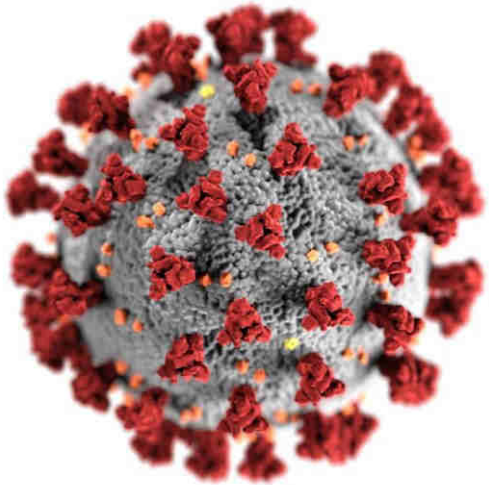
Defectos inmunitarios y COVID-19



Xavier Solanich Moreno
Servei de Medicina Interna
Hospital Universitari de Bellvige

SARS-CoV2 y la COVID-19

En diciembre de 2019 se detectaron los primeros casos de una nueva enfermedad (**COVID-19**) causada por un nuevo coronavirus humano (**SARS-CoV-2**).

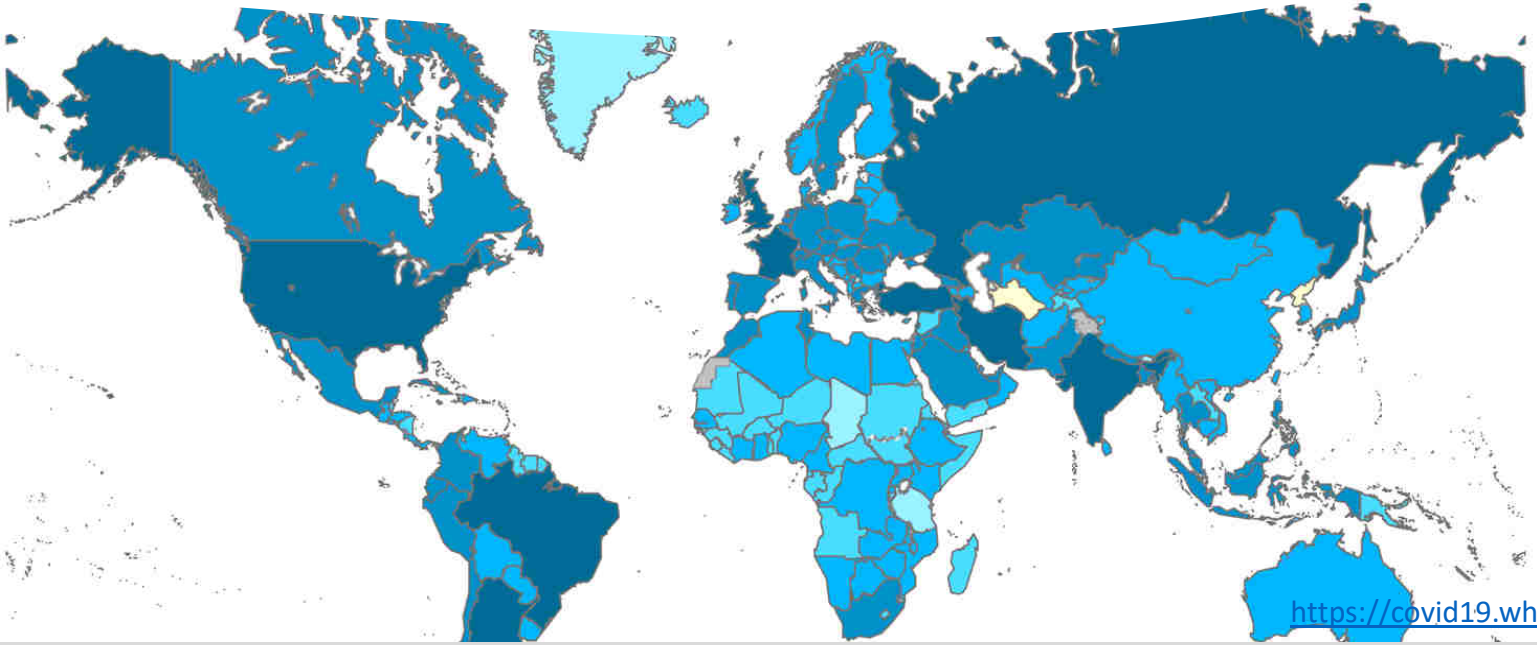
Fue reconocida por primera vez en Wuhan, China, i **se ha extendido por todo el mundo rápidamente**

La OMS declaró la COVID-19 como **pandemia** el 11 de marzo de 2020

15 de Octubre 2021

239,437,517
cumulative cases

4,879,235
cumulative deaths



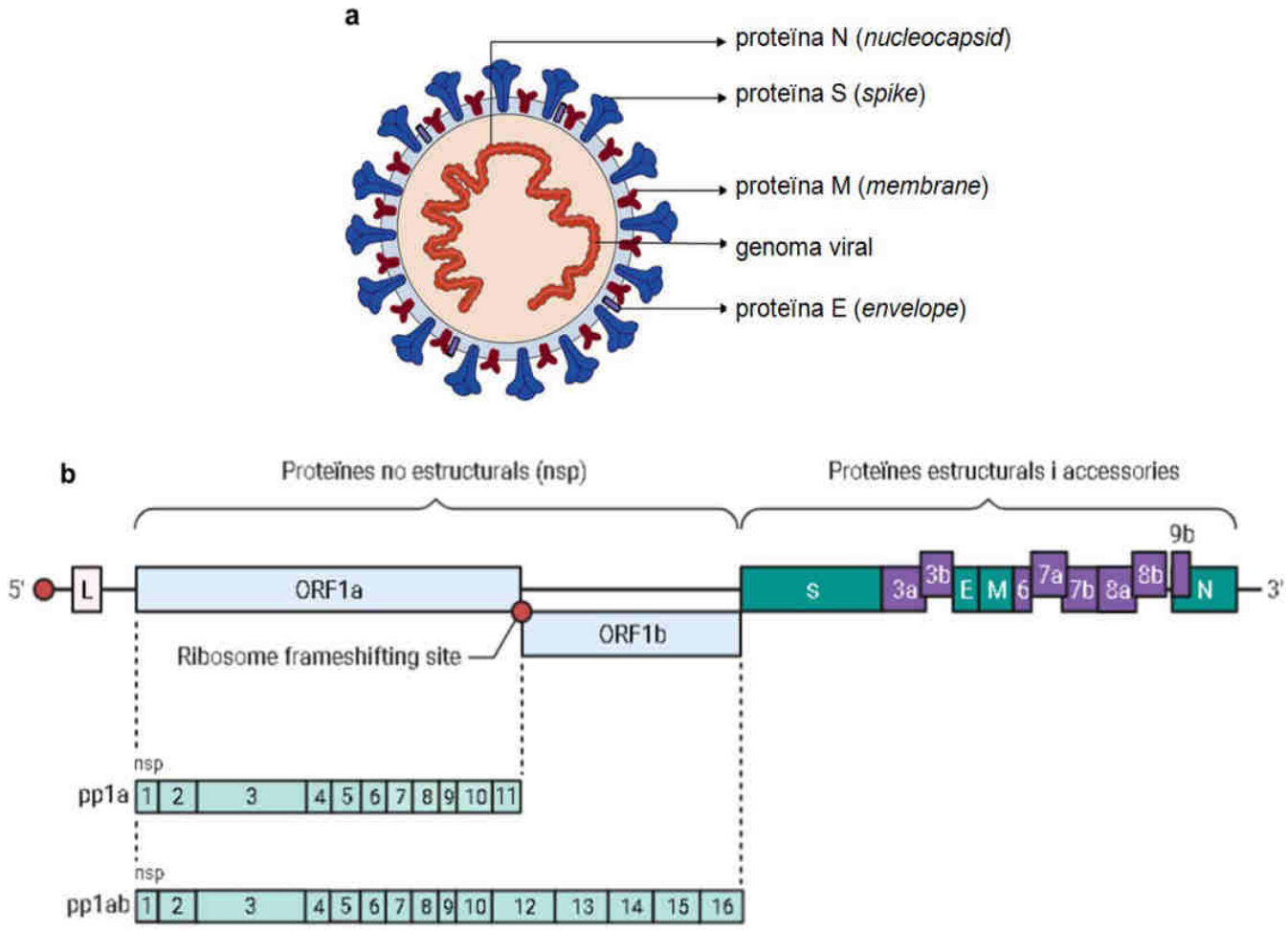
https://covid19.who.int

SARS-CoV2 y la COVID-19

SARS-CoV-2 es un nuevo betacoronavirus altamente patogénico.

Virus de 100-160 nm de diámetro
con bicapa lipídica
con RNA monocatenario (**ssRNA**)
~30kb de longitud

Se traduce en
-Proteinas no estructurales (nsp)
-Proteinas estructurales
-Proteinas accessorias

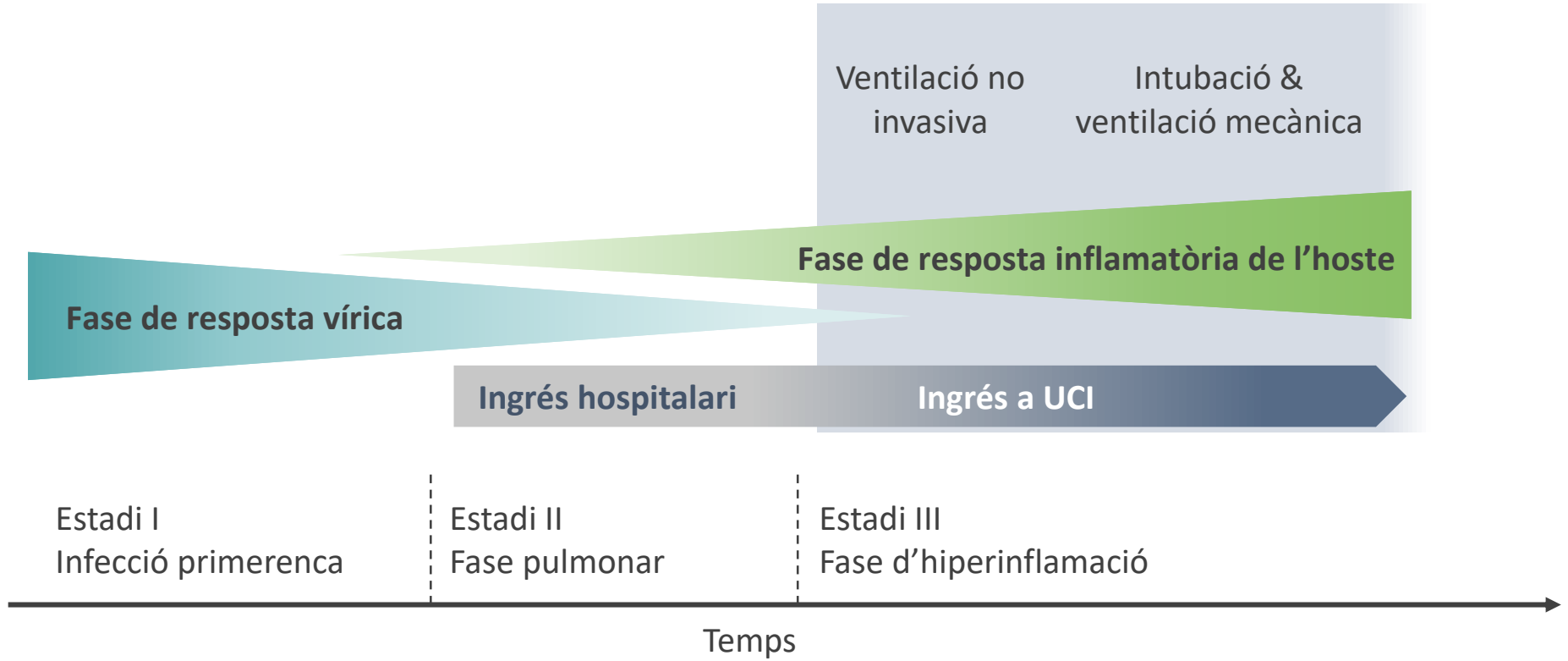


Adaptado de Hartemian et al. J Biol Chem. 2020

SARS-CoV2 y la COVID-19

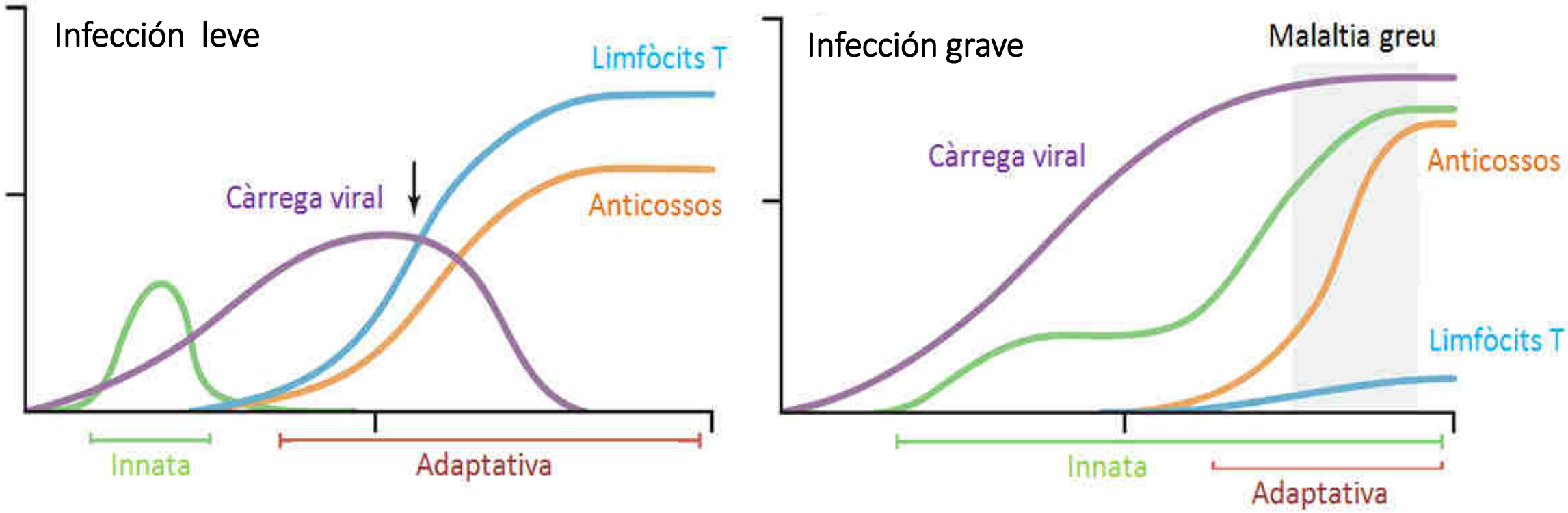
I. Estadios clínicos

La infección por SARS-CoV-2 se puede clasificar en **tres estadios clínicos** de gravedad creciente



Siddiqi HK, et al. *J Heart Lung Transplant* 2020

Respuesta inmune del huésped a SARS-CoV-2



Adaptat de Sette et al, Cell, 2021

¿Qué individuos tienen un mayor riesgo de COVID-19 grave?

1 Demografia y Comorbilidades

Risk Factor	Risk Estimates	Frequency
Male	1.54 / 2.07	0.50 / 0.91
Obesity: BMI $\geq$ 40 / BMI $\geq$ 35	1.52 / 1.22	0.06 / 0.19
Diabetes	1.24 / 1.40	0.25 / 0.38
Hypertension	NS / 1.30	0.43 / 0.62
Chronic pulmonary disease	NS / NS	0.18 / 0.19
Coronary artery disease	NS / NS	0.13 / 0.22

La mayoría de estas condiciones se asocian **riesgos estimados bajos**

Zhang Q et al. Med (N Y). 2020

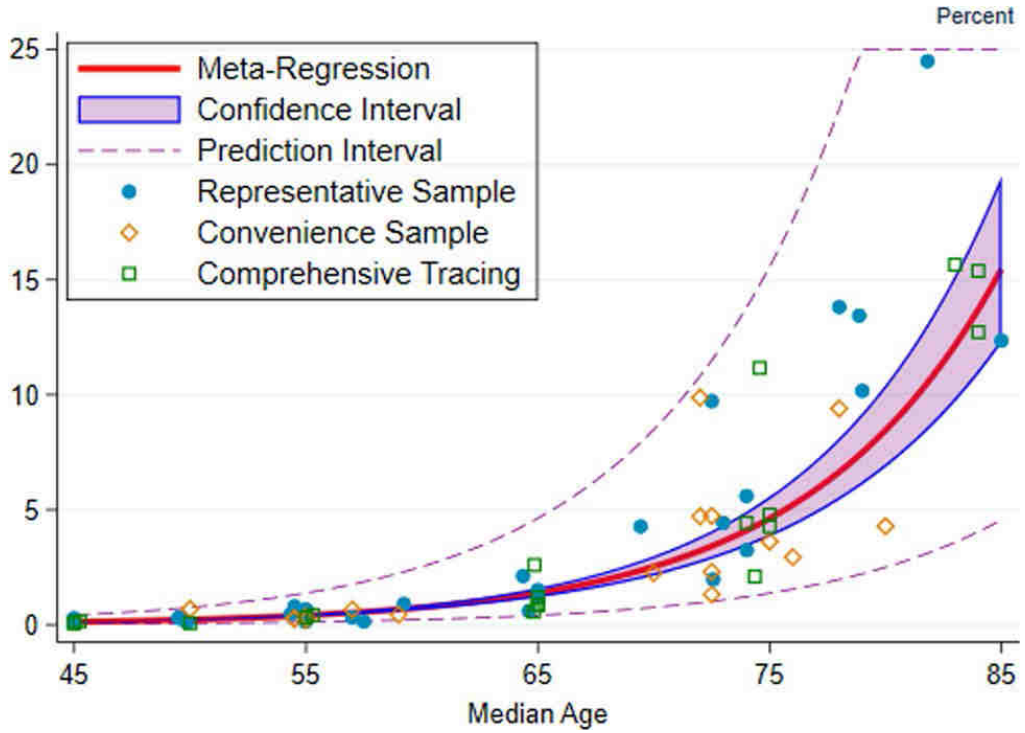
1 Demografia y Comorbilidades

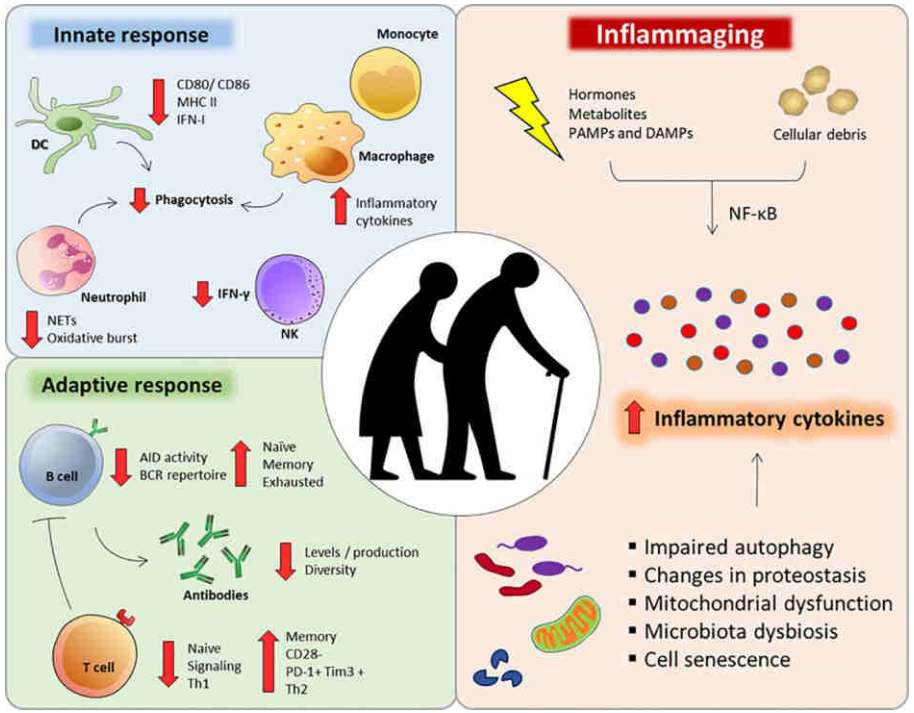
	Deaths: n (%)	N	OR (95% CI)	aOR* (95% CI)	p*
Non-IS	2143 (19.3)	11095	1	1	
IS	661 (31.3)	2111	1.90 (1.72–2.11)	1.60 (1.43–1.79)	<0.001
Patients with specific diseases and conditions					
All cancers (SO and H)	465 (33.3)	1398	2.08 (1.81–2.38)	1.59 (1.38–1.82)	<0.001
SO cancer	343 (31.7)	1081	1.94 (1.66–2.27)	1.39 (1.18–1.63)	<0.001
SO cancer with MT	84 (30.4)	276	1.82 (1.37–2.43)	1.87 (1.33–2.63)	<0.001
SO cancer, no MT	259 (32.2)	805	1.98 (1.63–2.41)	1.27 (1.05–1.54)	0.013
Hematologic cancer	139 (38.8)	358	2.42 (1.92–3.05)	2.31 (1.76–3.03)	<0.001
Leukaemia	66 (39.3)	168	2.70 (1.89–3.84)	2.20 (1.49–3.25)	<0.001
Lymphoma	77 (40.0)	194	2.75 (2.16–3.51)	2.94 (2.19–3.95)	<0.001
Transplant	57 (34.3)	166	2.18 (1.60–2.99)	3.12 (2.23–4.36)	<0.001

La mayoría de estas condiciones se asocian **riesgos estimados bajos**
Elevada variabilidad clínica interindividual dentro de estas categorias demográficas

Suárez-García I, et al. PLoS One. 2021

1 Demografia y Comorbilidades



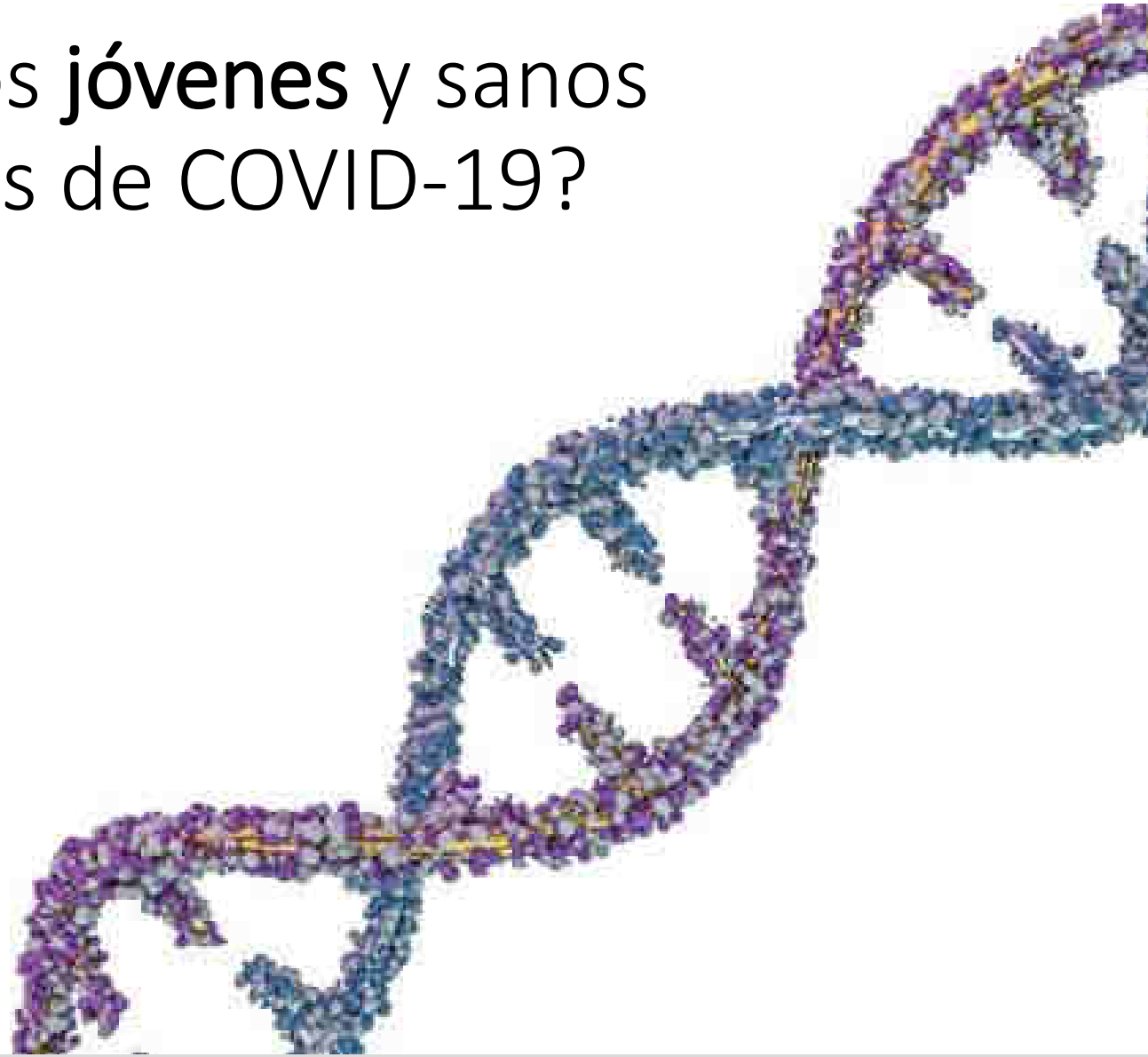


La mayoría de estas condiciones se asocian **riesgos estimados bajos**
Elevada variabilidad clínica interindividual dentro de estas categorias demográficas

Levin AT. Eur J Epidemiol. 2020

Pietrobon AJ. Front Immunol. 2020

¿Porqué algunos individuos **jóvenes** y sanos desarrollan formas graves de COVID-19?



2

Genética del huesped

Variant genètica o haplotip	Risc [OR]	Freqüència [MAF]	Referències
rs769208985—missense variant of *FURIN*	N.A	<0.001	Latini et al.
rs150892504—missense variant of *ERAP2*	N.A	0.002	Hu et al.
rs138763430—missense variant of *BRF2*	N.A	0.002	Hu et al.
rs147149459—missense variant of *ALOXE3*	N.A	0.002	Hu et al.
rs117665206—missense variant of *TMEM181*	N.A	0.006	Hu et al.
rs114363287—missense variant of *TMPRSS2*	N.A	0.006	Latini et al.
rs61756766—missense variant of *TNFRSF13C*	12.3	0.008	Russo et al.
rs7626962—missense variant of *SCN5A*	8.7	0.008	SeyedAlinaghi et al.
rs1805128—missense variant of *KCNE1*	9.0	0.009	SeyedAlinaghi et al.
HLA-DRB*27:07	N.A	0.02	*Novelli* et al.
rs72711165—intronic variant of *TMEM65*	1.2	0.02	COVID-19 H.G.I.
rs115492982—intronic variant of *MRPS21*	2.5	0.02	Dite et al.
rs74956615—3'UTR variant of *TYK2*	1.6	0.03	Pairo-Castineira et al.
rs2034831—intronic variant of *ITGA4*	1.2	0.05	Dite et al.
rs76374459—intronic variant of *LZTFL1*	1.2	0.05	Dite et al.
rs35652899—intronic variant of *LZTFL1*	1.2	0.05	Dite et al.
rs10490770—intronic variant of *LZTFL1*	2.0	0.06	COVID-19 H.G.I.
rs333—CCR5-Δ32	0.7	0.07	Cuesta-Llavona et al.
rs73064425—intronic variant of *LZTFL1*	2.1	0.08	Pairo-Castineira et al. Ellinghaus et al.
rs11385942—intronic variant of *LZTFL1*	1.8	0.07	Ellinghaus et al.
rs1886814—intronic variant of *FOXP4*	1.3	0.07	COVID-19 H.G.I.
rs76488148—intronic variant of *GYG1*	1.3	0.07	Dite et al.
rs2271616—5'UTR variant of *SLC6A20*	1.1	0.08	COVID-19
HLA-DQB1*06:02	N.A	0.0	
rs143334143—intronic variant of *CCHCR1*			
HLA-DRB1*15:01			
rs12252:G allele of *IFITM3*			Alghamdi et al.
rs4801778—intronic variant of *PLEKHA4*	1.0	0.16	COVID-19 H.G.I.
rs6598045—5'UTR variant of *IFITM3*	N.A	0.19	Kim et al.
rs429358—missense variant of *APOE*	2.3–2.4	0.20	Kuo et al.
rs12610495—intronic variant of *DPP9*	N.A	0.25	Moon et al.
rs12329760—intronic variant of *TMPRSS2/MX1*	0.9	0.25	Andolfo et al.
rs2298661—missense variant of *TMPRSS2/MX1*	0.9	0.25	Andolfo et al.
rs3787946—intronic variant of *TMPRSS2/MX1*	0.9	0.28	Andolfo et al.
rs9983330—intronic variant of *TMPRSS2/MX1*	0.9	0.28	Andolfo et al.
rs9380142—3'UTR variant of *HLA-G*	13	0.29	Pairo-Castineira et al.
rs2109069—intronic variant of *DPP9*	1.4	0.33	Pairo-Castineira et al., COVID-19 H.G.I.
rs9985159—intronic variant of *TMPRSS2/MX1*	0.9	0.33	Andolfo et al.
rs75603675—missense variant of *TMPRSS2*	N.A	0.36	Latini et al.
rs1405655—intronic variant of *NR1H2*	1.1	0.37	COVID-19 H.G.I.
rs12329760—missense variant of *TMPRSS2*	0.9	0.39	Hou et al.
rs657152—intronic variant of *ABO*	1.3	0.41	Ellinghaus et al.
rs677800—intronic variant of *ABO*	N.A	0.55	Moon et al.
rs6020298—intronic variant of *TMEM189-UBE2V1*	1.2	0.58	Wang et al.
rs10735079—intronic variant of *OAS1/3*	1.3	0.64	Pairo-Castineira et al.
rs8065800—intronic variant of *MAPT*	1.7	0.65	COVID-19 H.G.I.
rs10774671—intronic, splicing variant of *OAS1*	1.1	0.67	COVID-19 H.G.I.
rs13050728—intronic variant of *IFNAR2*	0.9	0.69	COVID-19 H.G.I.
rs2236757—intronic variant of *IFNAR2*	1.3	0.71	Pairo-Castineira et al.
rs3131294—intronic variant of *NOTCH4*	1.5	0.90	Pairo-Castineira et al.
HLA-A*11	N.A	N.A	Fricke-Galindo et al.
HLA-A*11:01:01:01	2.3	N.A	Khor et al.
HLA-A*25:01	N.A	N.A	Fricke-Galindo et al.
HLA-B*46:01	2.1	N.A	Lin et al.
HLA-B*51:01			
HLA-B*54:01			
		N.A	Fricke-Galindo et al.
	N.A	N.A	Fricke-Galindo et al.
HLA-C*12:02:02:01-HLA*52:01:02:02	2.3	N.A	Khor et al.
HLA-C*14:02	N.A	N.A	Fricke-Galindo et al.
HLA-C*17	N.A	N.A	Bonaccorsi et al.
HLA-DQB1*04	N.A	N.A	Fricke-Galindo et al.
HLA-DQB1*08	N.A	N.A	Fricke-Galindo et al.
HLA-E*0101/0103	2.1– 2.7	N.A	Vietzen et al.
*KLRC2*del	2.6–7.1	N.A	Vietzen et al.
ACE1 I/D genotype	2.5	N.A	Verma et al.
C9orf72 with HREs > 10 units	2.4	N.A	Zanella et al.
rs140312271—missense variant of *ACE2*	N.A	N.A	Novelli et al.

Riesgos estimados bajos para la mayoría de variantes

Colona VL, et al. Hum Genomics. 2021

2 Genética del huesped

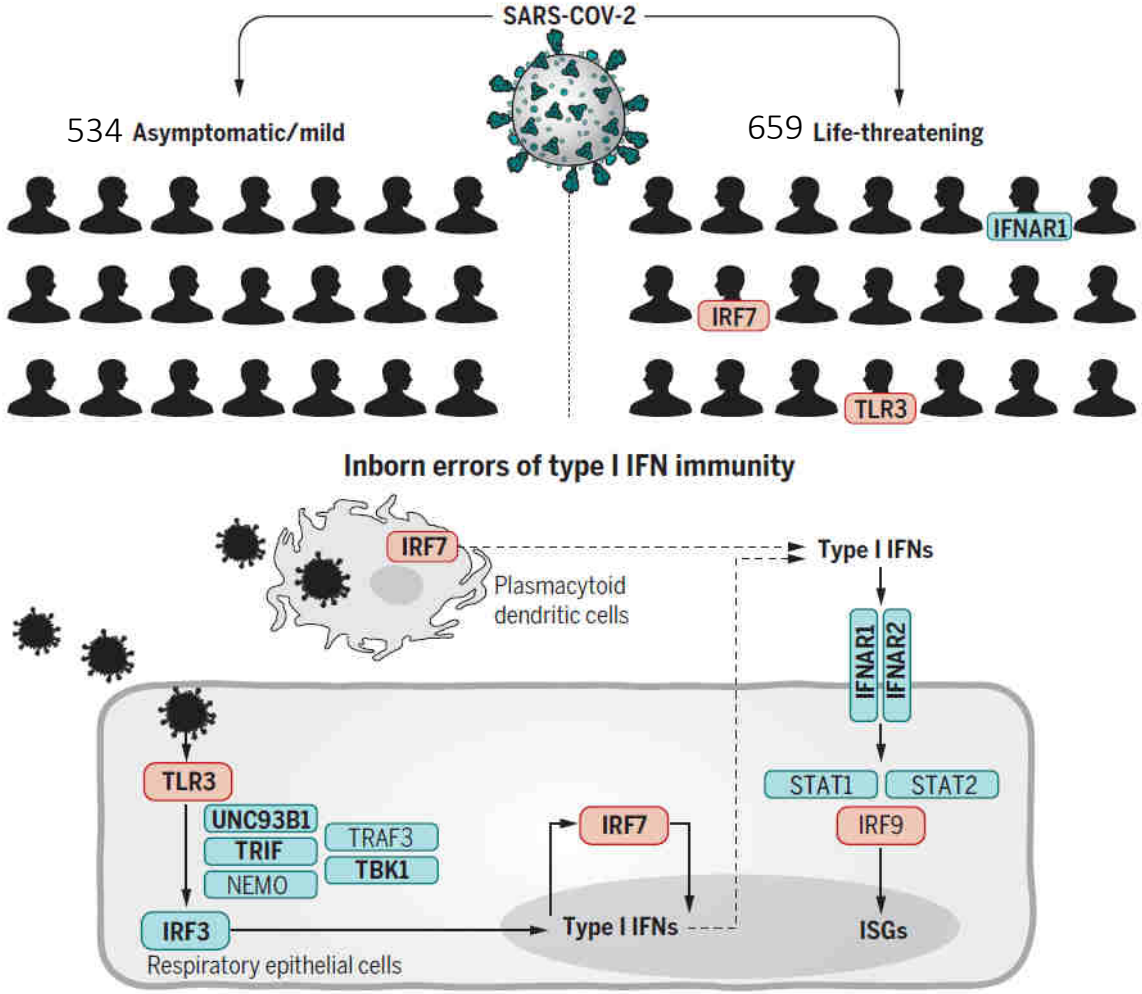
Via de IFN-I dependiente de TLR3 y IRF7

COVID HUMAN GENETIC EFFORT

WGS (13 locis)

3.5 %

Autosómica dominante (RR 9)
TLR3, UNC93B1, TICAM1, TBK1, IRF3, IRF7, IFNAR1, IFNAR2
Autosómica recesiva (RR > 50)
IRF7, IFNAR1



Zhang Q. Science. 2020

2 Genética del huesped

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The COVID-19 Host Genetics Initiative

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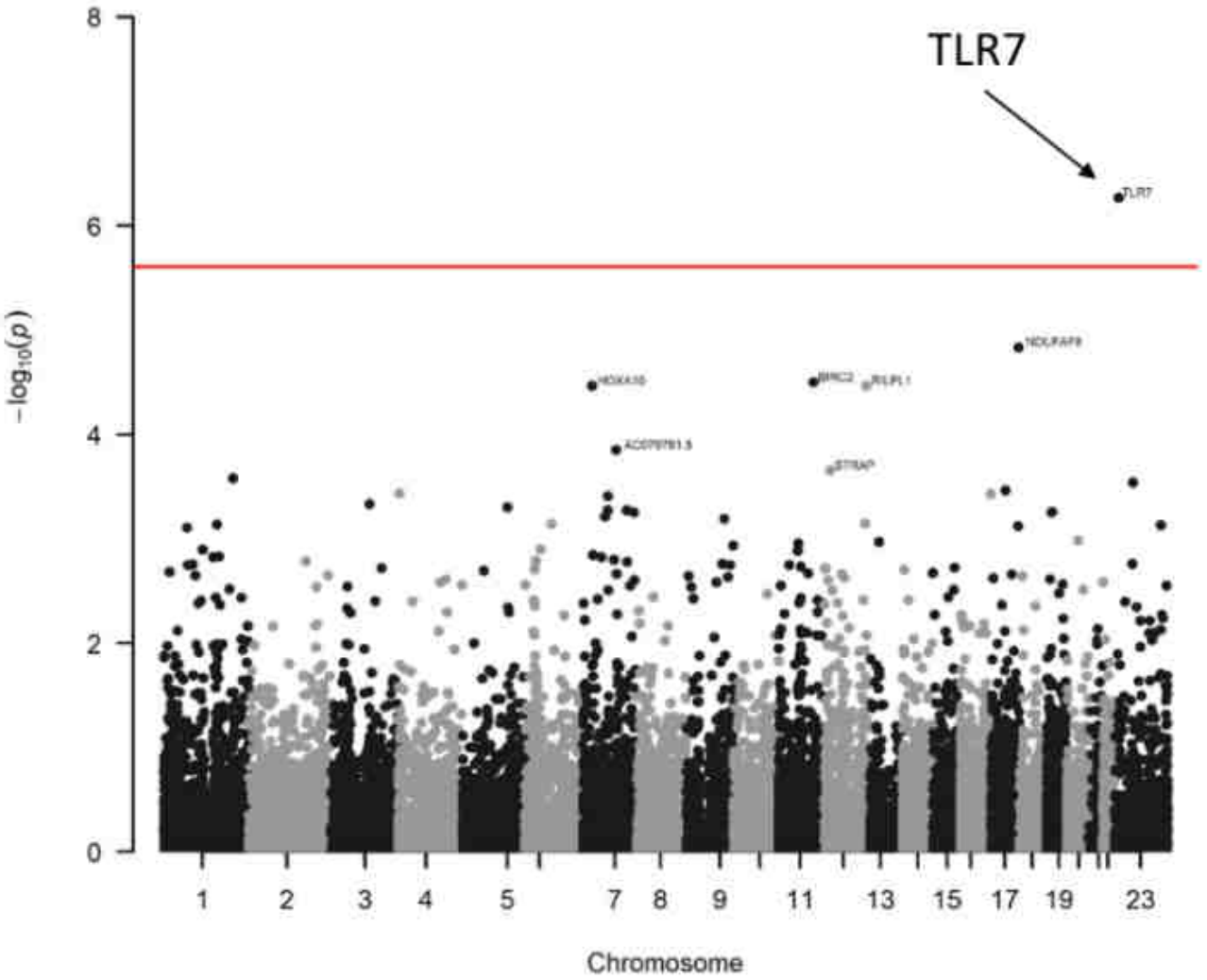


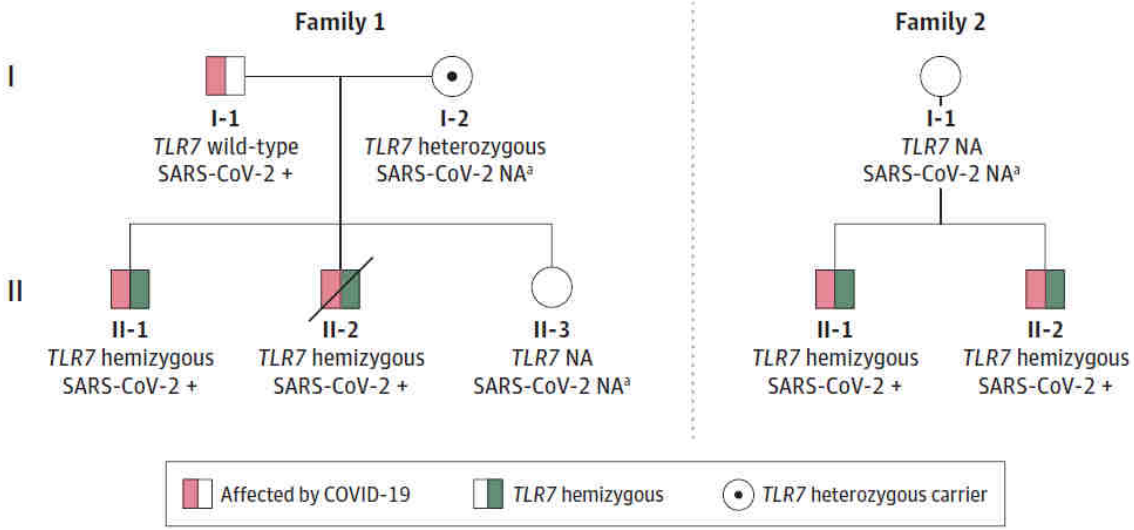
2 Genética del huesped

TLR7

Radboud University Medical Center

Receptor de virus **ssRNA**
1.036 aa (LRR, transmembrana, TIR)
Se expresa en **CDp**, monocitos, Mc, LB

Gen situado en **cromosoma X**

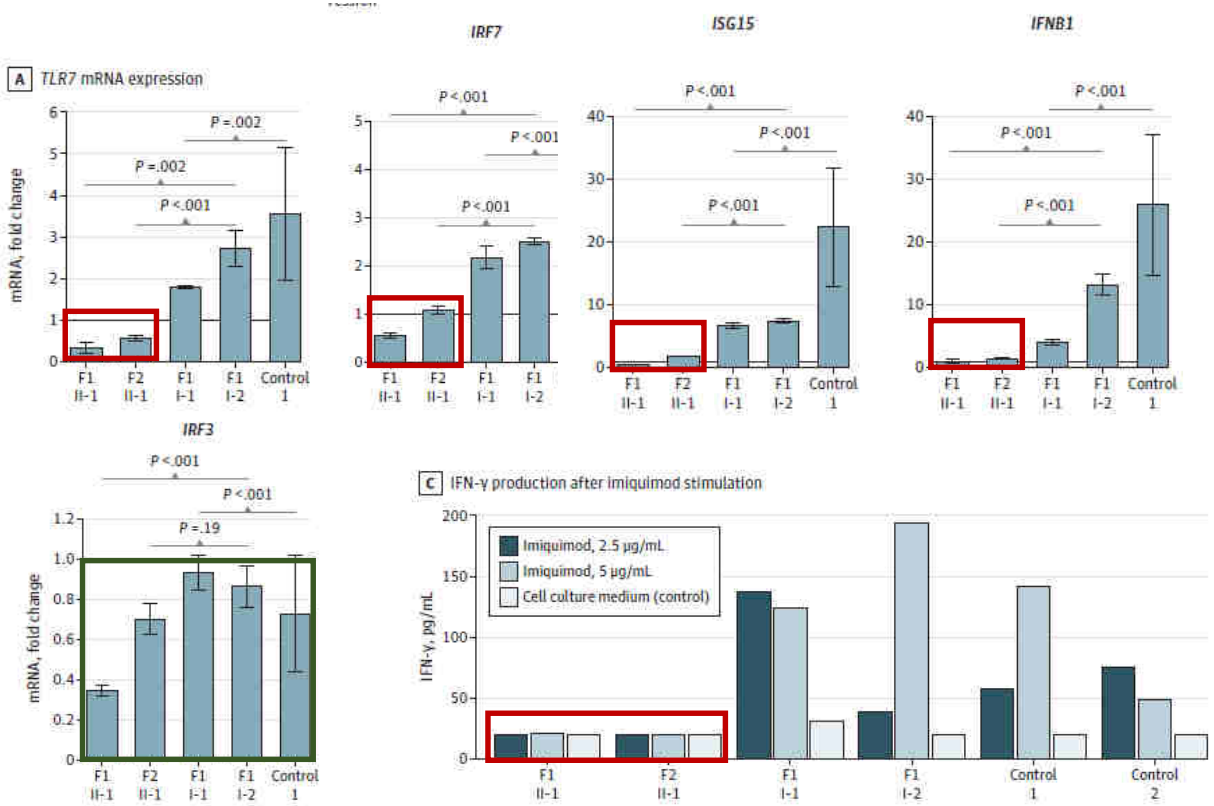


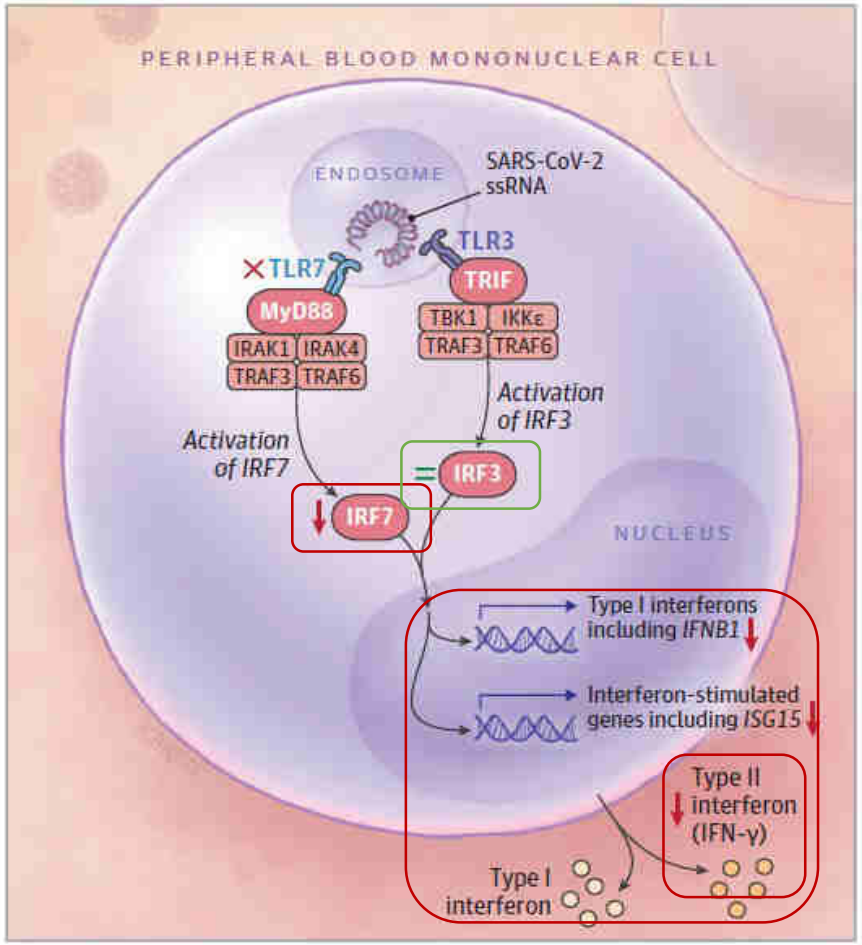
delección de 4 nucleótidos (c.2129_2132del; p.(Gln710Argfs*18))
variante *missense* (c.2383G>T; p.(Val795Phe))

van der Made CI, et al. JAMA 2020

2 Genética del huesped

TLR7





van der Made CI, et al. JAMA 2020

2 Genética del huesped

Estudio	Pacientes (n)	Tipo de paciente	% de portadores de variantes raras en TLR7 en < 60 años
GEN-COVID Multicenter Study	239	< 60 años - 135 C-19 graves - 104 C-19 leves o asintomáticos	**2,1%**
COVIDHGE	1533	0.5 y 102 años -332 C-19 leves o asintomáticos -1202 C-19 críticos	**1.8%**
ICO – HUB – IDIBELL Radboud Univ Medical Center Erasmus Medical Center	14	18 a 50 anys; Sin comorbilidades asociadas a C-19 grave Dispositivos alto flujo o ventilación mecánica.	**14.3%**

Fallerini C, et al. Elife 2021

Variantes de *TRL7* relacionadas con una COVID-19 grave publicadas en la literatura

Asano	c.223A>C	p.(Asn75His)	missense	LOF	Middle East
Asano	c.471delC	p.(Asn158Thrfs*11)	deletion	LOF	European NF
Fallerini	c.655G>A	p.(Val219Ile)	missense	Hypomorphic	European NF
Asano	c.730G>T	p.(Asp244Tyr)	missense	LOF	Middle East
Asano	c.928T>C	p.(Phe310Leu)	missense	LOF	Middle east
Asano	c.1514T>C	p.(Ile505Thr)	missense	LOF	European NF
Asano	c.1970T>C	p.(Ile657Thr)	missense	Hypomorphic	European NF
Asano	c.2050A>T	p.(Lys684*)	nonsense	LOF	European NF
Asano	c.2143C>T	p.(Pro715Ser)	missense	Hypomorphic	Latino
Van der Made	c.2383G>T	p.(Val795Phe)	missense	LOF	African
Fallerini	c.2759G>A	p.(Arg920Lys)	missense	-	European NF
Asano	c.2963T>C	p.(Leu988Ser)	missense	LOF	Middle East

2 Genética del huesped

Antes de la pandemia por SARS-CoV-2, **no se habían descrito alteraciones en TLR7 asociadas a una mayor predisposición a padecer infecciones** en humanos.

La deficiencia completa de TLR7 es extremadamente rara porque los TLR endosómicos (TLR3, TLR7, TLR8 y TLR9) tienen un **papel biológico esencial y no redundante en la supervivencia** de los individuos

Per lo tanto, es **poco probable que variantes raras de pérdida de función en *TLR7*** expliquen el desarrollo de una COVID-19 grave en una **proporción grande de la población**.

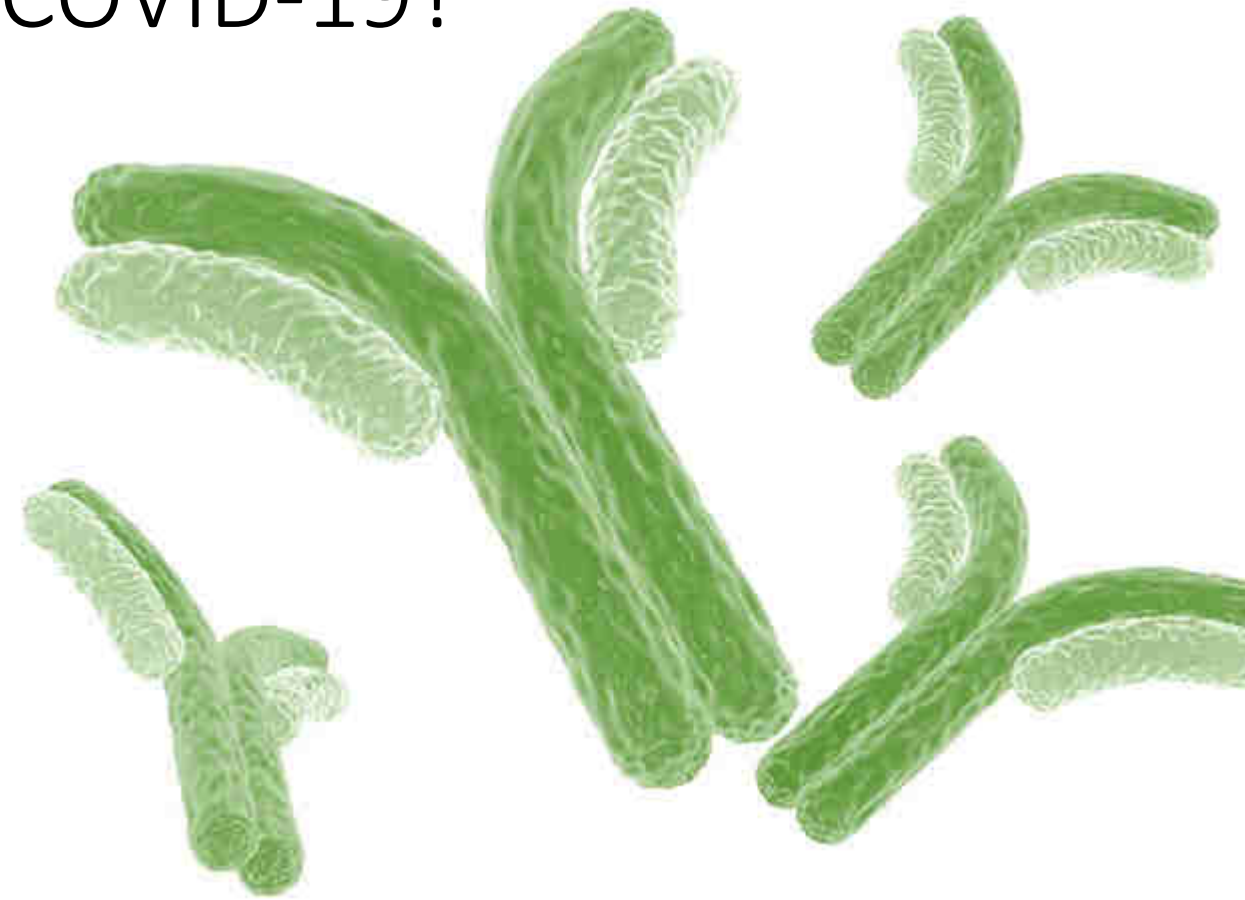
Mayor rendimiento

Biomarcadores genómicos

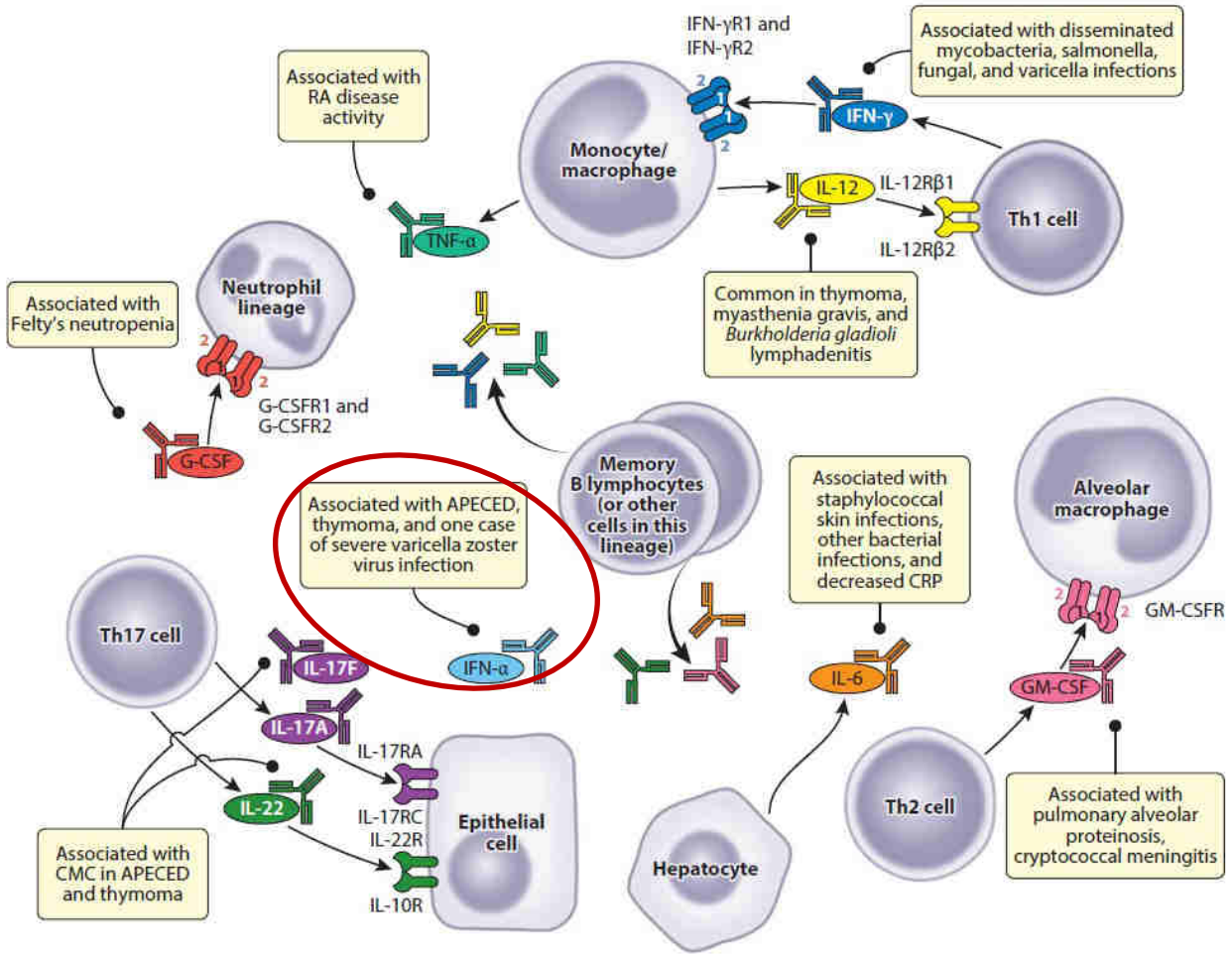
Medidas preventivas y terapéuticas específicas

Menor rendimiento

¿Porqué algunos **ancianos** desarrollan formas mas graves de COVID-19?



3 Fenocopias de las IDP



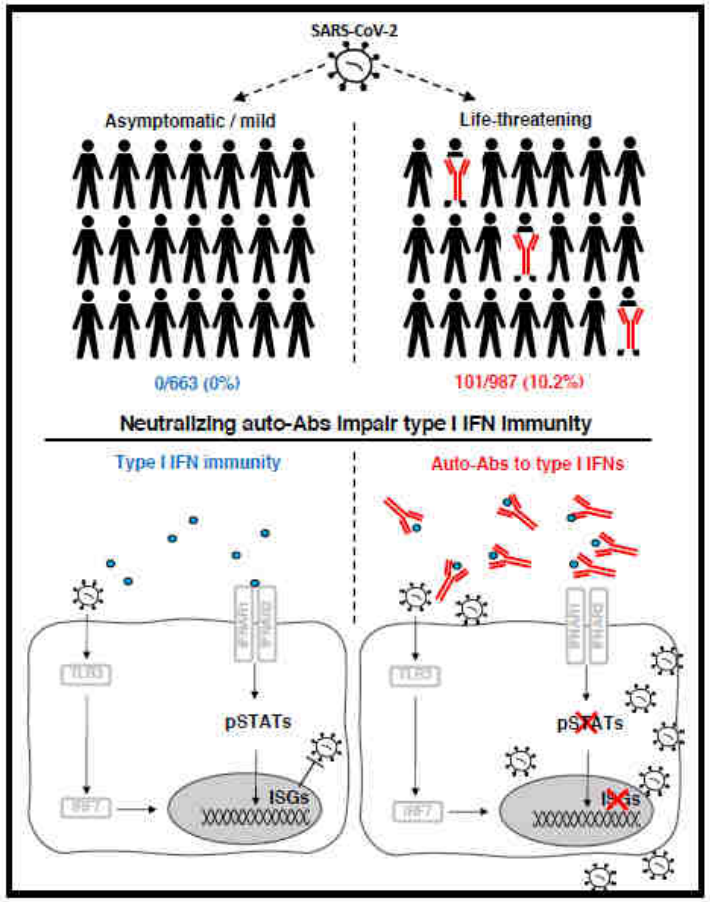
Browne SK. Annu Rev Immunol. 2014

3 Autoanticuerpos neutralizantes IFN-I

10 ng / mL
(altas)

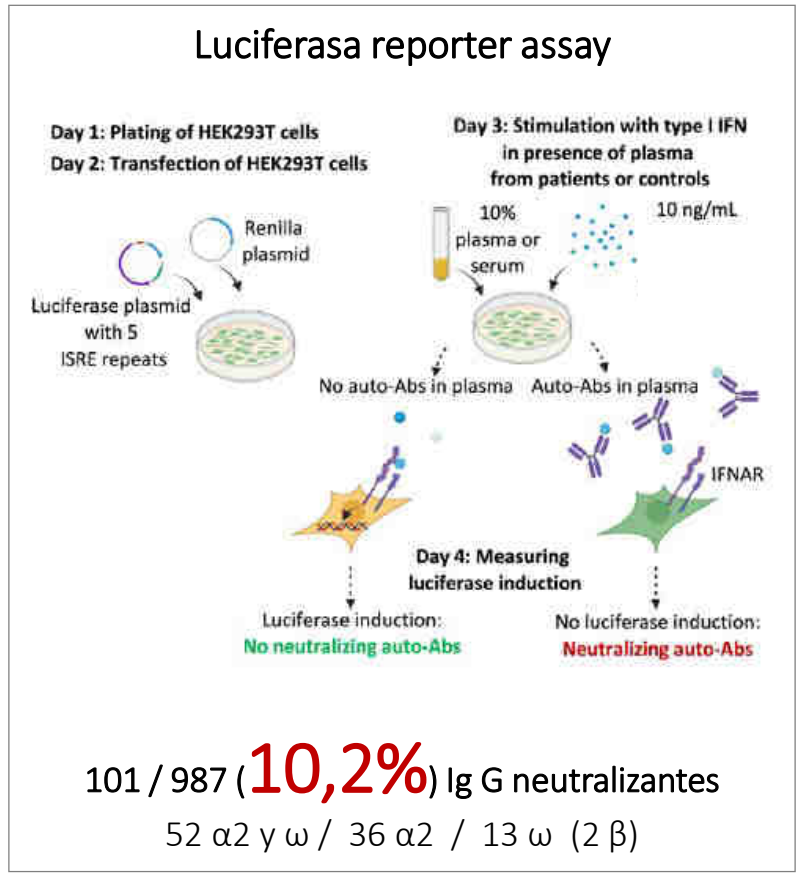
Determina gravedad
Preexistentes

↑ edad
↑ hombres
También:
APECED, IPEX, RAG1/RAG2 hipomorf, Sd Good, *Incontinentia pigmenti,* LES, Miastènia Gravis, Ttm previo IFN-α o IFN-β.



4 (0.33%) positivos de 1227 **controles sanos** (preCOVID-19)

135 / 987 (13,6%) positivos por ELISA o Luminex
49 α2 y ω / 45 α2 / 41 ω (19 β)

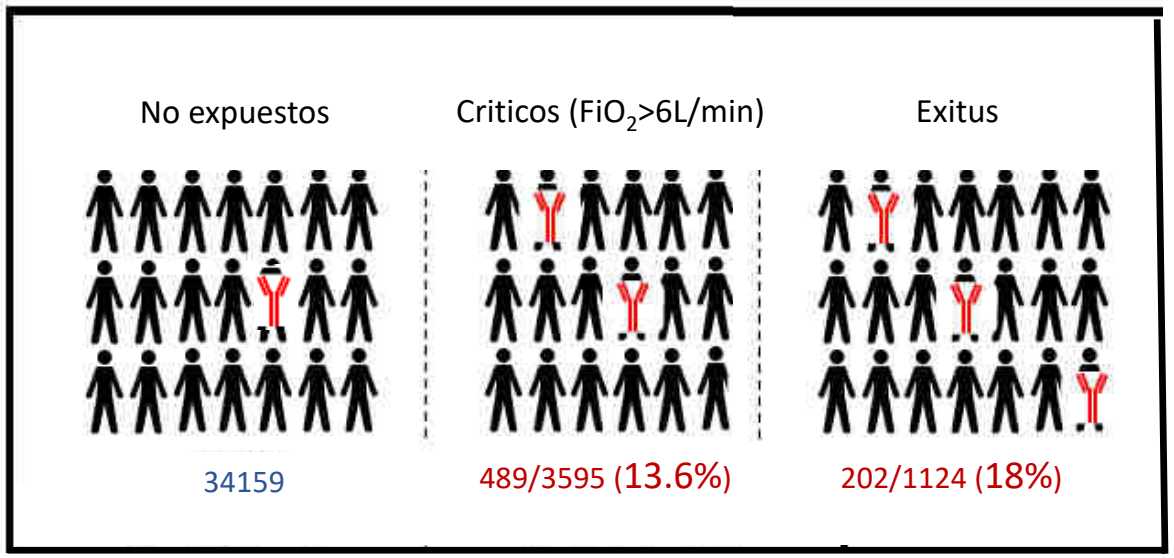


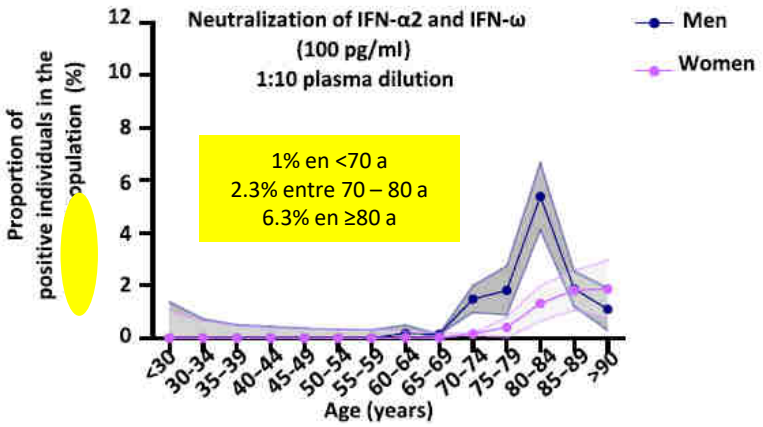
101 / 987 (**10,2%**) Ig G neutralizantes
52 α2 y ω / 36 α2 / 13 ω (2 β)

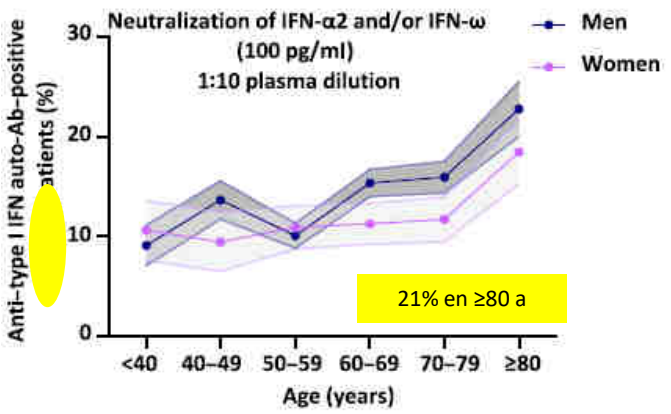
Bastard P, et al. Science. 2020

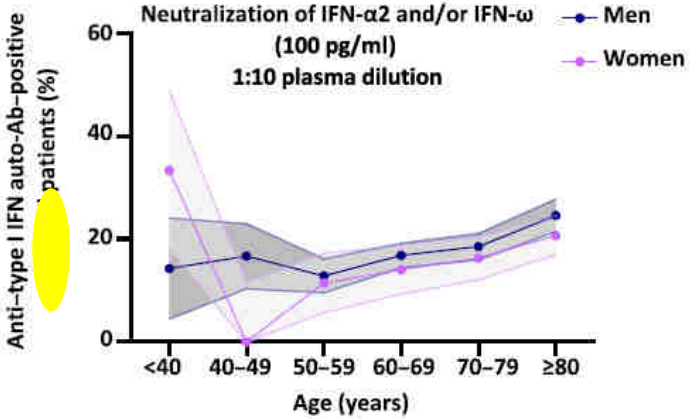
3 Autoanticuerpos neutralizantes IFN-I

100 pg / mL (fisiológico)



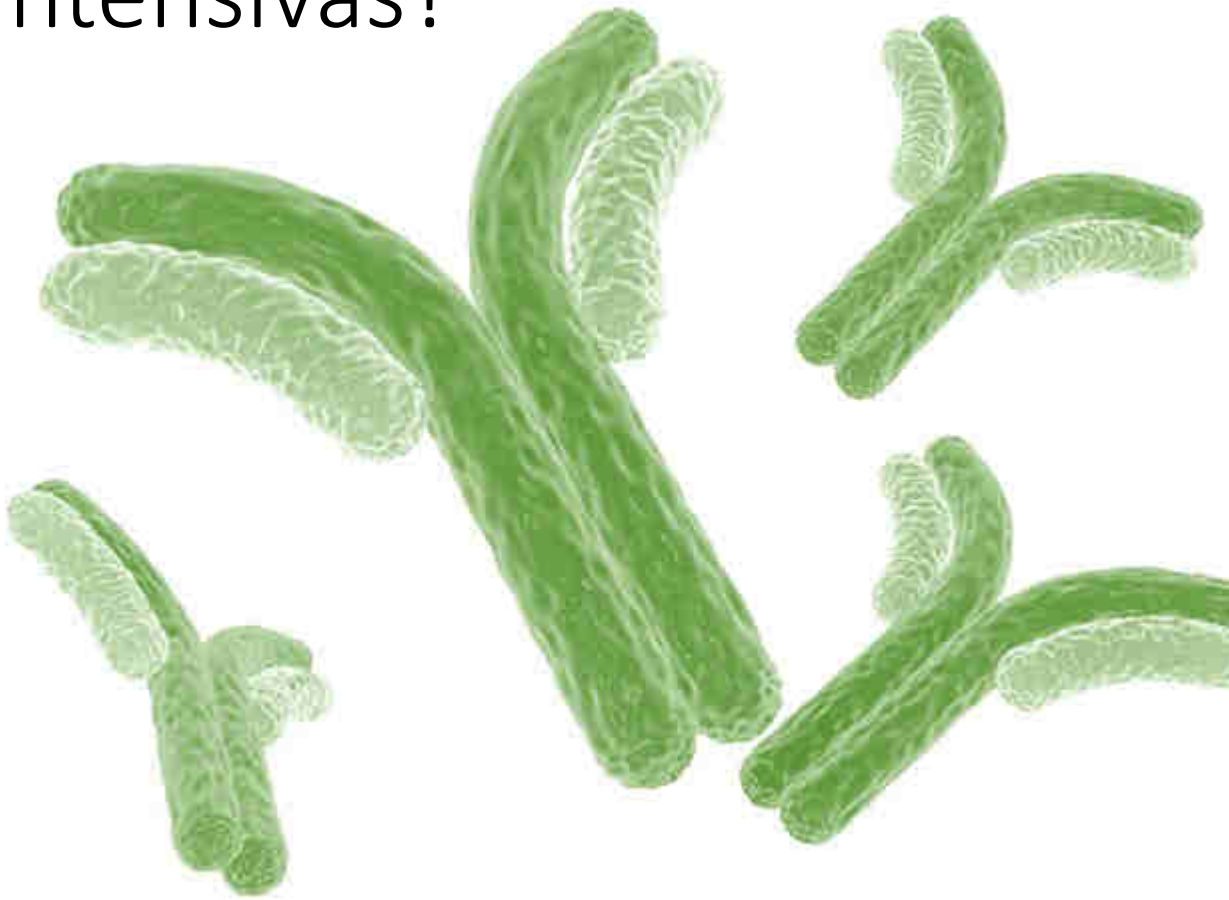






Bastard P, et al. Science Immunol. 2021

¿Es útil determinar estos autoanticuerpos en los pacientes de curas intensivas?



3 Autoanticuerpos neutralizantes IFN-I

Retrospectivo
03/2020 a 03/2021

- Adultos (**≥ 18 años**);
- Infección por **SARS-CoV-2 confirmada por RT-PCR**;
- Ingreso en **Unidad de Curas Intensivas** por neumonía por C-19
- **Disponibilidad de muestra sanguínea del ingreso**

Hospital Universitari de Bellvitge

Variables demográficas, comorbilides, análisis ingreso UCI, evolutivas, tratamiento

Autoanticuerpos frente IFN-α2 y IFN-ω por **ELISA** segun procedimient de St. Giles

IMAGINE institute / INSERM

Capacidad para neutralizar 10ng/mL d'IFN-α2 y IFN-ω mediante ensayo **Luciferasa** reportada

3 Autoanticuerpos neutralizantes IFN-I

Del 10 de Marzo de 2020 al 6 de Marzo de 2021

3216 pacientes con C-19

390 (12.1%) en UCI

275 (70.5%) tenian muestra

49 (el 17,8%) de los 275 pacientes fueron positivos para autoAbs contra IFN-α2 y/o IFN-ω (ELISA)
[19 (6,9%) solo contra IFN-α2, 8(2,9%) solo contra IFN-ω , y 22 (8,0%) contra todos dos]

26 (53,1%) de estos 49 pacientes mostraron actividad de bloqueo de 10 ng/mL de IFN α2 y/o –ω
[21 (80,8%) contra IFN-α2 y -ω, solo contra IFN-α2 en 4 (15,4%) y solo contra IFN-ω en 1 (3,8%)]

9.5%

3 Autoanticuerpos neutralizantes IFN-I

Variable	All results for auto-Abs to type I IFNs ($n=275$)	Neutralizing positive results for some or both auto-Abs to type I IFNs ($n=26$)	Neutralizing negative results for both auto-Abs to type I IFNs ($n=249$)	p-value	OR (95% CI)
		13 (50.0)	112 (45.0)	0.820	n.a
		1 (3.8)	22 (8.8)		
		12 (46.2)	115 (46.2)		
Demographics					
Age; median (IQC)	64 (55–71)	63 (57–73)	64 (55–71)	0.712	n.a
Comorbidities					
Cancer; *n* (%)	31 (11.3)	2 (7.7)	29 (11.6)	0.750	0.632 (0.142–2.815)
Cardiac disease; *n* (%)	44 (16.0)	4 (15.4)	40 (16.1)	1.000	0.950 (0.311–2.905)
Chronic kidney disease; *n* (%)	38 (13.8)	3 (11.5)	35 (14.1)	1.000	0.798 (0.227–2.798)
Chronic liver disease; *n* (%)	24 (8.7)	3 (11.5)	21 (8.4)	0.484	1.416 (0.392–5.111)
Chronic obstructive pulmonary disease; *n* (%)	45 (16.4)	3 (11.5)	42 (16.9)	0.590	0.643 (0.185–2.239)
Diabetes; *n* (%)	78 (28.4)	7 (26.9)	71 (28.5)	0.864	0.924 (0.372–2.293)
Dyslipidemia; *n* (%)	135 (49.1)	13 (50.0)	122 (49.0)	0.922	1.041 (0.464–2.335)
Hypertension; *n* (%)	146 (53.1)	13 (50.0)	133 (53.4)	0.740	0.872 (0.389–1.957)
Obesity; *n* (%)	137 (49.8)	11 (42.3)	126 (50.6)	0.421	0.716 (0.316–1.620)
Smoking; *n* (%)	20 (7.3)	0 (0.0)	20 (8.0)	0.233	n.a

No diferencias demográficas a excepción de mas hombres

3 Autoanticuerpos neutralizantes IFN-I

Variable	All results for auto-Abs to type I IFNs ($n=275$)	Neutralizing positive results for some or both auto-Abs to type I IFNs ($n=26$)	Neutralizing negative results for both auto-Abs to type I IFNs ($n=249$)	p-value	OR (95% CI)
Symptom onset and admission					
Number of days from the appearance of clinical symptoms to admission to the hospital; median (IQR)	8 (6–11)	7 (6–8)	8 (6–11)	**0.009**	n.a
Number of days from the hospital admission to the ICU; median (IQR)	2 (0–6)	3.5 (1–7)	2 (0–6)	0.352	n.a
Biological quantities at the first day in ICU					
median (IQR)					
median (IQR)					
LYM, $\times 10^9$ cells/L; median (IQR)	0.64 (0.38–0.96)	0.51 (0.41–0.72)	0.66 (0.37–0.98)	0.067	n.a
median (IQR)					
apH, 1; median (IQR)	7.35 (7.29–7.43)	7.35 (7.30–7.39)	7.35 (7.29–7.43)	0.800	n.a
$paCO_2$, mmHg; median (IQR)	46 (40–56.5)	47 (40–53)	46 (40–57)	0.856	n.a
paO_2, mmHg; median (IQR)	96.5 (76–125)	90 (73–127)	97 (76–124.5)	0.574	n.a
$aSatO_2$, %; median (IQR)	97.1 (94.5–98.7)	96.7 (94.3–98.4)	97.2 (94.5–98.7)	0.420	n.a
ALB, g/L; median (IQR)	31.6 (27.4–35.0)	32.0 (26.4–35.0)	31.5 (27.7–35.0)	0.741	n.a
LDH, U/L; median (IQR)	471.5 (367.5–610.8)	444.5 (354–538)	474.5 (370–613)	0.395	n.a
ALT, U/L; median (IQR)	34 (23–56.3)	38.5 (28–61)	34 (23–56)	0.421	n.a
AST, U/L; median (IQR)	45 (31–64.8)	41 (27–52)	45 (32–68)	0.165	n.a

↑ LEU, NEU, PLT

3 Autoanticuerpos neutralizantes IFN-I

Variable	All results for auto-Abs to type I IFNs ($n=275$)	Neutralizing positive results for some or both auto-Abs to type I IFNs ($n=26$)	Neutralizing negative results for both auto-Abs to type I IFNs ($n=249$)	p-value	OR (95% CI)
BIL, µmol/L; median (IQR)	9.2 (6.5–13.9)	10.4 (6.0–15.0)	9.0 (6.7–13.7)	0.819	n.a
CREA, µmol/L; median (IQR)	81 (61–114)	80 (61–117)	81 (60–111)	0.767	n.a
UREA, mmo/L; median (IQR)	7.9 (5.2–11.5)	8.1 (5.7–11.7)	7.9 (5.2–11.4)	0.588	n.a
TROP-T, ng/L; median (IQR)	14.7 (9.4–28.2)	11.3 (8.4–14.7)	15.8 (9.8–30.9)	0.121	n.a
DD, µg/L; median (IQR)	879 (454–2862)	963 (482–3507)	878 (452–2811)	0.671	n.a
PT, 1; median (IQR)	1.16 (1.08–1.28)	1.23 (1.11–1.25)	1.15 (1.08–1.29)	0.230	n.a
PROCAL, µg/L; median (IQR)	0.26 (0.13–0.68)	0.29 (0.14–0.51)	0.26 (0.13–0.73)	0.875	n.a
FERRI, mg/L; median (IQR)	1495 (874–2325)	1240 (919–2389)	1498 (862–2291)	0.664	n.a
IL6, ng/L; median (IQR)	91.3 (19.5–455.2)	40.4 (30.2–207.9)	95.3 (19.7–474)	0.778	n.a

3 Autoanticuerpos neutralizantes IFN-I

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Specific ICU treatment and mechanical ventilation data					
Patients with CRRT; n (%)	28 (10.2)	3 (11.5)	25 (10.0)	0.736	1.169 (0.328–4.170)
Patients with ECMO; n (%)	25 (9.1)	2 (7.7)	23 (9.2)	1.000	0.819 (0.182–3.688)
paO_2/FiO_2, mmHg/%; median (IQR)	116.5 (86–166)	111 (85–153)	120 (86.5–167)	0.313	n.a
Patients treated with IMV; n (%)	232 (84.4)	22 (84.6)	210 (84.3)	1.000	1.021 (0.334–3.127)
Patients with nitric oxide administration during IMV; n (%)	38 (13.8)	4 (15.4)	34 (13.7)	0.767	1.150 (0.373–3.542)
Patients positioned in prone position during IMV; n (%)	205 (74.5)	18 (69.2)	187 (75.1)	0.513	0.746 (0.309–1.800)
Number of days with IMV; median (IQR)	13 (4–27)	11 (3–17)	13 (4–28)	0.291	n.a
Drugs administration					
Patients treated with hydroxychloroquine; n (%)	126 (45.8)	13 (50.0)	113 (45.4)	0.653	1.204 (0.536–2.701)
Patients treated with lopinavir/ritonavir; n (%)	85 (30.9)	11 (42.3)	74 (29.7)	0.186	1.734 (0.761–3.954)
Patients treated with remdesivir; n (%)	53 (19.3)	5 (19.2)	48 (19.3)	0.995	0.997 (0.358–2.778)
Patients treated with azithromycin; n (%)	69 (25.1)	5 (19.2)	64 (25.7)	0.469	0.688 (0.249–1.901)
Patients treated with tocilizumab; n (%)	84 (30.5)	9 (34.6)	75 (30.1)	0.636	1.228 (0.524–2.880)
Patients treated with corticosteroids; n (%)	253 (92.0)	25 (96.2)	228 (91.6)	0.705	2.303 (0.297–17.85)
Patients treated with interferon beta 1; n (%)	29 (10.5)	3 (11.5)	26 (10.4)	0.744	1.119 (0.314–3.983)
Patients treated with enoxaparin; n (%)	250 (91.2)	26 (100.0)	224 (90.3)	0.144	n.a
Patients treated with anticoagulants with prophylactic or therapeutic goal; n (%)	275 (100)	26 (100.0)	249 (100.0)	n.a	n.a

No diferencias en los tratamientos recibidos

3 Autoanticuerpos neutralizantes IFN-I

Variable	All results for auto-Abs to type I IFNs ($n=275$)	Neutralizing positive results for some or both auto-Abs to type I IFNs ($n=26$)	Neutralizing negative results for both auto-Abs to type I IFNs ($n=249$)	p-value	OR (95% CI)
Length of hospital and ICU stay					
Number of admitted days to the ICU; median (IQR)	15 (7–31)	13.5 (4–24)	15 (7–31)	0.500	n.a
Number of admitted days to the hospital; median (IQR)	29 (15–49)	30.5 (14–46)	29 (16–50)	0.819	n.a
Complications during ICU stay					
Patients with neurological complications; *n* (%)	77 (28.0)	5 (19.2)	72 (28.9)	0.295	0.585 (0.213–1.612)
Patients with thrombotic complications; *n* (%)	50 (18.2)	5 (19.2)	45 (18.1)	0.795	1.079 (0.389–3.015)
Patients with hemorrhagical complications; *n* (%)	27 (9.8)	4 (15.4)	23 (9.2)	0.301	1.787 (0.567–5.634)
Patients with cardiovascular complications; *n* (%)	56 (20.4)	5 (19.2)	51 (20.5)	0.880	0.924 (0.332–2.570)
Patients with superinfection; *n* (%)	207 (75.3)	19 (73.1)	188 (75.5)	0.785	0.881 (0.353–2.195)
Patients with sepsis; *n* (%)	134 (48.7)	11 (42.3)	123 (49.4)	0.491	0.751 (0.332–1.700)
Patients with septic shock; *n* (%)	70 (25.5)	4 (15.4)	66 (26.5)	0.215	0.504 (0.167–1.517)
Patients with multiple organ failure; *n* (%)	56 (20.4)	5 (19.2)	51 (20.5)	0.880	0.924 (0.332–2.570)
Final status					
Exitus; *n* (%)	143 (52.0)	12 (46.2)	131 (52.6)	0.531	0.772 (0.343–1.736)

No diferencias en la evolución a excepción de mas insuf renal aguda

3 Autoanticuerpos neutralizantes IFN-I

En fases iniciales

Ayuda a identificar a pacientes con un riesgo elevado de desarrollar cuadros críticos de COVID-19

Bastard P, et al. Science 2020
Troya et al. J Clin Immunol 2021
Koning et al. Intensive Care Med. 2021
Abers MS, et al. Immunol Cell Biol. 2021

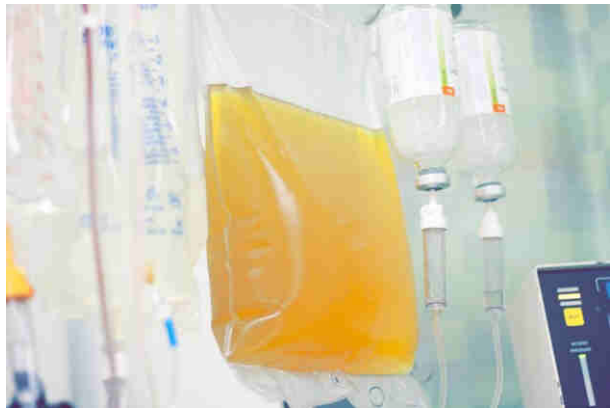
En Curas Intensivas

Característicasdemogràficas, analíticas i evolutivas similares

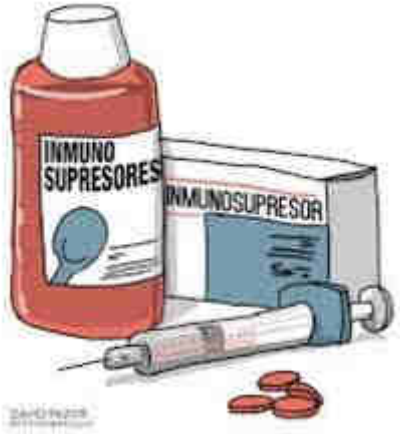
Solanich X, et al. J Clin Immunol. 2021
Goncalves D, et al. Clin Transl Immunology. 2021

3 Autoanticuerpos neutralizantes IFN-I

A diferencia de otros factores relacionados con el aumento de la gravedad de la COVID-19, la detección de estos NautoAbs en pacientes críticos permite plantear la administración de **tratamientos específicos**



Recanvios plasmáticos
Inmunoglobulinas



Corticoides
Deplección linfocitaria
JAK inhibitors

IFN-β
IFN-ʎ

Vinh DC, et al. J Clin Immunol. 2021

Conclusiones

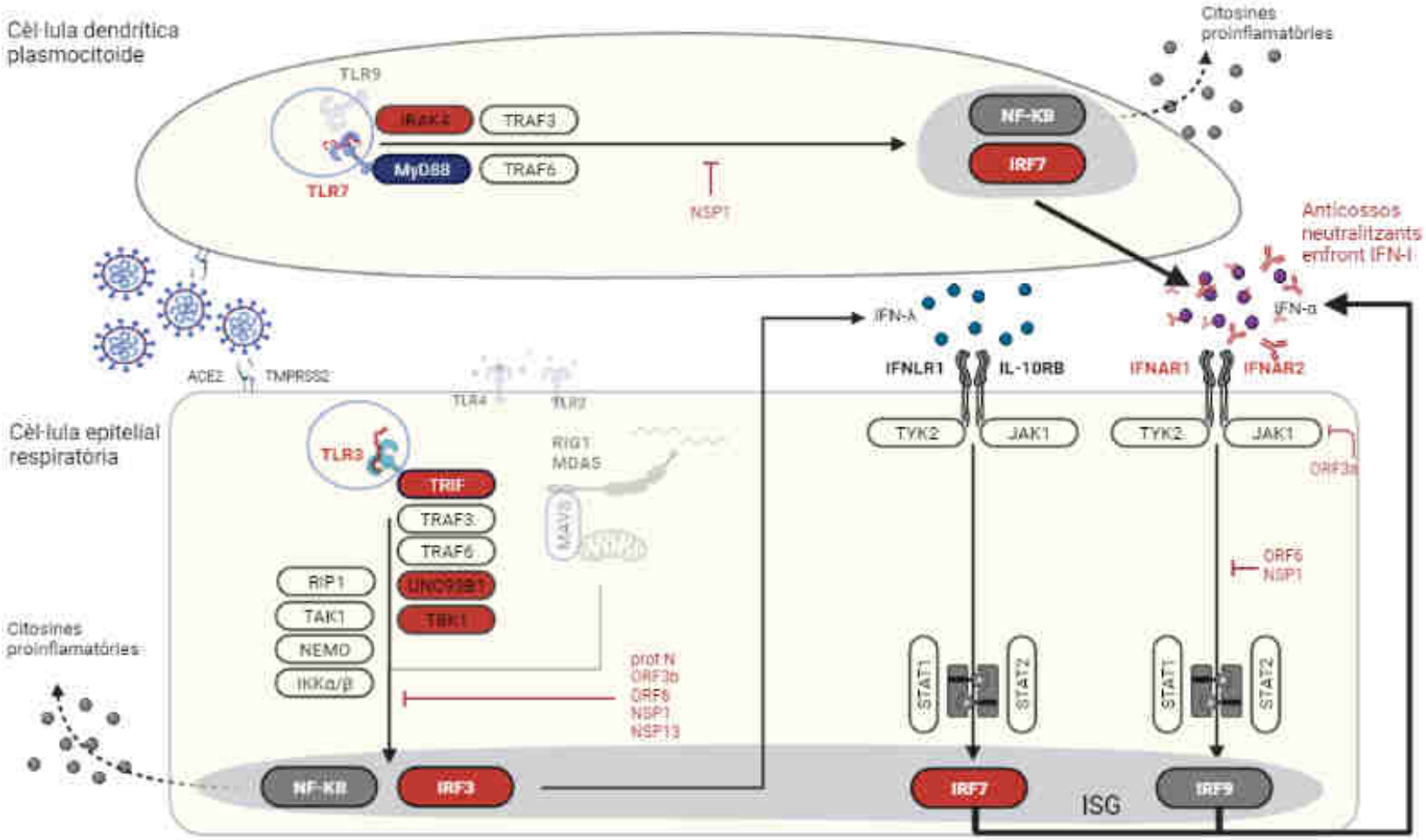
Conclusiones

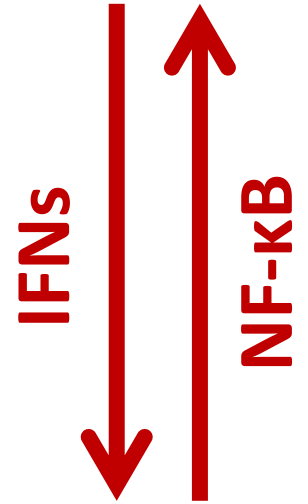
Edad o ciertas comorbilidades

Susceptibilidad genética

Autoanticuerpos neutralitzantes frente IFN-I

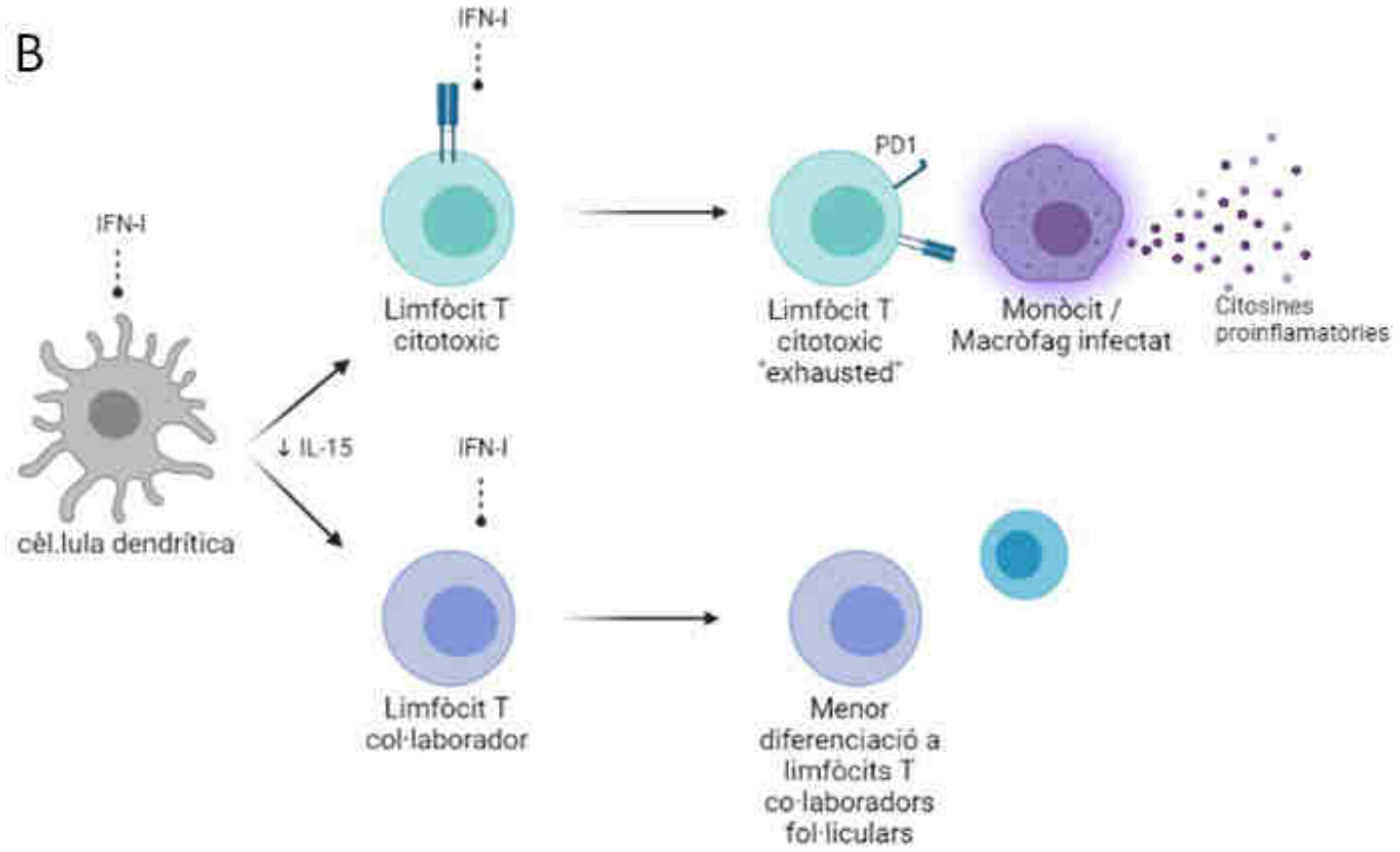
SARS-CoV-2





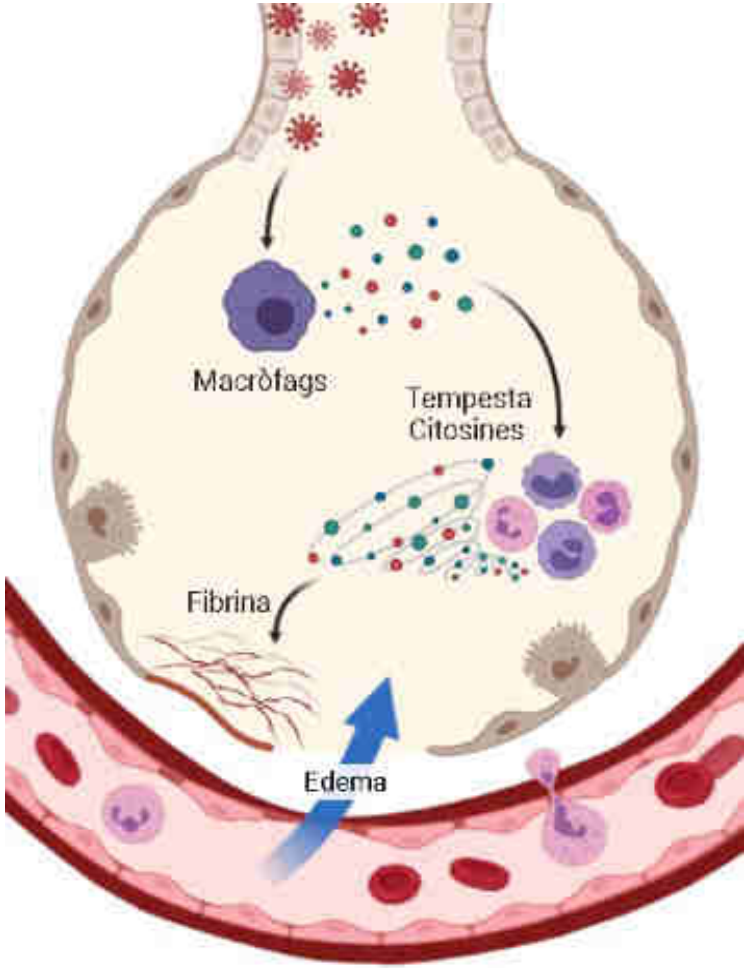
Adaptado de Schultze et al. Cell 2021

Respuesta inmune del huésped a SARS-CoV-2



Adaptat de King C et al. Trends Immunol, 2021

Respuesta inmune del huésped a SARS-CoV-2



Adaptat de Pillalamari et al. Transl Oncol. 2021

Mil gràcies !!!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