopio: 1575K-R

Resumen clínico / Resum Clínic
Estudio de infiltrados pulmonares en paciente con leucemia linfoblastica.
Sospecha de aspergilosis angioinvasiva.

Resultados / Resultats
Cuerdas vocales normales. Tráquea y árbol bronquial sin alteraciones.
Permeabilidad de todos los segmentos bronquiales. No lesiones endobronquiales. Se realizan:
1. BAS para estudio microbiológico.
2. LBA en LM con 100ml de suero fisiológico recuperándose 45ml para estudio microbiológico y citológico (se cursa como protocolo inmunodeprimido).

Conclusiones / Conclusions
Ver resultados.

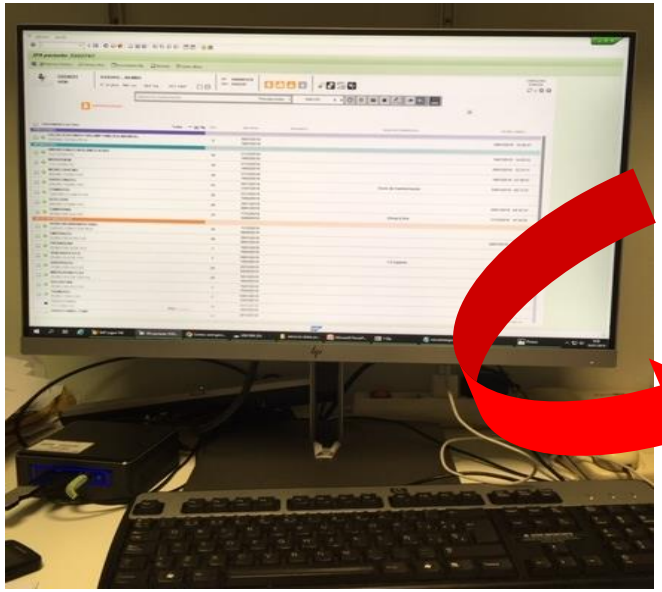
Observaciones / Observacions
Sin complicaciones inmediatas. Deberá permanecer en ayunas 2 horas tras la finalización del procedimiento.

Garcia-Vidal C, et al. Artificial intelligence to support clinical decision-making processes. Ebiomedicine 2019; 46:27-29

SILD

S4M
Smart Support System for Medicine

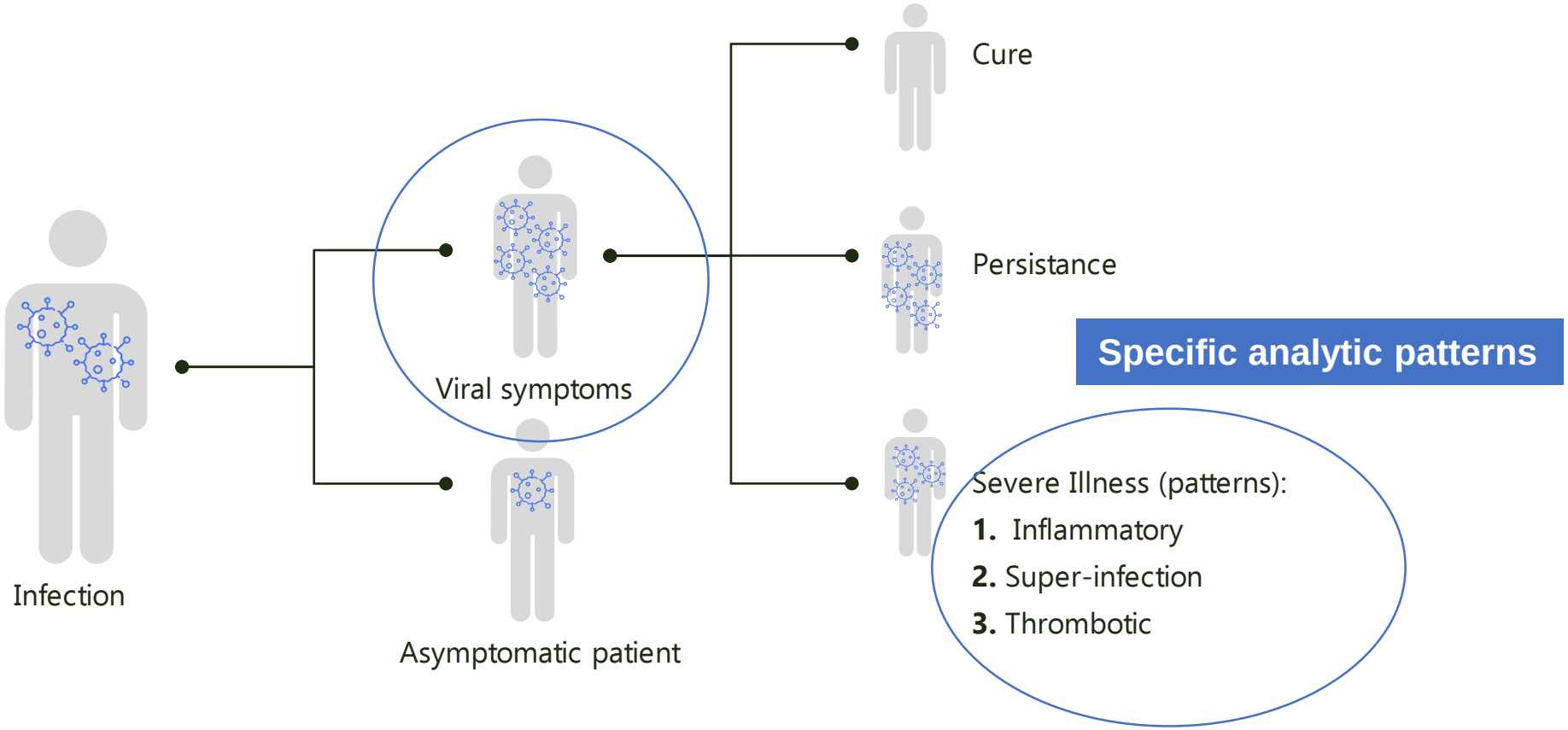
An intelligent system to read and provide high-quality pieces of data retrieved from EHRs in real time



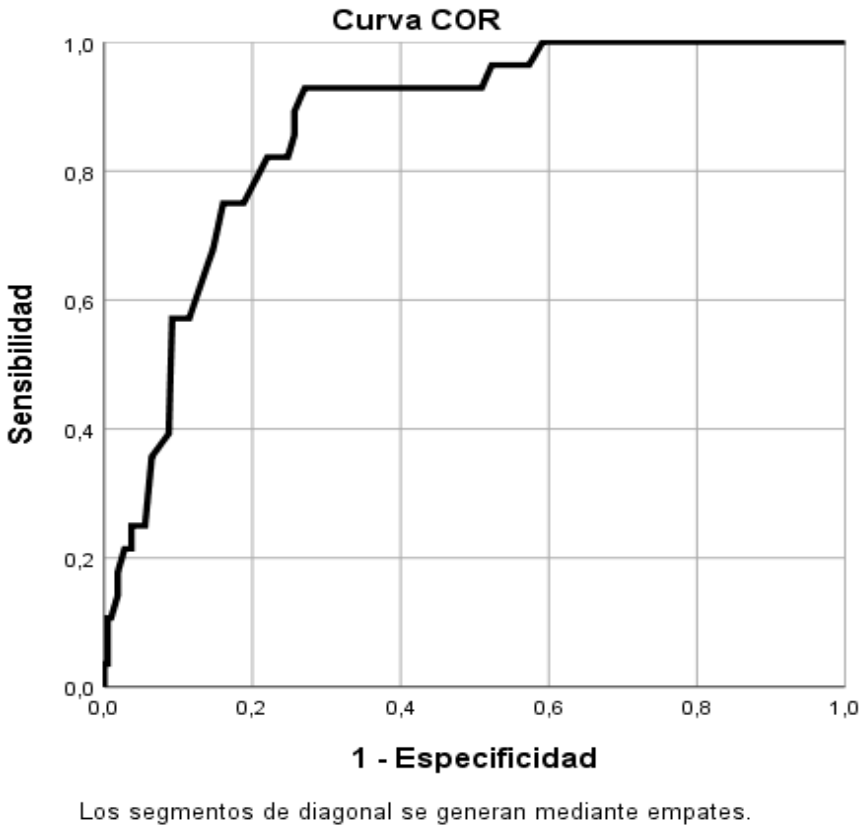
id	NHC	UCI	SEXO	Edad	FREC_RESP_0	EXITUS
315	4887936	0	2	93	20.0	0
316	5205668	1	2	56	20.0	0
317	5286474	0	2	88	22.0	0
318	5297324	0	1	74	NI	0
321	5307066	0	1	88	24.0	1
323	70167389	0	1	73	18.0	0
324	70414503	0	2	87	NI	0
	6124	0	1	53	NI	0
	48	1	2	70	22.0	0
	9	1	1	65	NI	0
328	530 6	1	1	70	NI	0
329	407080	0	2	43	NI	0
330	7024749	0	1	87	NI	1
331	132	0	2	57	19.0	0
332	14	0	2	83	NI	0
333	1	0	1	79	18.0	1
334	0	0	1	79	20.0	0
335	71	0	2	80	18.0	1
336	174	1	1	60	NI	0
	36145	0	1	33	21.0	0
	396607	0	1	54	18.0	0
	429395	0	2	64	NI	0
	522182	0	1	89	NI	0
341	612527	0	2	70	20.0	0
342	663331	0	1	65	22.0	0
343	686259	0	2	52	16.0	0
344	743694	0	2	72	32.0	0
345	4051163	0	1	72	16.0	0
347	4248417	0	1	53	18.0	0
348	4363976	0	1	69	NI	0
349	4420805	0	1	66	16.0	0
350	4639890	0	2	65	NI	0
352	5165357	1	2	71	32.0	0
Total	**32797906994**	**213**	**2312**	**88717**		**151**

MORE THAN 3 TRILLION PIECES OF DATA FROM PATIENTS WITH COVID-19

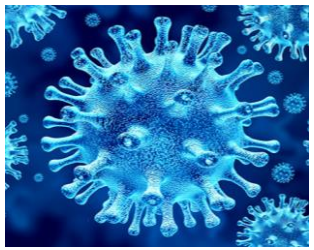
Garcia-Vidal C, et al. Personalized therapy approach for hospitalized patients with COVID-19. Clinical Infectious Disease 2020; doi: 10.1093



Garcia-Vidal C, et al.Personalized therapy approach for hospitalized patients with COVID-19. Clinical Infectious Disease 2020; doi: 10.1093



- Multivariate analyses showed that personalized therapy was independently associated with decreased early mortality (OR 0.144; 95% confidence interval [CI], 0.03–0.686; p=0.015).
- Increasing age (OR 1.06; 95% CI, 1.003-1.121; p=0.038) and therapeutic effort limitation (OR 9.684; 95% CI, 2.934-31.959; p<0.001) were found as independent factors associated with higher mortality.
- The goodness of fit of the model -> Hosmer-Lemeshow test (p=0.275). The discriminatory power of the model had an AUC of 0.907 (95% CI, 0.847–0.967), demonstrating an excellent ability to predict mortality.

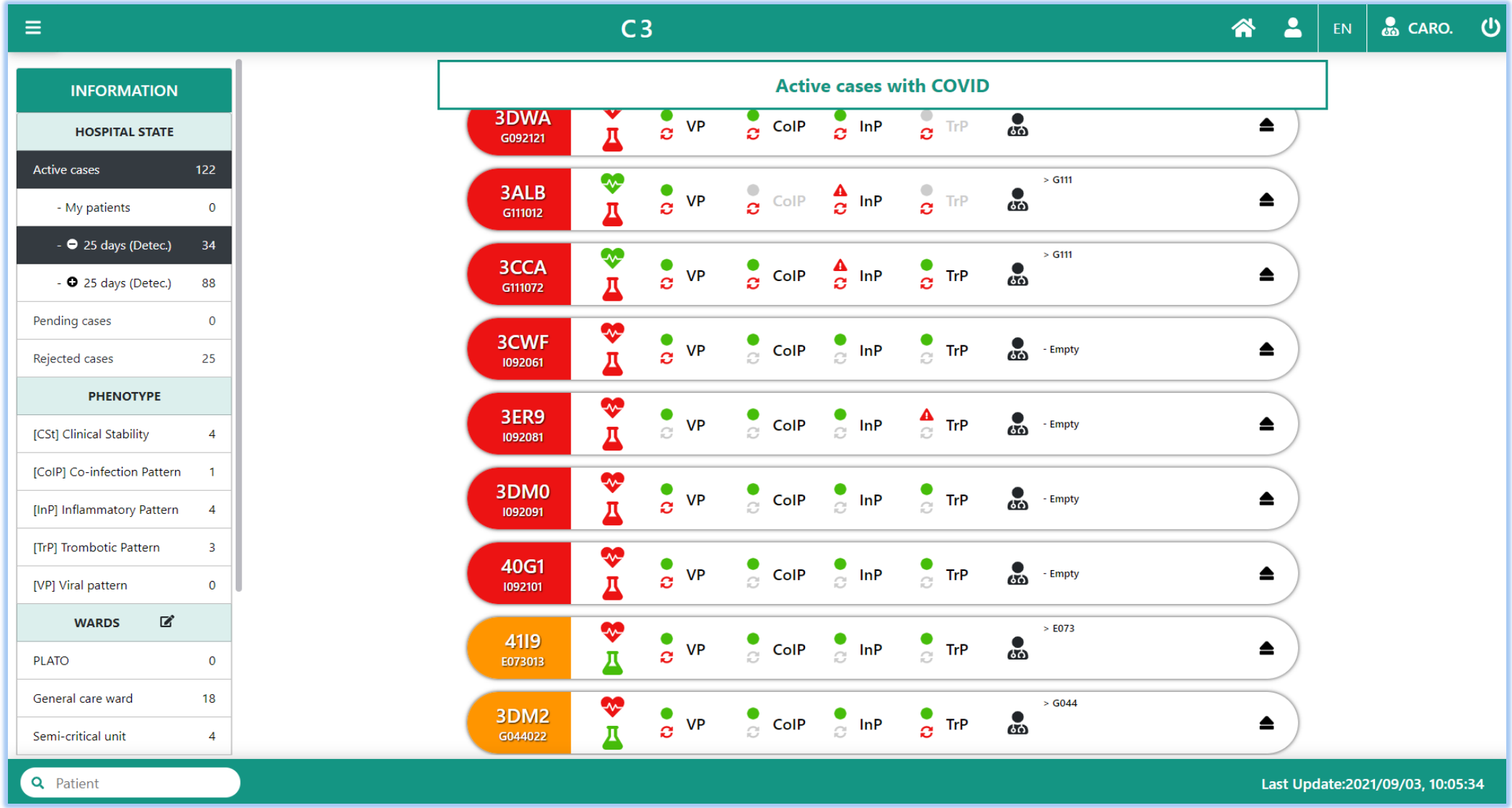


Disnea, fiebre, tos, …

Día 1
Día 2

	Virus	Inflamación	Co-infección	Trombopatía	Otros
Paciente 1	x x	x			
Paciente 2	x	x x	x		
Paciente 3		x	x	x	
…					

Remdesivir Plasma Ac monoclonales …	Tocilizumab Dexametasona Anakinra Baricitinib …	Antibiótico Antifúngico	Anticoagulación	Otros


C3
EN
CARO.
INFORMATION
HOSPITAL STATE
Active cases 122
- My patients 0
- 25 days (Detec.) 34
- 25 days (Detec.) 88
Pending cases 0
Rejected cases 25
PHENOTYPE
[CSt] Clinical Stability 4
[CoIP] Co-infection Pattern 1
[InP] Inflammatory Pattern 4
[TrP] Trombotic Pattern 3
[VP] Viral pattern 0
WARDS
PLATO 0
General care ward 18
Semi-critical unit 4
Active cases with COVID
3DWA G092121 VP CoIP InP TrP
3ALB G111012 VP CoIP InP TrP > G111
3CCA G111072 VP CoIP InP TrP > G111
3CWF I092061 VP CoIP InP TrP - Empty
3ER9 I092081 VP CoIP InP TrP - Empty
3DM0 I092091 VP CoIP InP TrP - Empty
40G1 I092101 VP CoIP InP TrP - Empty
41I9 E073013 VP CoIP InP TrP > E073
3DM2 G044022 VP CoIP InP TrP > G044
Patient
Last Update:2021/09/03, 10:05:34

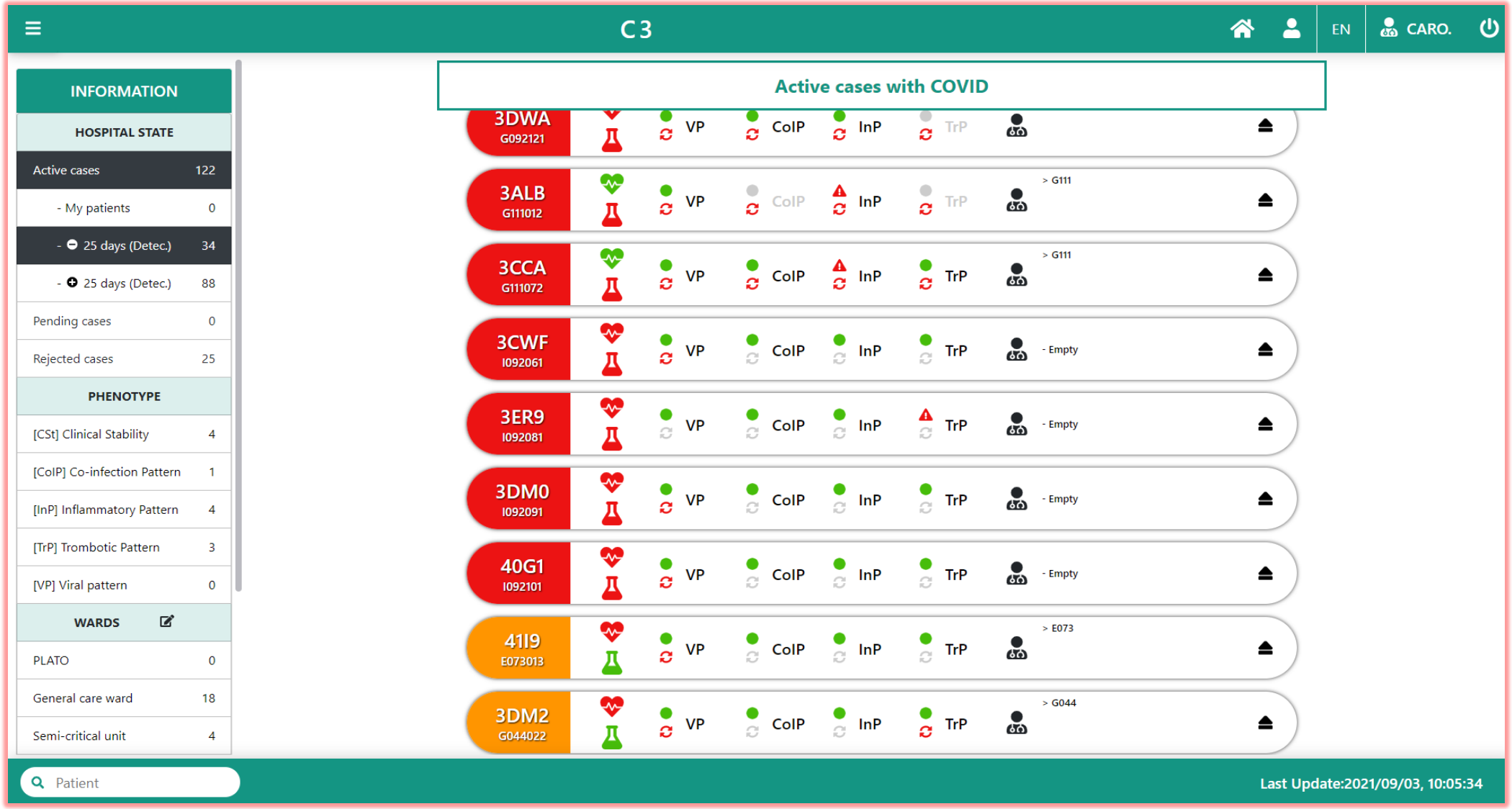
S4M
Smart Support System for Medicine

COVID-19 Central Control (C3)

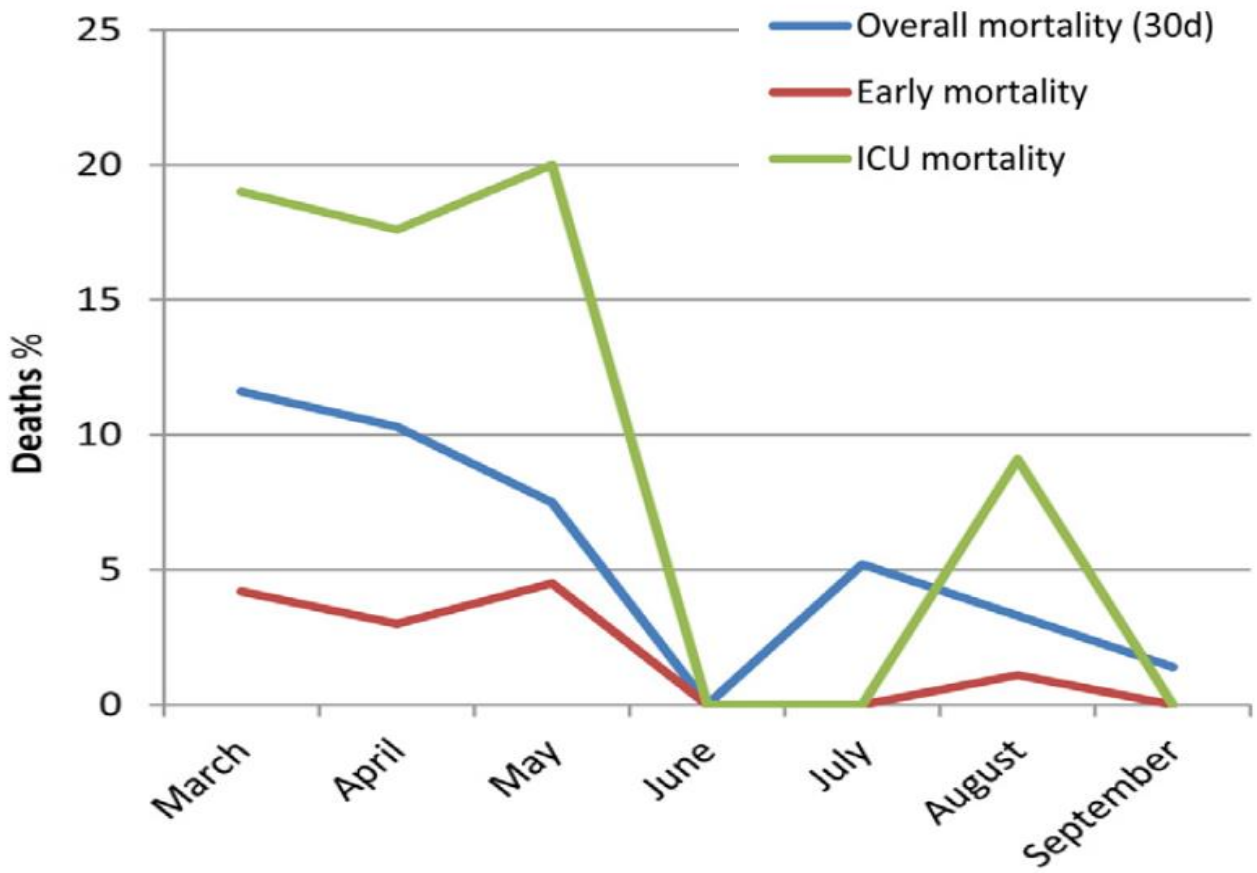
- Co-infection
- Patients with suspiction of thrombotic diseases
- Ready for hospital discharge!
- Antiinflammatory Treatment

EIT health award 2020

(European Union-Innovative Technology Department)!!!!



Garcia-Vidal C, et al. Trends in mortality of hospitalized COVID-19 patients: A single centre observational cohort study from Spain. The Lancet Regional Health 2021



Overall mortality decreased from 11.6% in the first month to 1.4% in the last month, reflecting a progressive, significant downward trend (p for trend <0.001).

Fig. 1. Overall mortality trends for patients admitted with COVID-19 (distribution by months).

Garcia-Vidal C, et al. Trends in mortality of hospitalized COVID-19 patients: A single centre observational cohort study from Spain. The Lancet Regional Health 2021

Table 1. Mortality by 10-year age intervals throughout the study periods

Mortality %	Period 1 March (n=810)	Period 2 April (n=504)	Period 3 May (n=67)	Period 4 June (n=22)	Period 5 July (n=77)	Period 6 August (n=91)	Period 7 September (n=74)	p
<40 y	1/90 (1%)	0/55 (0%)	0/9 (0%)	0/6 (0%)	0/14 (0%)	0/13 (0%)	0/7 (0%)	.465
40-49 y	1/105 (1%)	0/62 (0%)	0/7 (0%)	0/0 (0%)	0/13 (0%)	0/12 (0%)	0/17 (0%)	.474
50-59y	6/155 (4%)	4/86 (5%)	0/7(0%)	0/4 (0%)	0/17(0%)	0/12 (0%)	0/19(0%)	.173
60-69 y	9/180 (5%)	8/90 (9%)	0/14 (0%)	0/2 (0%)	0/8 (0%)	0/25 (0%)	1/11 (9%)	.482
70-79 y	38/186 (20%)	9/84 (11%)	2/10 (20%)	0/6 (0%)	1/11 (9%)	1/15 (7%)	0/11 (0%)	.012
80-89 y	31/80 (39%)	22/94 (24%)	2/11 (18%)	0/3 (0%)	1/5 (20%)	2/12 (17%)	0/8 (0%)	.005
>90 y	8/14 (57%)	9/33 (27%)	1/9 (11%)	0/1 (0%)	2/4 (50%)	0/2 (0%)	0/1 (0%)	.133
All patients	94/810 (11.6%)	52/504 (10.3%)	5/67 (7.5%)	0/22 (0%)	4/77 (5.2%)	3/91 (3.3%)	1/74 (1.4%)	<.001

FENOTIPO VIRAL

Primeros diez días desde el inicio de los síntomas

CT bajos

Infecciones persistentes

Rico V, et al. Impact of SARS-CoV-2 Viral load measured by cycle threshold and days from symptoms onset to admission on the mortality of hospitalized patients with COVID-19. *Under revision*

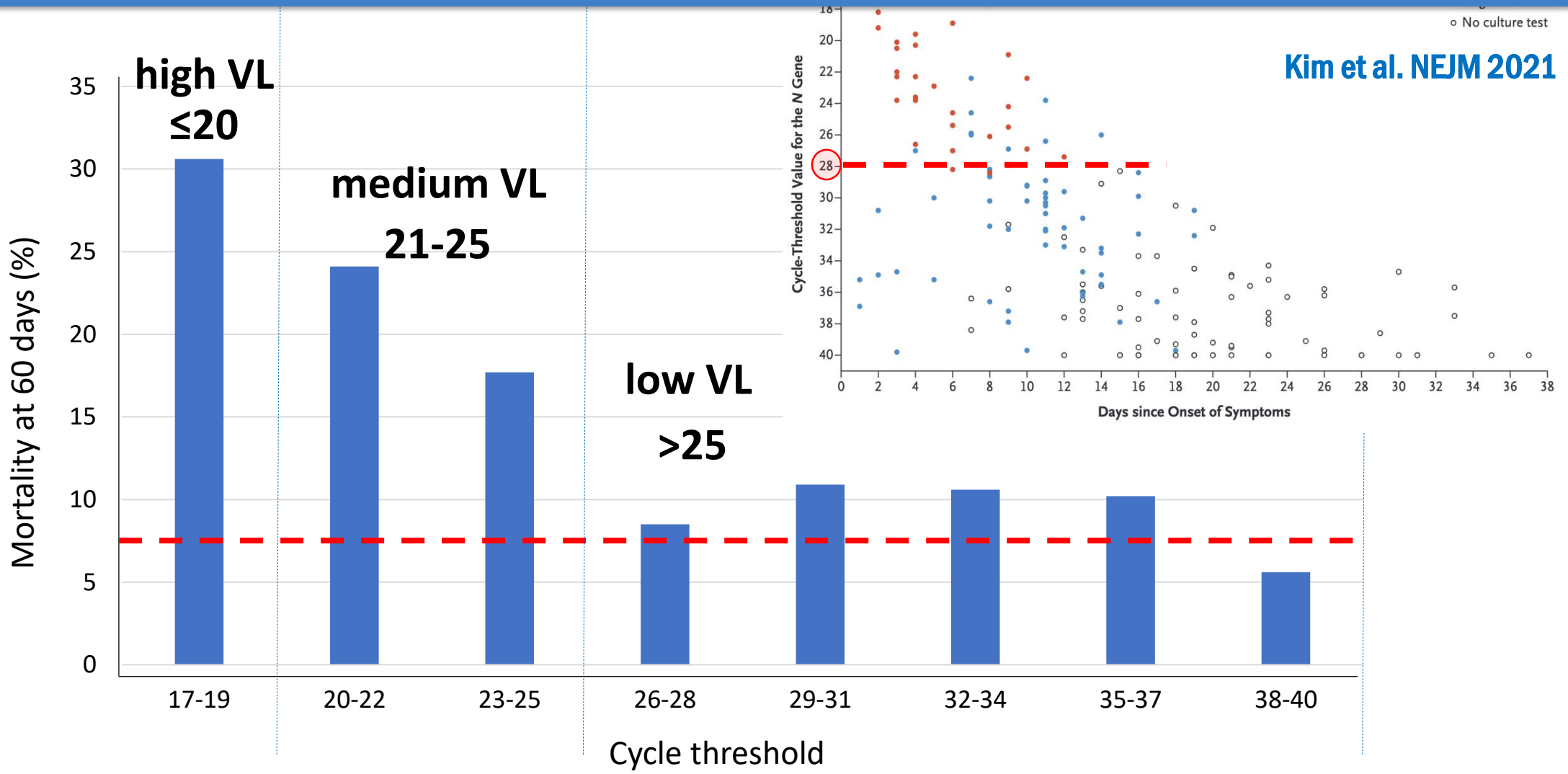


Figure 1. Mortality at 60 days according to the Ct value at admission (author's data)

Garcia-Vidal C, et al. Impact of remdesivir according to the pre-admission symptom duration in patients with COVID-19. *JAC 2021*

Remdesivir impact on COVID-19 mortality

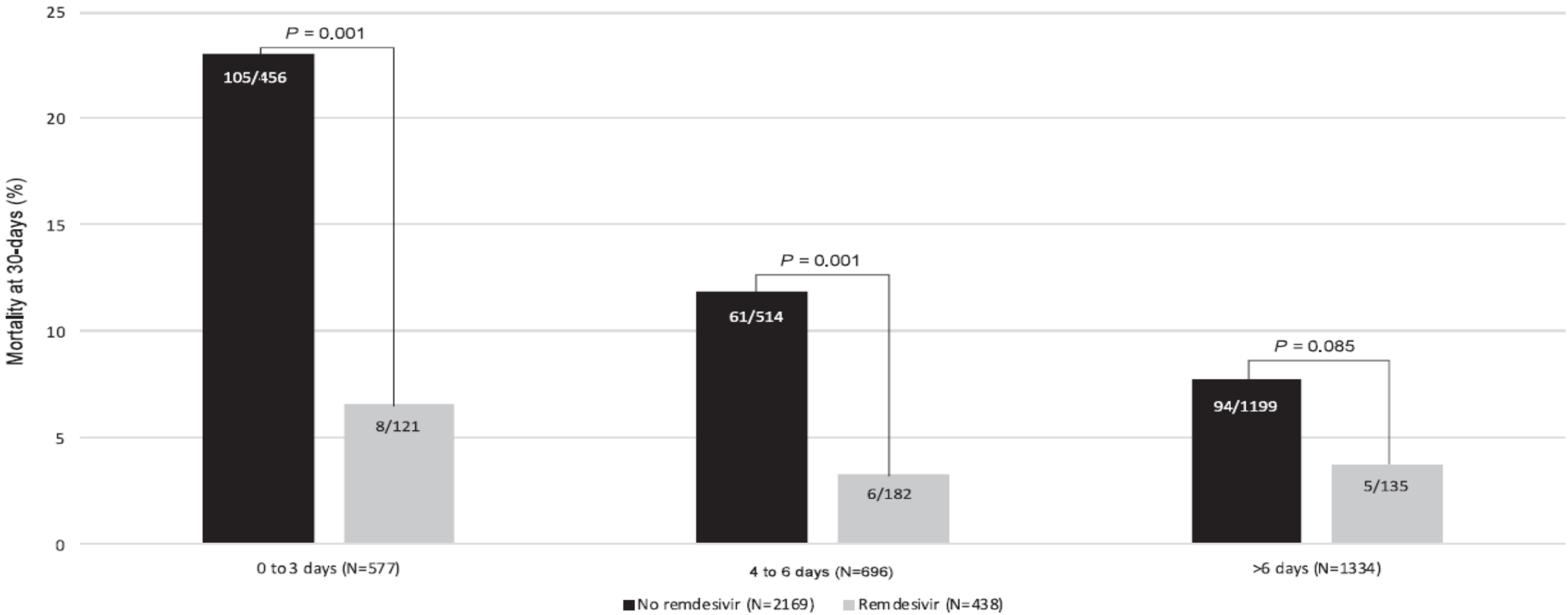
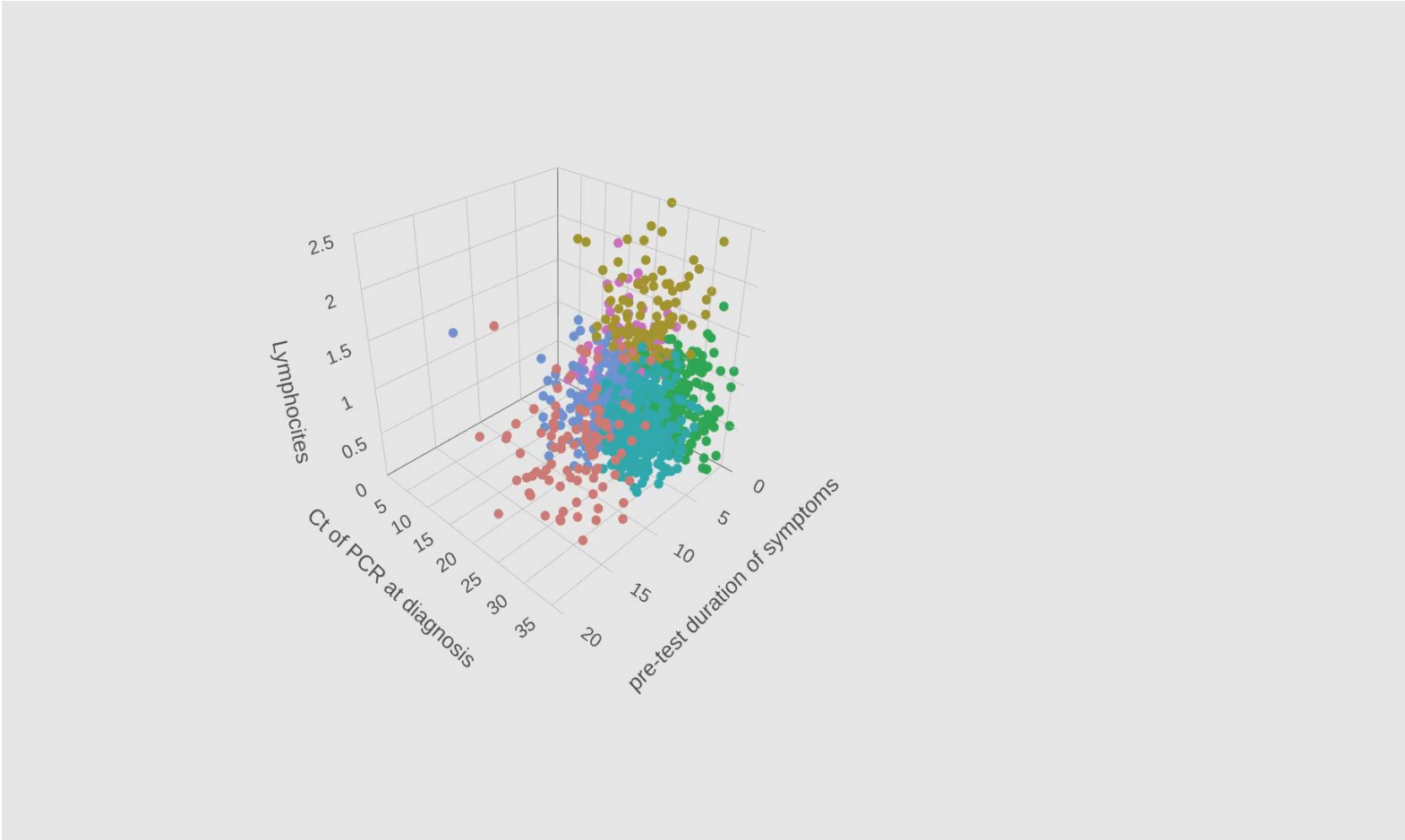


Figure 2. Mortality rate at 30 days by remdesivir treatment and the pre-test duration of symptoms (proportion comparisons using χ^2 test).

Garcia-Vidal C, et al. Clinical phenotypes of patients with COVID19 in whom remdesivir decreased mortality: non-supervised identification of clusters by artificial intelligence. Submitted



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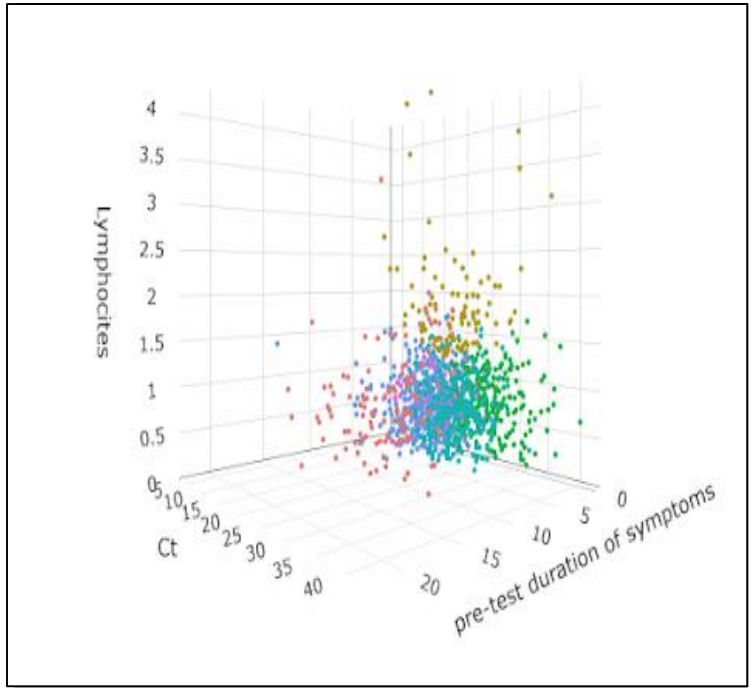
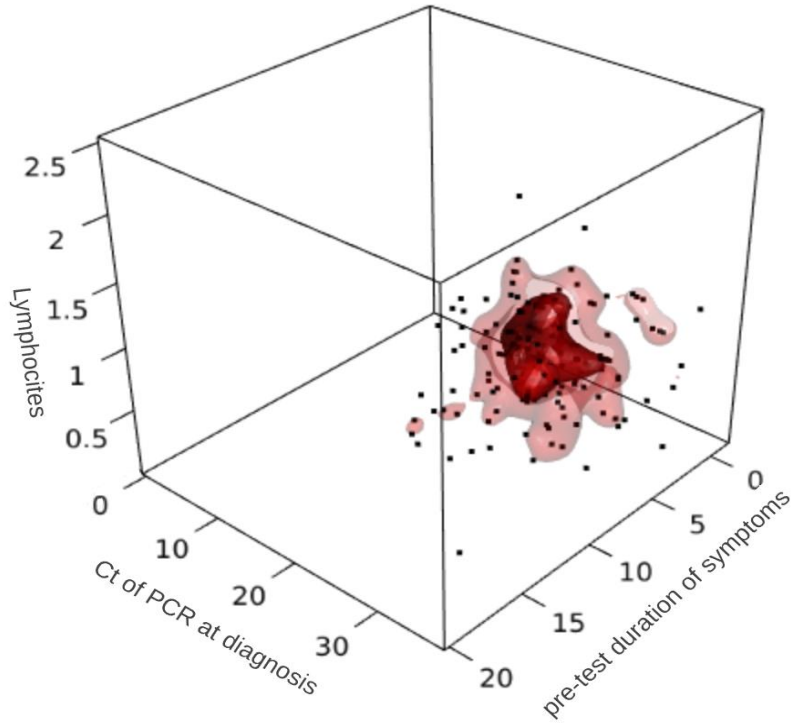


Clusters

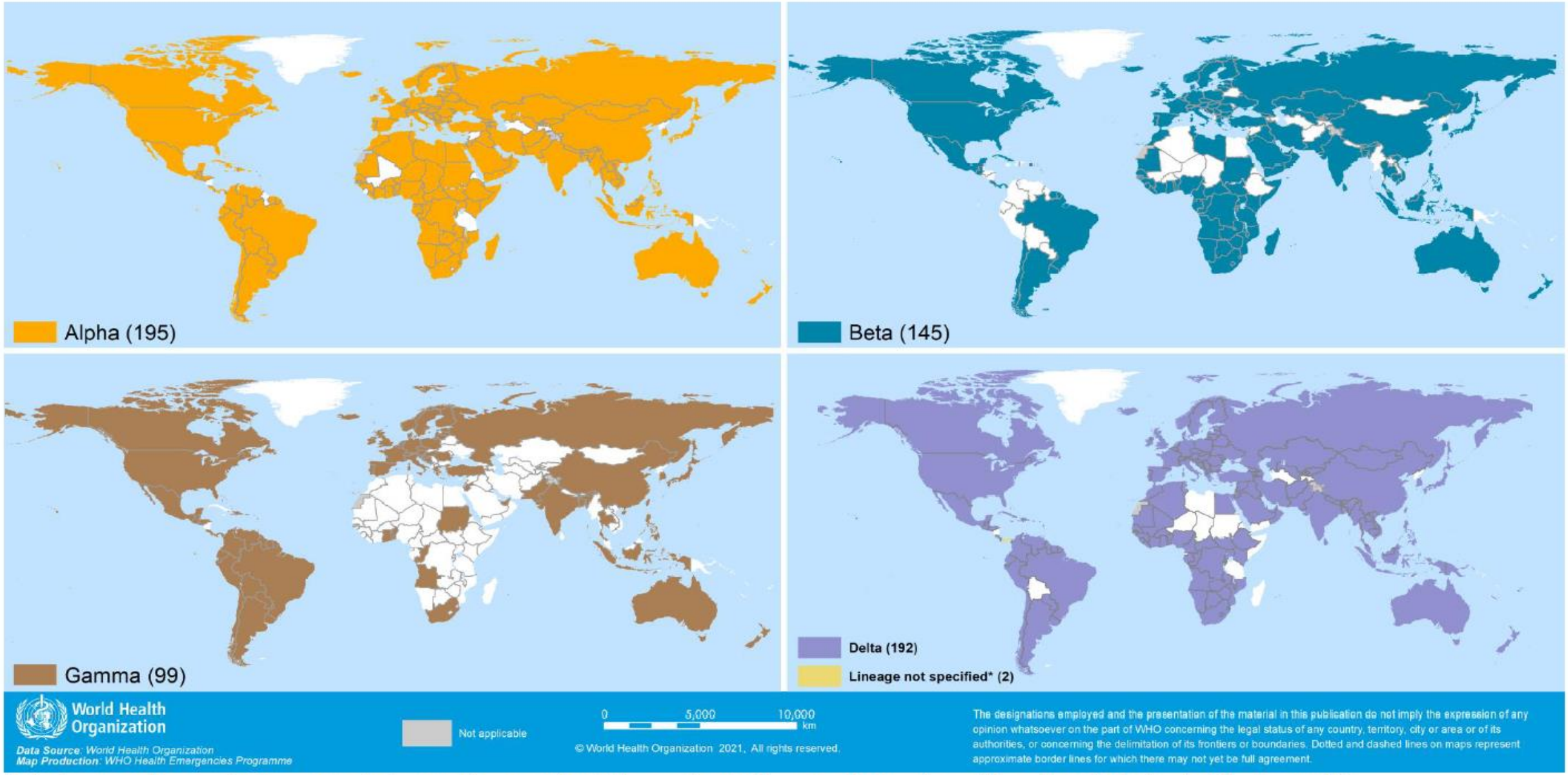


Mortality

Garcia-Vidal C, et al. Clinical phenotypes of patients with COVID19 in whom remdesivir decreased mortality: non-supervised identification of clusters by artificial intelligence. Submitted

K-means cluster	Median age (IQR)	Median Ct (IQR)	Median days of pre-test symptom duration (IQR)	Median lymphocyte number (IQR)	60-day mortality (%)	60-day mortality/ pts receiving remdesivir (%)	60-day mortality/ pts who did not receive remdesivir (%)	p-value
1 (n=101)	66 (56-76)	28.1 (24.53-32.8)	13 (12-15)	0.9 (0.6-1.2)	7.9%	0/6	8/95 (8.4)	1
2 (n=96)	61 (48-70.25)	26.22 (23-29.925)	5 (3-7)	1.75 (1.5-2.1)	2.1%	0/23	2/73 (2.7)	1
3 (n=222)	67.5 (55-76.75)	29.28 (26.87-31.97)	3 (2-4)	0.8 (0.6-1)	15,3%	2/45 (4.4)	32/177 (18)	0.023
4 (n=276)	61 (52-70)	30.96 (29-32.91)	8 (7-10)	0.8 (0.6-1)	7.6%	1/28 (3.6)	20/248 (8)	0.64
5 (n=242)	68 (55.25-79)	23.16 (21.49-25)	7 (6-8)	0.7 (0.5-1)	14.0%	2/53 (3.8)	32/189 (16.9)	0.015
6 (n=223)	75 (60.5-84)	19.3 (16.5-21.74)	2 (1-4)	0.7 (0.5-0.9)	29.6%	7/64 (10.9)	59/159 (37.1)	< 0.001

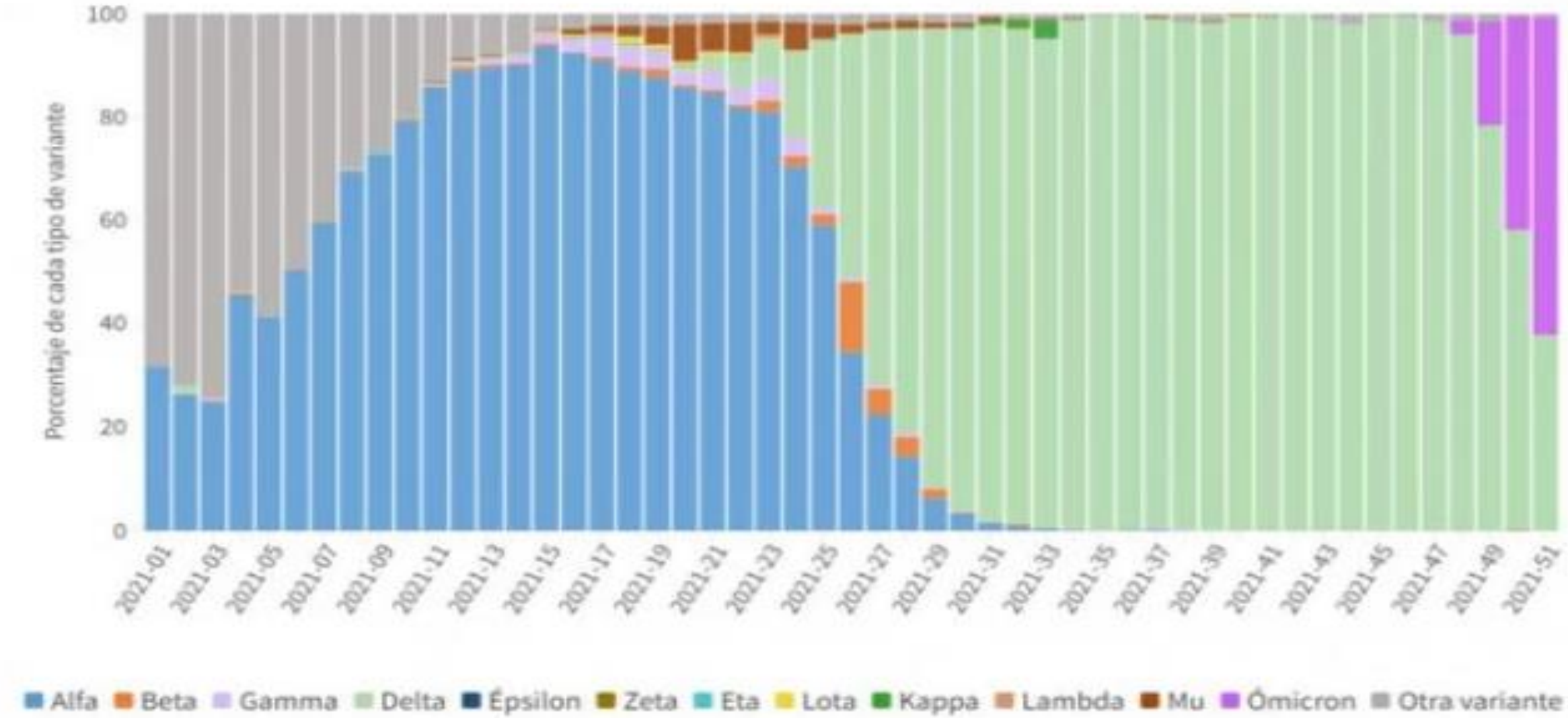
Figure 5. Countries, territories and areas reporting variants Alpha, Beta, Gamma and Delta, as of 5 October 2021**



**Includes countries/territories/areas reporting the detection of B.1.617 without further specification of lineage at this time. These will be reallocated as further details become available.*

***Countries/territories/areas highlighted include both official and unofficial reports of VOC detections, and do not presently differentiate between detections among travellers (e.g., at Points of Entry) or local community cases. Please see Annex 2 for further details*

Transición de Wuhan a Omicron



TF Aiello, et al. The Omicron variant of SARS-CoV2 determined a different clinical picture in hospitalized patients with COVID19. Submitted

	Cohorte anterior (n=3134)	Omicron (n=90)	Mi planta hoy (n=19)
Age (median)	66 (54-78)		78 (65-85)
Comorbilidity	68.3		-
Severe IS	22%		-
Age (Excluding IS)	63 (52-76)	74 (63-86)	-

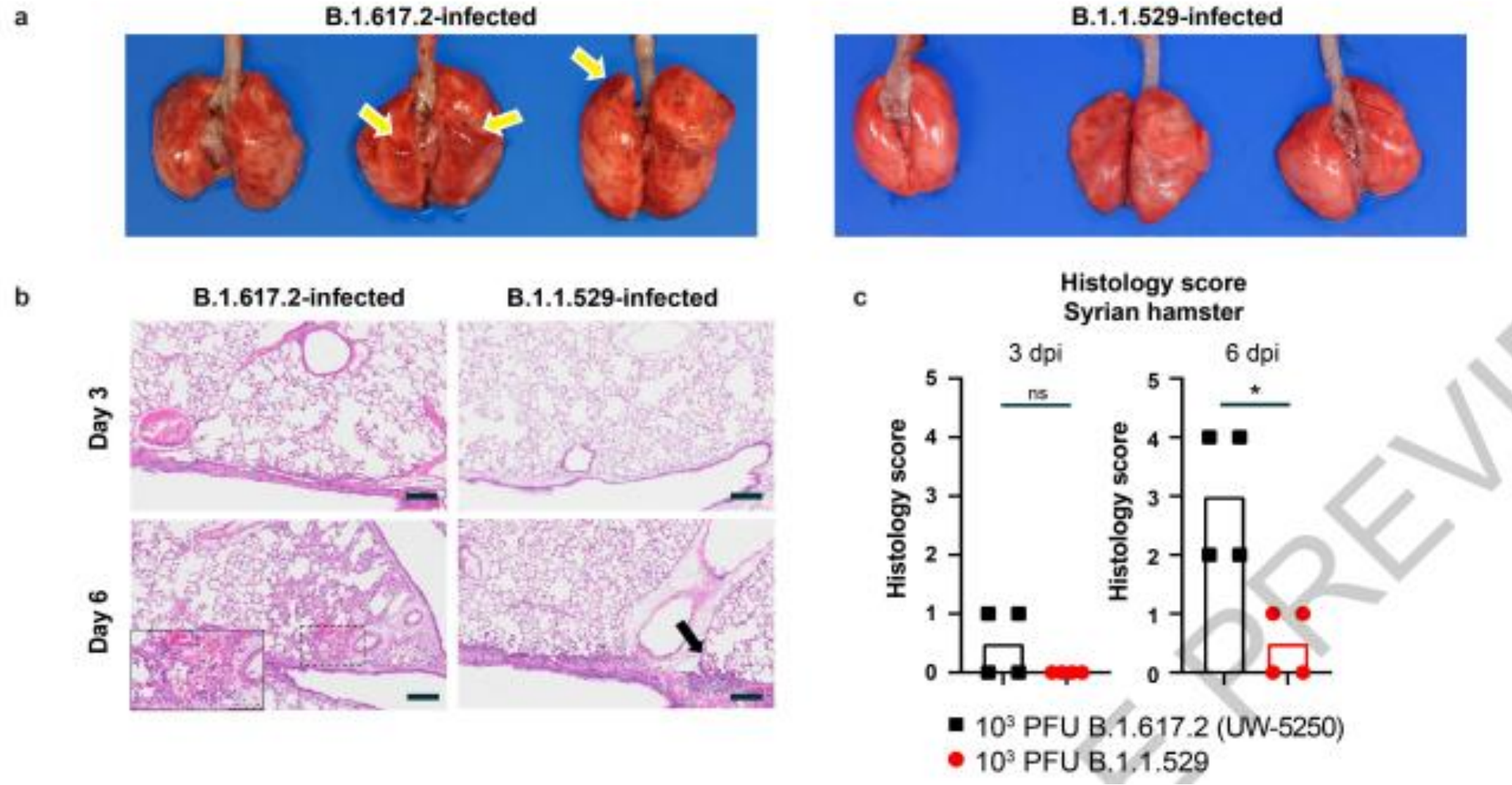
Ct 26 vs 19

TF Aiello, et al. The Omicron variant of SARS-CoV2 determined a different clinical picture in hospitalized patients with COVID19. Submitted

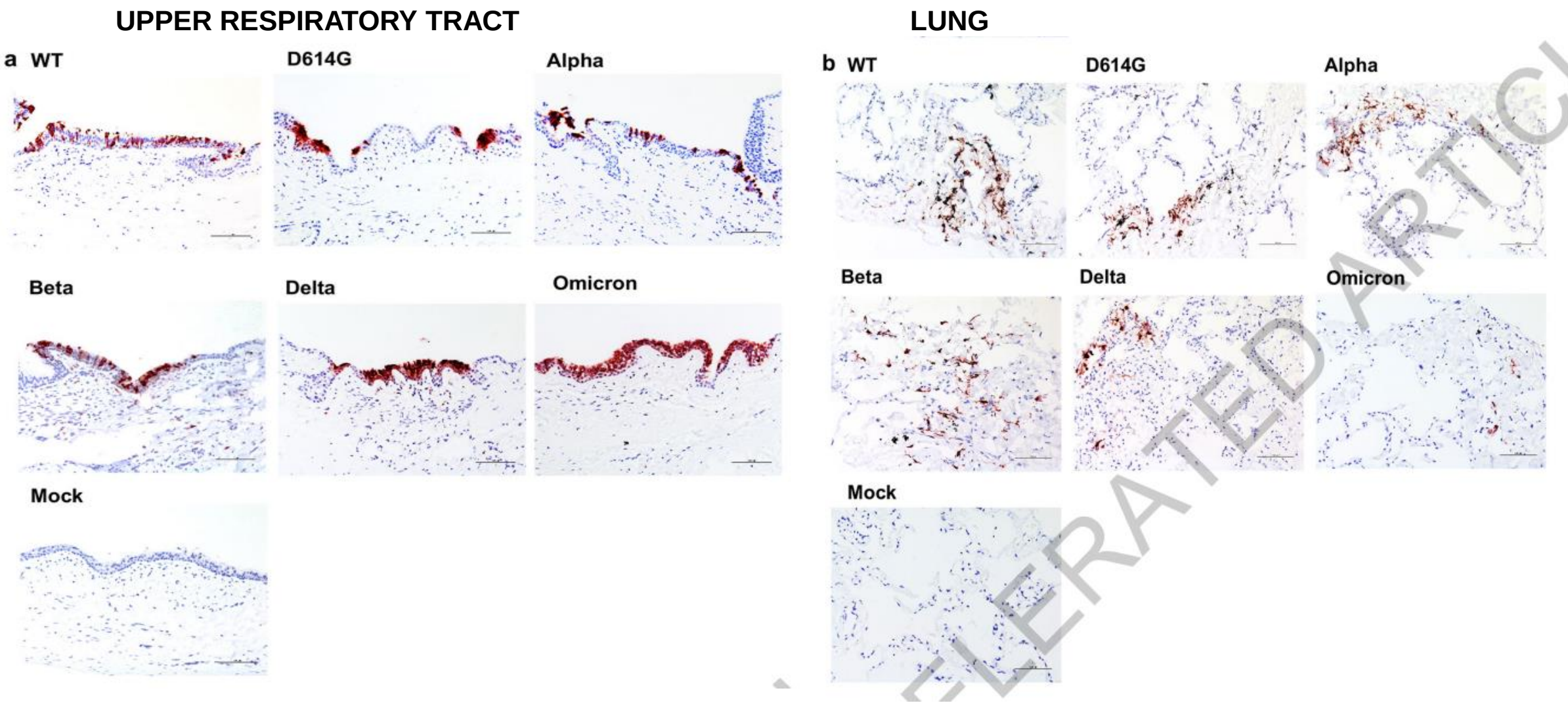
Al ingreso en el hospital…

	Virus	Inflamación	Co-infección
Omicron	97%	53%	30%
No Omicron	61.8%	68.1%	50%
p	<.001	.003	0.001

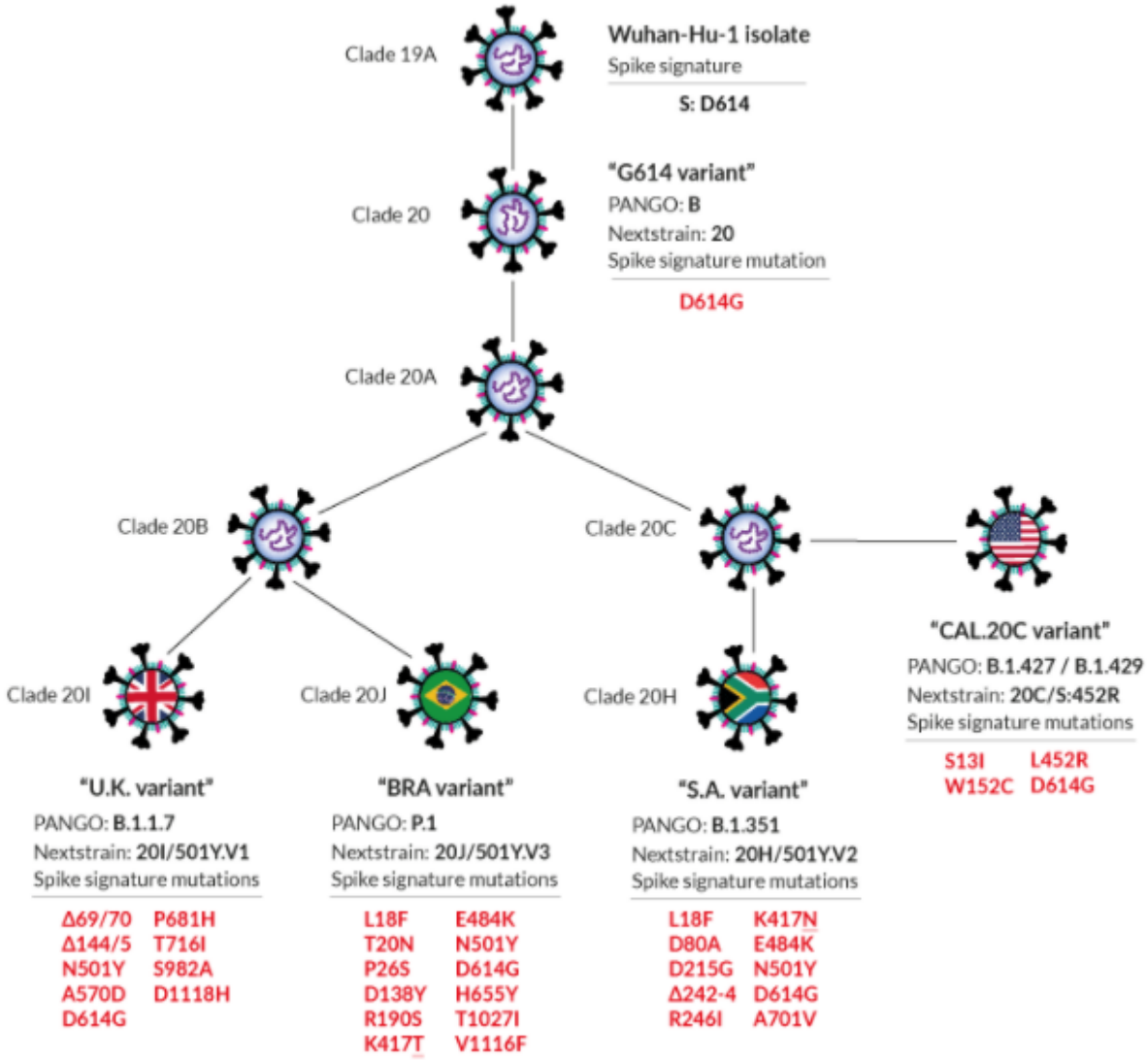
Halfmann P, et al. SARS-CoV-2 Omicron virus causes attenuated disease in mice and hamsters. Nature; 21 January 2022



Hui KPY, et al. SARS-CoV2 Omicron variant replication in human bronchus and lung ex vivo; Nature; 27 January 2022



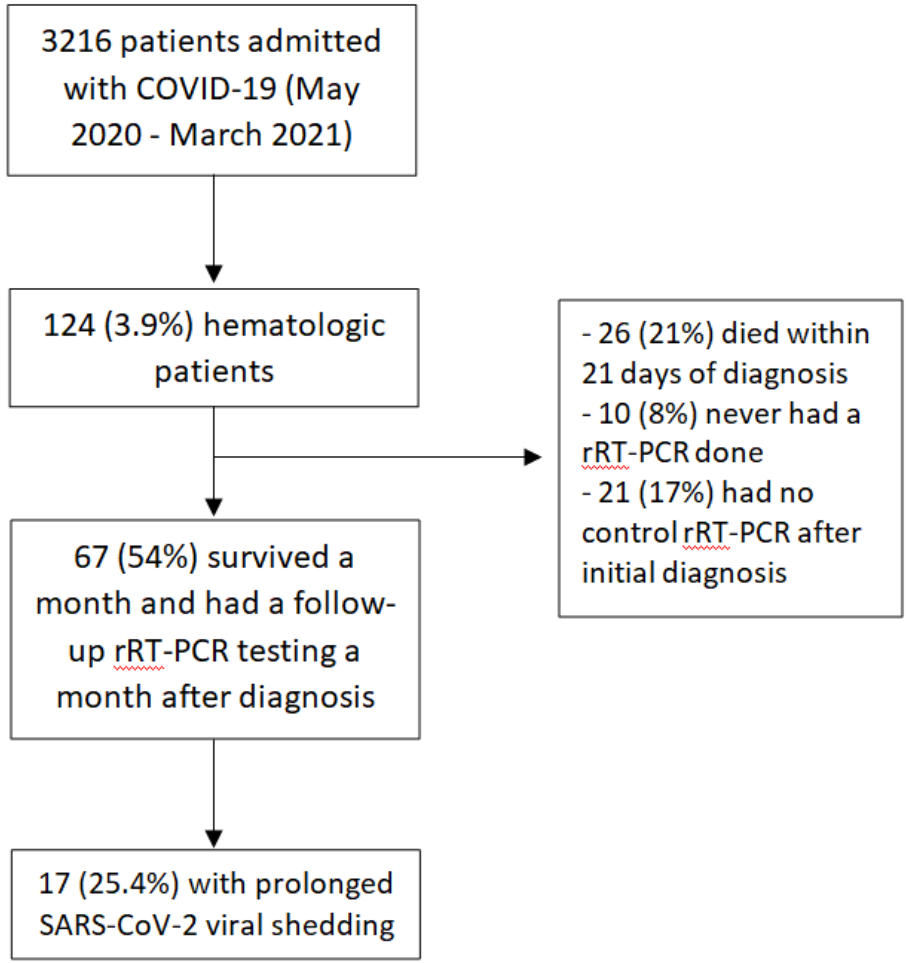
New variants emerged due to…



- High number of virus
- Prolonged infections

Garcia-Vidal C, et al. Prolonged viral replication in hematologic patients hospitalized with COVID19. Under review.

Figure 1. Flowchart.



High concern: Adequate antiviral strategies!!!!!

Garcia-Vidal C, et al. Prolonged viral replication in hematologic patients hospitalized with COVID19. Under review.

Table 1. Main epidemiological and clinical characteristics of hematologic patients.

	Patients N=67 (%)
Patient characteristics	
Median (IQR) age, in years	65 (54-77)
Age > 65 years (%)	32 (47.8)
Sex male, n (%)	42 (62.7)
Hematologic diseases (%)	
Lymphoma*	30 (44.8)
Chronic lymphocytic leukemia	10 (14.9)
Multiple myeloma	7 (10.4)
Acute leukemia	6 (9)
Myelodysplastic syndrome	5 (7.5)
Others	6 (9)
Prior hematopoietic stem cell transplant (HSCT)	14 (20.9)
Prior CAR-T cell therapy	3 (4.5)
Other important clinical features (%)	
Prior corticosteroid use (3 months)	35 (52.2)
Prior chemotherapy (3 months)	36 (53.7)
Prior rituximab use (12 months)	15 (22.4)
Neutropenia (< 500 neutrophils/mm^3)	6 (9.0)
Long-term lymphopenia	32 (47.8)
Hypogammaglobulinemia	23/62 (34.3)
Active hematologic disease	40 (59.7)
Median (IQR) days from symptom onset to hospital admission	4 (2-6)

17 patients with prolonged viral shedding (10.6%):

- **Hypogammaglobulinemia: 81%**
- **Corticosterois within the last 3 m: 70%**
- **Active hematologic disease: 82%**
- **Prior rituximab: 20%**
- **QMT within the last 3 m: 82%**
- **Prolonged lymphopenia: 53%**

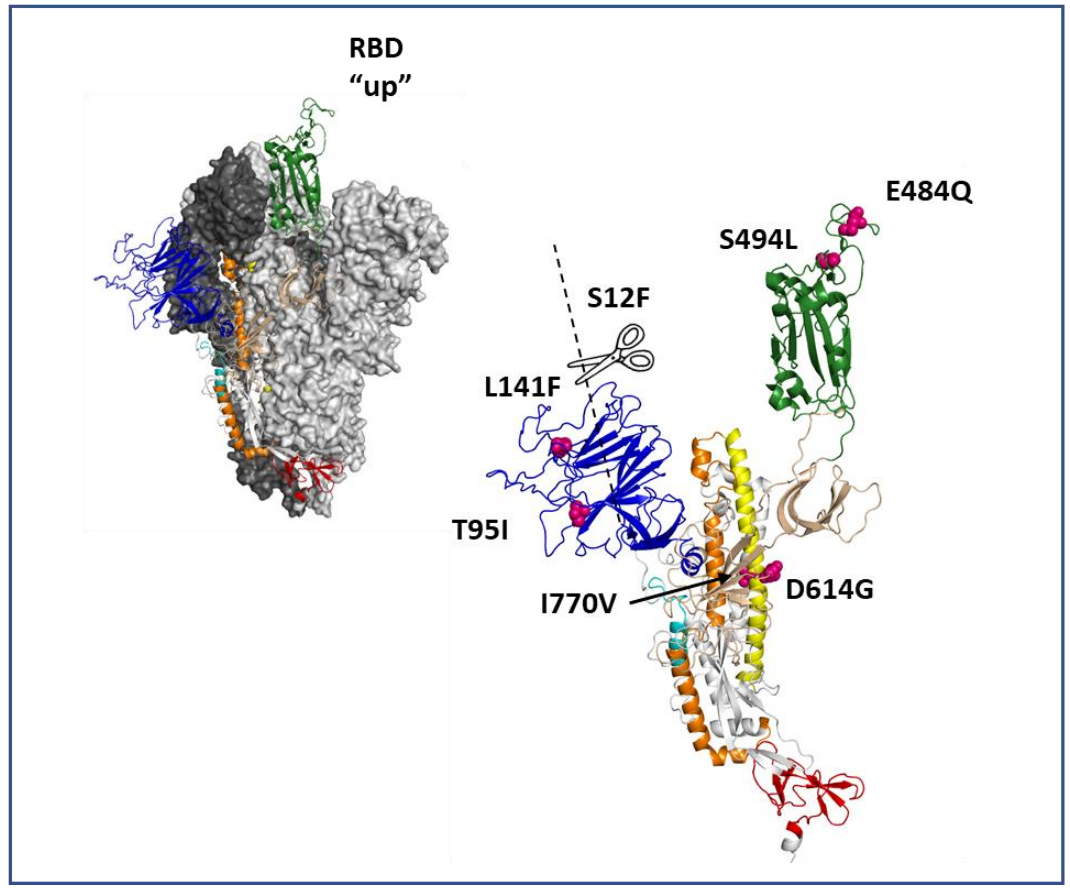
The clinical spectrum of these infections range from chronic asymptomatic infection to death

Garcia-Vidal C, et al. Occurrence of progressive mutations in a hematological patient with SARS-CoV-2 and prolonged viral replication. *Frontiers Microbiology 2022.*

Table 1. Summary of 12 samples of SARS-Cov-2 genetic study.

Sample number	Date of collection	Days since the first sampling	Nucleotid mutations *	Amino acid mutations *	Completed by Sanger	Lineage
1	2020-03-24	0	7	2		B.1
2	2020-03-30	6	8	3		B.1
3	2020-04-28	35	8	3		B.1
4	2020-05-18	55	11	5	Yes	B.1
5	2020-06-02	70	12	6		B.1
6	2020-06-22	90	14	8		B.1
7	2020-07-30	128	20	15		B.1
8	2020-08-03	132	18	12	Yes	B.1
9	2020-08-07	136	16	10		B.1
10	2020-11-06	227	17	10		B.1
11	2020-11-12	233	21	13	Yes	B.1
12	2020-11-16	237	29	22		B.1

* Compared with the reference SARS-CoV-2 Wuhan-1 (GenBank accession number: NC 045512).



Protein representation of the spike homotrimer in open conformation. The residues involved in amino acid substitutions are pointed in the structure representation.

Antiviral strategies

Antivirals

Remdesivir

Molnupiravir

Paxlovid

Immunologic strategies

Monoclonal antibodies

(uso compasivo: sotromivab)

Hiperimmune plasma

FENOTIPO CO-INFECCION

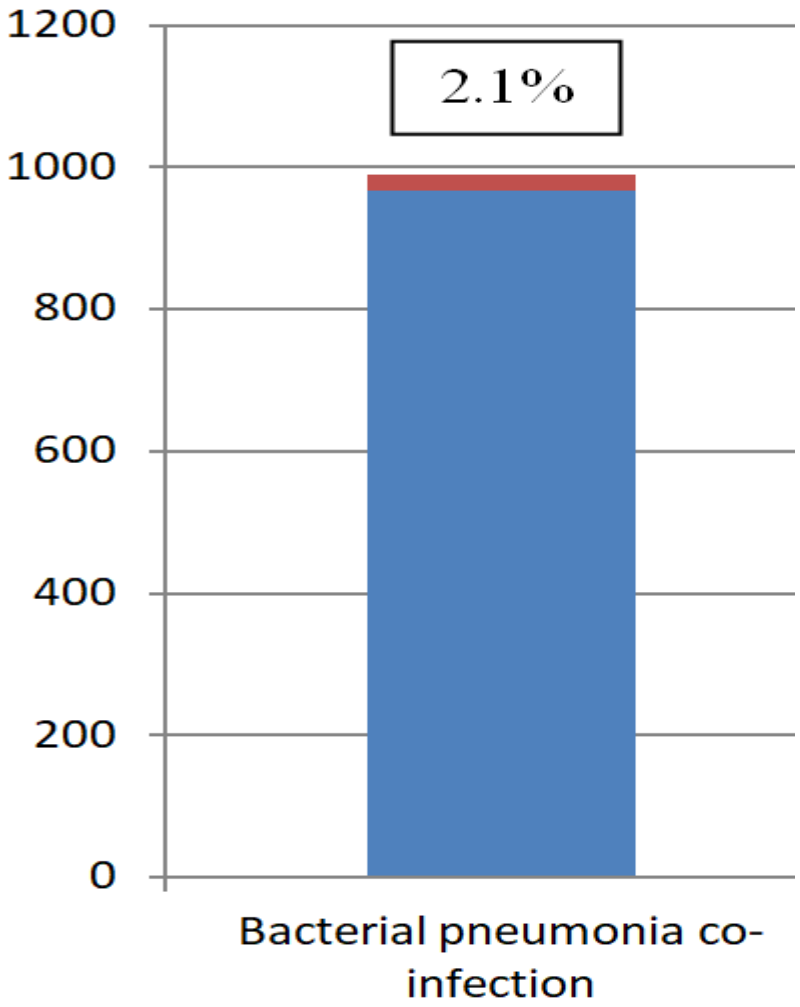
Cultivo esputo

Antigeno neumococo

Procalcitonina

OJO SUPRAINFECCIÓN

Garcia-Vidal C, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clinical Microbiology and Infection 2020; doi: 10.1016



989 consecutive patients

510 (55.6% man)

Age median 61 years old

Median days of LHS: 11 days

Garcia-Vidal C, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clinical Microbiology and Infection 2020; doi: 10.1016

Bacterial co-infection	*n*/*N* (%)
Infection at COVID-19 diagnosis	30/74 (40.5)
Community-acquired pneumonia co-infection	21/30 (70)
Streptococcus pneumoniae	12/21 (57.1)
Staphylococcus aureus	6/21 (28.6)
Haemophilus influenzae	2/21 (9.5)
Moraxella catarrhalis	1/21 (4.8)
Lower respiratory co-infection in patients with bronchiectasis	2/30 (6.6)
Pseudomonas aeruginosa	2/2 (100)
Concurrent urinary tract infection	7/30 (23.3)
Escherichia coli	1/7 (14.2)
Klebsiella pneumoniae	1/7 (14.2)
Enterococcus faecium	1/7 (14.2)
Proteus mirabilis	1/7 (14.2)
Citrobacter koseri	1/7 (14.2)
S. aureus	1/7 (14.2)

Moreno-Garcia E, et al. Bacterial co-infection at hospital admission in COVID19 patients: how to optimise the use of empirical antibiotics. Under review

Microbiological test ordered by the attending physicians were one or more of the following:

- **blood cultures in 803 patients, in whom 8 (1%) were positive**
- **pneumococcal UAT in 780 patients, in whom 79 (10.1%) were positive**
- **legionella UAT in 776 patients, all of them negative**
- **culture of good quality sputum in 145 pts, in whom 17 (11.7%) were positive.**

Moreno-Garcia E, et al. Bacterial co-infection at hospital admission in COVID19 patients: how to optimise the use of empirical antibiotics. Under review

Table 3. Sensitivity, specificity, predictive negative value and predictive positive value of different PCT cut-off for co-infection detection.

	PCT ≥0.20ng/ml	PCT ≥0.50ng/ml	PCT ≥1ng/ml	PCT ≥2 ng/ml
Sensitivity	0.40	0.19	0.14	0.14
Specificity	0.71	0.89	0.95	0.97
Negative predictive value	0.92	0.92	0.92	0.92
Positive predictive value	0.12	0.14	0.21	0.34

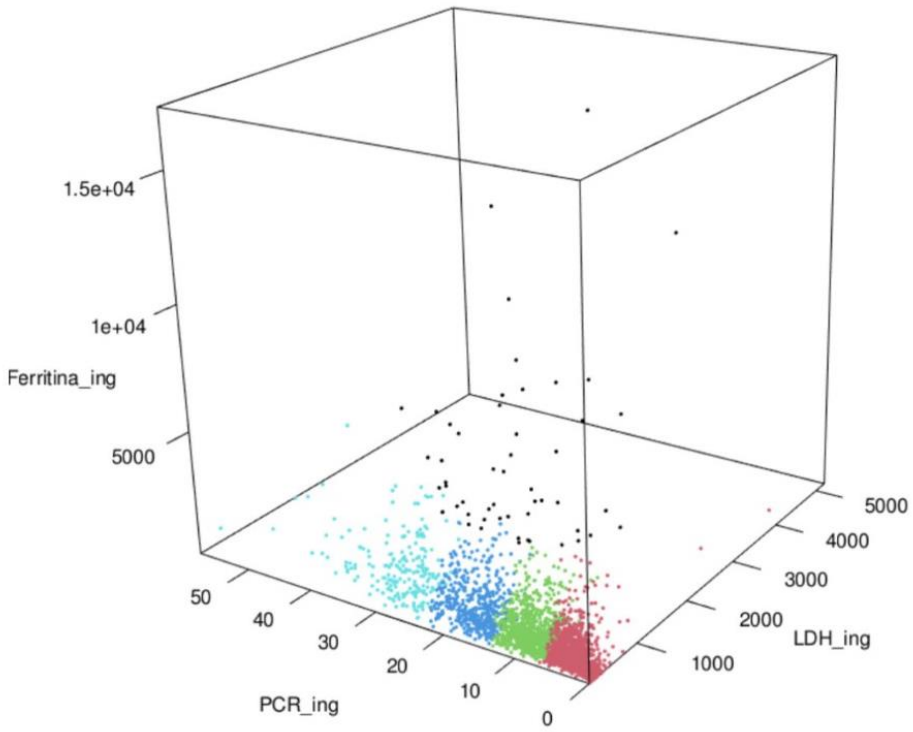
FENOTIPO INFLAMACIÓN

PCR

Ferritina

LDH

Garcia-Vidal, et al. Different inflammatory phenotype in hospitalized patients with COVID19. In process.



PCR-> IL-6

Ferritina -> IL-1

DIFERENTES PATRONES DE INFLAMACIÓN– COVID19

Datos propios

→ PCR mayor de 8 + Ferritina mayor de 1000 IL-6 IL-1

→ PCR mayor de 8 + Ferritina menor de 1000 IL-6

→ PCR menor de 8 + Ferritina mayor de 1000 IL-1

Estrategias antiinflamatorias

Tocilizumab

Anakinra

Baricitinib

Dexametasona

JAK1 is a human tyrosine kinase protein essential for signaling for certain type I and type II cytokines. It interacts with the common gamma chain (γc) of type I cytokine receptors, to elicit signals from the IL-2 receptor family (e.g. IL-2R, IL-7R, IL-9R and IL-15R), the IL-4 receptor family (e.g. IL-4R and IL-13R), the gp130 receptor family (e.g. IL-6R, IL-11R, LIF-R, OSM-R, cardiotrophin-1 receptor (CT-1R), ciliary neurotrophic factor receptor (CNTF-R), neurotrophin-1 receptor (NNT-1R) and Leptin-R). It is also important for transducing a signal by type I (IFN-α/β) and type II (IFN-γ) interferons, and members of the IL-10 family via type II cytokine receptors.[5] Jak1 plays a critical role in initiating responses to multiple major cytokine receptor families. Loss of Jak1 is lethal in neonatal mice, possibly due to difficulties suckling.[6] Expression of JAK1 in cancer cells enables individual cells to contract, potentially allowing them to escape their tumor and metastasize to other parts of the body.[7]

Janus kinase 2 (commonly called **JAK2**) is a non-receptor tyrosine kinase. It is a member of the Janus kinase family and has been implicated in signaling by members of the type II cytokine receptor family (e.g. interferon receptors), the GM-CSF receptor family (IL-3R, IL-5R and GM-CSF-R), the gp130 receptor family (e.g., IL-6R), and the single chain receptors (e.g. Epo-R, Tpo-R, GH-R, PRL-R).[5][6]

Jak 1 y 2

Mucho

FENOTIPO COAGULOPATÍA

D-Dimero

Troponina

Mensajes finales

- **Los pacientes con COVID19 presentan diferentes fenotipos de enfermedad que pueden evolucionar con los días.**
- **Se debe identificar cuando el paciente presenta un fenotipo viral, inflamatorio, de co-infección, trombótico y/o otras situaciones clínicas.**
- **Las diferentes variantes se presentan clínicamente con diferentes características fenotípicas.**
- **Es importante ofrecer un tratamiento personalizado y precoz a nuestros pacientes.**

Gracias por vuestra atención

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