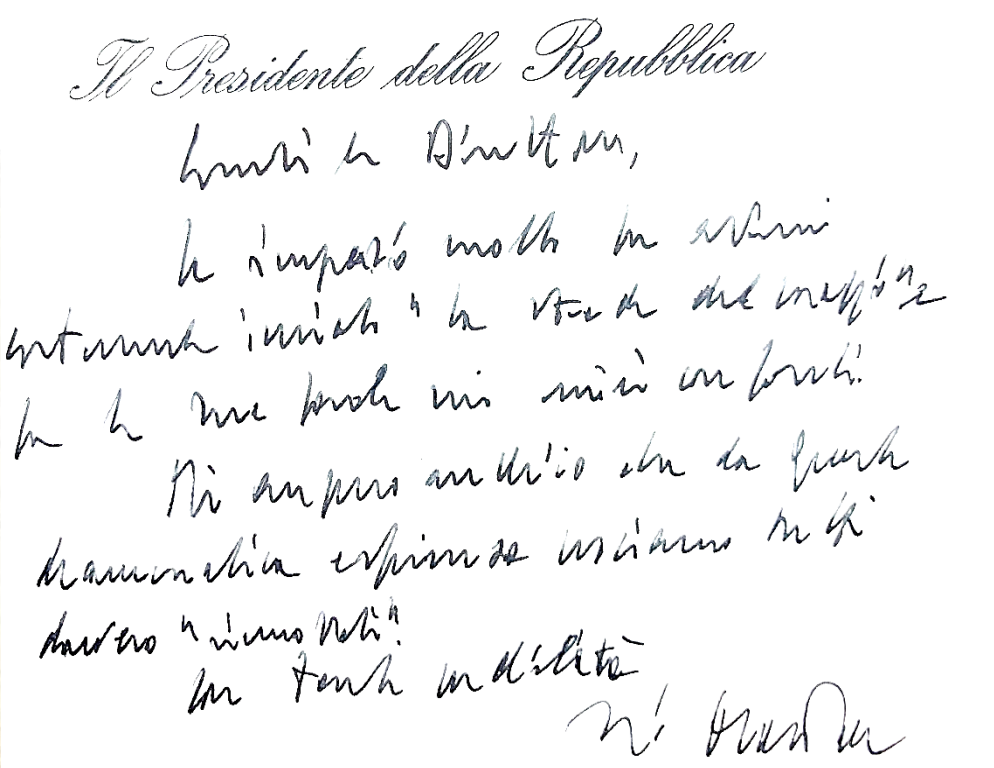
RIDEFINIRE LE PRIORITÀ DELLE MALATTIE CARDIOVASCOLARI DURANTE LA PANDEMIA COVID 19: MOLTE DOMANDE, POCHE RISPOSTE

FRANCESCO MARIA BOVENZI



Egregio Direttore,

*La ringrazio molto per avermi cortesemente inviato «**la strada del coraggio**» e per le sue parole nei miei confronti.*

Mi auguro anch'io che da questa drammatica esperienza usciremo tutti davvero «rinnovati».

Con tanta cordialità,
Sergio Mattarella

I numeri del Covid-19 (Dashboard)

Il personale sanitario ha affrontato con sacrificio le insidie di un nemico invisibile che ha infettato

in oltre **200 Paesi del mondo**

- quasi **230 milioni di persone**
- con oltre **4,8 milioni di decessi**

In Italia: 4,7 milioni di persone con 131.000 decessi

- nel primo anno sono deceduti **17.000 operatori della salute**
- Circa **40 milioni** di cittadini nel mondo **sono stati in lutto**

ESC Guidance

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

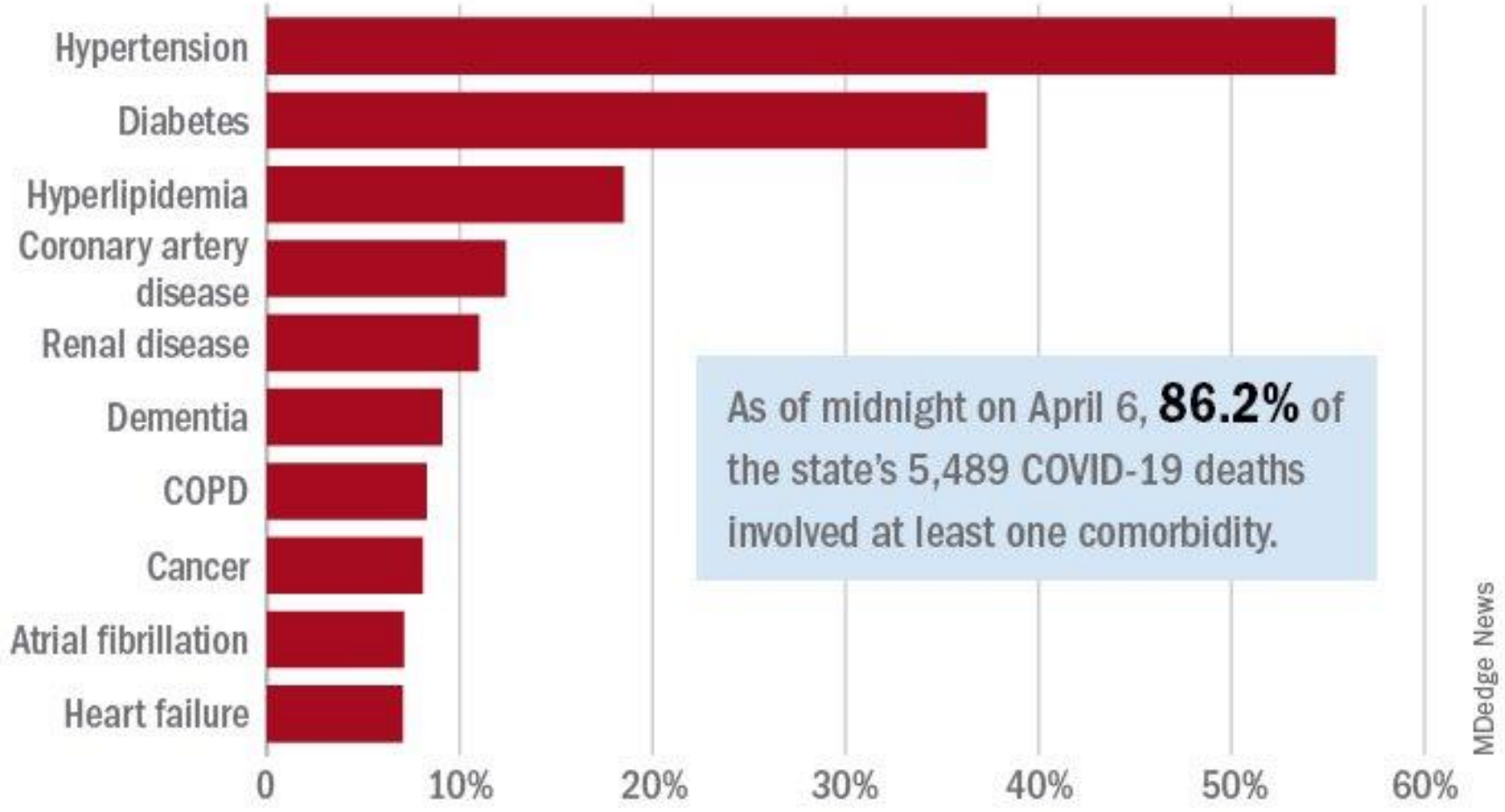
ESC European Society of Cardiology

ESC, 10 June 2020

1. **SARS-CoV-2** (Severe acute respiratory syndrome coronavirus 2) causing **Covid-19** (coronavirus disease 2019) **has reached pandemic levels**
2. **Pts with cardiovascular risk factors and established CVD represent a vulnerable population** when suffering from COVID-19
3. **Pts with cardiac injury** in the context of COVID-19 **have an increased risk of morbidity and mortality**

Cardio LUCCA

Leading comorbidities among COVID-19 deaths in New York



Note: Data reported on a daily basis by hospitals, nursing homes, and other health care facilities.

Source: New York State Department of Health

The New York Times

Opinion

Covid-19 Is Creating a Wave of Heart Disease

Emerging data show that some of the coronavirus's most potent damage is inflicted on the heart.

By Haider Warraich

Dr. Warraich is a cardiologist.

Aug. 17, 2020, 5:00 a.m. ET

VIEWPOINT

Cardiology and COVID-19

Bonow R. JAMA 2020

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Viewpoints pages 1131-1155 and Editorial page 1159

The initial reports on the epidemiology of coronavirus disease 2019 (COVID-19) emanating from Wuhan, China, offered an ominous forewarning of the risks of severe complications in elderly patients and those with underlying cardiovascular disease, including the development of acute respiratory distress syndrome, cardiogenic shock, thromboembolic events, and death. These observations have been confirmed subsequently in numerous reports from around the globe, including studies from Europe and the US. The mechanisms responsible for this vulnerability have not been fully elucidated, but there are several possibilities. Some of these adverse consequences could reflect the basic fragility of older individuals with chronic conditions subjected to the stress of severe pneumonia similar to influenza infections. In addition, development of type 2 myocardial infarction related to increased myocardial oxygen demand in the setting of hypoxia may be a predominant concern, and among patients with chronic coronary artery disease, an episode of acute systemic inflammation might also contribute to plaque instability, thus precipitating acute coronary syndromes, as has also been reported during influenza outbreaks.

However, in the brief timeline of the current pandemic, numerous publications highlighting the constellation of observed cardiovascular consequences have emphasized certain distinctions that appear unique to COVID-19.[1] Although the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gains entry via the upper respiratory tract, its affinity and selective bind-

Thrombosis, arterial or venous, is a hallmark of severe COVID-19 infections, related both to vascular injury and the prothrombotic cytokines released during the intense systemic inflammatory and immune responses.[3] This sets the stage for serious thrombotic complications including acute coronary syndromes, ischemic strokes, pulmonary embolism, and ischemic damage to multiple other organ systems. Such events can complicate the course of any patient with COVID-19 but would be particularly devasting to individuals with preexisting cardiovascular disease.

Another unique aspect of COVID-19 infections that is not encountered by patients with influenza is myocardial injury, manifested by elevated levels of circulating troponin, creatinine kinase-MB, and myoglobin. Hospitalized patients with severe COVID-19 infections and consequent evidence of myocardial injury have a high risk of in-hospital mortality.[4] Troponin elevations are most concerning, and when accompanied by elevations of brain natriuretic peptide, the risk is further accentuated. Although myocardial injury could reflect a COVID-19–related acute coronary event, most patients with troponin elevations who undergo angiography do not have epicardial coronary artery obstruction. Rather, those with myocardial injury have a high incidence of acute respiratory distress syndrome, elevation of D-dimer levels, and markedly elevated inflammatory biomarkers such as C-reactive protein and procalcitonin, suggesting that the combination of hypoxia, microvascular thrombosis, and systemic inflammation contributes to myocardial injury. Myocarditis is a candidate explanation for myocardial injury but has been difficult to confirm consistently. However, features of myocarditis have been reported

Thrombosis, arterial or venous, is a hallmark of severe COVID-19 infections...

I pts con distress respiratorio acuto grave hanno un alta incidenza di danno miocardico, un aumento di Livelli di D-dimero e PCR lasciando supporre che la combinazione di ipossia, danno microvascolare e **trombosi** con infiammazione sistemica possano contribuire al danno.

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Malattie CV al tempo del Covid-19: come possiamo stimarne il reale impatto?

1) **Riduzione degli accessi per SCA nella fase acuta**
2) La malattie CV rappresentano complicanze gravi e la principale **causa di morte** nel Covid-19
3) I pazienti con problematiche CV hanno **maggiore probabilità di essere infettati**
4) La presenza di danno miocardico è un marker di **peggiori outcome**
5) **Morti aritmiche** indotte anche da scelta di terapie inappropriate
6) **Miocarditi, embolia polmonare, infarto miocardico, danno microvascolare,** evoluzione vs **fibrosi polmonare** con ipertensione polmonare e disfunzione ventricolare dx persistente
7) **Burden del Long-Covid**
8) **Problematiche organizzative e assistenziali:** radicale cambiamento del lavoro degli operatori della salute
9) **Cambia la metodologia della ricerca clinica**

La risposta del mondo scientifico alla pandemia è stata forte e globale

- I virus ha confermato di avere **una propria intelligenza biologica** che sostiene il vivere da **parassita** nelle cellule dell'uomo

- Sono **migliaia gli articoli pubblicati** sulle riviste mediche invase da contributi al punto che avere **un articolo inviato ai *referee* è considerato un grande successo, perché tanti studi sono subito rifiutati.**

- Dall'inizio 2020 ad oggi **alla voce Covid-19 sul sito ClinicalTrials.gov** sono stati registrati **oltre 7000 i programmi di ricerca clinica** e sempre più numerosi sono quelli di intervento.

- La pandemia ha persino **cambiato la metodologia e il rigore scientifico delle ricerca clinica:** da aneddotica e osservazionale avanzano nuovi **modelli «adattivi»**

doi:10.1093/eurheartj/ehaa675

Adapting to survive

Are 'classic' clinical trials at risk for extinction in the post-COVID era?

In current times, all of us are 'forced to adapt' to the new, unexpected environment created by the Coronavirus pandemic. Indeed, the ability to adapt to a changing environment is the key to successful evolution. People, healthcare systems, hospitals, economy, governments, etc., all have to adapt! Clinical science, which is typically linked to rigid schemes and protocols, is not exempt and large classic clinical trials are embracing the so-called 'adaptive designs'.

Why the switch to adaptive trials?

It is a necessity. In the last two decades, the world has experienced six large viral epidemics: influenza H1V1, HIV-AIDS, Ebola, SARS-1, METS, and the present COVID-19 (or SARS-2). The last three belong to the same family: the Corona viruses. All the previous epidemics ceased, more or less, spontaneously. Actually, they became and still remain endemic. The scientific world was not particularly upset, mainly because these epidemics remained confined to a few areas with local specificities. Several new drugs were tested but at the end, no cure was found nor were vaccines produced.

An adaptive trial? What is it?

An 'adaptive' trial is defined as 'a design that allows for prospectively planned modifications to one or more aspects of the trial based on accumulating data from subjects in the trial' (FDA).[4] Several papers carefully describe the principles and applications.[5–7] In principle, the adaptive trial designs are based on a flexible methodology aimed at 'adapting' the trial design and performance to specific dynamic characteristics of the study, emerging from the investigator observations and from interim analyses (blinded or not-blinded), to allow to achieve the expected answers quickly and (hopefully) precisely. For instance, a trial arm may be stopped for efficacy, futility, harm, but also for evidence of benefit or damage emerging from another well-designed contemporary trial. Hence, the trial can be concluded when an answer is obtained instead of when a prefixed sample size is achieved. The central characteristics of the trial can also be changed during its course, inclusion and exclusion criteria can be modified, the criteria for randomization, and even the endpoints can be changed, switching from non-inferiority to superiority and adapting the alpha spending functions. Often, adaptive trials test multiple treatments and treatment groups can be adapted: participants to a group which is promising can be enlarged or, vice versa, reduced or just limited to a specific phenotype. New arms can also be activated during the course of the main trials and so on.

Our considerations

These are the reasons why, in the present outbreak, scientists and regulators have decided to implement the adaptive design for clinical research. We believe it is the right decision considering the pressing urgency and the uncertainty on what to do or not to do, providing that the necessary rigor and integrity is preserved, as the results of the current trials will decide the life or death of hundreds of thousands of people. Outside the COVID-19 outbreak, a new era for the flexible trials design may arise, also in cardiology. Meantime, an unprecedented spread of different scientific methodological approaches to the same target—the COVID-19 infection—allows a unique experimental exercise worldwide. This leads to a great increase of knowledge, experience and ultimately will make the world ready for future viral epidemics.

The 'Ebola story' is grounds for some optimism. During the 2014–2016 Ebola outbreak in West Africa, many small studies were launched, in the end all inconclusive. The virus remained endemic with periodic smaller outbreaks until 2018–2020 when in the Democratic Republic of the Congo two effective therapies were finally identified.[9] Let us wait and hope for the best.

Acknowledgements

We thank Silvia Felloni and Elisa Ghizzardi for editing and assistance.

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Luigi Tavazzi[1], Claudio Rapezzi[1,2], Aldo Pietro Maggioni[1,3], and Roberto Ferrari[1,2]

- **Uno studio "adattivo" è definito come "un disegno che consente modifiche pianificate in modo prospettico a uno o più aspetti dello studio sulla base dei dati provenienti dai soggetti in studio".**
- Cambia la dimensione del campione prefissata, cambiano le caratteristiche centrali dello studio che possono essere modificate anche durante il suo corso
- Possono essere modificati i criteri di inclusione ed esclusione
- Possono essere modificati i criteri per la randomizzazione e persino gli endpoint, passando dalla non inferiorità alla superiorità.

Ricoveri x STEMI nel period critico COVID-19: la Survey dell'ESC

Ovunque la pandemia COVID-19 ha avuto un forte impatto

- **su dipartimenti di emergenza**
- **sull'assistenza territoriale**
- **sui professionisti**
- **sui pazienti**

MA …

La malattia da COVID-19 ha tenuto più della metà dei pazienti con infarto lontana dagli ospedali!

ESC – STEMI Admission during COVID

ESC European Society of Cardiology

Cardio LUCCA

Reduced Rate of Hospital Admissions for ACS during Covid-19 Outbreak in Northern Italy

Diminuzione significativa dei tassi di ospedalizzazione correlati a SCA nei diversi centri del nord Italia durante i primi giorni dell'epidemia di Covid-19.

Il tasso medio di ricoveri per SCA durante il periodo di studio è stato di 13,3 vs 18,0 dello stesso periodo del precedente anno (P < 0,001)

Table 1. Comparison of Hospital Admissions for Acute Coronary Syndrome (ACS) in Northern Italy between the Onset of the Covid-19 Outbreak and Two Control Periods.*

ACS Subtype	No. of Patients	Study Period (N=547)	Control Periods	
			Same Year (N=899)	Previous Year (N=756)
All ACS	2202			
No. of daily admissions		13.3	18.0	18.9
Incidence rate ratio (95% CI)			0.74 (0.66–0.82)	0.70 (0.63–0.78)
P value			<0.001	<0.001
STEMI	957			
No. of daily admissions		6.1	7.8	8.0
Incidence rate ratio (95% CI)			0.77 (0.66–0.91)	0.75 (0.64–0.89)
NSTEMI	832			
No. of daily admissions		4.2	7.1	7.5
Incidence rate ratio (95% CI)			0.59 (0.49–0.71)	0.56 (0.46- 0.67)
Unstable angina	413			
No. of daily admissions		3.1	3.1	3.4
Incidence rate ratio (95% CI)			1.00 (0.79–1.26)	0.91 (0.72–1.16)

* The study period was defined as the time between the first confirmed case of Covid-19 in Italy (February 20, 2020) and March 31, 2020. The two control periods were from January 1 to February 19, 2020 (same year) and from February 20 to March 31, 2019 (previous year). The 95% confidence intervals are not adjusted for multiple testing and therefore should not be used to infer definitive effects. CI denotes confidence interval, NSTEMI non–ST-segment cardial infarction, and STEMI ST-segment elevation myocardial infarction.

Ovidio De Filippo, M.D.
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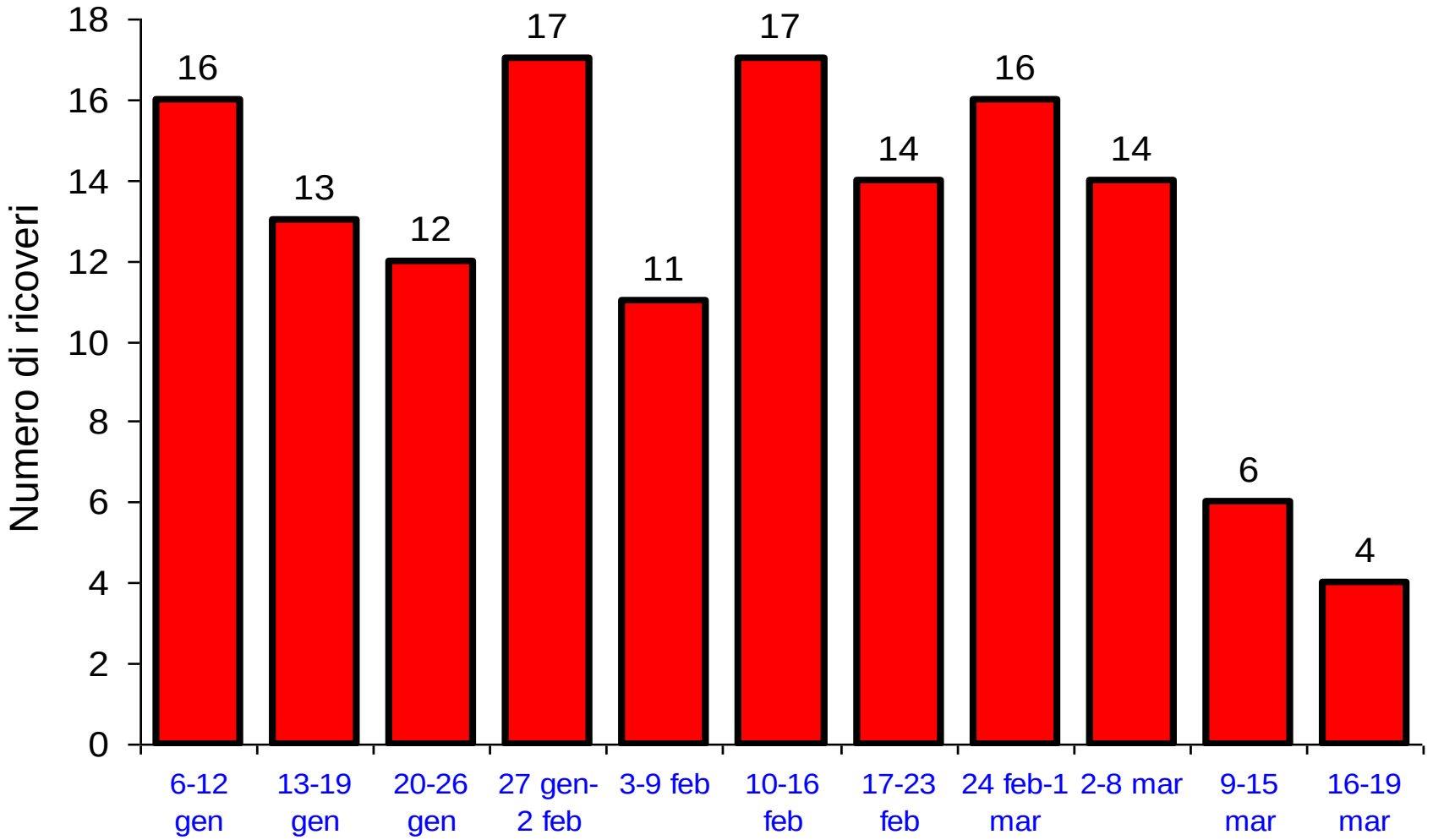
Pier Paolo Bocchino, M.D.
Federico Conrotto, M.D.
Andrea Saglietto, M.D.

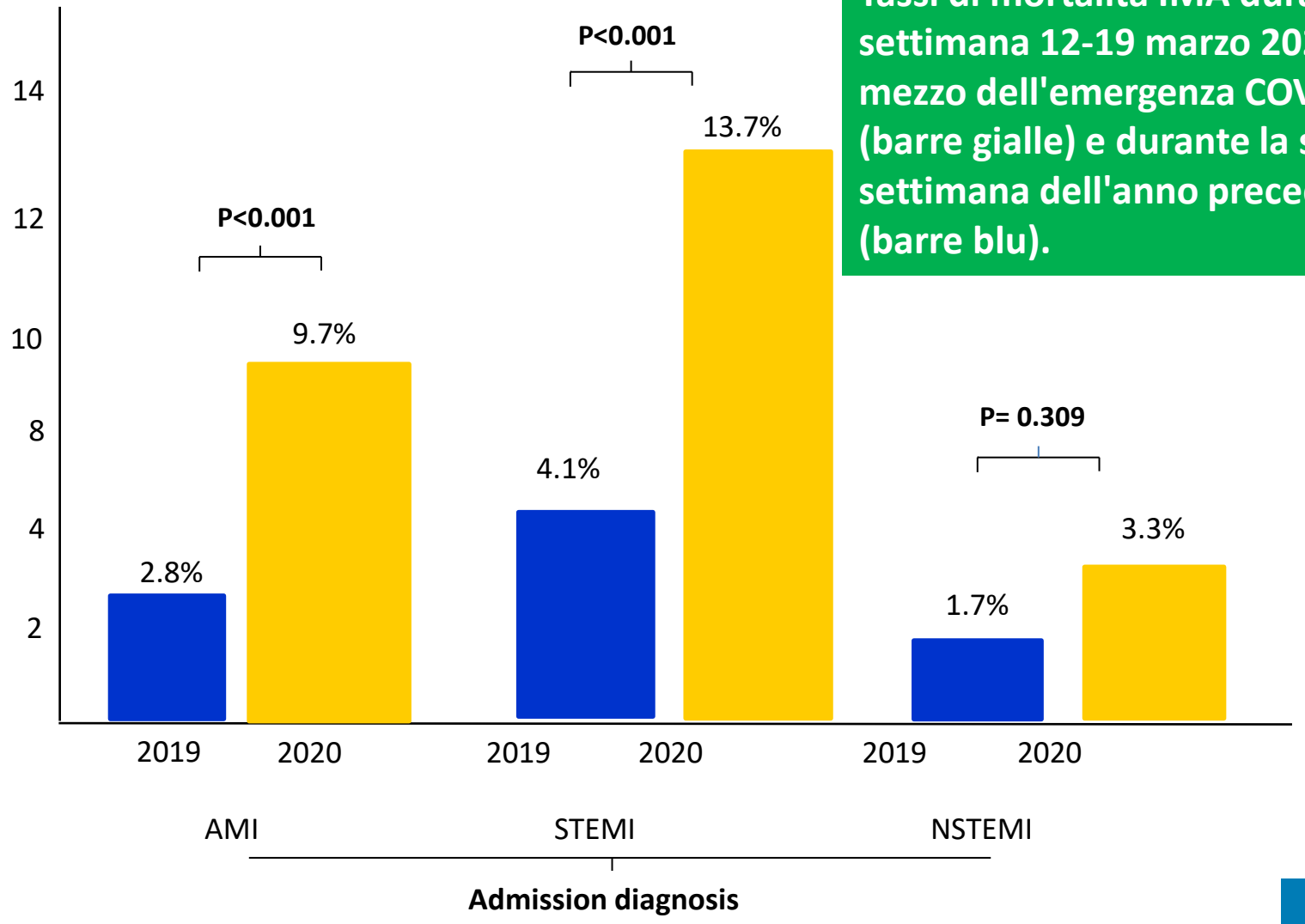
140 ricoveri per patologie acute UTIC Lucca
6 gennaio-19 marzo 2020

83 SCA, 30 scompensp cardiaco (*la gran parte dei ricoveri cardiologici*),
16 aritmie ipocinetiche, 4 aritmie ventricolari ipercinetiche,
3 embolie polmonari, 3 pericarditi, 1 tako-tsubo



Case fatality rates for acute myocardial infarction

Tassi di mortalità IMA durante la settimana 12-19 marzo 2020, nel mezzo dell'emergenza COVID-19 (barre gialle) e durante la stessa settimana dell'anno precedente (barre blu).

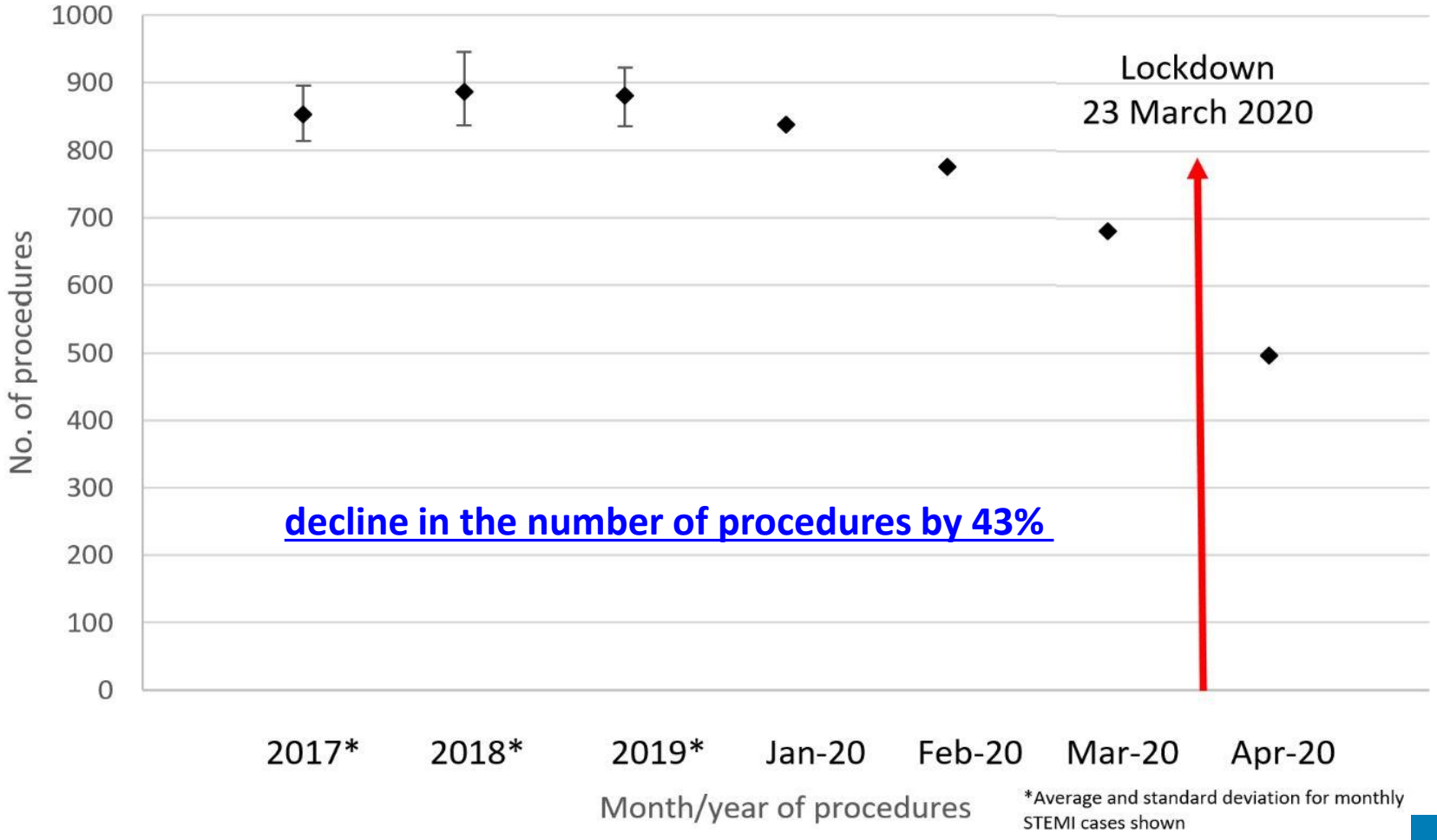


De Rosa et al, Eur Heart J 2020, 0, 1–6 doi: 10.1093/eurheartj/ehha409

Questo aumento significativo della mortalità **non può essere spiegato solo con il peggior andamento nei casi Covid-19**

… i pazienti con infarto sono morti perché non curati in ospedale durante la pandemia Covid-19 **ma anche per un eccesso di ritardo nell'assistenza** territoriale e intra-ospedaliera a tutti i livelli

Number of procedures for primary PCI for STEMI



Kwok at al, Heart, 27 July 2020, in press

Gestione Covid-19 in Cardiologia Invasiva e Cardiostimolazione

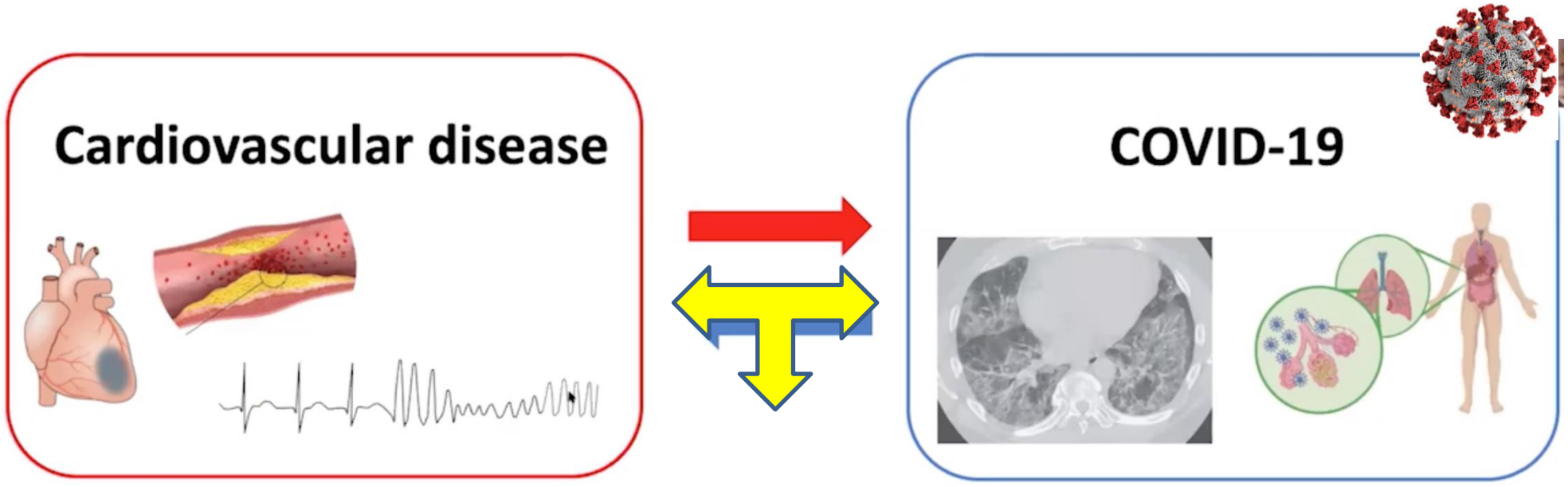
Ospedale San Luca, Lucca

Questo documento viene redatto per la gestione nell'Ospedale San Luca dei pazienti Covid-19 sospetti, probabili o confermati, differibili o non differibili, con l'obiettivo di:

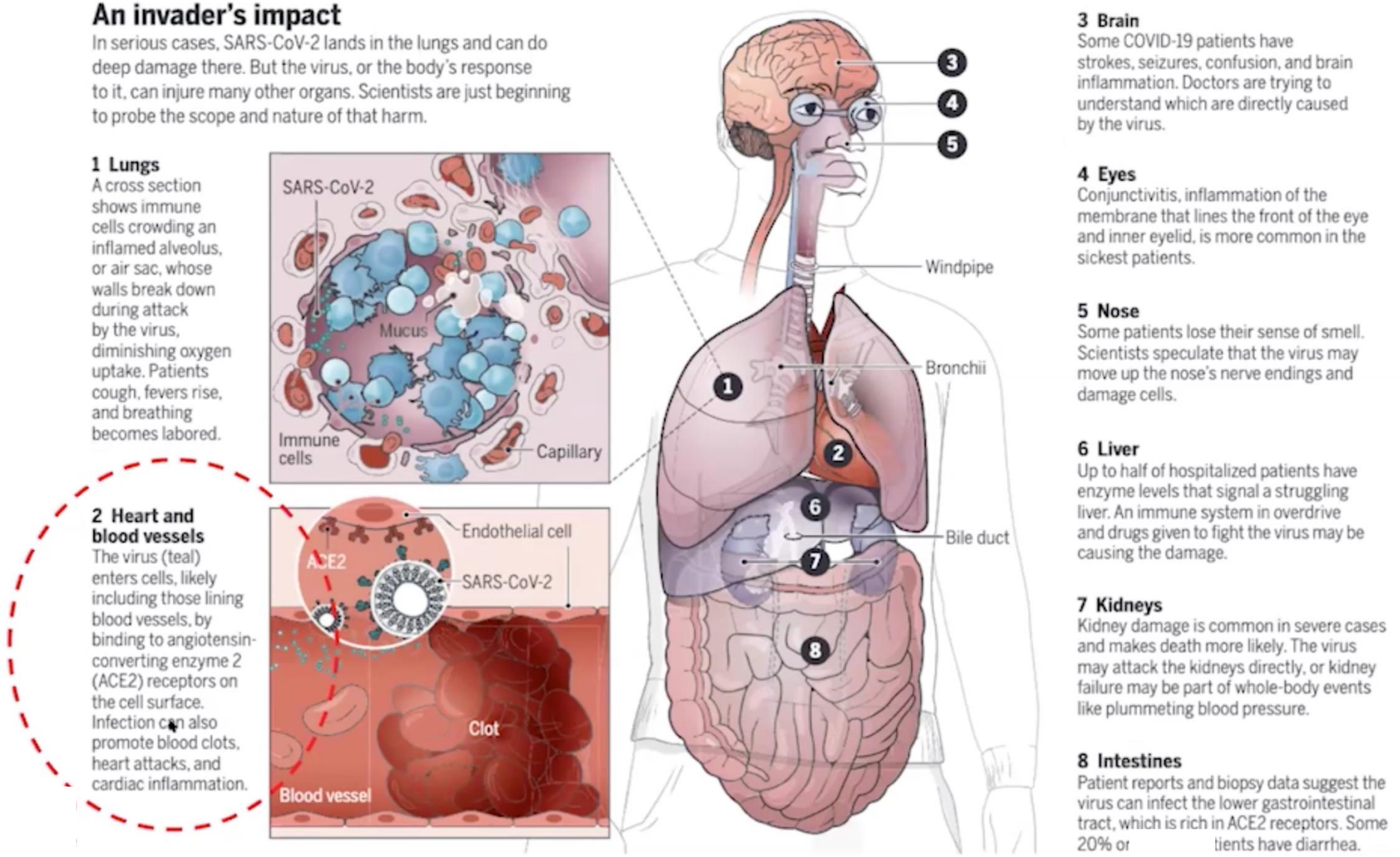
1. Distinguere un percorso tra:
   - **Casi differibili,** la gran parte che potremmo quindi chiamare elettivi pur in un contesto di SCA-NSTEMI, a meno di differente giudizio clinico condiviso e certamente limitato solo ad alcuni di questi come nel dolore persistente o subentrante, gravi aritmie complesse, scompenso cardiaco avanzato etc
   - **Casi NON differibili**, questi ultimi perché nelle condizioni tempo-dipendenti: STEMI, PM temporanei per blocco avanzato non responsivi di cardiostimolazione esterna, pericardiocentesi urgente non differibile per grave tamponamento cardiaco etc. Questi non saranno soggetti a triage, molti di essi provenienti direttamente dal Territorio come gran parte degli STEMI o i blocchi AV avanzati non responsivi alla cardiostimolazione esterna, ma potranno continuare ad arrivare come sempre, eccetto situazioni limite secondo giudizio clinico, **direttamente in sala di emodinamica MA COME TALI andranno necessariamente considerati alla stregua dei probabili o sospetti o confermati COVID-19.**

La notte del 2 aprile 2020 dopo aver trattato uno STEMI

Fisiopatologia del coinvolgimento CV

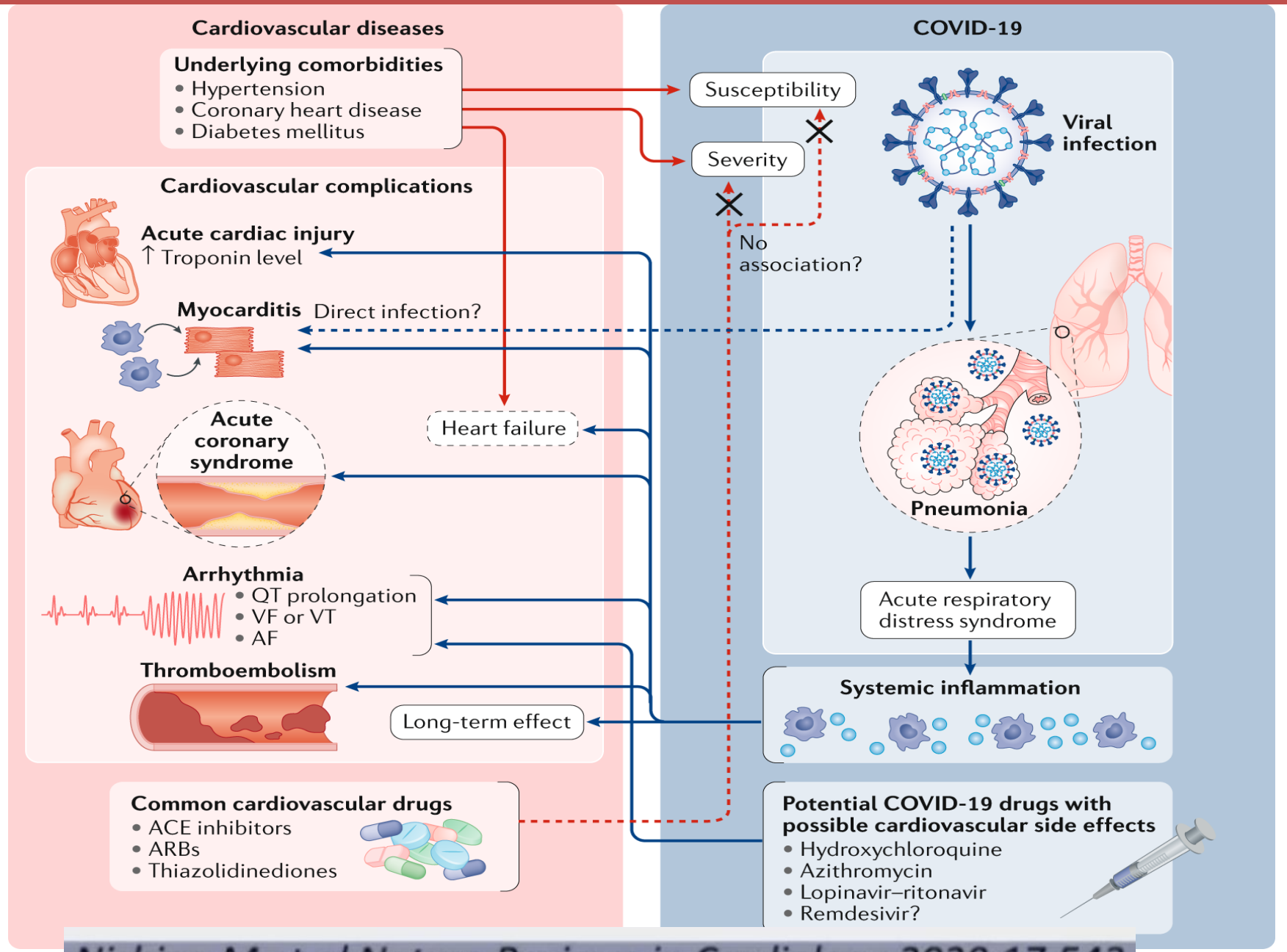


Conseguenze sistemiche della «Tempesta Citochinica»



Wadman et al. Scienze 2020

Bidirectional interaction between cardiovascular diseases and COVID-19



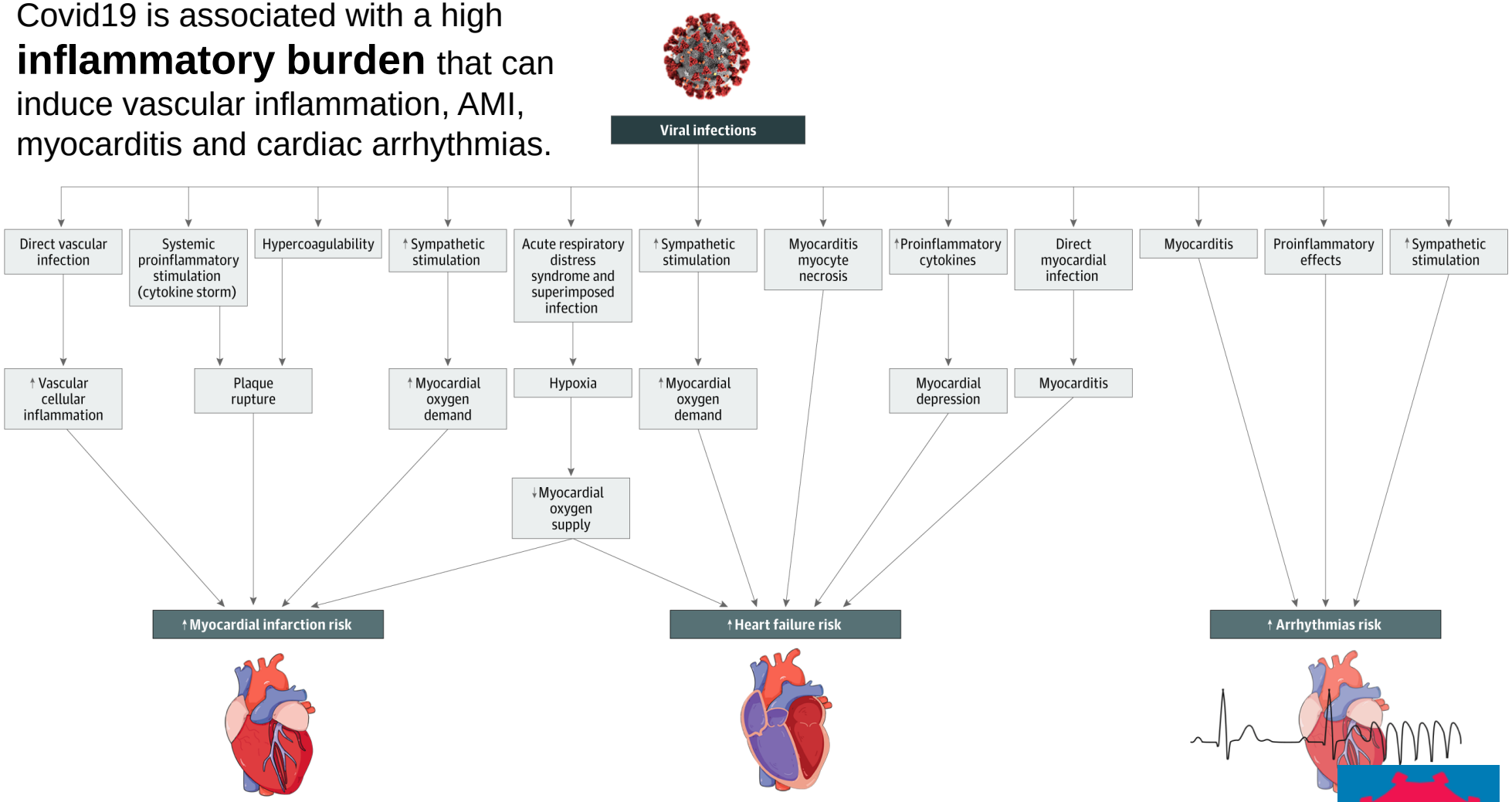
Nishiga M et al Nature Reviews in Cardiology 2020;17:543

Potential Effects of Coronaviruses on the Cardiovascular System: A Review

Potential Mechanisms for Acute Effects of Viral Infections on Cardiovascular System

JAMA Network™

Covid19 is associated with a high **inflammatory burden** that can induce vascular inflammation, AMI, myocarditis and cardiac arrhythmias.



JAMA Cardiol. 2020;5(7):831-840

Cardio LUCCA

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 1879–1882
doi:10.1093/eurheartj/ehab145

EDITORIAL

What we (don't) know about myocardial injury after COVID-19

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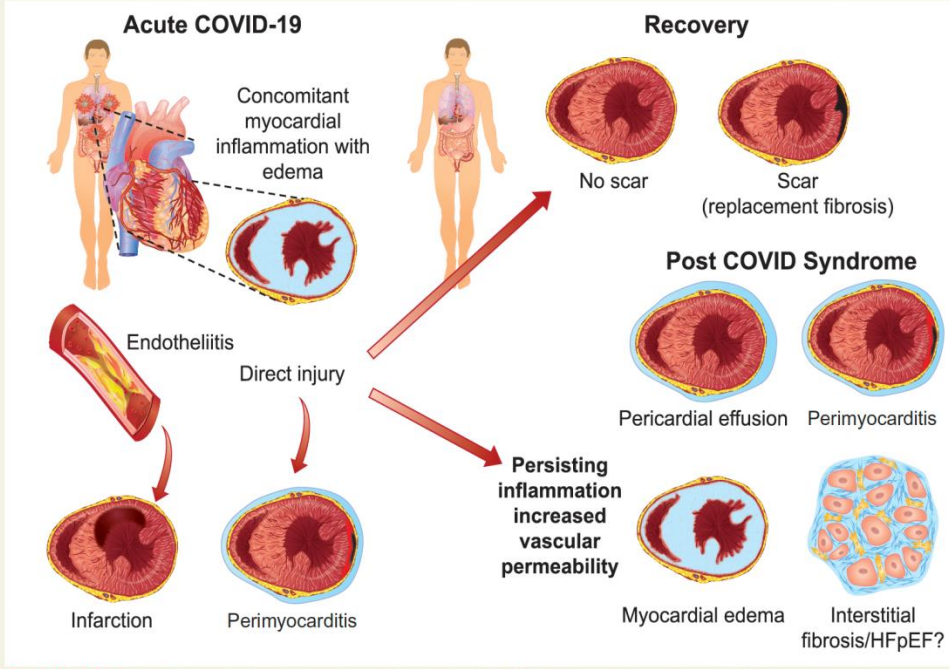
Online publish-ahead-of-print 13 March 2021

Listen to the podcast associated with this article, which can also be found at ESC CardioTalk https://www.escardio.org/The-ESC/Whatwe-do/news/ESC-Cardio-Talk

This editorial refers to 'Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance'†, by T. Kotecha *et al.*, on page 1866.



Graphical Abstract Acute and chronic outcomes of symptomatic COVID-19 infection for the heart. HFpEF, heart failure with preserved ejection fraction.

- La frequenza del danno cardiaco tra i pazienti ospedalizzati con COVID-19 associato a maggiore mortalità è stimata al 13-41% definito da elevati livelli di troponina.
- Meccanismi multipli possono portare a danno cardiaco, tra cui ischemia da > domanda, ipossia sistemica, trombosi intravascolare e danno endoteliale e miocardite.
- Post Covid Syndrome

Abnormal biomarkers in COVID-19 patients

General chemistry	• Albumin • Alanine/Aspartate aminotransferase • Bilirubin • Creatinine • Lactate • Lactic dehydrogenase
Cell counts	• Leukocyte count (leukocytosis with lymphopenia) • Platelet count (thrombocytopenia) • Red blood cell distribution width
Inflammatory/acute phase markers	• C-reactive protein • Ferritin • Interleukin-1 • Interleukin-2R • Interleukin-6 • Interleukin-10 • Procalcitonin • Tumor necrosis factor α
Thrombosis/hemostasis	• D-dimer
Cardiac markers	• B-type natriuretic peptide • N-terminal pro-B type natriuretic peptide • Troponin T and I • Creatine kinase-MB • Myoglobin

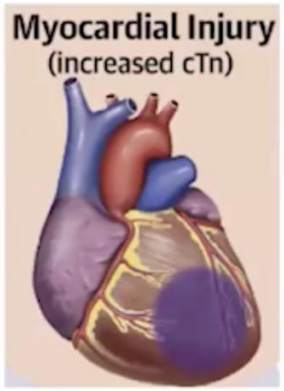
- A large number of abnormal lab findings are present in those with COVID-19
- These findings are generally worse in those with more severe disease…
- Abnormal labs are associated with adverse outcome

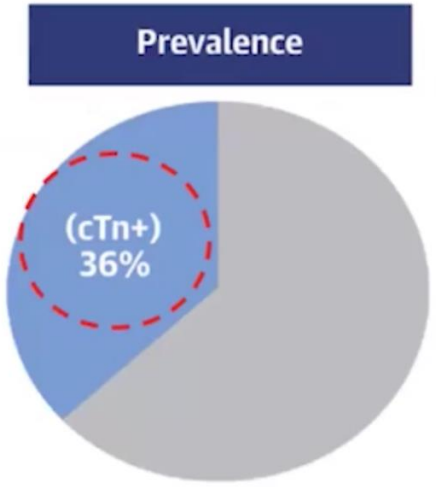
Zou, et al, the Lancet 2020.

Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection

Anuradha Lala, MD,[a,b,*] Kipp W. Johnson, PhD,[c,d,*] James L. Januzzi, MD,[e,f] Adam J. Russak, MD,[c,g] Ishan Paranjpe, BS,[c] Felix Richter, PhD,[c,d] Shan Zhao, MD, PhD,[c,h] Sulaiman Somani, BS,[c] Tielman Van Vleck, PhD,[i] Akhil Vaid, MD,[c,d] Fayzan Chaudhry, MS,[c] Jessica K. De Freitas, BS,[c,d] Zahi A. Fayad, PhD,[j,k] Sean P. Pinney, MD,[a] Matthew Levin, MD,[b,d,l,m] Alexander Charney, MD, PhD,[d,n,o] Emilia Bagiella, PhD,[a,b] Jagat Narula, MD, PhD,[a] Benjamin S. Glicksberg, PhD,[c,d,j] Girish Nadkarni, MD, MPH,[c,g,i] Donna M. Mancini, MD,[a,b,†] Valentin Fuster, MD, PhD,[a,†] on behalf of the Mount Sinai COVID Informatics Center

Lala A, et al. **J Am Coll Cardiol**. 2020;76(5

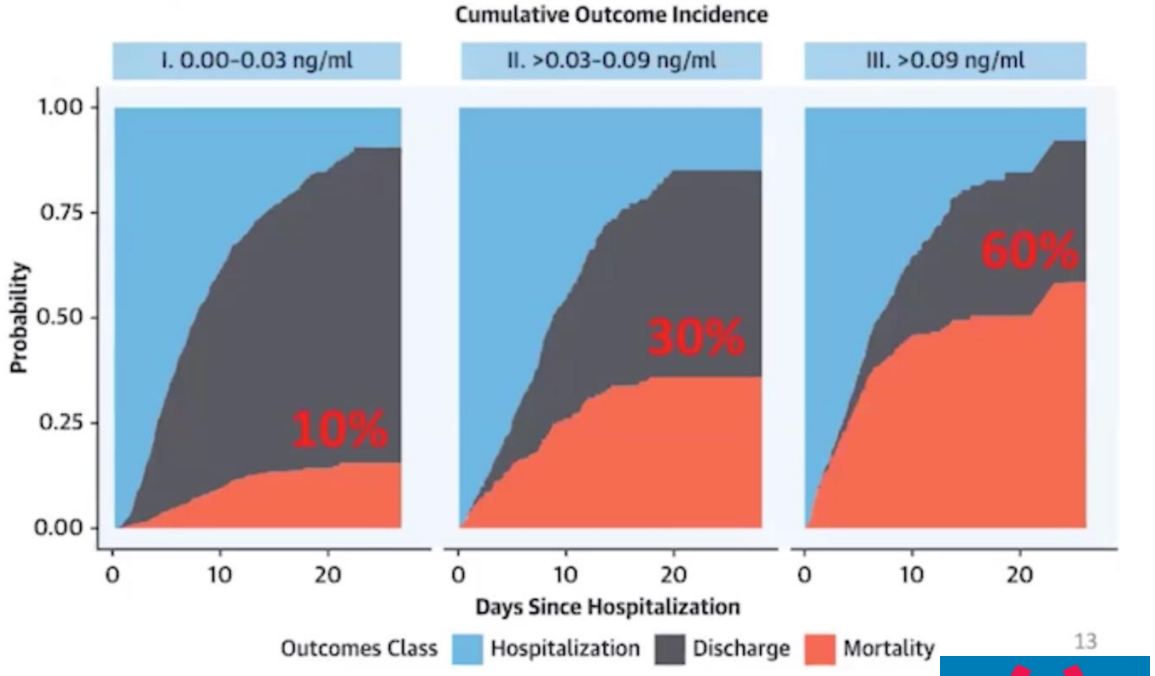




Poor outcomes

High-sensitive troponin I

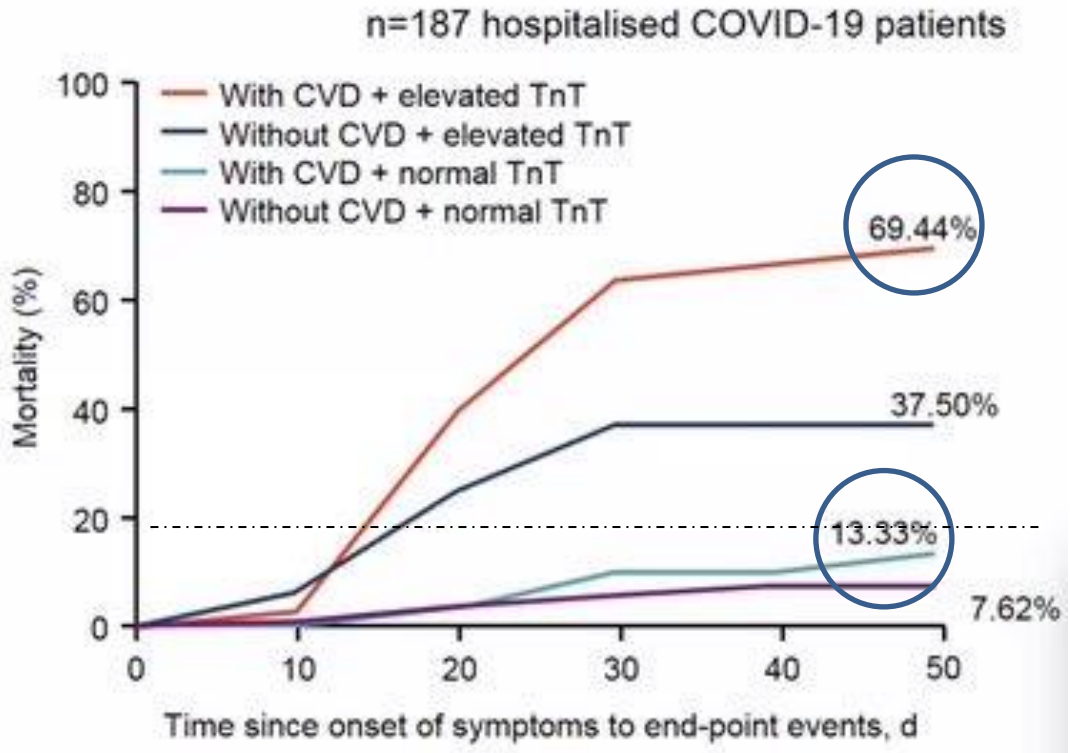
normal **modest** **high**



Myocardial injury in COVID-19

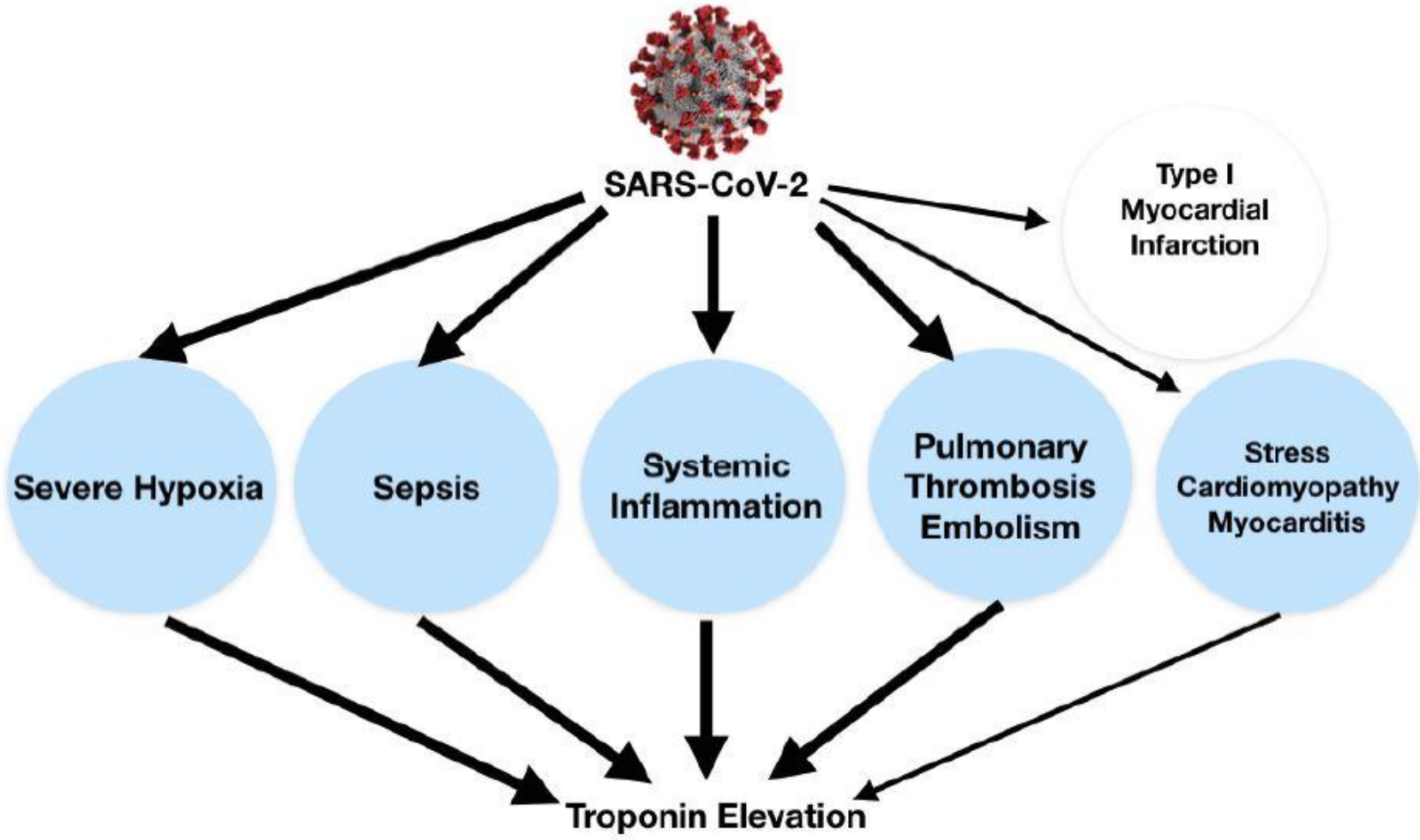
predictive value of troponin beyond CVD

- Patients with **underlying CVD** more likely to develop myocardial injury (55% versus 13%)
- **Favourable prognosis** in patients with underlying CVD and normal cTnT levels (mortality rate **13.33%** vs. **69.44%** in patients with elevated cTnT and underlying CVD)



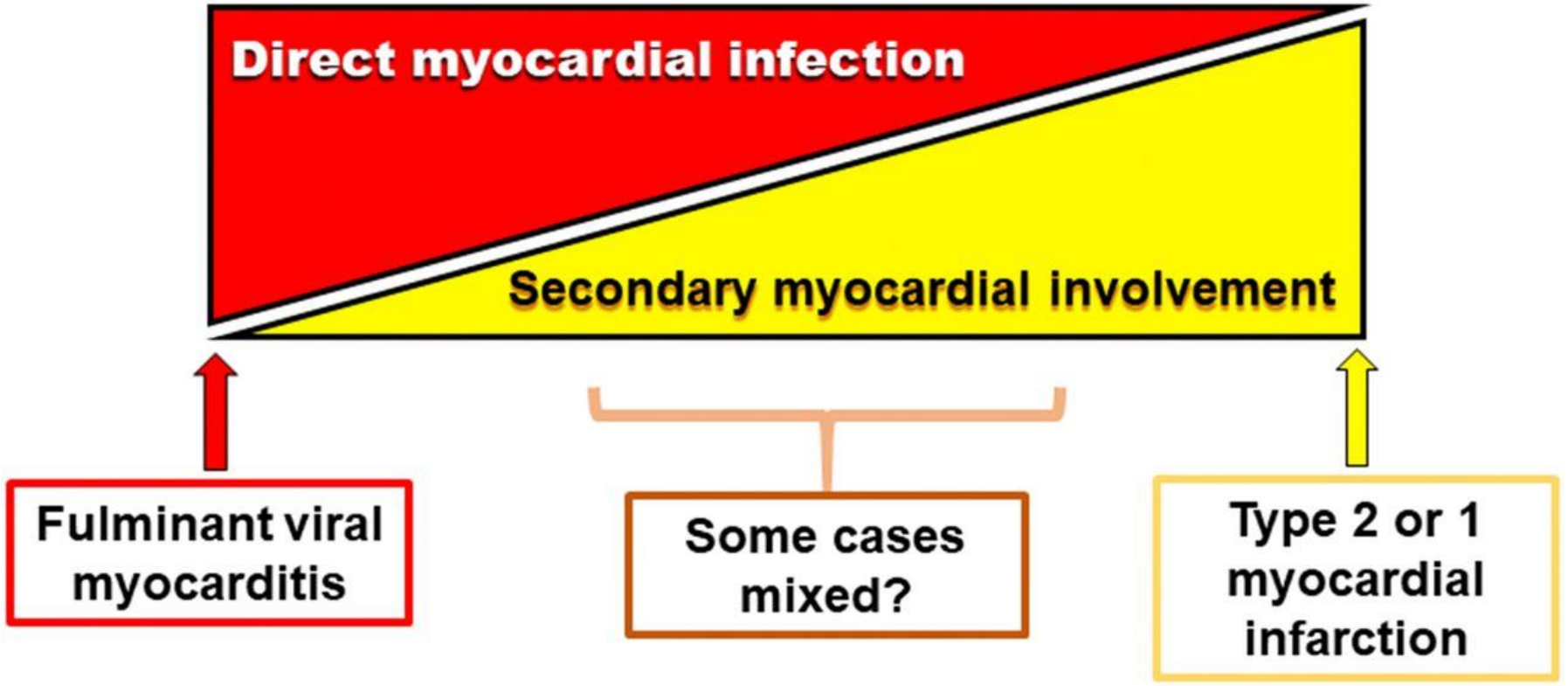
Guo T, et al. JAMA Cardiol. 2020; DOI: 10.1001/jamacardio.2020.1017.

Troponin elevation in COVID-19



Imazio et al, Heart 2020;106:1127-1131 doi: 10.1136/heartjnl-2020-317186

The Heart in COVID19: Primary Target or Secondary Bystander?



Peter Libby, JACC 2020

Should patients with COVID-19 undergo cardiac biomarker testing?

ESC
European Society of Cardiology

- Suggest to measure cTn only if the diagnosis of type 1 MI is being considered on clinical grounds, or in new onset LV dysfunction
- Routine measurements of cTn and/or NT-proBNP in patients with COVID-19 are discouraged given the current limited evidence of incremental value in clinical-decision making

AMERICAN COLLEGE of CARDIOLOGY

- cTn should only be measured if diagnosis of acute MI is being considered on clinical grounds
- BNP or NT-proBNP elevation should not necessarily trigger evaluation or treatment for h[...] failure unless there is clear clinical eviden[...] the diagnosis

rather restrictive handling

University Hospital Basel

Circulation

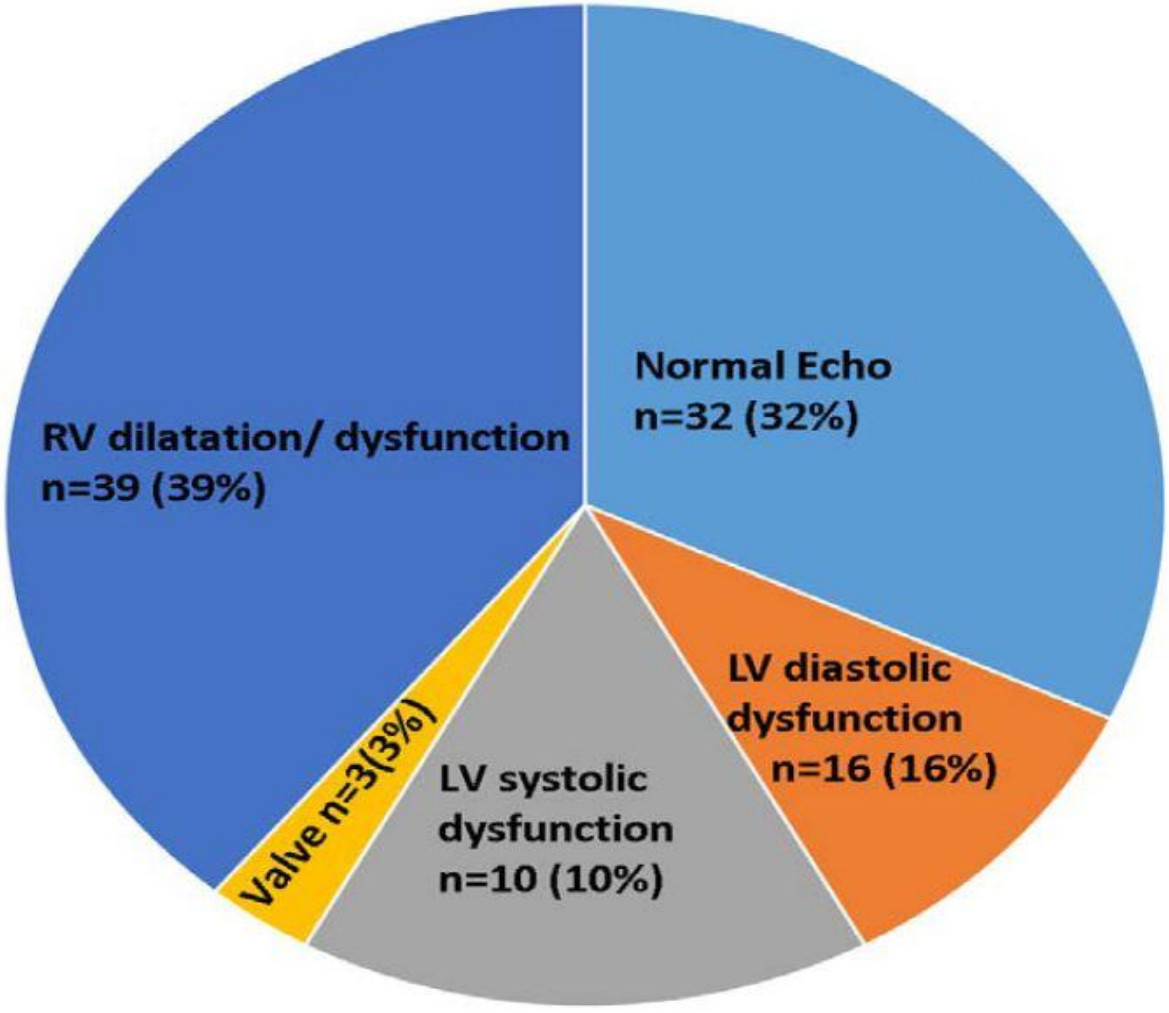
ORIGINAL RESEARCH ARTICLE

Spectrum of Cardiac Manifestations in COVID-19

A Systematic Echocardiographic Study

Szekely et al, Circulation 2020;142:342-353 doi: 10.1161/circulationaha.120.047971

Patterns of cardiac disease in hospitalized patients with Coronavirus disease 2020



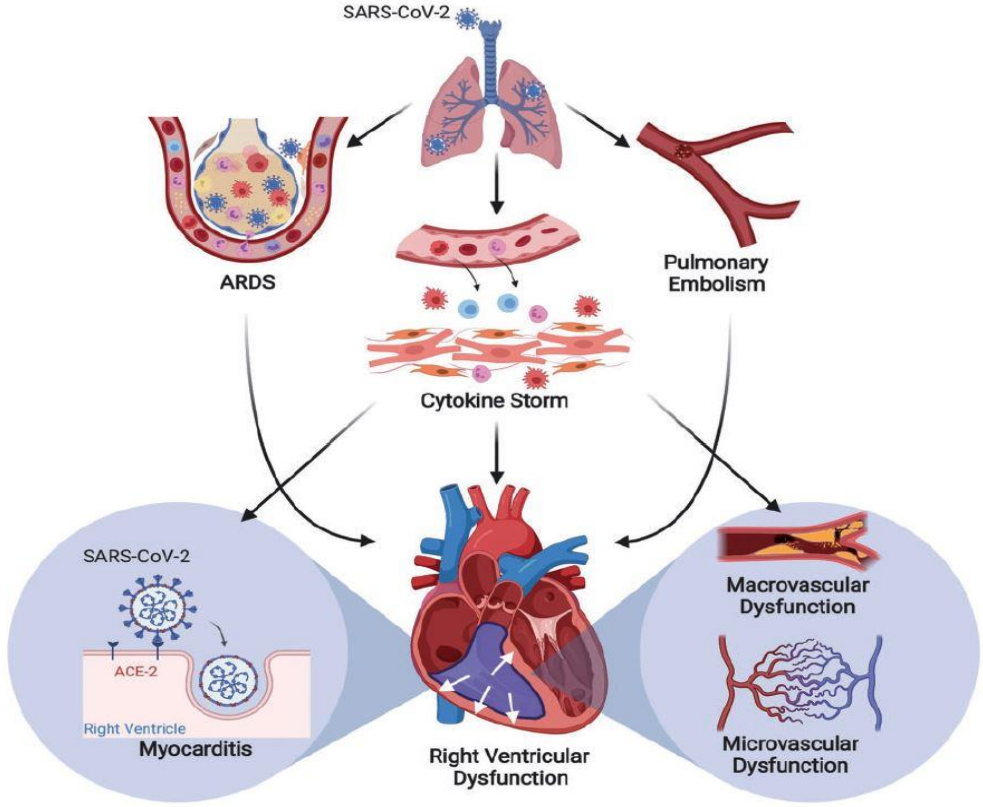
Szekely et al, Circulation 2020;142:342-353 doi: 10.1161/circulationaha.120.047971

In the eye of the storm: the right ventricle in COVID-19

John F. Park, Somanshu Banerjee and Soban Umar

Plausible mechanisms of development of right ventricular dysfunction in COVID 19

Direct angiotensis-converting enzyme 2 (ACE2 aminopeptidase) mediated effects of SARS-CoV-2 virus on the right ventricle.



Long – term follow - up of cardiopulmonary function will be necessary for COVID-19 patients, and further investigation of VR dysfunction should be considered

Park et al, Pulmonary Circulation 2020;10(3) 1-7

ESC European Society of Cardiology

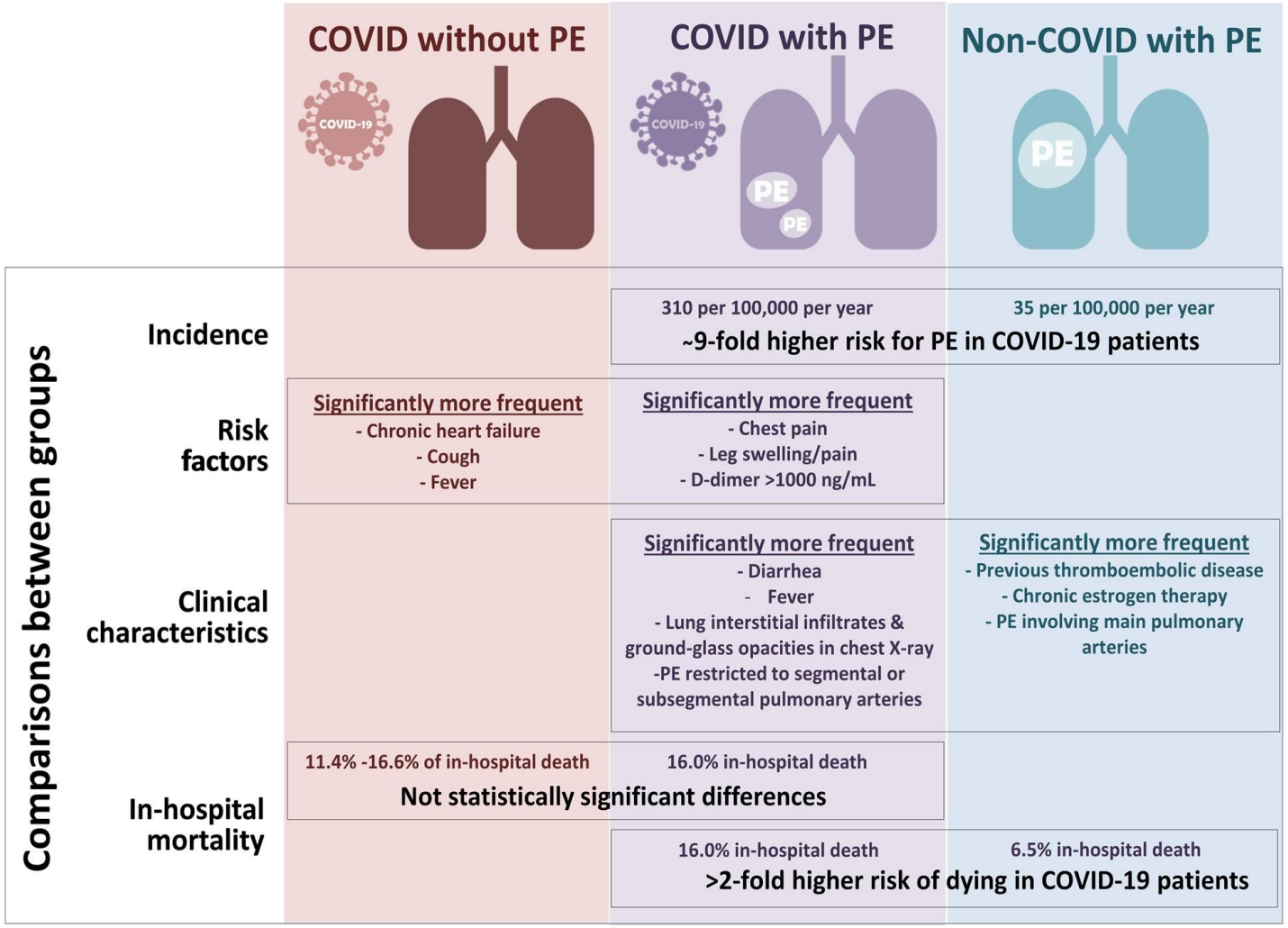
- Un'elevata prevalenza di TEV è stata segnalata durante il ricovero in TI in gravi COVID-19.
- Nella maggior parte dei casi, la **diagnosi di EP** è stata **casuale** a seguito di CTPA x aggravamento delle condizioni respiratorie.
- **E' riportata un'elevata prevalenza di EP in TI (20,6-27%)**

ESC European Society of Cardiology European Heart Journal (2021) 42, 3127–3142 doi:10.1093/eurheartj/ehab314

CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome

Summary of the main findings of the study



Oscar Mirò et al, Eur Heart J, Volume 42, Issue 33, 1 September 2021, Pages 3127–3142

OXFORD UNIVERSITY PRESS

Letters

Takotsubo Cardiomyopathy in COVID-19

The coronavirus disease-2019 (COVID-19) is a global pandemic caused by the novel severe acute respiratory-syndrome coronavirus-2 that is resulting in substantial morbidity and mortality across the globe (1). Emerging data suggest that patients presenting with COVID-19 requiring hospitalization may have objective evidence of myocardial injury, which has been shown to be associated with increased risk of in-hospital morbidity and mortality (2).

JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. ■, NO. ■, 2021

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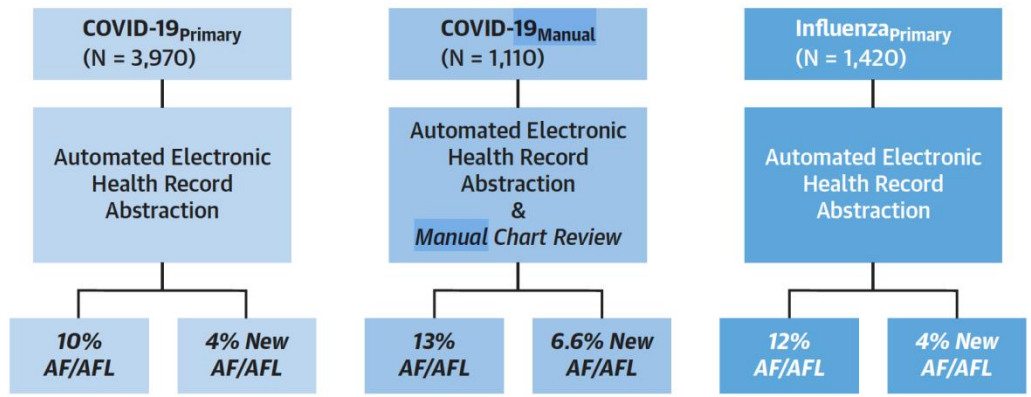
Atrial Fibrillation in Patients Hospitalized With COVID-19

Incidence, Predictors, Outcomes and Comparison to Influenza

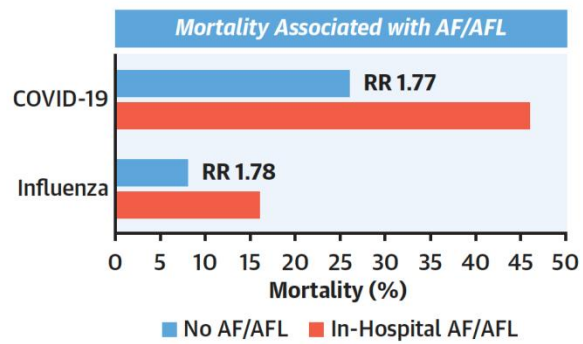
Daniel R. Musikantow, MD,[a,*] Mohit K. Turagam, MD,[a,*] Samantha Sartori, PhD,[a] Edward Chu, MD,[a]

CENTRAL ILLUSTRATION **Incidence, Predictors, and Outcomes of Atrial Arrhythmias in Patients Admitted With Coronavirus Disease 2019 Versus Influenza**



Risk Factors for New AF/AFL in COVID-19Primary

- ↑ Inflammatory Markers
- ↑ Myocardial Injury
- ↑ Intubation and Vasopressor requirement
- ↑ Use of steroids



Musikantow, D.R. et al. J Am Coll Cardiol EP. 2021;■(■):■-■.

AF = atrial fibrillation; AFL = atrial flutter; COVID-19 = coronavirus disease 2019; RR = relative risk.

www.thelancet.com **Vol 396**
September 5, 2020

COVID-19: a new lens for non-communicable diseases

- COVID-19 è una pandemia che deve evidenziare anche **l'elevato carico che le malattie non trasmissibili** impongono alle risorse sanitarie (**causano i tre quarti dei decessi globali**).
- COVID-19 ha dimostrato che **molti degli strumenti necessari per combattere una pandemia sono anche quelli necessari per combattere le malattie non trasmissibili**: sorveglianza delle malattie, una società civile forte, solida salute pubblica, comunicazione chiara e accesso equo a sistemi sanitari universali resilienti.
- **COVID-19 potrebbe fornire nuove informazioni sulle interazioni tra il sistema immunitario e le malattie non trasmissibili** e potenzialmente cambiare il modo in cui comprendiamo e trattiamo queste malattie.
- COVID-19 **potrebbe anche generare nuove disabilità a lungo termine (Long Covid)** che aumenteranno l'onere delle malattie non trasmissibili.
- La relazione tra malattie trasmissibili e malattie non trasmissibili è cruciale e non da sottovalutare perché infliggono un pedaggio inaccettabile alla **vita umana**.
- COVID-19 deve **stimolare un'azione politica di gran lunga maggiore per superare l'inerzia attorno alle malattie non trasmissibili**.

POST-Covid

- Con il progredire della pandemia globale di COVID-19 sono emerse evidenze su alcuni pazienti che manifestano **sintomi e complicazioni multiorgano** prolungati **oltre il periodo iniziale di infezione acuta** e di malattia (73%)
- L'elenco dei sintomi nuovi e persistenti è ampio tra cui: **un'estrema inspiegabile stanchezza (60%), a tosse cronica, la mancanza di respiro, l'oppressione toracica, la disfunzione cognitiva («brain fog»)**
- Tutte implicazioni e conseguenze cliniche che rappresentano **una nuova e crescente preoccupazione per la salute**

6-month consequences of COVID-19 in patients discharged from hospital: a cohort study

Chaolin Huang*, Lixue Huang*, Yeming Wang*, Xia Li*, Lili Ren*, Xiaoying Gu*, Liang Kang*, Li Guo*, Min Liu*, Xing Zhou, Jianfeng Luo, Zhenghui Huang, Shengjin Tu, Yue Zhao, Li Chen, Decui Xu, Yanping Li, Caihong Li, Lu Peng, Yong Li, Wuxiang Xie, Dan Cui, Lianhan Shang, Guohui Fan, Jiuyang Xu, Geng Wang, Ying Wang, Jingchuan Zhong, Chen Wang, Jianwei Wang†, Dingyu Zhang†, Bin Cao†

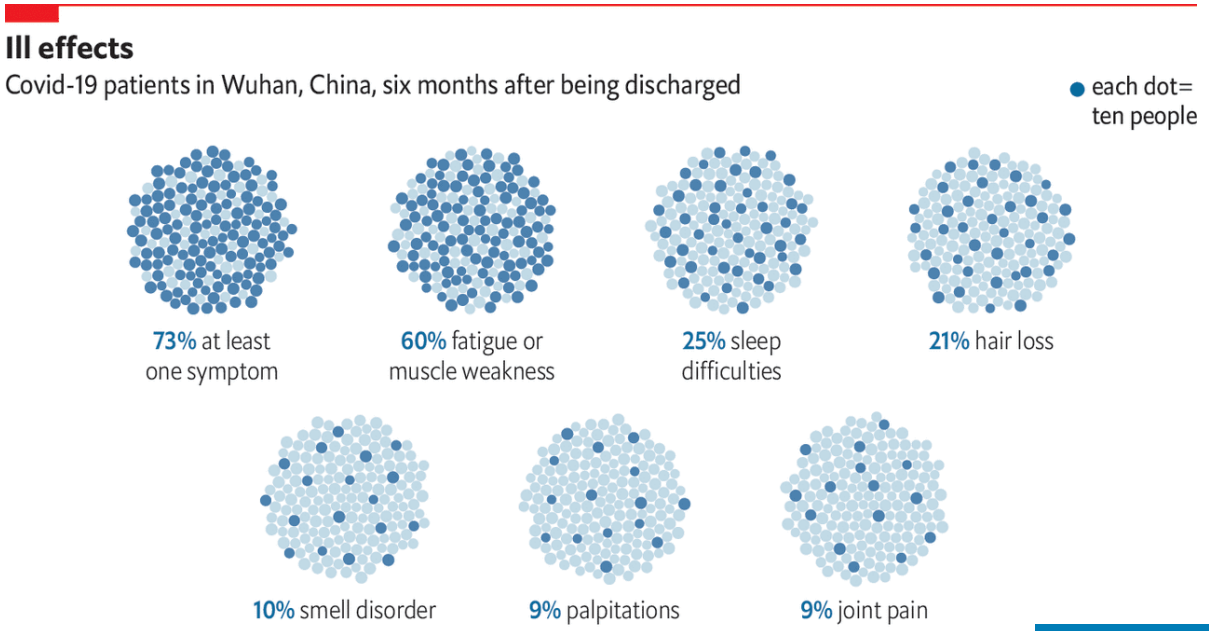
Summary

Background The long-term health consequences of COVID-19 remain largely unclear. The aim of this study was to describe the long-term health consequences of patients with COVID-19 who have been discharged from hospital and investigate the associated risk factors, in particular disease severity.

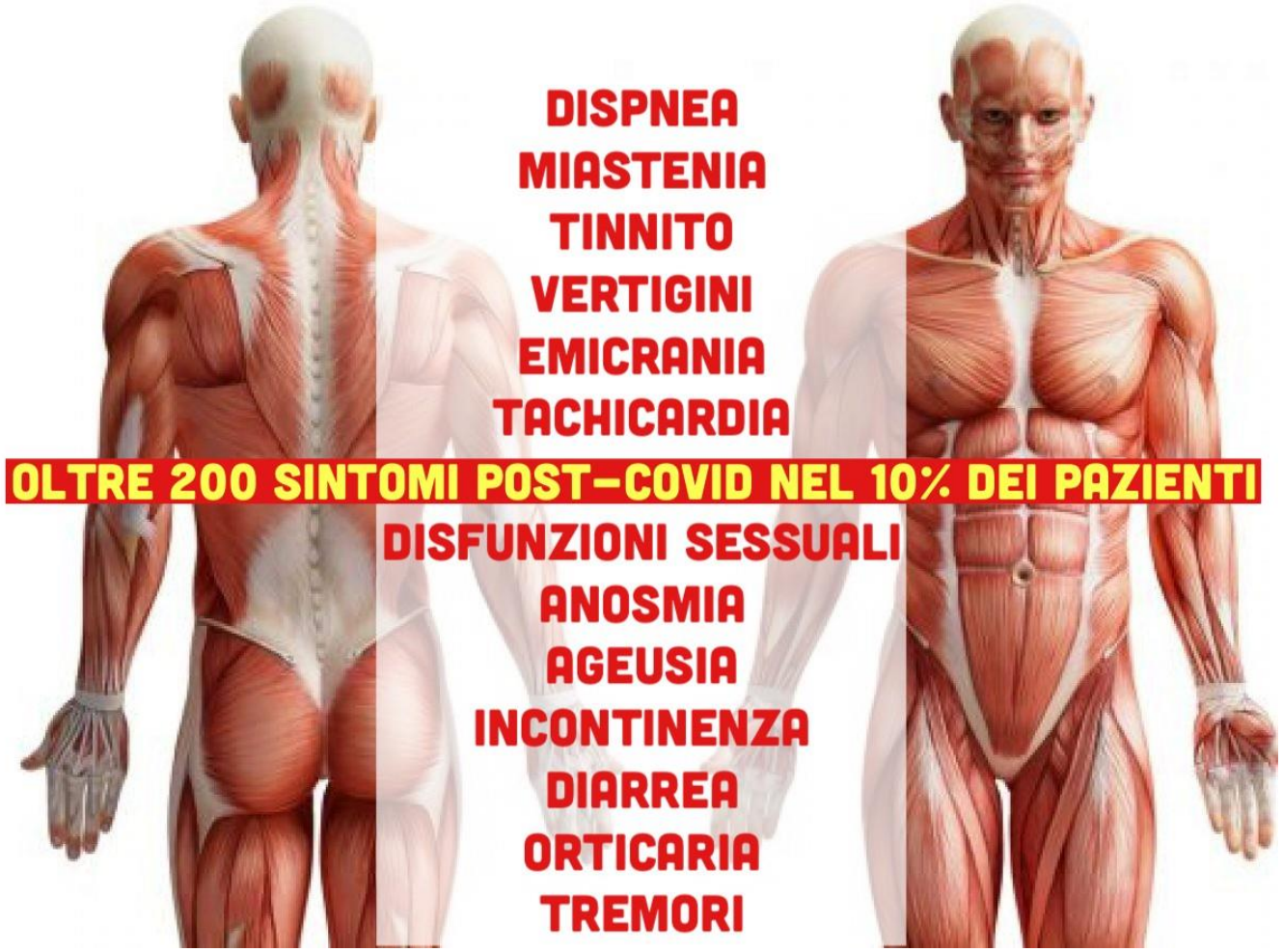
Methods We did an ambidirectional cohort study of patients with confirmed COVID-19 who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7, 2020, and May 29, 2020. Patients who died before follow-up, patients for whom follow-up would be difficult because of psychotic disorders, dementia, or re-admission to hospital, those who were unable to move freely due to concomitant osteoarthropathy or immobile before or after discharge due to diseases such as stroke or pulmonary embolism, those who declined to participate, those who could not be contacted, and those living outside of Wuhan or in nursing or welfare homes were all excluded. All patients were interviewed with a series of questionnaires for evaluation of symptoms and health-related quality of life, underwent physical examinations and a 6-min walking test, and received blood tests. A stratified sampling procedure was used to sample patients according to their highest seven-category scale during their hospital stay as 3, 4, and 5–6, to receive pulmonary function test, high resolution CT of the chest, and ultrasonography. Enrolled patients who had participated in the Lopinavir Trial for Suppression of SARS-CoV-2 in China received severe acute respiratory syndrome coronavirus 2 antibody tests. Multivariable adjusted linear or logistic regression models were used to evaluate the association between disease severity and long-term health consequences.

Findings In total, 1733 of 2469 discharged patients with COVID-19 were enrolled after 736 were excluded. Patients had a median age of 57·0 (IQR 47·0–65·0) years and 897 (52%) were men. The follow-up study was done from June 16, to Sept 3, 2020, and the median follow-up time after symptom onset was 186·0 (175·0–199·0) days. Fatigue or muscle weakness (63%, 1038 of 1655) and sleep difficulties (26%, 437 of 1655) were the most common symptoms. Anxiety or depression was reported among 23% (367 of 1617) of patients. The proportions of median 6-min walking distance less than the lower limit of the normal range were 24% for those at severity scale 3, 22% for severity scale 4, and 29% for severity scale 5–6. The corresponding proportions of patients with diffusion impairment were 22% for severity scale 3, 29% for scale 4, and 56% for scale 5–6, and median CT scores were 3·0 (IQR 2·0–5·0) for severity scale 3, 4·0 (3·0–5·0) for scale 4, and 5·0 (4·0–6·0) for scale 5–6. After multivariable adjustment, patients showed an odds ratio (OR) 1·61 (95% CI 0·80–3·25) for scale 4 versus scale 3 and 4·60 (1·85–11·48) for scale 5–6 versus scale 3 for diffusion impairment; OR 0·88 (0·66–1·17) for scale 4 versus scale 3 and OR 1·77 (1·05–2·97) for scale 5–6 versus scale 3 for anxiety or depression, and OR 0·74 (0·58–0·96) for scale 4 versus scale 3 and 2·69 (1·46–4·96) for scale 5–6 versus scale 3 for fatigue or muscle weakness. Of 94 patients with blood antibodies tested at follow-up, the seropositivity (96·2% *vs* 58·5%) and median titres (19·0 *vs* 10·0) of the neutralising antibodies were significantly lower compared with at the acute phase. 107 of 822 participants without acute kidney injury and with estimated glomerular filtration rate (eGFR) 90 mL/min per 1·73 m² or more at acute phase had eGFR less than 90 mL/min per 1·73 m² at follow-up.

Interpretation At 6 months after acute infection, COVID-19 survivors were mainly troubled with fatigue or muscle weakness, sleep difficulties, and anxiety or depression. Patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations, and are the main target population for intervention of long-term recovery.



Characterizing Long Covid in an international cohort: 7 months of symtoms and ther impact



EClinicalMedicine by THE LANCET 2021

Cardio LUCCA

Il «**Long COVID**» **è definita** come una condizione della sindrome post-acuta da COVID-19, in cui i sintomi persistono **tra le 4 e le 12 settimane** dopo l'infezione e include anche la **malattia cronica COVID-19 in cui i sintomi persistono ≥12 settimane**

La **fisiopatologia** del Long COVID rimane **poco chiara**: le attuali ipotesi formulate richiamano la **viremia persistente, il decondizionamento, una recidiva o reinfezione, le reazioni immunitarie e infiammatorie e vari fattori psicologici**

Interessa il 15% dei Covid-19: età avanzata, sesso femminile, BPCO, più sintomi alla presentazione

Coronavirus Disease 2019 (COVID-19) and the Heart—Is Heart Failure the Next Chapter?

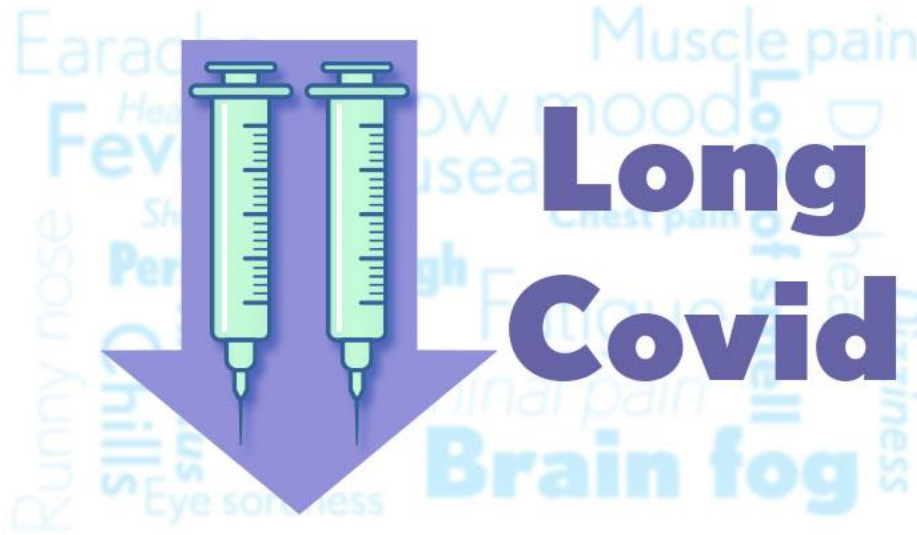
Clyde W. Yancy, MD, MSc; Gregg C. Fonarow, MD

Alcuni mesi dopo una diagnosi di COVID-19

Una possibile **disfunzione ventricolare sinistra residua** con associato **stato infiammatorio persistente rappresentano** una condizione preoccupante, perché sarebbero un potenziale fondamento per **un'insufficienza cardiaca di nuova insorgenza o di altre complicanze cardiovascolari**

Yancy et al, Jama Cardiol. July 2020 . doi:10.1001/jamacardio.2020.3575

Cardio LUCCA



Non c'è dubbio che **i vaccini stiano facendo un'enorme differenza nella protezione di individui e intere comunità contro infezioni e malattie gravi come COVID-19**.

In questo caso esiste **un altro motivo per vaccinarsi** per avere anche meno probabilità di sviluppare una **Long Covid che vede protagonisti i MMG e specialisti**

IL VIRUS E IL MEDICO

Ci voleva un virus per ridare decoro, dignità e valore al lavoro del medico travolto in questi ultimi anni da una deriva culturale e sociale della sua storica anima ippocratica. La salute è un bene intangibile, non una merce o un valore materiale, un insieme complesso di interventi multidisciplinari garantiti dal ragionamento clinico del medico e dall'organizzazione del sistema sanitario che oggi, in piena pandemia, auspico rifletta e riconsideri il dogma della medicina al servizio delle risorse economiche.

Mentre il lutto ospedaliero continua da più parti a conquistare il ruolo di notizia scandalistica, contro l'ordine delle cose possibili e di una storia naturale propria della biologia, sommessamente da novembre ad oggi il virus COVID-19 mette in crisi l'indissolubile supposto binomio salute-terapia e la solida persuasione che un uomo non muore perché si ammala, ma per una terapia sbagliata.

Ridare dignità al sacrificio del medico e degli operatori della salute, che in prima linea orgogliosi mettono a disposizione come veri eroi moderni la propria vita per il nostro Paese, diventa l'imperativo dominante di queste lunghe giornate di necessarie restrizioni. Le testimonianze di solidarietà, stima, vicinanza umana e sociale al ruolo vocativo del medico ridonano finalmente onorabilità, riaffermano l'autonomia e la libertà decisionale di una professione speciale, antica quanto l'uomo.

L'attuale clima di paura generalizzata che si percepisce per il rischio di contrarre l'infezione da nuovo coronavirus invita a riflettere. Siamo stati abituati ad essere protetti da una rete assistenziale e da un sistema sanitario capace di offrire terapie in grado di modificare in misura importante la prognosi e la qualità di vita. Per contro, il disagio scientifico nei confronti di questa epidemia, che avanza come sciame sismico, mette a dura prova l'impegno etico e scientifico del medico sempre pronto, ieri come oggi, ad offrire la sua umanità, esperienza e conoscenza per difendere la vita nel rispetto dei diritti individuali dell'uomo.

Non conosciamo il comportamento del coronavirus, come non sappiamo ancora arginare la sua virulenza, ma sappiamo che le misure di prevenzione e isolamento sociale disposto dal nostro governo sono vitali per tutti noi. Quando la medicina è umiliata dall'incertezza scientifica è l'umanità intera che va in crisi d'identità, perché percepisce la minaccia sul bene primario: la vita. In questi momenti difficili la medicina diventa la forza e l'energia, il medico è il coraggio e la speranza, gli operatori della salute sono gli angeli e le sentinelle del bene, il sistema sanitario resta per tutti il bene comune e il riferimento da seguire.

Solo lavorando insieme responsabilmente potremo combattere la diffusione del virus, proprio come nella storica alleanza medico-paziente, con l'aiuto della cultura sociale, le conoscenze pratiche e la consapevolezza che la medicina non sempre procede per gradi, a volte per rivoluzioni periodiche, come accadrà in questa emergenza in attesa della risposta che verrà dalle rigorose evidenze della ricerca clinica. E quando questo accadrà, quando vinceremo questa sfida, non dovremo dimenticare di coinvolgere i medici nelle complesse scelte della salute, ma ancor di più di investire ed espandere la nostra capacità assistenziale.

In questa devastante dimensione sociale ed economica, in questo storico disagio scientifico e in parte organizzativo, sono oggi più che mai fiero di essere medico, altruista e consapevole che solo l'umanizzazione e la scienza potranno riannodare il filo spezzato di una medicina capace ancora di ricevere sorrisi, gratitudine e di guardare al futuro di un abbraccio, perché tutto andrà bene.

Francesco Maria Bovenzi

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e-mail: fr.bovenzi@gmail.com