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Vicepresidencia Segunda y Consejería de Sanidad y Servicios Sociales

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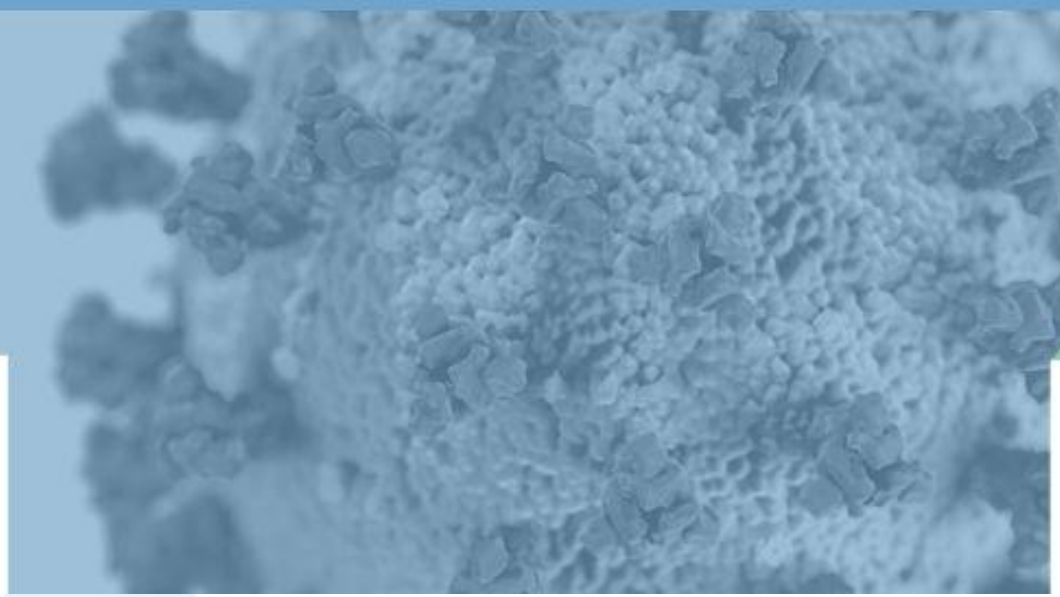
WEBINAR: COVID-19 Y RIESGO CARDIOVASCULAR

MARTES 9 DE JUNIO. 17:30 H. (CEST)

DURACIÓN: 90'

INSCRIPCIONES AQUÍ.

Solicitada acreditación a Comisión de formación continuada de las profesiones sanitarias en Extremadura



Con la colaboración de :

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Ponentes:

Dr. Daniel Fernández-Bergés

Dr. Francisco Carramiñana Barrera

Escuela de Ciencias de la Salud y de la Atención Sociosanitaria

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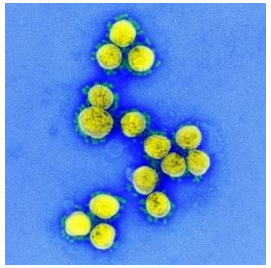


COVID-19 Y ENFERMEDADES CARDIOVASCULARES: ANÁLISIS Y REFLEXIÓN DE LA INFORMACIÓN CIENTÍFICA GENERADA A RAÍZ DE LA PANDEMIA.

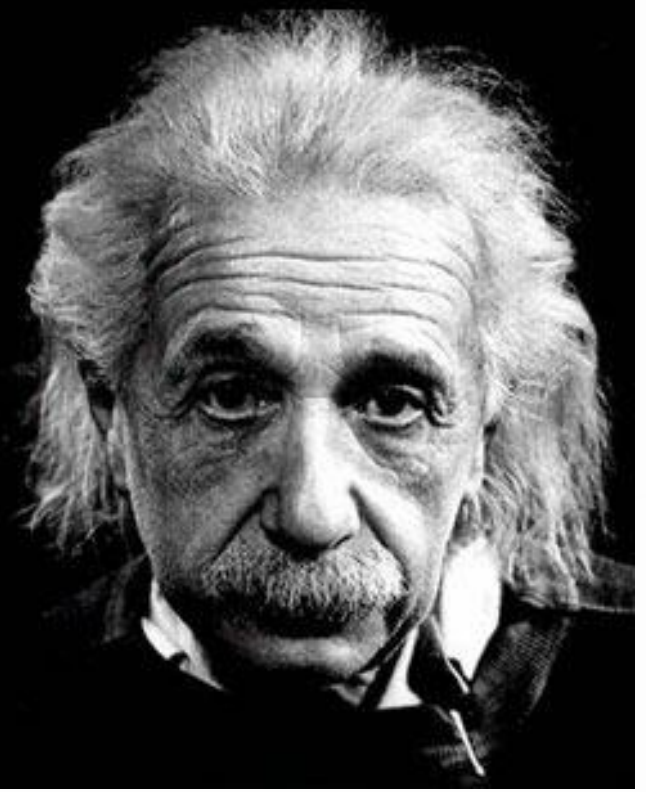
Daniel Fernández-Bergés MD PhD FESC

INUBE
Instituto Universitario de Investigación BIOSANITARIA de Extremadura

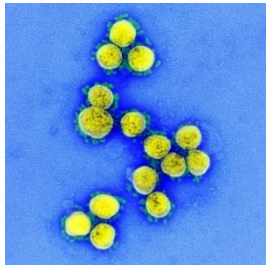
Grimex
Grupo Investigador Multidisciplinar Extremeño

TODOS SOMOS MUY IGNORANTES,
LO QUE OCURRE ES QUE
NO TODOS IGNORAMOS
LAS MISMAS COSAS.

Albert Einstein



Contenido



- Información básica del SARS Co 2.
- El tsunami informativo.
- SARS Co 2 y el sistema cardiovascular.
- Asociación del SARS CoV2 con FRCV y ECV.
- SARS Co2: injuria miocárdica y consecuencias.
- Los efectos colaterales del SARS Co 2.
- La lectura crítica de la literatura científica
- Conclusiones

El VIRUS: SARS CoV 2

El conocimiento “básico”

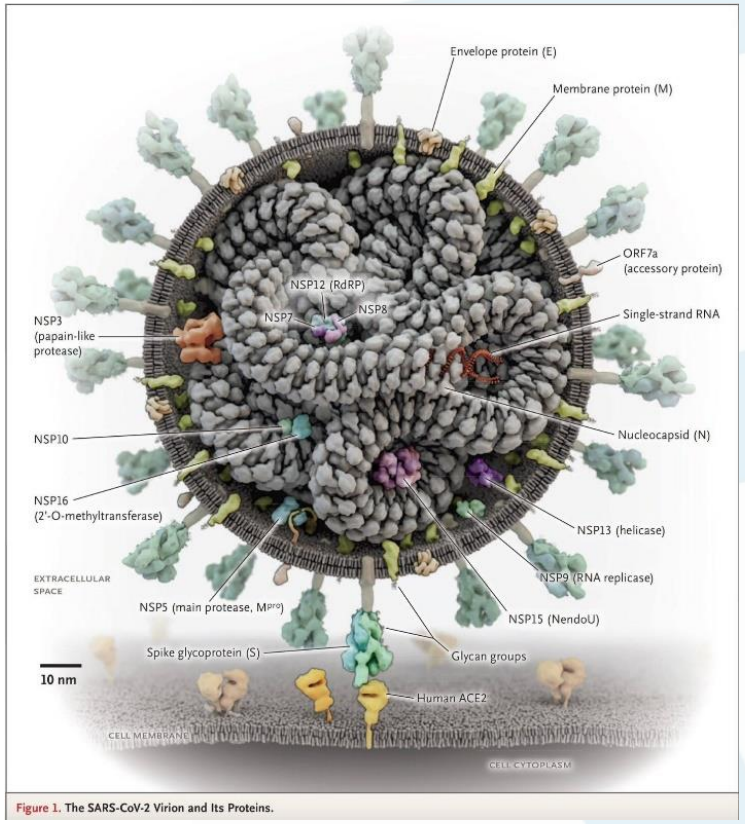


Figure 1. The SARS-CoV-2 Virion and Its Proteins.

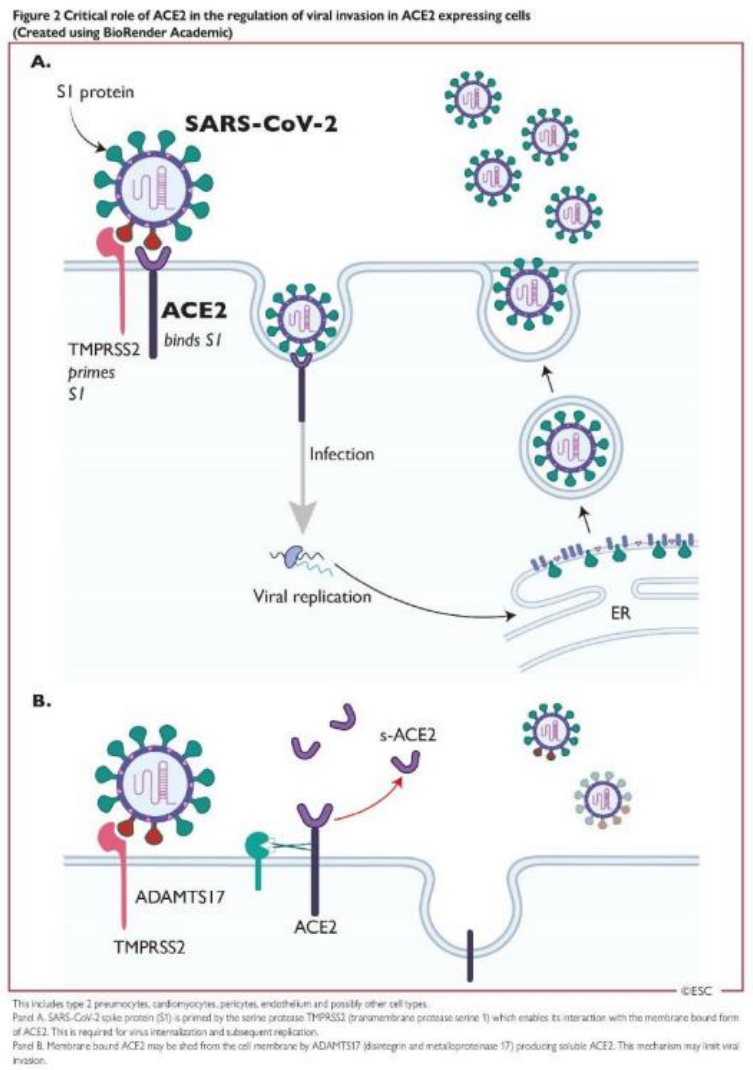
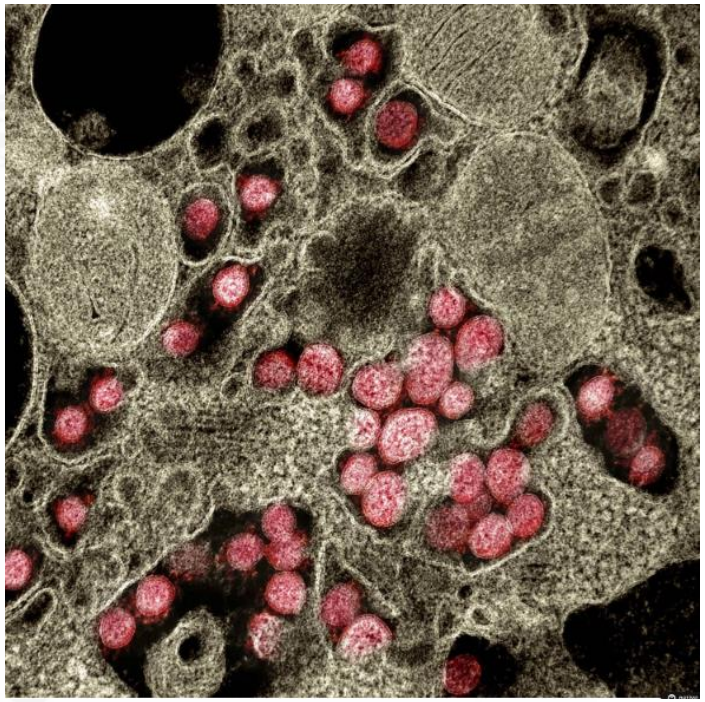
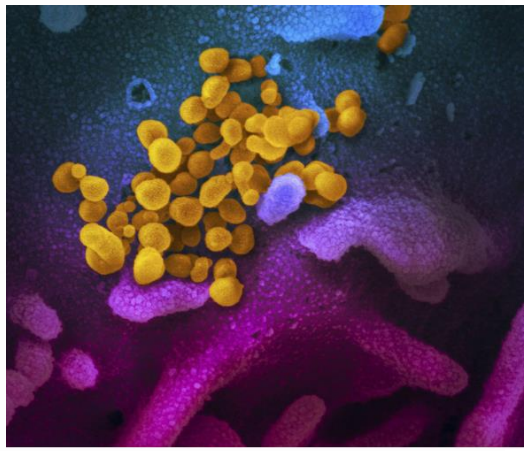


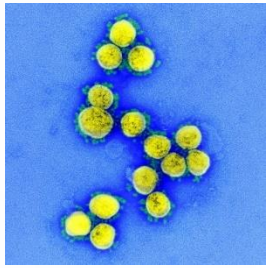
Figure 2 Critical role of ACE2 in the regulation of viral invasion in ACE2 expressing cells (Created using BioRender Academic)

This includes type 2 pneumocytes, cardiomyocytes, pericytes, endothelium and possibly other cell types.
Panel A. SARS-CoV-2 spike protein (S1) is primed by the serine protease TMPRSS2 (transmembrane protease serine 1) which enables its interaction with the membrane bound form of ACE2. This is required for virus internalization and subsequent replication.
Panel B. Membrane bound ACE2 may be shed from the cell membrane by ADAMTS17 (disintegrin and metalloproteinase 17) producing soluble ACE2. This mechanism may limit viral invasion.





El Tsunami informativo



If we don't flatten the curve, there will be about 50 million COVID papers by the end of the year.

Traducir Tweet

Scientists are drowning in COVID-19 papers. Can new tools keep them afloat?

La información que no fue conocimiento

CLINICAL MICROBIOLOGY REVIEWS, Oct. 2007, p. 660–694 Vol. 20, No. 4
0893-8512/07/$08.00+0 doi:10.1128/CMR.00023-07

Severe Acute Respiratory Syndrome Coronavirus as an Agent of Emerging and Reemerging Infection

Vincent C. C. Cheng, Susanna K. P. Lau, Patrick C. Y. Woo, and Kwok Yung Yuen*

State Key Laboratory of Emerging Infectious Diseases, Department of Microbiology, Research Centre of Infection and Immunology, The University of Hong Kong, Hong Kong Special Administrative Region, China

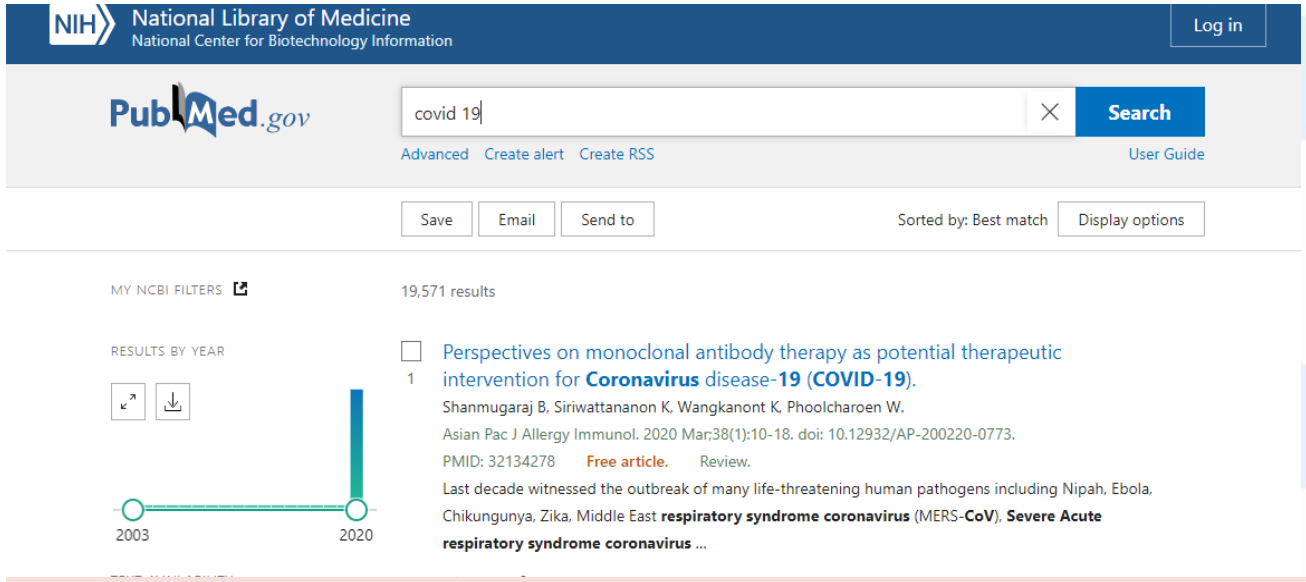
2007

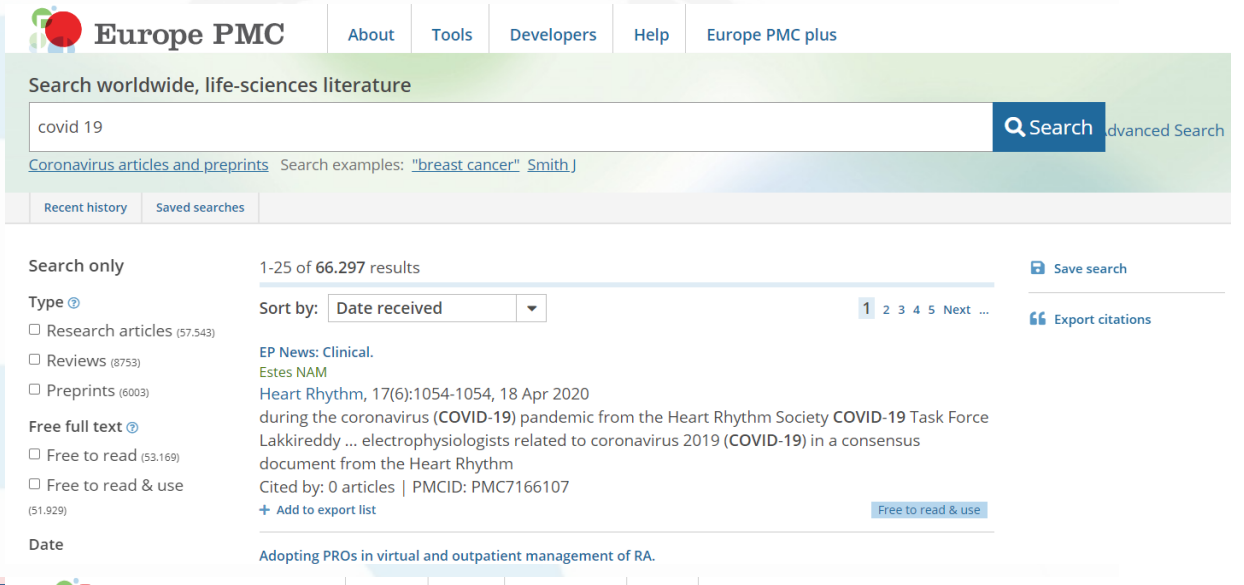
12 years ago!

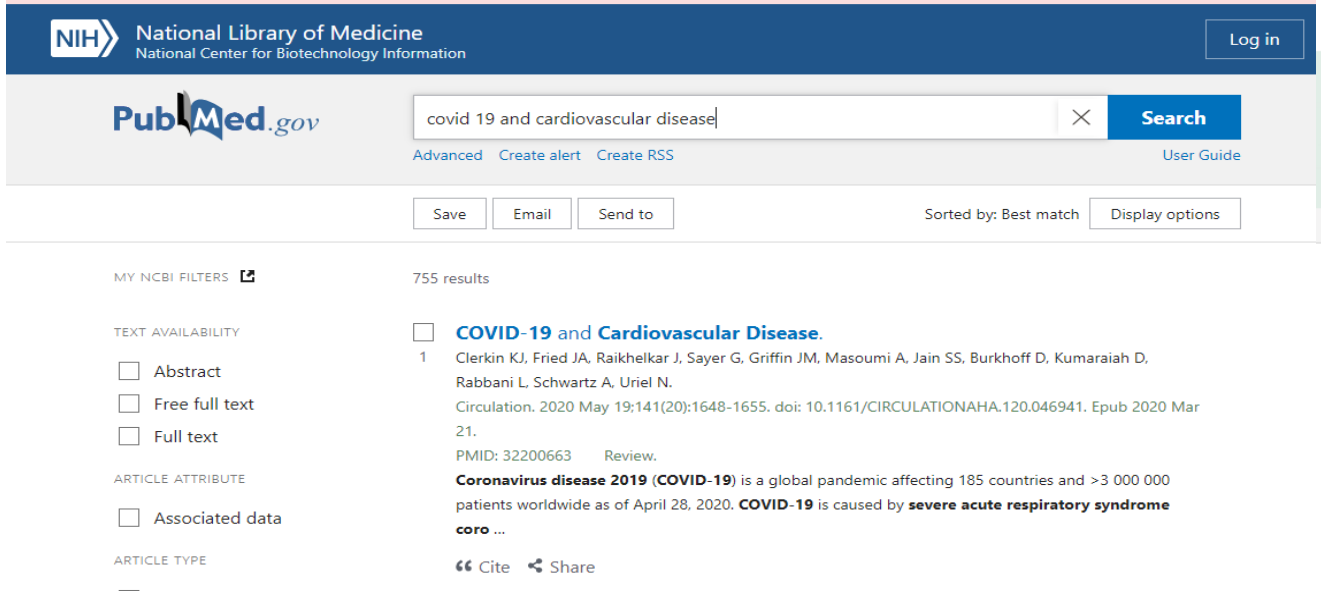
SHOULD WE BE READY FOR THE REEMERGENCE OF SARS?

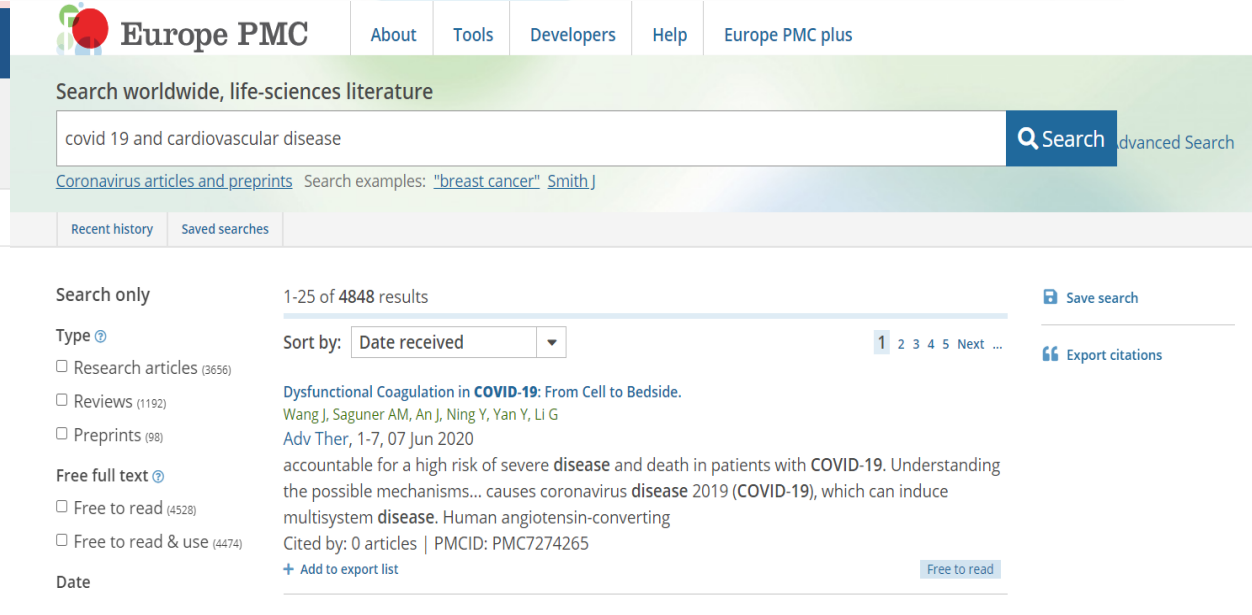
The medical and scientific community demonstrated marvelous efforts in the understanding and control of SARS within a short time, as evident by over 4,000 publications available online. Despite these achievements, gaps still exist in terms of the molecular basis of the physical stability and transmissibility of this virus, the molecular and immunological basis of disease pathogenesis in humans, screening tests for early or cryptic SARS cases, foolproof infection control procedures for patient care, effective antivirals or antiviral combinations, the usefulness of immunomodulatory agents for late presenters, an effective vaccine with no immune enhancement, and the immediate animal host that transmitted the virus to caged civets in the market at the beginning of the epidemic. Coronaviruses are well known to undergo genetic recombination (375), which may lead to new genotypes and outbreaks. The presence of a large reservoir of SARS-CoV-like viruses in horseshoe bats, together with the culture of eating exotic mammals in southern China, is a time bomb. The possibility of the reemergence of SARS and other novel viruses from animals or laboratories and therefore the need for preparedness should not be ignored.

Bases de datos: pub med; Europe PMC









COVID-19 and Cardiology

ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic

Last updated on 21 April 2020

The document is not a guideline but rather a guidance document. The recommendations are the result of observations and personal experience from health care providers at the forefront of the COVID-19 pandemic.

doi:10.1093/eurheartj/ehaa280

CAPACITY-COVID: a European Registry to determine the role of cardiovascular disease in the COVID-19 pandemic

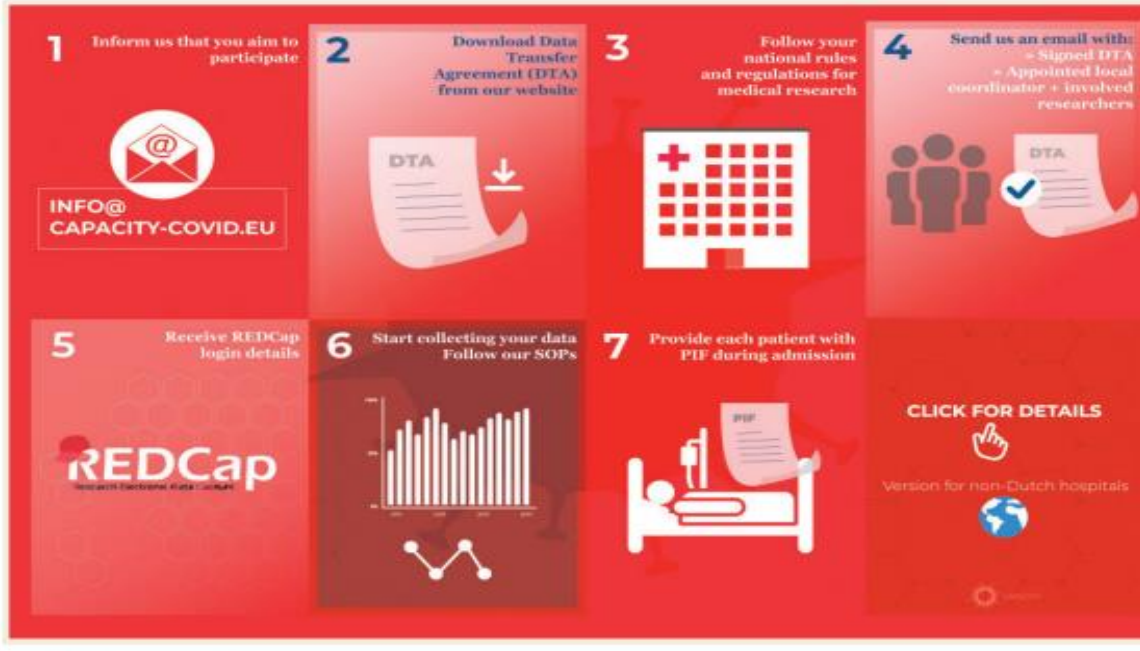
From the emerging literature, cardiovascular disease appears to play a prominent role in the COVID-19 pandemic on multiple levels: (i) patients with cardiovascular risk factors and pre-existent cardiovascular disease seem to have an increased risk of a poor outcome;[1,2,3] (ii) patients with COVID-19 have been, also in the absence of underlying cardiovascular disease, reported to develop cardiovascular complications;[3,4,5] (iii) therapeutics currently prescribed in an experimental setting such as antimalarial and antiviral drugs have known cardiovascular side effects; and (iv) there are concerns, especially on social media, regarding the safety of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in relation to COVID-19.[3,6] Insufficient evidence is currently available to guide clinicians in the management of these patients.

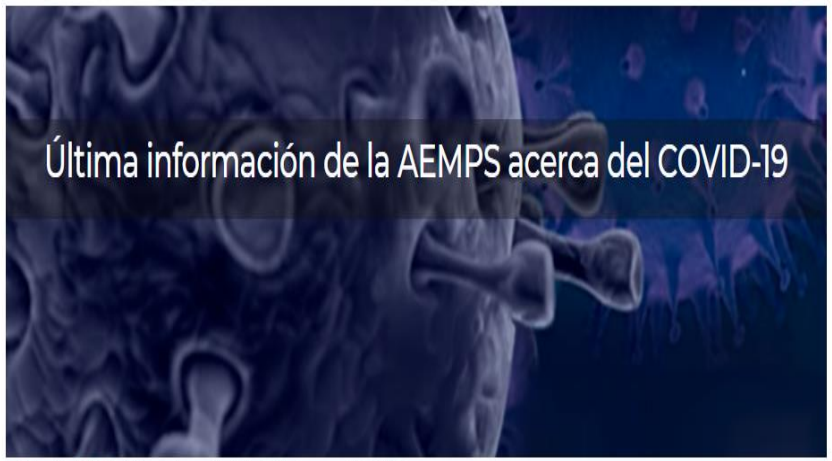
To accelerate knowledge on the role of cardiovascular disease in the COVID-19 pandemic, standardized and coordinated data collection on a large scale is of pivotal importance.

For this reason, we launched the CAPACITY-COVID (www.ity-covid.eu) registry on the 23rd of March (Figure 1).

CAPACITY-COVID offers a comprehensive data collectio that facilitates uniform data collection of patients infected with CoV-2. The registry builds upon the Case Report Form (CRF) (isaric.tghn.org/covid-19-clinical-research-resources/) released International Severe Acute Respiratory and Emerging Inf Consortium (ISARIC) and World Health Organization (WHO) sponse to the COVID-19 outbreak. By collecting information registry in a standardized manner, we hope this initiative can aid viding more insight into (i) the incidence and pattern of cardiova complications in patients with COVID-19 and (ii) the vulnerabili clinical course of COVID-19 in patients with an underlying card cular disease.

Within CAPACITY-COVID, the ISARIC-WHO CRF has be tended with multiple additional data collection instruments on c vascular risk factors, the use of cardiovascular medication and





Compartir:

- **Tratamientos disponibles sujetos a condiciones especiales de acceso para el manejo de la infección respiratoria por SARS-CoV-2**, (actualizado a 28 de mayo de 2020)
- **Información sobre investigación clínica sobre la COVID-19**, (actualizado a 29 de mayo de 2020)
- **Sospechas de reacciones adversas notificadas con tratamientos utilizados en COVID-19**, (actualizado a 22 de mayo de 2020)

Remdesivir

Lopinavir/ritonavir (LPV/r)

Cloroquina/Hidroxicloroquina

Tocilizumab (TCZ)

Sarilumab

Ruxolitinib (RXT)

Siltuximab (STX)

Baricitinib (BAR)

Anakinra (ANK)

Interferón Beta-1B (IFNb) e Interferón Alfa-2B

Ensayos clínicos

En el enlace a continuación, se muestran una herramienta para la visualización agregada de una serie de datos de los ensayos clínicos autorizados en España que tratan de generar evidencia en el tratamiento para SARS-CoV-2. Los datos provienen de **REec.**

La intención es proporcionar a los investigadores, médicos y pacientes una base de datos fácilmente filtrable que permita identificar, entre otros filtros, la tipología de ensayo, centros donde se está llevando a cabo el estudio, tratamiento investigado y población estudiada. El objetivo es informar sobre las distintas líneas de investigación que se están llevando a cabo en los centros de nuestro país y alentar la colaboración entre los investigadores. Se recomienda realizar estudios clínicos aleatorizados y multicéntricos que generen conocimiento útil.

A medida que el número de ensayos vaya aumentando, mantendremos esta información actualizada diariamente con los ensayos clínicos que se autoricen.

Visualización de datos sobre ensayos clínicos para evaluar medicamentos sobre COVID- 19

Estudios observacionales

Además de los ensayos clínicos, la investigación clínica también se desarrolla a través de estudios observacionales con medicamentos es decir, investigaciones en las que se recogen datos de salud de los pacientes con el fin de analizar el uso, la seguridad o la efectividad de los medicamentos en el contexto de la asistencia sanitaria real, sin intervenir en la práctica clínica. Esto convierte a ambos métodos en complementarios para extraer mucha información relevante del tratamiento con los diferentes medicamentos.

Una proporción importante de estos estudios son multicéntricos. Casi todos ellos son iniciativas de los propios profesionales del Sistema Nacional de Salud, y en muchos casos, para llevarlos a cabo, utilizan los datos ya registrados en las historias clínicas electrónicas, mientras que en otros casos se obtienen además los datos durante la propia atención sanitaria de los pacientes.

Lista completa de estudios observacionales con medicamentos sobre COVID-19 clasificados

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COVID-19

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Cardiología

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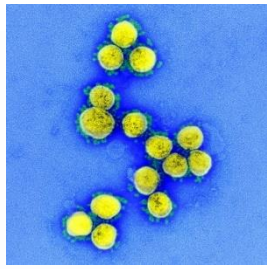
- Estudios Observacionales
- Guías de Práctica Clínica
- Otros
- Revisiones Narrativas
- Revisiones Rápidas
- Revisiones Sistemáticas

- Cardiología
- Cirugía
- Cirugía Cardiovascular
- Medicina de Familia
- Medicina Interna
- Medicina Paliativa
- Nefrología
- Neumología
- Psiquiatría
- Radiología
- Otorrinolaringología
- Patología
- Pediatría
- Psiquiatría
- Radiología
- Rehabilitación
- Reumatología
- Transplante
- UCI Anestesia
- Urología
- Virología, Biología Molecular

Generalidades del SARS Co V 2 y ECV



- El Sars-Cov 2 produce centralmente un Síndrome de fallo respiratorio agudo.
- Pacientes con factores de riesgo cardiovascular y enfermedad cardíaca establecida constituyen una población vulnerable a la exposición del SARS Co V 2.
- Pacientes con daño miocardico en el contexto de una infección por SARS Co V 2 tienen un incremento de morbi-mortalidad.
- El Sars Co V 2 puede desencadenar una reaccion inflamatoria severa con multiples trastornos de la coagulación y fenómenos tromboembólicos.
- Peligro de interacción o efectos secundarios con ciertos medicamentos
- Efectos colaterales del Sars Co V 2 sobre la atención del paciente cardiovascular

https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance

Características clínicas de pacientes afectados

Características demográficas, clínicas y epidemiológicas

Tabla 2. Características demográficas, clínicas y antecedentes epidemiológicos de riesgo. Casos de COVID-19 notificados a la RENAVE[1] (N=250.287)

Características	n*	Total N (%)	Mujeres N (%)	Hombres N (%)	p-valor
Sexo	248335		141581 (56,6)	106754 (42,7)	
Edad. Mediana (RIC)[2]	247169	60 (46-79)	59 (44-81)	62 (48-77)	<0,001
Grupo de edad (años)					
<2		381 (0,2)	165 (0,1)	216 (0,2)	
2-4		192 (0,1)	98 (0,1)	94 (0,1)	
5-14		826 (0,3)	389 (0,3)	437 (0,4)	
15-29		15421 (6,2)	10225 (7,3)	5196 (4,9)	
30-39		23489 (9,5)	14785 (10,5)	8704 (8,2)	
40-49		36042 (14,6)	21307 (15,1)	14735 (13,9)	
50-59		43668 (17,7)	24921 (17,7)	18745 (17,6)	
60-69		35074 (14,2)	16824 (11,9)	18246 (17,2)	
70-79		33345 (13,5)	14990 (10,6)	18355 (17,3)	
≥80		58731 (23,8)	37102 (26,3)	21628 (20,3)	<0,001
Síntomas[1]					
Fiebre o reciente historia de fiebre	101179	73691 (72,8)	36936 (68,2)	36746 (79,2)	<0,001
Tos	92806	63960 (68,9)	33796 (67,8)	30157 (71,2)	<0,001
Dolor de garganta	38193	8312 (21,8)	5313 (24,8)	2997 (18,5)	<0,001
Disnea	87578	41533 (47,4)	20606 (43,8)	20925 (52,3)	<0,001
Escalofríos	37908	8737 (23,0)	4788 (22,6)	3947 (24,5)	<0,001
Vómitos	37903	3245 (8,6)	2104 (9,9)	1141 (7,1)	<0,001
Diarrea	39684	10546 (26,6)	6202 (27,9)	4343 (25,8)	<0,001
Neumonía (radiológica o clínica)	124671	67120 (53,8)	29246 (44,7)	37871 (64,6)	<0,001
Síndrome de distrés respiratorio agudo	85496	5807 (6,8)	2227 (4,8)	3580 (9,4)	<0,001
Otros síntomas resp.	69594	6417 (9,2)	2721 (7,2)	3696 (11,8)	<0,001
Fallo renal agudo	85735	4479 (5,2)	1710 (3,6)	2769 (7,3)	<0,001
Enfermedades y factores de riesgo[1]					
Una o más	159110	103440 (65,0)	53788 (61,5)	48340 (68,7)	<0,001
Enfermedad cardiovascular	149307	43278 (29,0)	20251 (24,7)	22804 (34,3)	<0,001
Enfermedad respiratoria	149307	16399 (11,0)	6957 (8,5)	9269 (13,9)	<0,001
Diabetes	149307	24163 (16,2)	11094 (13,5)	12923 (19,4)	<0,001
Hipertensión arterial†	149307	31761 (21,3)	17154 (20,9)	14213 (21,4)	0,037
Hospitalización	239628	92087 (38,4)	40570 (30,1)	51352 (49,7)	<0,001
Ventilación mecánica	77059	5781 (7,5)	1899 (4,7)	3882 (10,6)	<0,001
Admisión UCI[3]	196959	7691 (3,9)	2341 (2,1)	5339 (6,2)	<0,001
Defunción	250287	20527 (8,2)	8914 (6,3)	11604 (10,9)	<0,001
Contacto estrecho con casos COVID-19 probable o confirmado	13706	7354 (53,7)	4617 (60,2)	2737 (45,3)	<0,001
Contacto con persona con infección respiratoria aguda	15417	8006 (51,9)	5051 (57,0)	2955 (45,1)	<0,001
Profesional sanitario	169598	40921 (24,1)	31325 (32,1)	9592 (13,3)	<0,001
Visita a centro sanitario	8475	1207 (14,2)	728 (16,2)	479 (12,0)	<0,001

[1]Los porcentajes se calculan sobre los casos de COVID-19 de los que se dispone de información de cada variable. [2]RIC: rango intercuartil. [3]UCI: Unidad de cuidados intensivos. *n: número de casos con información sobre la variable. †La información sobre hipertensión arterial se recoge a partir del 18-03-2020. Datos actualizados a 21-05-2020.

Características clínicas de pacientes hospitalizados por COVID-19 en España

Table 4. Comparison of baseline characteristics and outcome of patients with COVID-19 included in series from different countries

	Guan et al [4].	Zhou et al [6].	Docherty et al (data unpublished).	Onder et al [8].		Richardson et al [7].		Borobia et al. (data unpublished)		SEMI-COVID-19	
City/Country/Source/Type of study	Wuhan/China/ multicenter cohort	China/multicenter cohort	UK/multicenter cohort	Italy/Italian National Institute of Health		New York/USA/ multicenter cohort		Madrid/Spain/single-center cohort		Spain/multicenter cohort	
Number of cases	1099	191	16749	22512		5700		2226		6424	
Median age in years, [IQR]	47 [35-58]	56 [46-67]	72 [57-82]			63 [52,75]		61 [46–78]		69.1 [56-79]	
Male sex	58.1%	62.0%	60.2%			60.3%		48.2%		56.9%	
Comorbidity											
Hypertension	15.0%	30.0%	-			56.0%		41.3%		50.2%	
Obesity	-	-	-			41.7		10.9%		21.2%	
Diabetes	7.4%	19.0%	19.0%*			33.8%		17.1%		18.7%	
Abnormal chest X-ray	59.0%	59%-75%	-			-		-		86.6%	
Clinical Outcomes											
Acute respiratory distress syndrome	3.4%	31.0%	-			-		4.9%		31.7%	
ICU admission	5.0%	26.0%	17%			12.2%		10.6%		7.5%	
Mortality	1.4%	28.3%	33.0%		7.2%		21.0%		20.7%		21.1%
Mortality by age group				**No. (%)**	**CFR %**	**No. (%)**	**CFR %**	**No. (%)**	**CFR %**	**No. (%)**	**CFR %**
<30	-	-	-	0	0%	97 (3.7)	4.1%	1 (0.2)	0.6%	1 (0.07)	0.9%
30-39	-	-	-	4 (0.3)	0.3%	211 (8.1)	3.8%	0 (0)	0.0%	2 (0.15)	0.6%
40-49	-	-	-	10 (0.6)	0.4%	353 (13.5)	6.2%	4 (0.9)	1.5%	15 (1.11)	2.4%
50-59	-	-	-	43 (2.7)	1.0%	515 (19.8)	10.3%	14 (3.0)	3.8%	45 (3.34)	4.4%
60-69	-	-	-	139 (8.6)	3.5%	533 (20.5)	15.8%	36 (7.8)	11.0%	131 (9.73)	10.6%
70-79	-	-	-	578 (25.6)	12.8%	451 (17.3)	32.1%	122 (26.5)	34.1%	407 (30.22)	25.7%
≥80	-	-		850 (52.3)	20.2%	441 (16.9)	53.7%	283 (61.5)	55.4%	746 (55.38)	49.7%

IQR: interquartile range; ICU: intensive care unit; CFR%: case fatality rate percentage: SEMI: Spanish Society of Internal Medicine. *Uncomplicated diabetes

Casas Rojo JM . Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMICOVID-19 Network. BMJ 2020; ahead of print

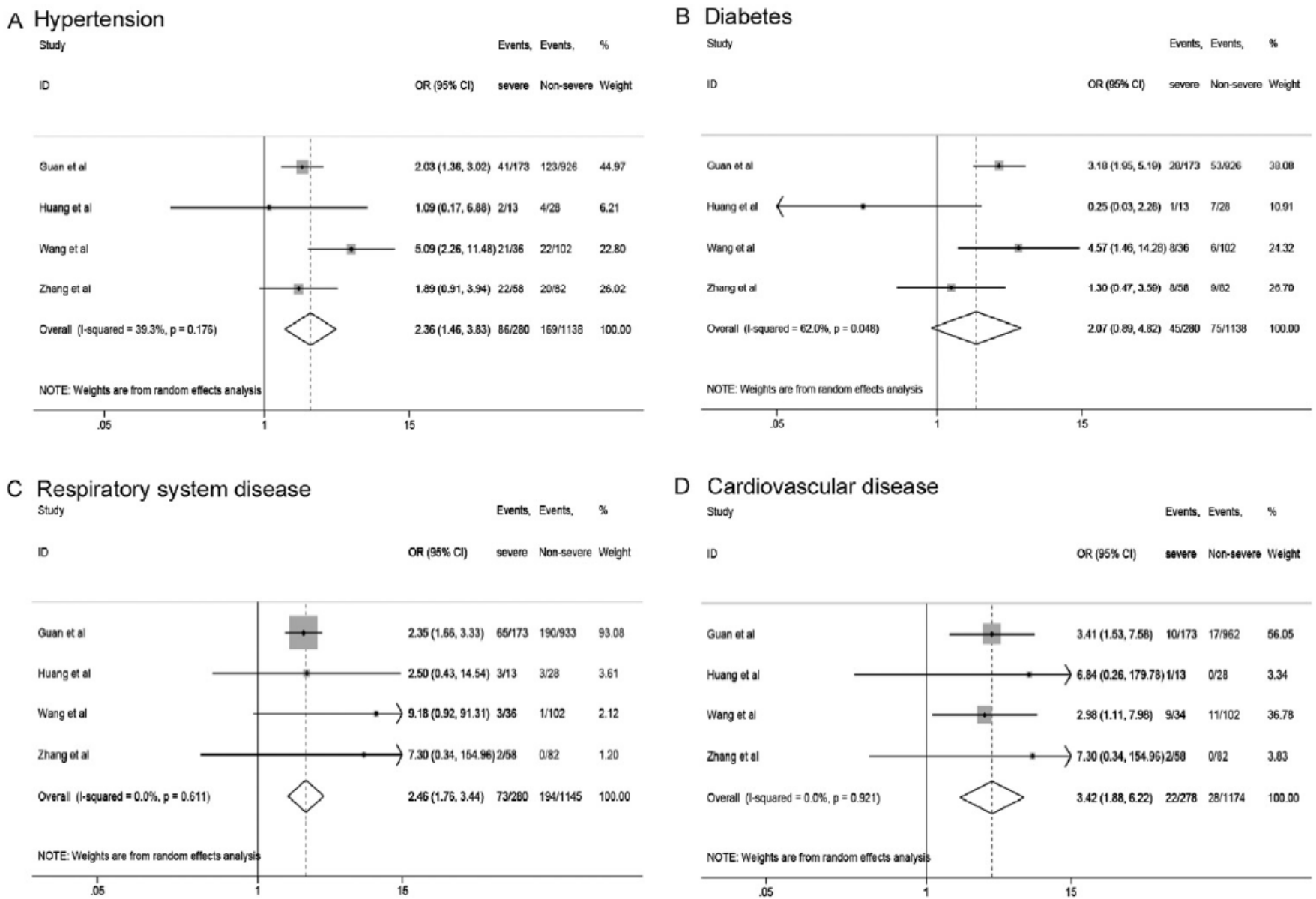


Figure 3. The risk of comorbidities in severe patients compared to non-severe patients. (A) hypertension, (B) diabetes, (C) respiratory system disease, (D) cardiovascular disease.

Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study

Simon de Lusignan, Jienchi Dorward, Ana Correa, Nicholas Jones, Oluwafunmi Akinyemi, Gayatri Amirthalingam, Nick Andrews, Rachel Byford, Gavin Dabrera, Alex Elliot, Joanna Ellis, Filipa Ferreira, Jamie Lopez Bernal, Cecilia Okusi, Mary Ramsay, Julian Sherlock, Gillian Smith, John Williams, Gary Howsam, Maria Zambon, Mark Joy, F D Richard Hobbs

Chronic kidney disease	..	..	<0·0001
No	519/3595 (14·4%)	1 (ref)	..
Yes	68/207 (32·9%)	2·90 (2·14–3·93)	..
Diabetes	..	..	<0·0001
No	473/3299 (14·3%)	1 (ref)	..
Yes	114/503 (22·7%)	1·75 (1·40–2·20)	..
Chronic heart disease	..	..	<0·0001
No	451/3202 (14·1%)	1 (ref)	..
Yes	136/600 (22·7%)	1·79 (1·44–2·20)	..
Chronic respiratory disease	..	..	<0·0001
No	529/3544 (14·9%)	1 (ref)	..
Yes	58/258 (22·5%)	1·65 (1·21–2·25)	..
Malignancy or immunocompromised	..	..	0·0010
No	460/3164 (14·5%)	1 (ref)	..
Yes	127/638 (19·9%)	1·46 (1·17–1·82)	..
BMI†	..	..	<0·0001
Normal weight	171/1296 (13·2%)	1 (ref)	..
Overweight	198/1095 (18·1%)	1·45 (1·20–1·80)	..
Obese	142/680 (20·9%)	1·74 (1·36–2·20)	..
Severely obese	26/145 (17·9%)	1·44 (0·91–2·27)	..
Missing	50/586 (8·5%)	0·61 (0·44–0·85)	..
Hypertension	..	..	<0·0001
No	378/2708 (14·0%)	1 (ref)	..
Yes	209/1094 (19·1%)	1·46 (1·20–1·75)	..
Smoking status	..	..	<0·0001
Non-smoker	201/1125 (17·9%)	1 (ref)	..
Active smoker	47/413 (11·4%)	0·59 (0·42–0·83)	..
Ex-smoker	303/1753 (17·3%)	0·96 (0·79–1·17)	..
Missing	36/511 (7·0%)	0·35 (0·24–0·51)	..

La Enfermedad en 3 fases

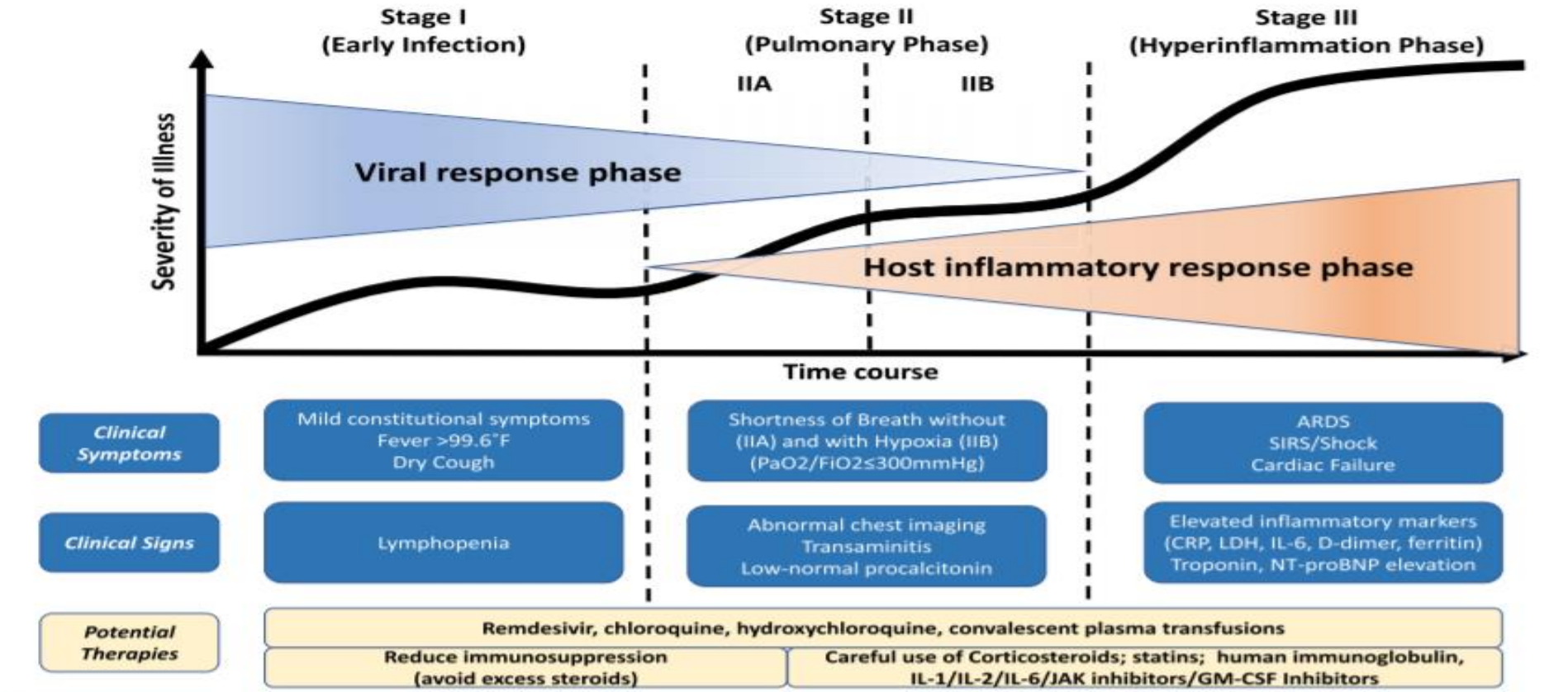
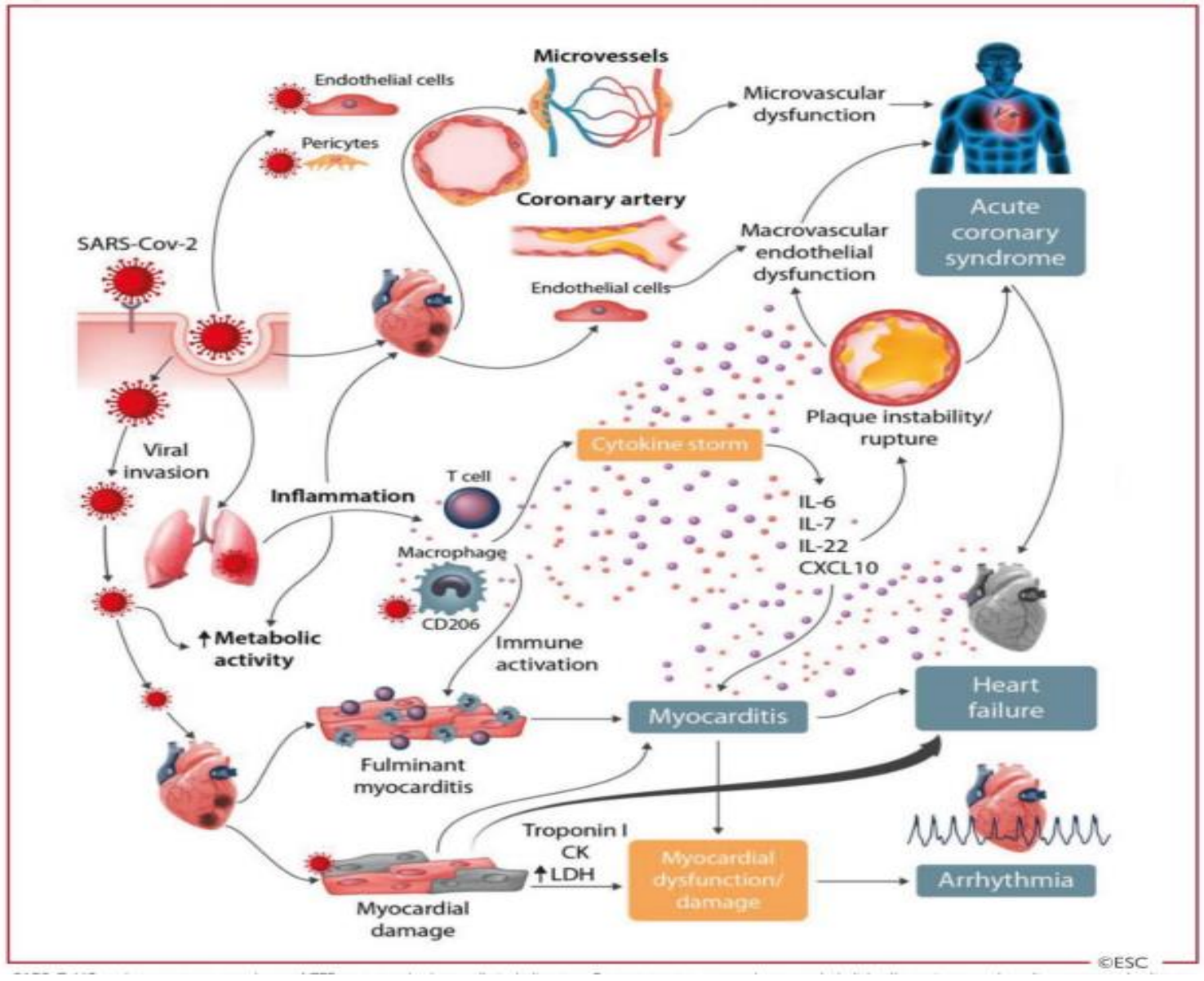
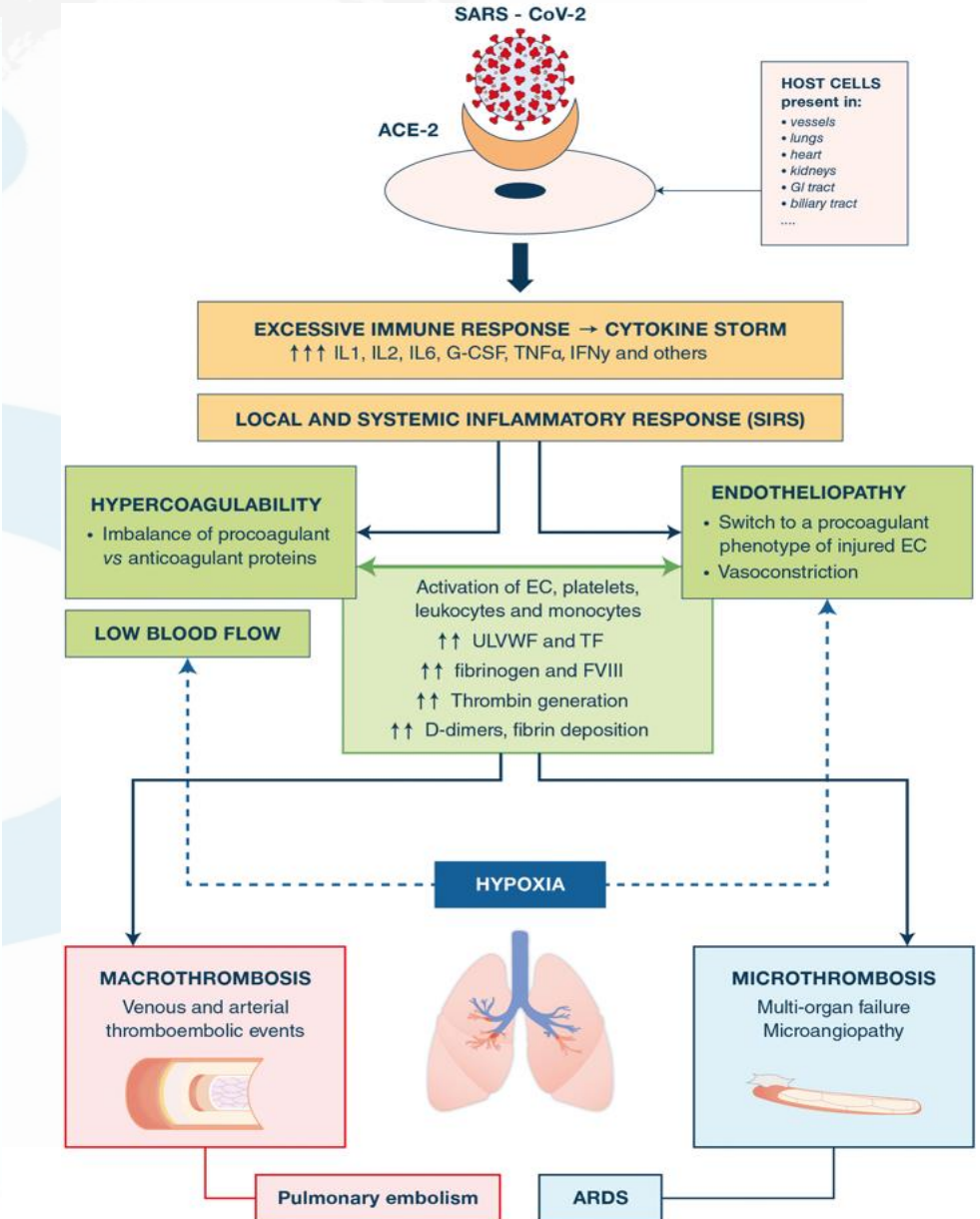


Figure 1 Classification of COVID-19 disease states and potential therapeutic targets. The figure illustrates 3 escalating phases of COVID-19 disease progression, with associated signs, symptoms, and potential phase-specific therapies. ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; JAK, janus kinase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro B-type natriuretic peptide; SIRS, systemic inflammatory response syndrome; GM-CSF, Granulocyte Macrophage Colony Stimulating Factor.

SARS Co 2: Hipótesis agresión cardiovascular

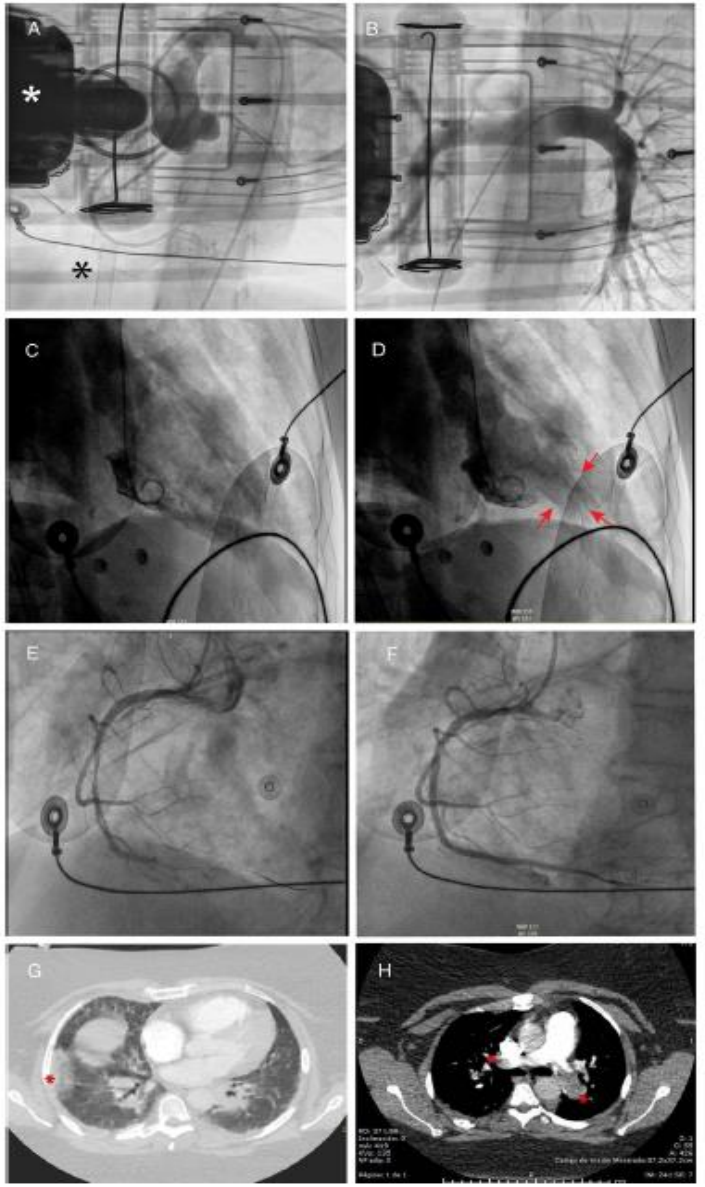




SARS Co 2: Shock Cardiogénico

Características clínicas, analíticas y de imagen, tratamientos y evolución de los 4 pacientes complicados con *shock* cardiogénico

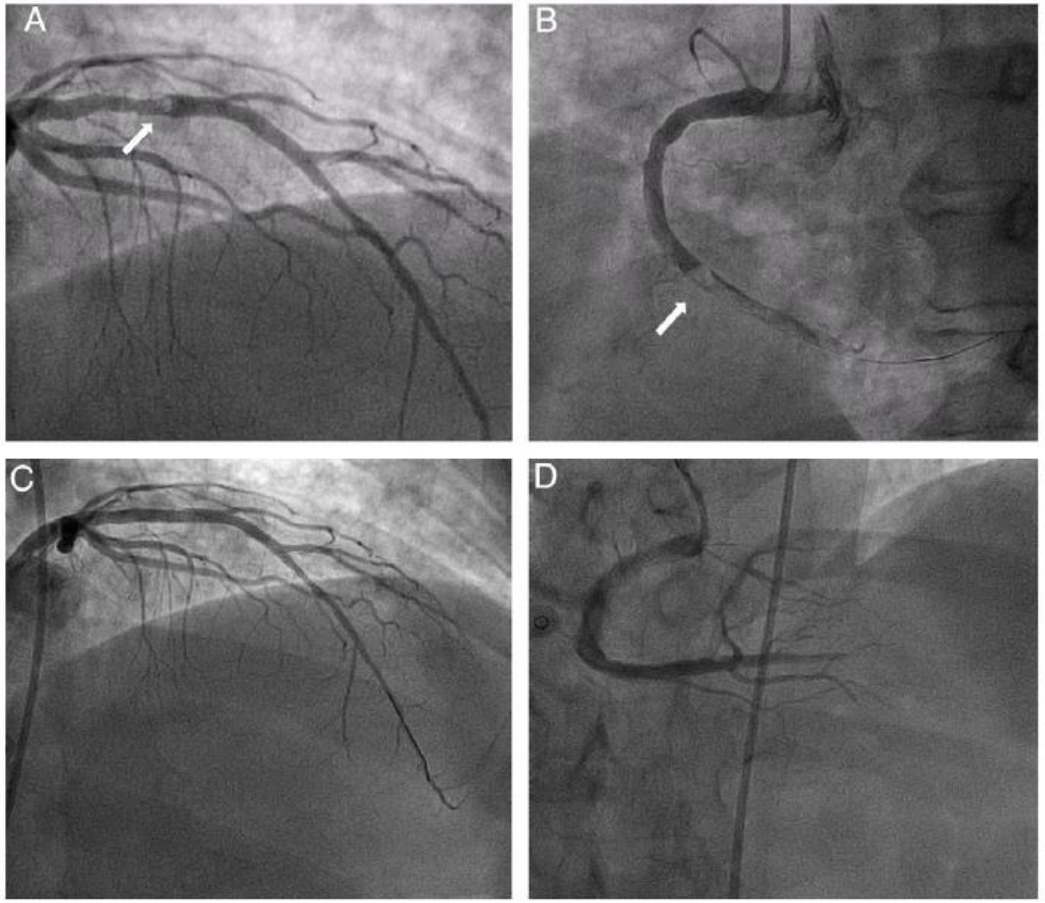
	Caso 1	Caso 2	Caso 3	Caso 4
Sexo	Mujer	Varón	Varón	Mujer
Edad (años)	42	50	75	37
Peso (kg)/IMC	50/19,5	66/21,7	65/22,9	120/43
FRCV	Dislipemia	Ninguno	Ninguno	Obesidad mórbida
Tratamiento crónico	Drospirenona-etinilestradiol 3/ 0,02 mg (anticonceptivo oral)	Ninguno	Ninguno	Ninguno
Comorbilidades	Ninguna	Trastorno del metabolismo del cobre no filiado Tumor benigno mediastínico derecho	Ninguna	Antecedente de TVP 8 años antes por inmovilización tras fractura
Cateterismo	Arterias coronarias normales Arterias pulmonares normales	Arterias coronarias normales Ventriculografía con patrón de *tako-tsubo* invertido	Oclusión trombótica del segmento medio de la coronaria derecha	Sin tiempo para realizarlo
Troponina I (ng/ml)	70,4 (VN < 0,1)	64,1	500	0,4
BNP (pg/ml)	No disponible	790,7	2.212,4	382
IL-6 (pg/ml)	No disponible	260,2	No disponible	50,93
Dímero D (ng/ml)	4.342 (VN < 500)	2.442	7.530	3.128
PCR (mg/l)	1	379,5	113,8	82,9
Evolución clínica	Parada cardiorrespiratoria Maniobras de RCP Tormenta arrítmica FV refractaria *Shock* cardiogénico ECMO-VA y BCIA Ventilación mecánica Fallecimiento	*Shock* mixto (cardiogénico inicial y séptico después) Ventilación mecánica Asistencia vasoactiva (3 días) Alta domiciliaria a los 11 días Normalización de las alteraciones en la contractilidad	Parada cardiorrespiratoria FV primaria ICP primaria *Shock* cardiogénico refractario a aminas vasoactivas Ventilación mecánica Fracaso multiorgánico Fallecimiento	*Shock* cardiogénico Parada cardiorrespiratoria y disociación electromecánica Fallecimiento tras maniobras de RCP

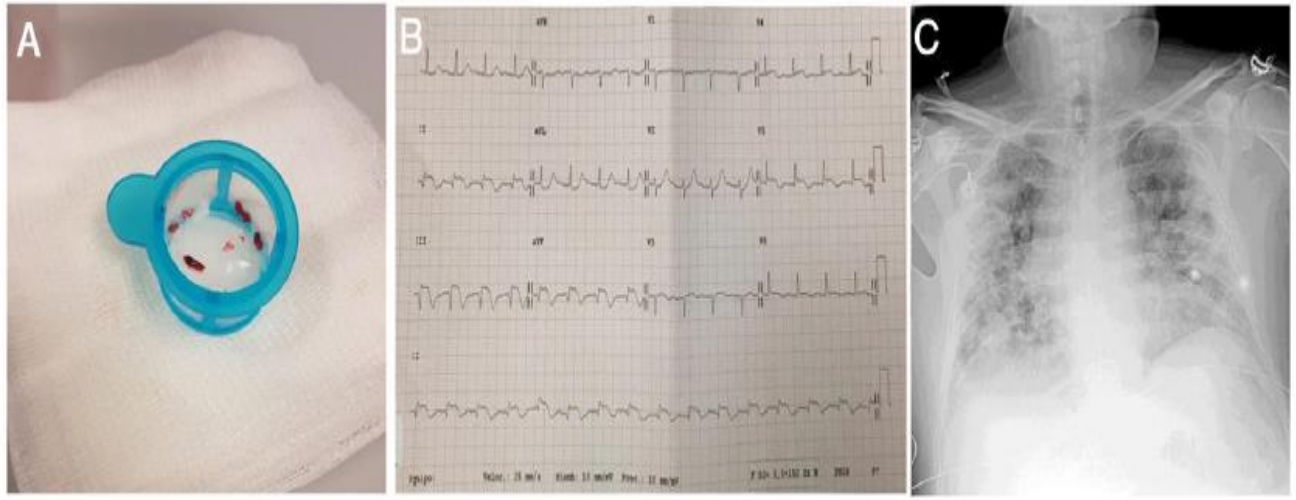


Sánchez Recalde A, et al. Covid 19 y shock cardiogénico: diferentes formas de presentación CV con alta mortalidad. Rev Esp Cardiol 2020: ahead of print

Carta científica

COVID-19 y trombosis simultánea en dos arterias coronarias





Rey J et al. Rev Esp Cardiol 2020; ahead of print.

SARS Co 2: Arritmias Cardíacas

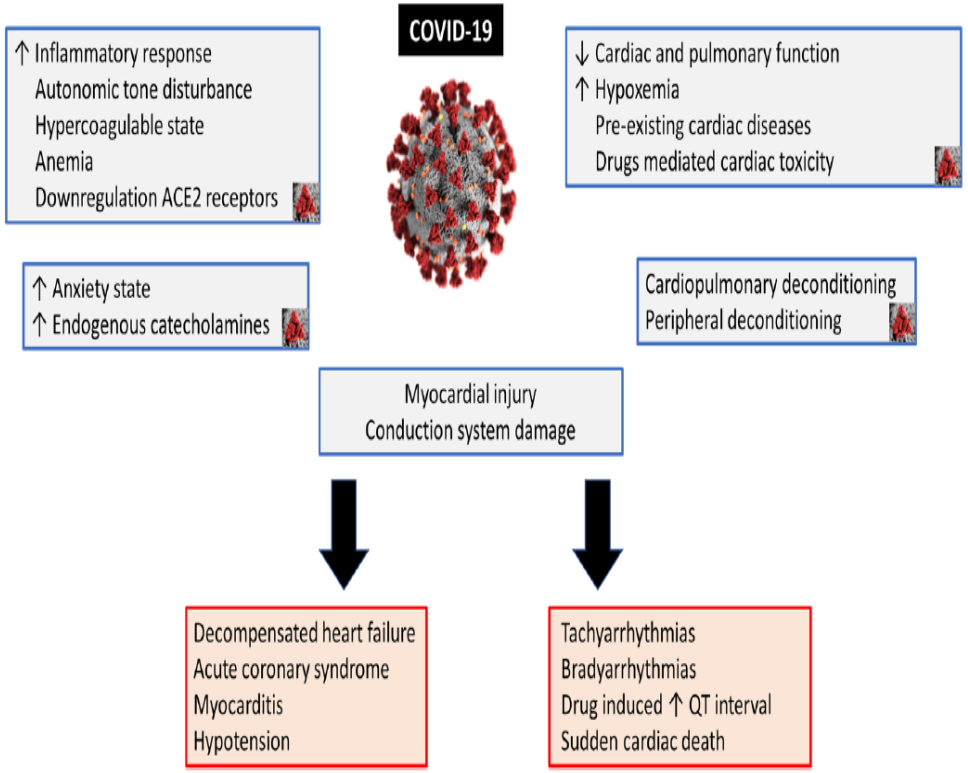
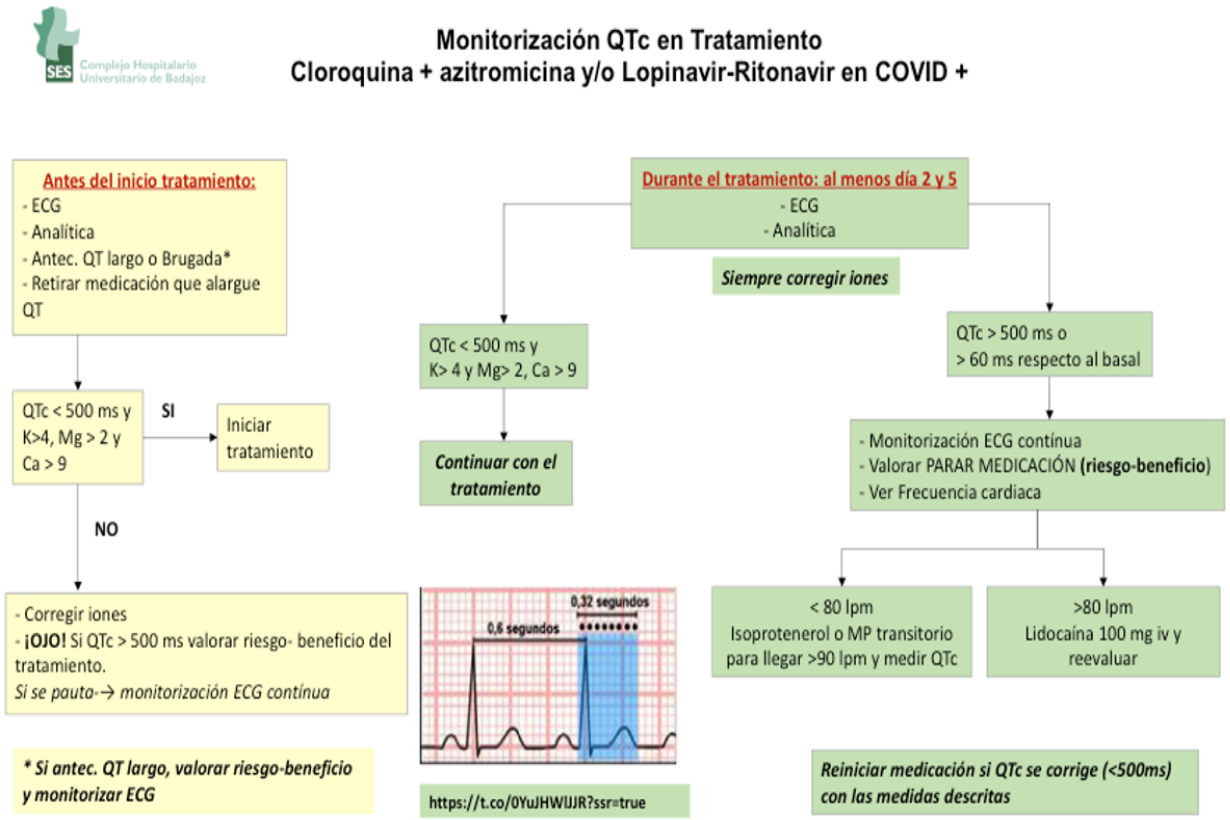


FIGURE 1 Mechanisms and consequences of COVID-19 myocardial damage. COVID-19, coronavirus disease



SARS Co 2: Enfermedad de Kawasaki

An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study

Lucio Verdoni, Angelo Mazza, Annalisa Gervasoni, Laura Martelli, Maurizio Ruggeri, Matteo Ciuffreda, Ezio Bonanomi, Lorenzo D'Antiga

Summary

Background The Bergamo province, which is extensively affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic, is a natural observatory of virus manifestations in the general population. In the past month we recorded an outbreak of Kawasaki disease; we aimed to evaluate incidence and features of patients with Kawasaki-like disease diagnosed during the SARS-CoV-2 epidemic.

Methods All patients diagnosed with a Kawasaki-like disease at our centre in the past 5 years were divided according to symptomatic presentation before (group 1) or after (group 2) the beginning of the SARS-CoV-2 epidemic. Kawasaki-like presentations were managed as Kawasaki disease according to the American Heart Association indications. Kawasaki disease shock syndrome (KDSS) was defined by presence of circulatory dysfunction, and macrophage activation syndrome (MAS) by the Paediatric Rheumatology International Trials Organisation criteria. Current or previous infection was sought by reverse-transcriptase quantitative PCR in nasopharyngeal and oropharyngeal swabs, and by serological qualitative test detecting SARS-CoV-2 IgM and IgG, respectively.

Findings Group 1 comprised 19 patients (seven boys, 12 girls; aged 3·0 years [SD 2·5]) diagnosed between Jan 1, 2015, and Feb 17, 2020. Group 2 included ten patients (seven boys, three girls; aged 7·5 years [SD 3·5]) diagnosed between Feb 18 and April 20, 2020; eight of ten were positive for IgG or IgM, or both. The two groups differed in disease incidence (group 1 *vs* group 2, 0·3 *vs* ten per month), mean age (3·0 *vs* 7·5 years), cardiac involvement (two of 19 *vs* six of ten), KDSS (zero of 19 *vs* five of ten), MAS (zero of 19 *vs* five of ten), and need for adjunctive steroid treatment (three of 19 *vs* eight of ten; all p<0·01).

Interpretation In the past month we found a 30-fold increased incidence of Kawasaki-like disease. Children diagnosed after the SARS-CoV-2 epidemic began showed evidence of immune response to the virus, were older, had a higher rate of cardiac involvement, and features of MAS. The SARS-CoV-2 epidemic was associated with high incidence of a severe form of Kawasaki disease. A similar outbreak of Kawasaki-like disease is expected in countries involved in the SARS-CoV-2 epidemic.

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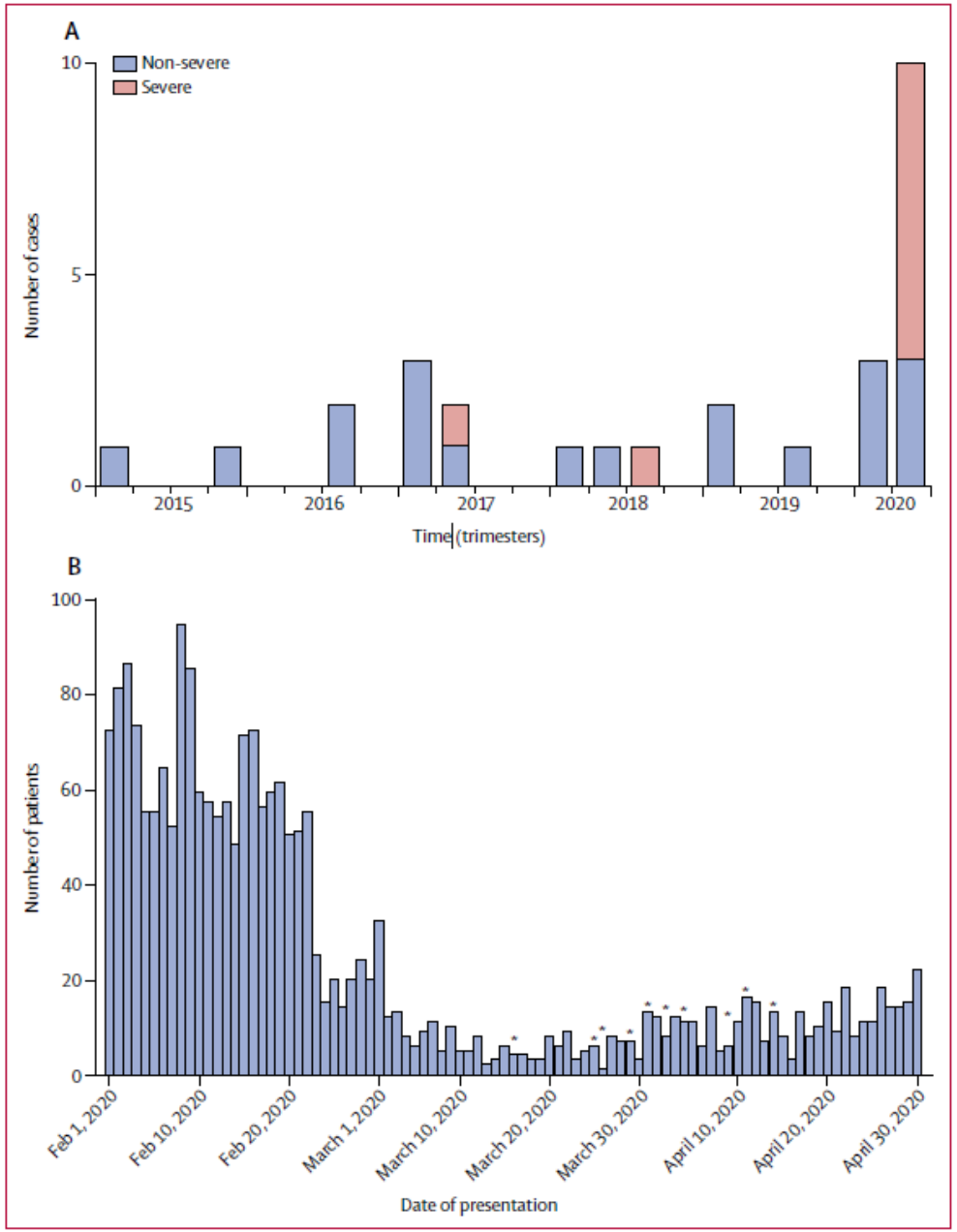


Figure: **Incidence of Kawasaki disease in the study period and in the past 5 years**
(A) Frequency of Kawasaki disease at the paediatric emergency department of Hospital Papa Giovanni XXIII of Bergamo, Italy, in the past 5 years, by case severity. (B) Number of patients presenting to the paediatric emergency department during the severe acute respiratory syndrome coronavirus 2 epidemic, and date of presentation of ten patients with Kawasaki-like disease (indicated by asterisks).

Efectos colaterales del COVID 2

- Incremento del sedentarismo en domicilio
- Disminución de control en seguimiento del paciente cardiológico
- Disminución de procedimientos diagnósticos y terapéuticos.
- Disminución de angioplastias primarias (Código Infarto)
- Aumento de la mortalidad por infarto de miocardio

Reducción de hospitalizaciones por Síndrome Coronario Agudo en tiempos del COVID-19

Table 1 Admissions for specific diagnoses

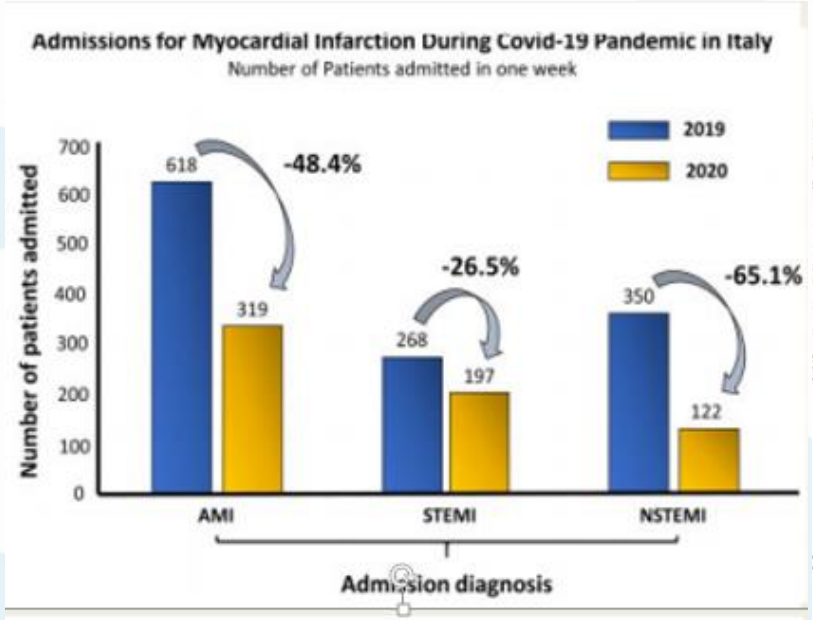
		2019			2020					
	Centres	Adm	Sex^F	Age	Adm	Sex^F	Age	Change	95% CI	P-value
AMI	54	618	176	67.1 ± 9.5	319	76	68.0 ± 9.0	48.4%	44.6–52.5	<0.001
STEMI	54	268	68	65.4 ± 9.7	197	40	66.5 ± 10.2	26.5%	21.7–32.3	0.009
NSTEMI	54	350	108	68.9 ± 9.3	122	36	69.6 ± 8.1	65.1%	60.3–70.3	<0.001
HF	50	154	59	72.3 ± 10.1	82	30	72.9 ± 9.7	46.8%	39.5–55.3	0.005
AF	48	88	29	70.0 ± 7.5	41	17	64.6 ± 12.3	53.4%	43.9–64.9	0.017
DF	49	19	6	76.9 ± 5.4	7	3	70.6 ± 15.2	63.2%	0.45–0.89	0.349
PE	34	17	6	69.1±13.3	12	2	70.8 ± 11.2	29.4%	0.14–0.61	0.667

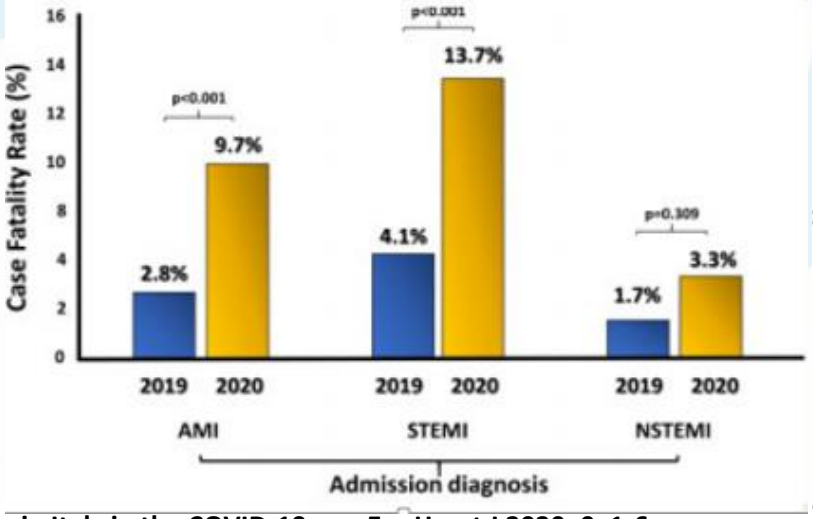
Absolute number of patients admitted during the 2019 (light blue columns) and the 2020 (yellow-shaded columns) index weeks are reported, along with sex and age. Percentage change in admissions in 2020 compared with 2020 is reported (Change). 95% confidence intervals (95% CI) are also reported, followed by the *P*-value.
Every line reports data on a single disease: AMI = acute myocardial infarction; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; HF = heart failure; AF = atrial fibrillation; DF = device failure; PE = pulmonary embolism; Adm = admissions; Sex^F = number of females.

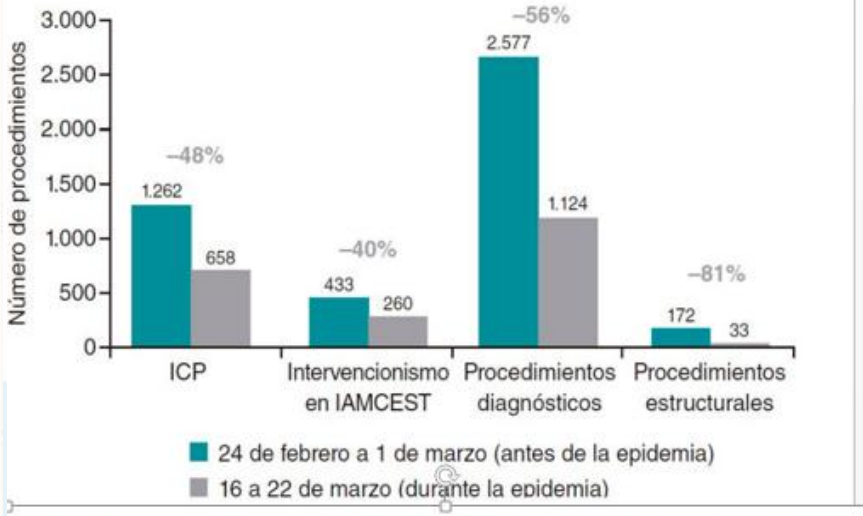
Table 2 Case fatality rate

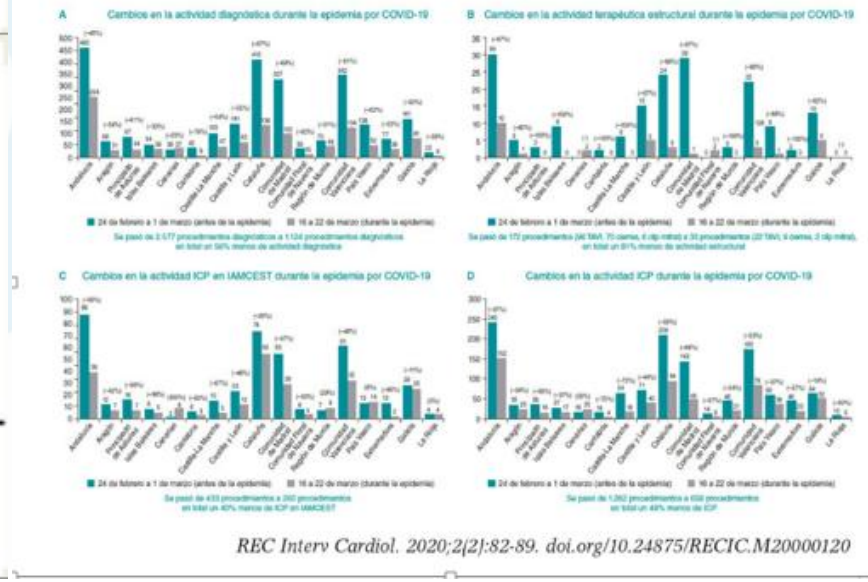
		2019		2020			
	Centres	Adm	Dead (%)	Adm	Dead (%)	RR (95% CI)	P-value
AMI	54	618	17 (2.8)	319	31 (9.7)	3.6 (2.0–6.4)	<0.001
STEMI	54	268	11 (4.1)	197	27 (13.7)	3.3 (1.7–6.6)	<0.001
NSTEMI	54	350	6 (1.7)	122	4 (3.3)	1.9 (0.5–6.7)	0.309

Absolute number of patients admitted and the number of deaths during the 2019 (light blue columns) and the 2020 (yellow-shaded columns) index weeks are reported. Risk ratios are reported in the next column, together with their 95% confidence intervals (95% CI), followed by the *P*-value.
Every line reports data on a single disease: AMI = acute myocardial infarction; STEMI = ST-segment elevation myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; Adm = admissions; RR = risk ratio.









REC Interv Cardiol. 2020;2(2):82-89. doi.org/10.24875/RECIC.M20000120

De Rosa S et al. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. Eur Heart J 2020; 0: 1-6

Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?

The most distinctive comorbidities of 32 non-survivors from a group of 52 intensive care unit patients with novel coronavirus disease 2019 (COVID-19) in the study by Xiaobo Yang and colleagues[1] were cerebrovascular diseases (22%) and diabetes (22%). Another study[2] included 1099 patients with confirmed COVID-19, of whom 173 had severe disease with comorbidities of hypertension (23·7%), diabetes mellitus (16·2%), coronary heart diseases (5·8%), and cerebrovascular disease (2·3%). In a third study,[3] of 140 patients who were admitted to hospital with COVID-19, 30% had hypertension and 12% had diabetes. Notably, the most frequent comorbidities reported in these three studies of patients with COVID-19 are often treated with angiotensin-converting enzyme (ACE) inhibitors; however, treatment was not assessed in either study.

Human pathogenic coronaviruses (severe acute respiratory syndrome coronavirus [SARS-CoV] and SARS-CoV-2) bind to their target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels.[4] The expression of ACE2 is substantially increased in patients with type 1 or type 2 diabetes, who are treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs). Hypertension is also treated with ACE inhibitors and ARBs, which results in an upregulation of ACE2.[5] ACE2 can a
by thiazolidinedione
These data sugg
expression is increa
and treatment with
and ARBs increases
Consequently, the inc
of ACE2 would facilita
COVID-19. We there
that diabetes and
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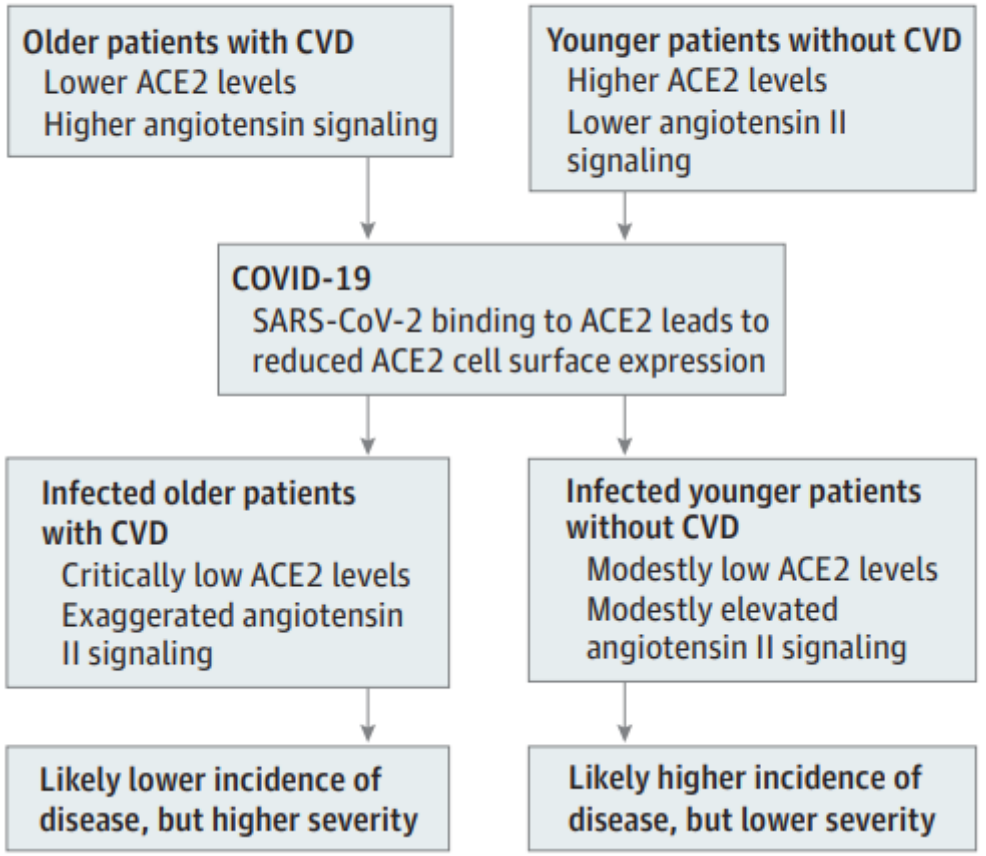
drugs increases the r
severe and fatal COVI

If this hypothes
confirmed, it could
regarding treatmen
reduces inflammatic
suggested as a poter
for inflammatory lung
diabetes, and hypert
aspect that should
is the genetic pre
an increased risk
infection, which m
ACE2 polymorphism
linked to diabetes
stroke, and hyperter
in Asian populatior
this information, th
an individual migh
combination of bo
ACE2 polymorphism.

We suggest that
cardiac diseases, h
diabetes, who are tre
increasing drugs, ar
for severe COVID-1
therefore, should b
ACE2-modulating m
as ACE inhibitors or
PubMed search on F
did not find any evi
that antihypertensive
blockers increased
or activity, therefore these could be a suitable alternative treatment in these patients.

Figure. Schematic of Inflammatory Profile Before and After Coronavirus Disease 2019 (COVID-19) Infection



POSITION STATEMENT OF THE ESC COUNCIL ON HYPERTENSION ON ACE-INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

ESC Council Hypertension

China, and subsequent evidence that arterial hypertension may be associated with
hospitalized COVID-19 infected subjects, hypotheses have been put forward to suggest a
giotensin converting enzyme inhibitors (ACE-i) or Angiotensin Receptor Blockers (ARBs). It
y on social media sites, that these commonly used drugs may increase both the risk of
ARS-CoV2. The concern arises from the observation that, similar to the coronavirus
irus binds to a specific enzyme called ACE2 to infect cells, and ACE2 levels are increased
-I and ARBs.
elated amplification, patients taking these drugs for their high blood pressure and their
ngly concerned, and, in some cases, have stopped taking their ACE-I or ARB medications.
fety of ACE-i or ARB treatment in relation to COVID-19 does not have a sound scientific
t. Indeed, there is evidence from studies in animals suggesting that these medications
ainst serious lung complications in patients with COVID-19 infection, but to date there is

of the European Society of Cardiology wish to highlight the lack of any evidence
ACE-I and ARB in the context of the pandemic COVID-19 outbreak.
strongly recommend that physicians and patients should continue treatment with their
py because there is no clinical or scientific evidence to suggest that treatment with ACEI or
because of the Covid-19 infection.

Prof. Giovanni de Simone,
Chair, ESC Council on Hypertension
On behalf of the Nucleus Members

Int J Antimicrob Agents. 2020 Apr; 55(4): 105932.
Published online 2020 Mar 4. doi: 10.1016/j.ijantimicag.2020.105932
PMCID: PMC7135139
PMID: 32145363

Chloroquine and hydroxychloroquine as available weapons to fight COVID-19

Philippe Colson,[a,b] Jean-Marc Rolain,[a,b] Jean-Christophe Lagier,[a,b] Philippe Brouqui,[a,b] and Didier Raoult[a,b,*]

‣ Author information ‣ Article notes ‣ Copyright and License

[1,12,13] (Table 1). We previously emphasised interest i
this journal [1], predicting its use in viral infections lack
in vitro activity of chloroquine against SARS-CoV-2, d
50% and 90% effective concentrations (EC_{50} and EC_{90}
(antiviral activity being observed when addition of this
of the cells) [3], we awaited with great interest the clini
communicated following the first results of clinical tria
enthusiasm among us. They showed that chloroquine c
the evolution of COVID-19 pneumonia [4,6], leading to
chloroquine twice a day in patients with mild, moderate
such a dosage, a therapeutic concentration of chloroqui
dosages of hydroxychloroquine during the past 5 years
know that with a dosage of 600 mg/day we reach a con
SARS-CoV-2 is an issue that will need to be assessed i
hydroxychloroquine on viruses is probably the same as
of these two molecules is identical, and we are used to
which would be therefore our first choice in the treatme
be necessary to administer a loading dose followed by a

Sin embargo, los **investigadores** advierten que "nuestro estudio tiene algunas **limitaciones**, incluido un tamaño de muestra pequeño, un seguimiento limitado de los resultados a largo plazo y el abandono de seis pacientes del estudio".

Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Published Online June 4, 2020 https://doi.org/10.1016/S0140-6736(20)31324-6

After publication of our *Lancet* Article,[1] several concerns were raised with respect to the veracity of the data and analyses conducted by Surgisphere Corporation and its founder and our co-author, Sapan Desai, in our publication. We launched an independent third-party peer review of Surgisphere with the consent of Sapan Desai to evaluate the origination of the database elements, to confirm the completeness of the database, and to replicate the analyses presented in the paper.

Our independent peer reviewers informed us that Surgisphere would not transfer the full dataset, client contracts, and the full ISO audit report to their servers for analysis as such transfer would violate client agreements and confidentiality requirements. As such, our reviewers were not able to conduct an independent and private peer review and therefore notified us of their withdrawal from the peer-review process.

We always aspire to perform our research in accordance with the highest ethical and professional guidelines. We can never forget the responsibility we have as researchers to scrupulously ensure that we rely on data sources that adhere to our high standards. Based on this development, we can no longer vouch for the veracity of the primary data sources. Due to this unfortunate development, the authors request that the paper be retracted.

We all entered this collaboration to contribute in good faith and at a time of great need during the COVID-19 pandemic. We deeply apologise to you, the editors, and the journal readership for any embarrassment or inconvenience that this may have caused.

MRM reports personal fees from Abbott, Medtronic, Janssen, Roivant, Triple Gene, Mesoblast, Baim Institute for Clinical Research, Portola, Bayer, NupulseCV, FineHeart, and Leviticus. FR has been paid for time spent as a committee member for clinical trials, advisory boards, other forms of consulting, and lectures or presentations; these payments were made directly to the University of Zurich and no personal payments were received in relation to these trials or other activities since 2018. Before 2018 FR reports grants and personal fees from SJM/Abbott, grants and personal fees from Servier, personal fees from Zoll, personal fees from Astra Zeneca, personal fees from Sanofi, grants and personal fees from Novartis, personal fees from Amgen, personal fees from BMS, personal fees from Pfizer, personal fees from Fresenius, personal fees from Vifor, personal fees from Roche, grants and personal fees from Bayer, personal fees from Cardiorentis, personal fees from Boehringer Ingelheim, other from Heartware, and grants from Mars. ANP declares no competing interests.

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1 Mehra MR, Desai SS, Ruschitzka F, Patel AN. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020; published online May 22. https://doi.org/10.1016/S0140-6736(20)31180-6.

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Summary

Background Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment ı COVID-19.

l registry analysis of the use of hydroxychloroquine or chloroquine with or without a ID-19. The registry comprised data from 671 hospitals in six continents. We included ec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. treatments of interest within 48 h of diagnosis were included in one of four treatment roquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a ceived none of these treatments formed the control group. Patients for whom one of iitiated more than 48 h after diagnosis or while they were on mechanical ventilation, remdesivir, were excluded. The main outcomes of interest were in-hospital mortality ventricular arrhythmias (non-sustained or sustained ventricular tachycardia or

age 53·8 years, 46·3% women) with COVID-19 were hospitalised during the study criteria. Of these, 14888 patients were in the treatment groups (1868 received oroquine with a macrolide, 3016 received hydroxychloroquine, and 6221 received rolide) and 81144 patients were in the control group. 10698 (11·1%) patients died in ultiple confounding factors (age, sex, race or ethnicity, body-mass index, underlying k factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, when compared with mortality in the control group (9·3%), hydroxychloroquine CI 1·223–1·457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), 8–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each n increased risk of in-hospital mortality. Compared with the control group (0·3%), 59, 1·935–2·900), hydroxychloroquine with a macrolide (8·1%; 5·106, 4·106–5·983), chloroquine (4·3%; 3·361, 2·760–4·596), and chloroquine with a macrolide (6·5%; 4·011, 3·344–4·812) were independently associated with an increased risk of de-novo ventricular arrhythmia during hospitalisation.

Interpretation We were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19.

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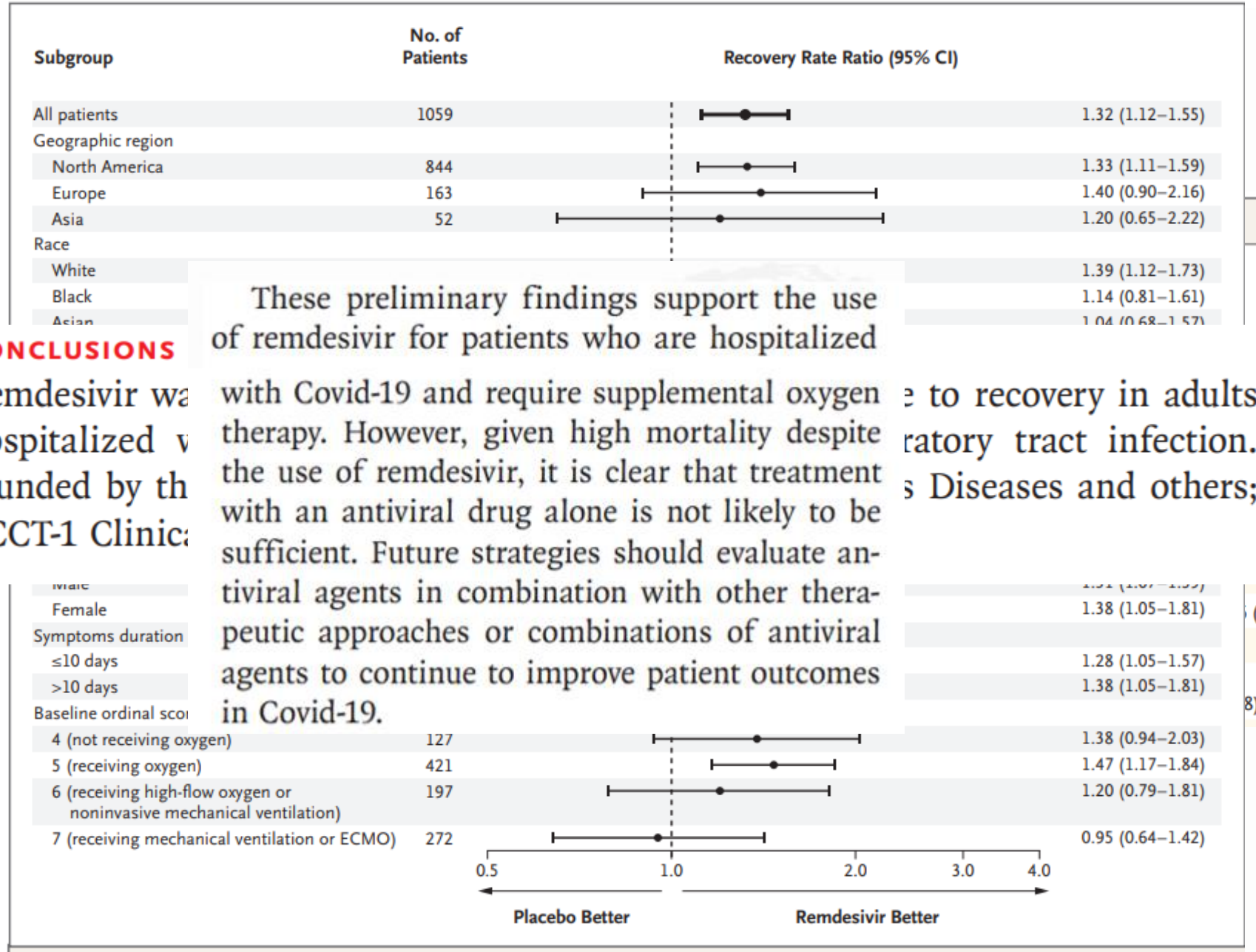

Figure 3. Time to Recovery According to Subgroup.

The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects.

CONCLUSIONS

Remdesivir wa … to recovery in adults hospitalized v … ratory tract infection. (Funded by th … s Diseases and others; ACCT-1 Clinica …

These preliminary findings support the use of remdesivir for patients who are hospitalized with Covid-19 and require supplemental oxygen therapy. However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient. Future strategies should evaluate antiviral agents in combination with other therapeutic approaches or combinations of antiviral agents to continue to improve patient outcomes in Covid-19.

Table 2. Outc…

		Placebo (N=147)
Recovery		
No. of rec…		51
Median ti… (95% …		28 (NE– 22)
Rate ratio …		…64–1.42)
Mortality		
Hazard ratio …		… (0.59–1.92)
No. of deaths		19
Kaplan–Meier … — % (95…		14.1 (9.2–21.2)

Reflexiones

- Extremar
- Prever las
- Integrar c
- Increment
- Huir de lo
- Las prisas

- Humildad
- Entrega
- Generosidad
- Objetividad

Conclusiones

- El SARS Co V 2 presenta asociación moderada con FRCV.
- También con la presencia de ECV y esto agrava su evolución, muy especialmente en la población de mayor edad.
- Se ignora su mecanismo de acción y se han expuesto algunas teorías relacionadas con la injuria miocárdica que deben investigarse.
- Durante la enfermedad es necesario ajustar algunos tratamientos.
- Algunos de los tratamientos dirigidos a combatir el virus tienen efectos adversos sobre el corazón.
- Su presencia disminuyó significativamente la realización de angioplastias primarias lo que puede haber incrementado la mortalidad debida a SCA.

MUCHAS GRACIAS