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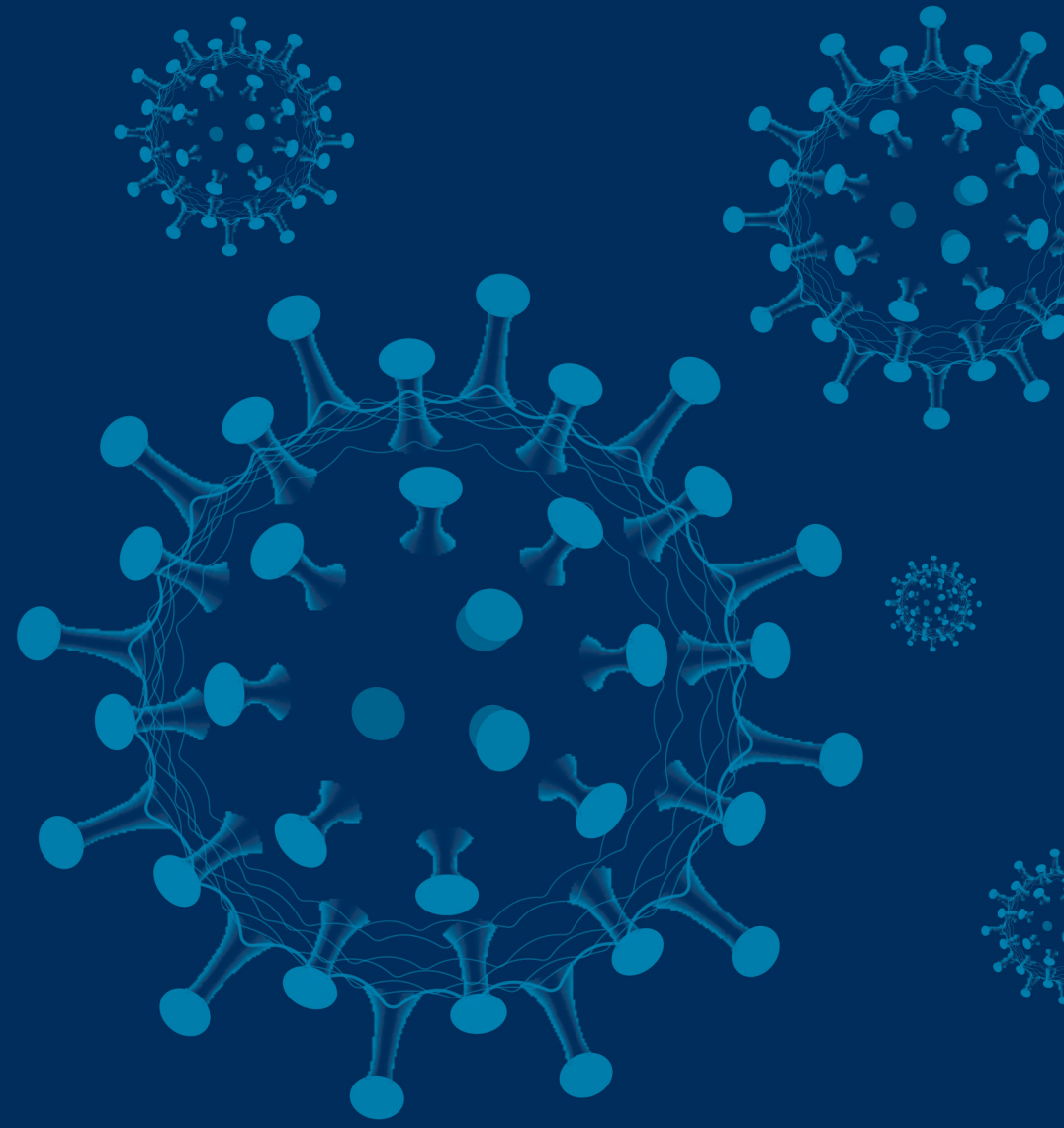
COVID-19

COVID-19 and the HEART:

Focus on Myocardial Injury



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Disclosures

NONE

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Clinical Characteristics of CoViD-19 Pneumonia in Wuhan, China

Table 1. Baseline Characteristics of Patients Infected With 2019-nCoV

	No. (%)			
	Total (N = 138)	ICU (n = 36)	Non-ICU (n = 102)	P Value[a]
Age, median (IQR), y	56 (42-68)	66 (57-78)	51 (37-62)	<.001
Sex				
Female	63 (45.7)	14 (38.9)	49 (48.0)	.34
Male	75 (54.3)	22 (61.1)	53 (52.0)	
Huanan Seafood Wholesale Market exposure	12 (8.7)	5 (13.9)	7 (6.9)	.30
Infected				
Hospitalized patients	17 (12.3)	9 (25.0)	8 (7.8)	.02
Medical staff	40 (29)	1 (2.8)	39 (38.2)	<.001
Comorbidities	64 (46.4)	26 (72.2)	38 (37.3)	<.001
Hypertension	43 (31.2)	21 (58.3)	22 (21.6)	<.001
Cardiovascular disease	20 (14.5)	9 (25.0)	11 (10.8)	.04
Diabetes	14 (10.1)	8 (22.2)	6 (5.9)	.009
Malignancy	10 (7.2)	4 (11.1)	6 (5.9)	.29
Cerebrovascular disease	7 (5.1)	6 (16.7)	1 (1.0)	.001
COPD	4 (2.9)	3 (8.3)	1 (1.0)	.054
Chronic kidney disease	4 (2.9)	2 (5.6)	2 (2.0)	.28
Chronic liver disease	4 (2.9)	0	4 (3.9)	.57
HIV infection	2 (1.4)	0	2 (2.0)	>.99
Signs and symptoms				
Fever	136 (98.6)	36 (100)	100 (98.0)	>.99
Fatigue	96 (69.6)	29 (80.6)	67 (65.7)	.10
Dry cough	82 (59.4)	21 (58.3)	61 (59.8)	.88
Anorexia	55 (39.9)	24 (66.7)	31 (30.4)	<.001
Myalgia	48 (34.8)	12 (33.3)	36 (35.3)	.83
Dyspnea	43 (31.2)	23 (63.9)	20 (19.6)	<.001
Expectoration	37 (26.8)	8 (22.2)	29 (28.4)	.35
Pharyngalgia	24 (17.4)	12 (33.3)	12 (11.8)	.003
Diarrhea	14 (10.1)	6 (16.7)	8 (7.8)	.20
Nausea	14 (10.1)	4 (11.1)	10 (9.8)	>.99
Dizziness	13 (9.4)	8 (22.2)	5 (4.9)	.007
Headache	9 (6.5)	3 (8.3)	6 (5.9)	.70
Vomiting	5 (3.6)	3 (8.3)	2 (2.0)	.13
Abdominal pain	3 (2.2)	3 (8.3)	0 (0)	.02
Onset of symptom to, median (IQR), d				
Hospital admission	7.0 (4.0-8.0)	8.0 (4.5-10.0)	6.0 (3.0-7.0)	.009
Dyspnea	5.0 (1.0-10.0)	6.5 (3.0-10.8)	2.5 (0.0-7.3)	.02
ARDS	8.0 (6.0-12.0)	8.0 (6.0-12.0)	8.0 (6.3-11.3)	.97
Heart rate, median (IQR), bpm	88 (78-97)	89 (81-101)	86 (77-96)	.14
Respiratory rate, median (IQR)	20 (19-21)	20 (16-25)	20 (19-21)	.57
Mean arterial pressure, median (IQR), mm Hg	90 (84-97)	91 (78-96)	90 (85-98)	.33

Wang D et al, JAMA 2020

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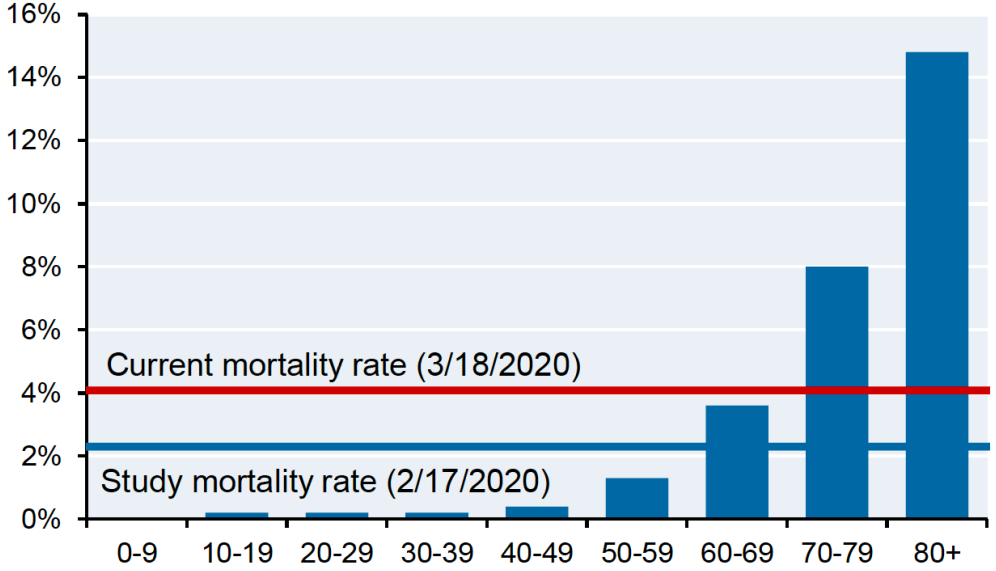
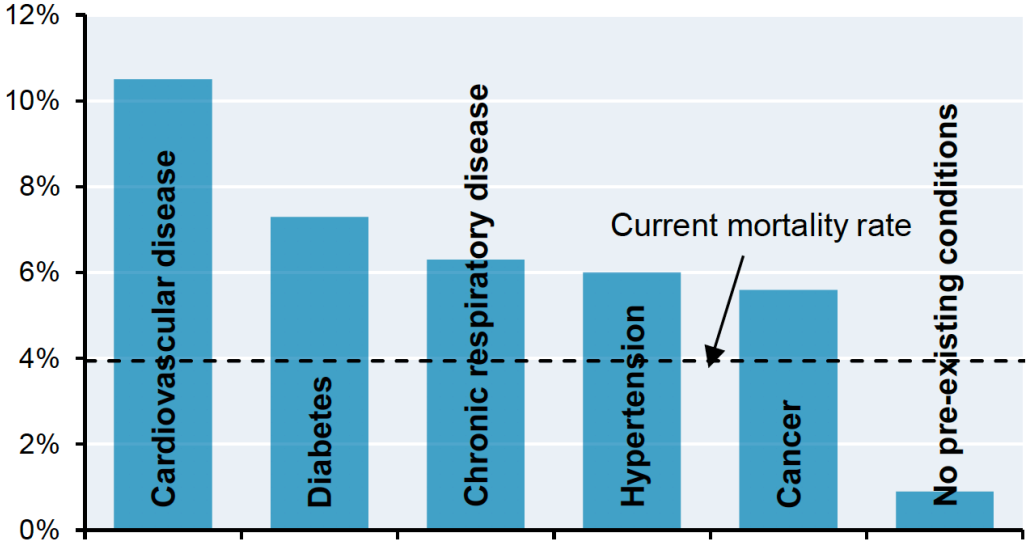
Infection and mortality rates

Coronavirus mortality rate by age

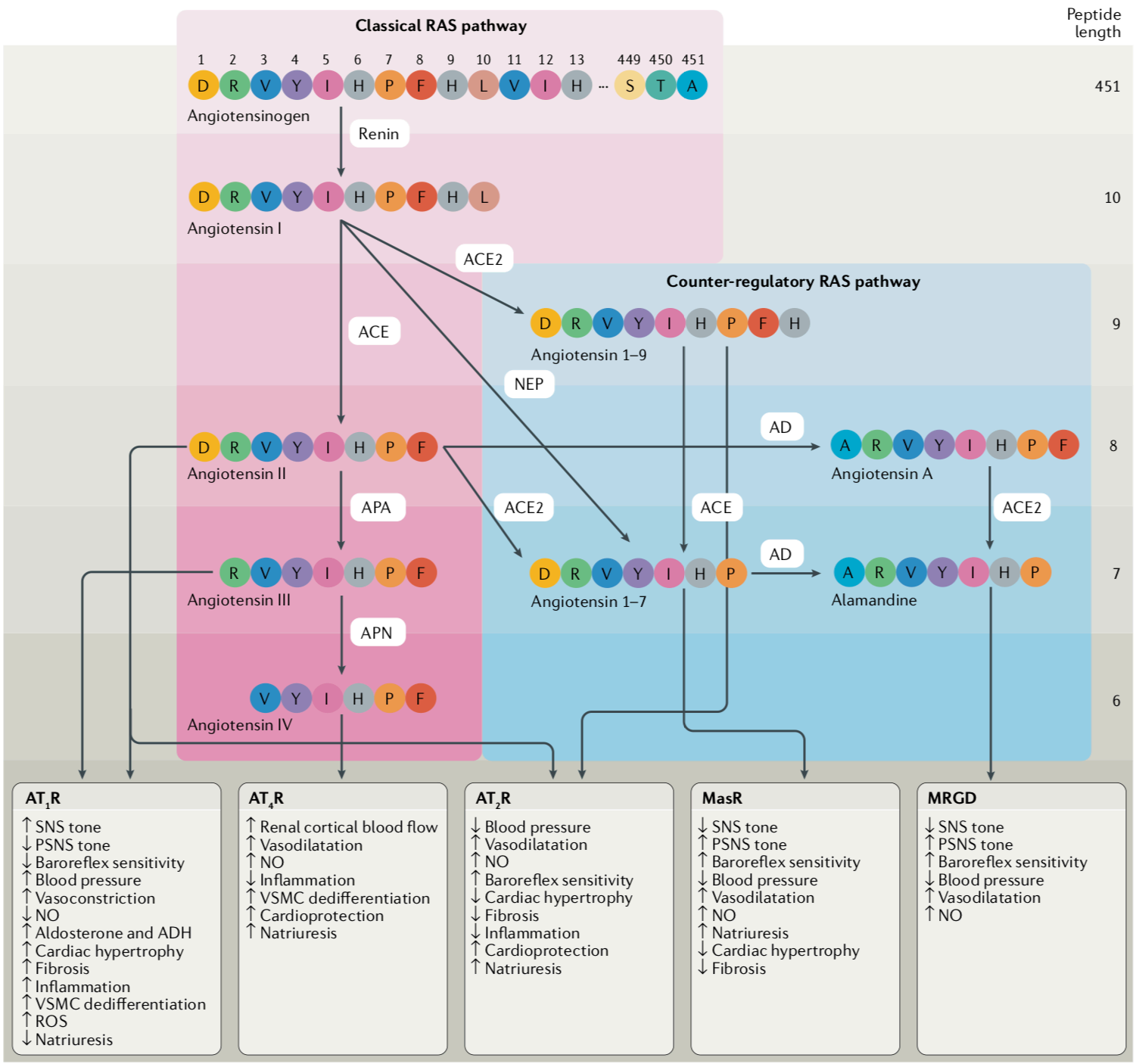


Source: Chinese CDC, WHO. February 2020.

Coronavirus mortality rate based on pre-existing conditions



Source: Chinese Center for Disease Control and Prevention. February 2020.



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RAS:

the renin-angiotensin system

Ocaranza MP et al.
Nat Rev Cardiol. 2020;17:116-129

aminopeptidase A (APA)
aminopeptidase N (APN)
aspartate decarboxylase (AD)
neprilysin (NEP)
proto-oncogene Massey receptor (MasR)
Mas-related GPCR member D (MRGD)

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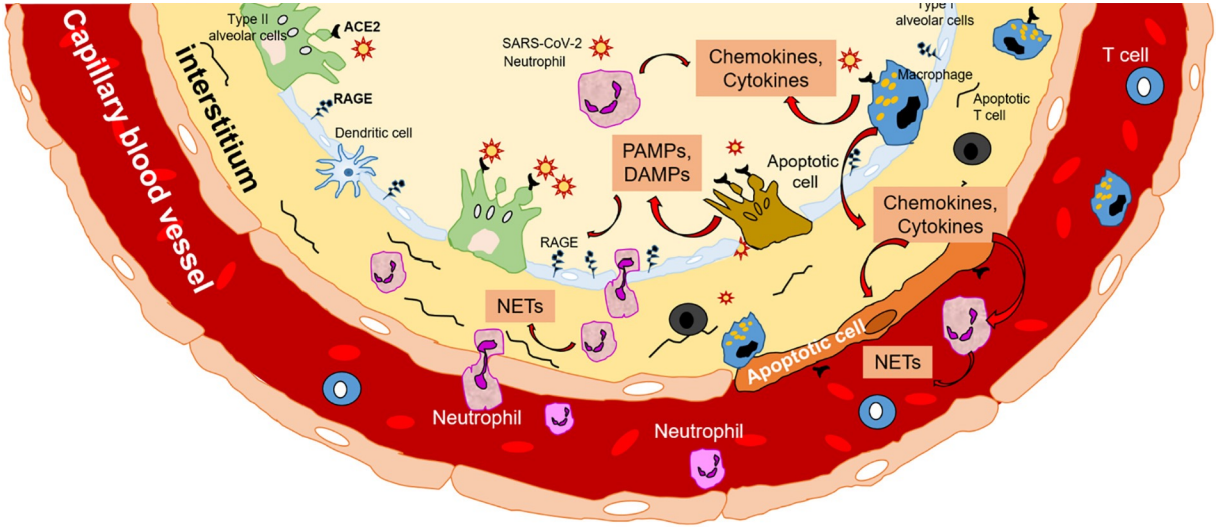

Putative mechanisms of SARS-CoV-2 infection within the alveolus. When SARS-CoV-2 infects the lower pulmonary airways, it can directly attack alveolar type II alveolar cells and resident macrophages, both expressing the ACE2 receptor. In response to viral infection, these cells produce various proinflammatory chemokines and cytokines. SARS-CoV-2 can also directly infect both capillary endothelial cell (increasing the permeability to plasma components at the infection site) and T cells (reducing the antiviral immune response). Stressed and necrotic cells release DAMPs and PAMPs mediators. These ligands interact with the RAGE, a highly expressed receptor in lung epithelial cells and stimulate downstream signalling that perpetuates an unfavourable proinflammatory state. Neutrophils can release NETs, which could damage endothelial cells. The hypercytokinemia attracts a greater number of monocytes-macrophages (the main sources of pro-inflammatory cytokines) and neutrophils from the bloodstream to the infection/inflammation site, to remove exudates. This massive cell infiltration into the alveolar or interstitial spaces causes a “cytokine storm” which promotes further cellular apoptosis and leads to further worsening of lung injury.

Serena Del Turco et al. Thrombosis Research 196 (2020) 143–151

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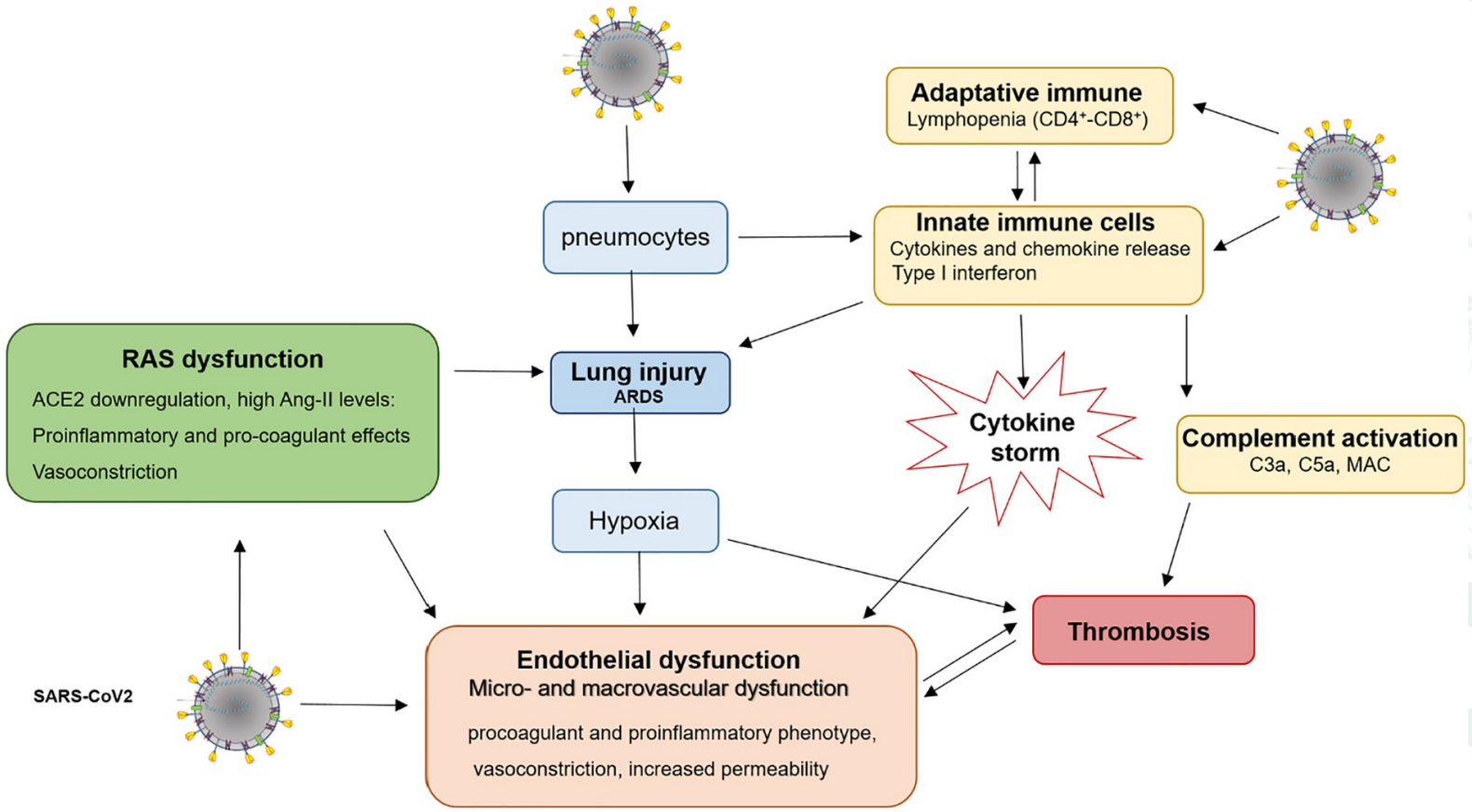

A comprehensive overview of SARS-CoV-2-induced endothelial injury and thrombotic complications. SARS-CoV2 infects a number of cell types, including type II alveolar cells, macrophages, T cells and endothelial cells, leading to hyperinflammation, hypoxia, apoptosis and imbalance of renin-angiotensin system. High levels of proinflammatory cytokines/chemokines can directly induce endothelial leak, cause cell apoptosis or also promote systemic inflammation and thrombosis. High levels of Ang-II switch endothelium to a proinflammatory and procoagulant phenotype. The ARDS- induced hypoxia can cause endothelial dysfunction by mitochondrial ROS generation, intracellular acidosis, cell signalling pathway activation, and can increase blood viscosity. Together, a dysregulated immune response, hypercytokinemia, imbalance of RAS, complement activation and hypoxemia induce an exacerbated endothelial dysfunction and thrombosis.

Serena Del Turco et al. Thrombosis Research 196 (2020) 143–151

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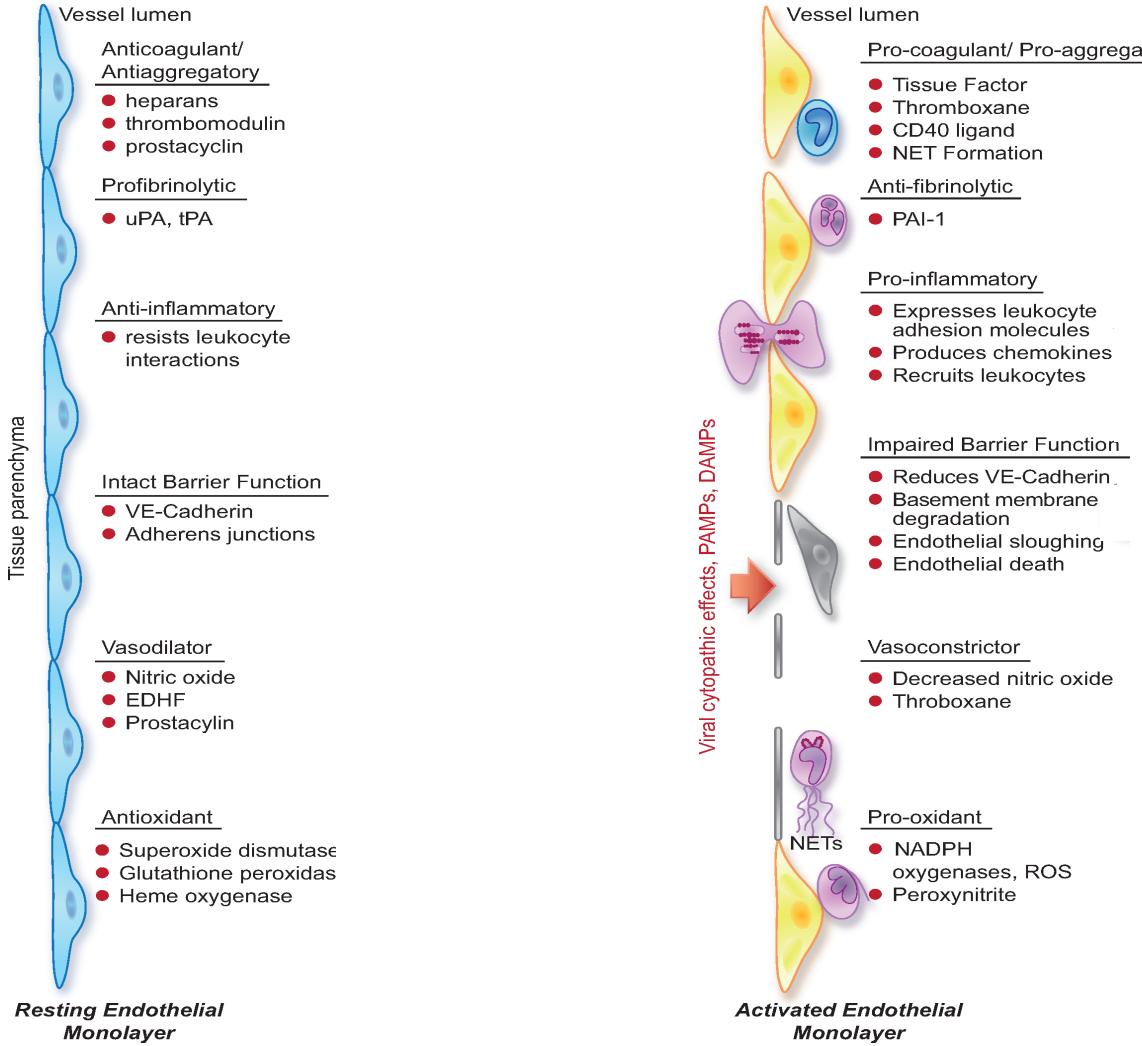
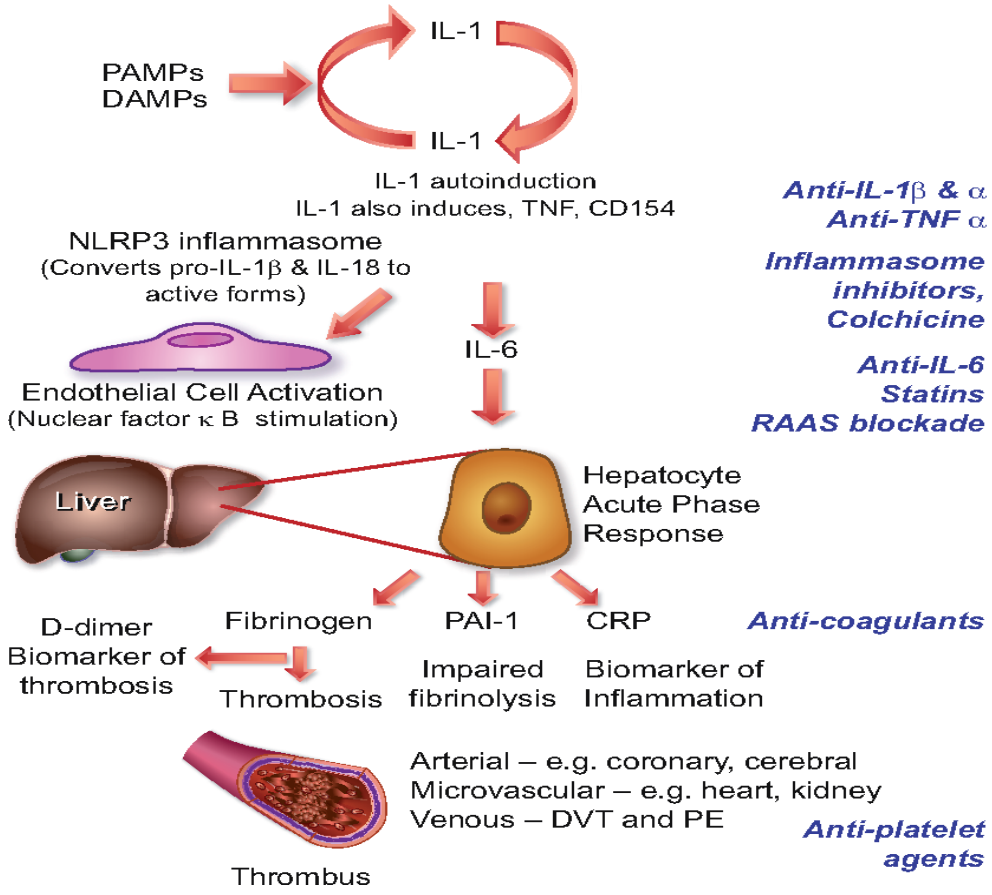
Resting and activated endothelial monolayer…



A resting endothelial cell monolayer on an intact basement membrane (L) plays an important homeostatic role. With cytopathic effect from a viral infection, or pathogen-associated molecular patterns (PAMPs, such as LPS), proinflammatory cytokines (such as IL-1 or TNF), or damage-associated molecular patterns (DAMPs derived from dead or dying cells) the endothelial cells become activated. They can express adhesion molecules (that attract leucocytes) and chemokines (that direct their migration into the subendothelial space), and MMP (that degrade BM). Sloughing of endothelial cells uncovers the thrombogenic BM. Inflammatory activation of endothelial cells can disrupt VE-cadherin responsible for the integrity of barrier function that can lead to capillary leak. Adherent neutrophils form NETs that amplify endothelial damage mediated by IL-1α. Microvascular as well macrovascular dysfunction can lead to thrombotic, ischemic and other injurious complications and could lead to multiorgan system failure characteristic of the advanced stages of COVID-19.

Libby & Luscher, Eur Heart J 41; 2020:3038–3044

The cytokine storm



Proinflammatory cytokines such as IL-1 and TNF-α induce gene expression of each other initiating an amplification loop, as they induce central proinflammatory hub- NF-κB in endothelial cells, as also IL-6- the instigator of the hepatocyte acute phase response including fibrinogen (the precursor of clot), PAI-1 (the inhibitor of endogenous fibrinolytic system) and CRP. This promotes thrombosis in arteries (including the microvasculature of myocardium and kidney), and in veins (causing deep vein thrombosis and predisposing to pulmonary embolism). The right side of this diagram aligns therapeutic agents that attack these mechanisms of the cytokine storm and may thus limit its devastating consequences.

Libby & Luscher, Eur Heart J 41; 2020:3038–3044

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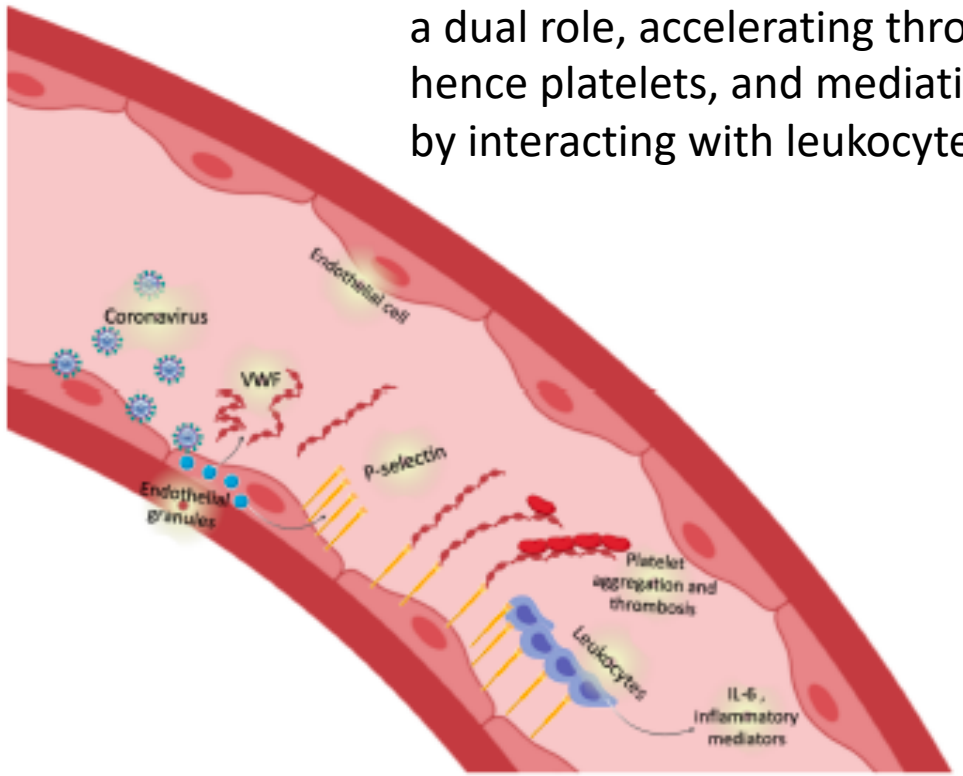
Endothelial exocytosis COVID-19.

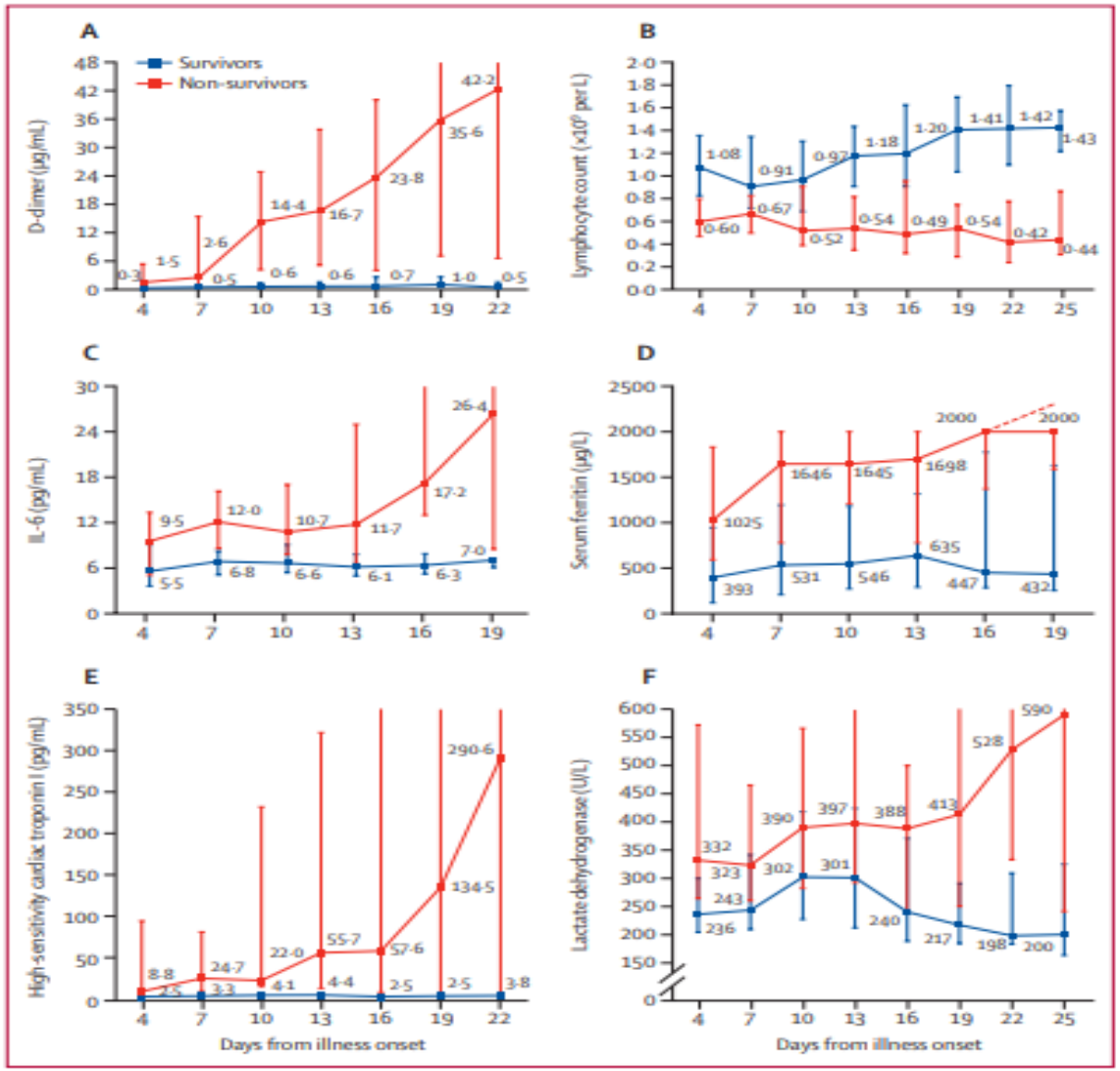
SARS-CoV-2 entry and polypeptide production induces exocytosis of granular complex from cytopathic endothelial cells - VWF and P-selectin. P-selectin plays a dual role, accelerating thrombosis by binding to vWF hence platelets, and mediating vascular inflammation by interacting with leukocytes.



Target interaction of P-selectin with ligand, P-Selectin Glycoprotein Ligand 1 (PSGL1):
Small molecules: quinoline salicylate derivatives (PSI-697)
Oligonucleotide aptamers (ARC5690)
Decoy ligands (recombinant PSGL-1)
Monoclonal antibodies (inclacumab, crizanlizumab)
Crizanlizumab approved for preventing vaso-occlusive crisis in SCD
CRITICAL (Crizanlizumab in COVID-19 Vasculopathy, NCT04435184) trial ongoing

Inhibition of VWF interfere with another part of the endothelial secretory pathway:
Abciximab or eptifibatide block platelet VWF receptor- GPIIbIIIa

Lowenstein CJ & Solomon SD.
10.1161/CIRCULATIONAHA.120.050354



Temporal changes in laboratory markers from illness onset in hospitalized COVID-19 patients

Temporal changes in D-dimer (A), lymphocytes (B), IL-6 (C), serum ferritin (D), high-sensitivity cardiac troponin I (E), and lactate dehydrogenase (F). Differences between survivors and non-survivors were significant for all timepoints shown, except for day 4 after illness onset for d-dimer, IL-6, and high-sensitivity cardiac troponin I. For serum ferritin (D), the median values after day 16 exceeded the upper limit of detection, as indicated by the dashed line. COVID-19=coronavirus disease 2019. IL-6=interleukin-6

Zhou F, Lancet 2020

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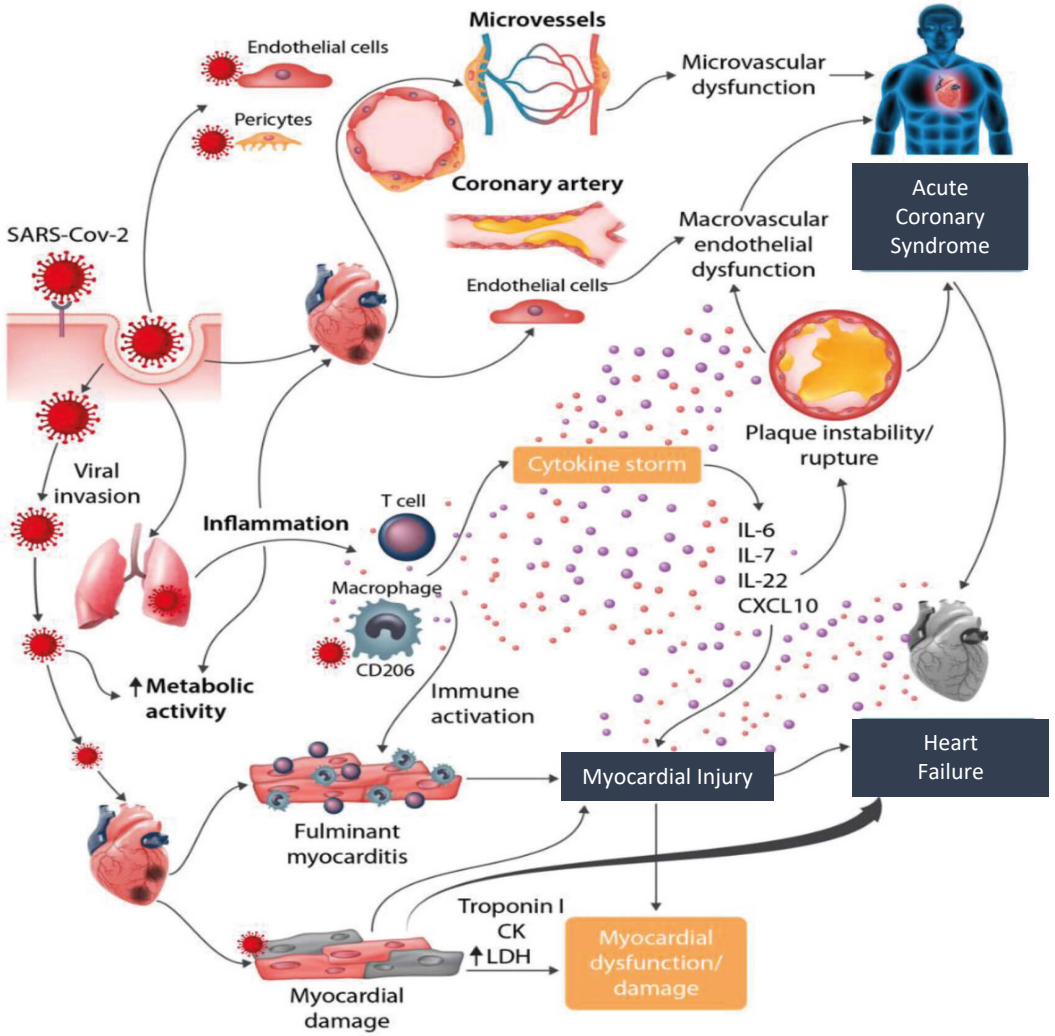

CV involvement in COVID-19: Key manifestations and hypothetical mechanisms

SARS-CoV-2 anchors on trans-membrane ACE2 to enter the host cells including type-2 pneumocytes, macrophages, endothelial cells, pericytes Infection of the respiratory tract, particularly type-2 pneumocytes results in local respiratory damage followed by progressive systemic inflammation often leading to cytokine storm with increased levels of IL-6, IL-7, IL-22 and CXCL-10. Cytokines could cause myocardial depression and microvascular thrombosis can contribute to myocyte damage. Immune over-reactivity can also destabilize atherosclerotic plaques and explain the development of ACS. Finally, endothelial involvement and immune activity when widespread could result in systemic micro- and macro-vascular dysfunction, thrombotic complications and multi-organ damage.

Modified from Cardiovasc Res. 2020, doi: 10.1093/cvr/cvaa106

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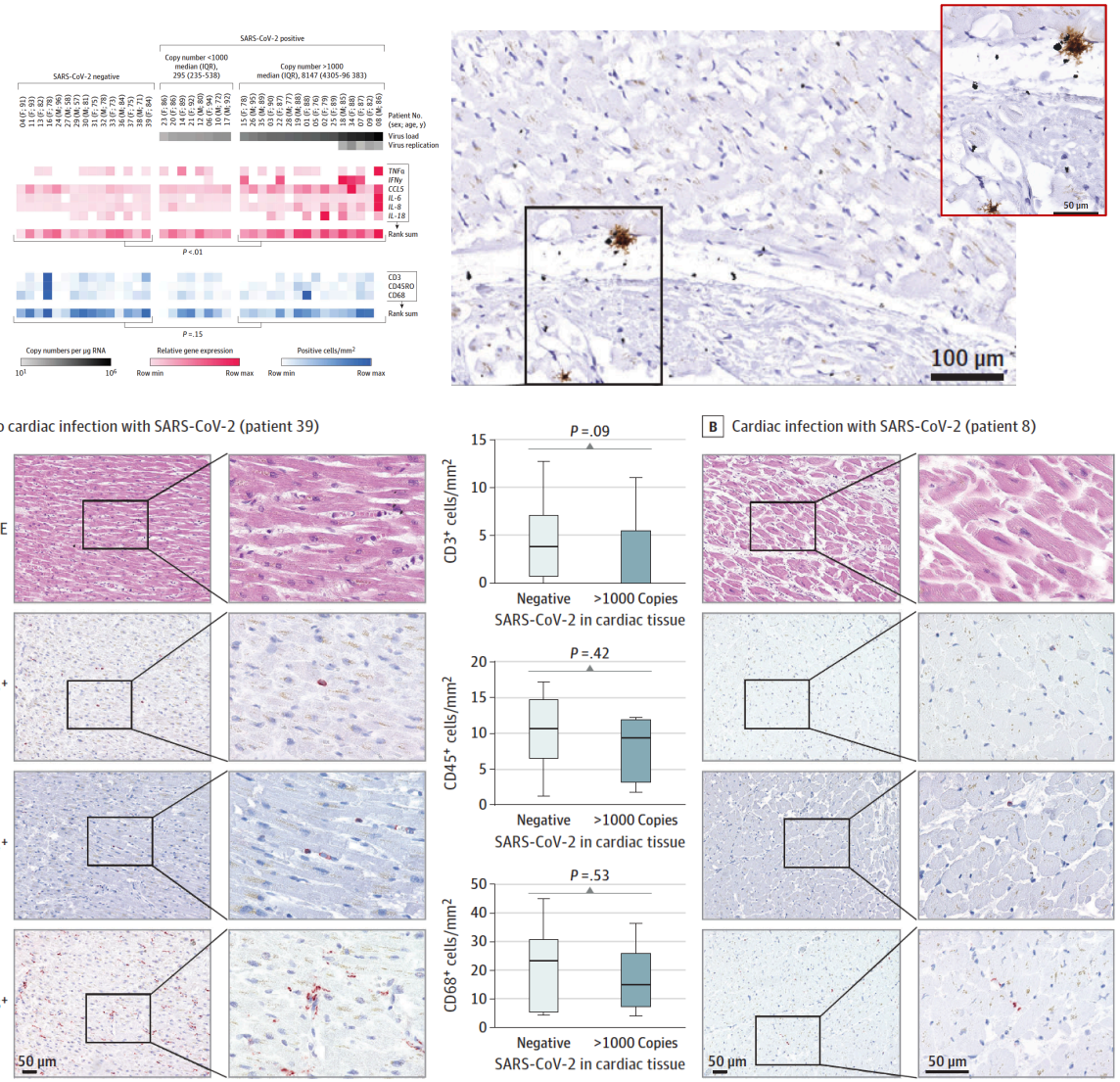
Does myocarditis occur in COVID-19?



COVID-19 myocarditis diagnosis requires:

- Clinical presentation, AND
- Histologic findings

  inflammatory lymphomonocytic infiltrates + myocyte necrosis not typical of ischemic injury
- SARS-CoV-2 genome in heart tissue
- Viral particles in cardiomyocytes
- Exclusion of known cardiotropic viruses (enterovirus, parvovirus)
- Troponin ≠ myocarditis

SARS-CoV-2 RNA was detected by RT-PCR in 24 of 39 patients (62%), and patients grouped according to copy numbers. Virus replication was determined in the 5 patients with the highest virus load. Gene expression data of a cytokine response panel revealed increased proinflammatory response in cardiac tissue with copy numbers >1000 compared with noninfected cardiac tissue, whereas IHC staining revealed no difference in leukocyte infiltrates.

Lindner et al. JAMA Cardiol. doi:10.1001/jamacardio.2020.3551; published online July 27, 2020

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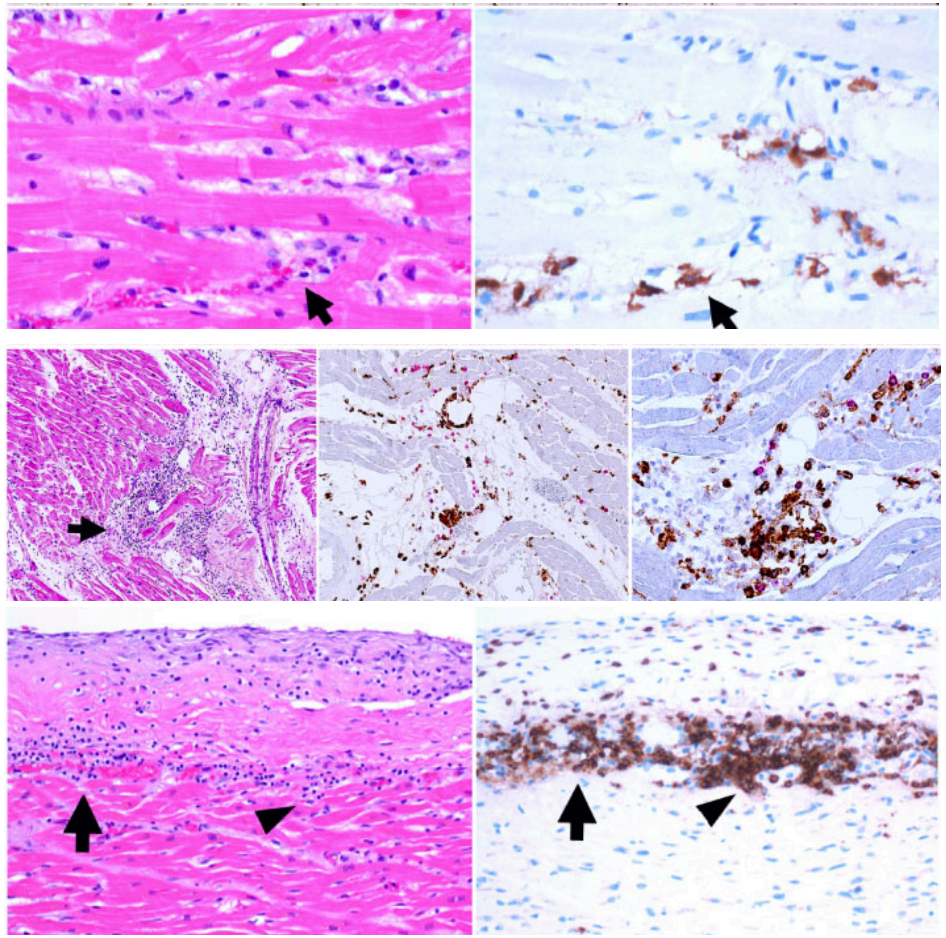


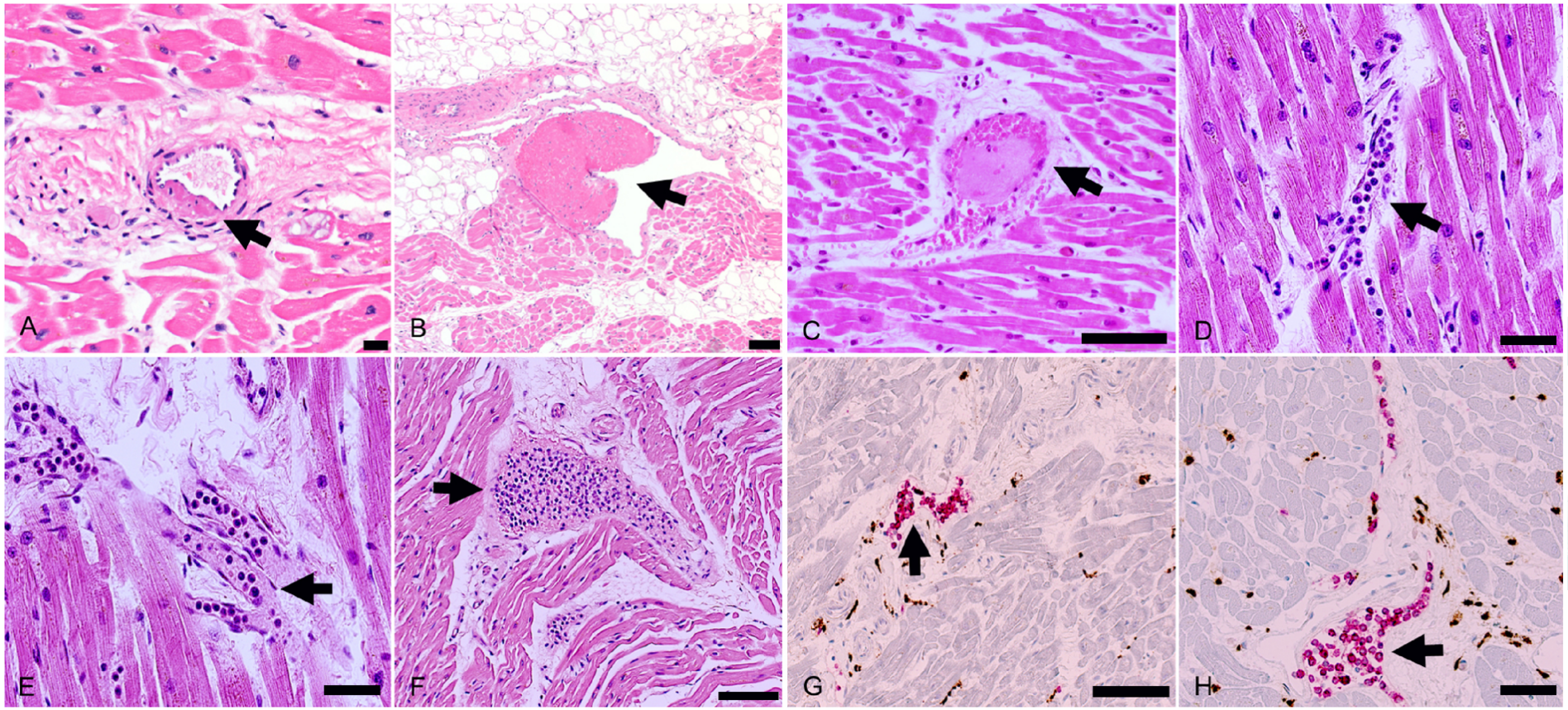
18/21

3/21

4/21

Basso et al. https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa664/5910781

Myocardial small vessel changes



Basso et al. https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa664/5910781

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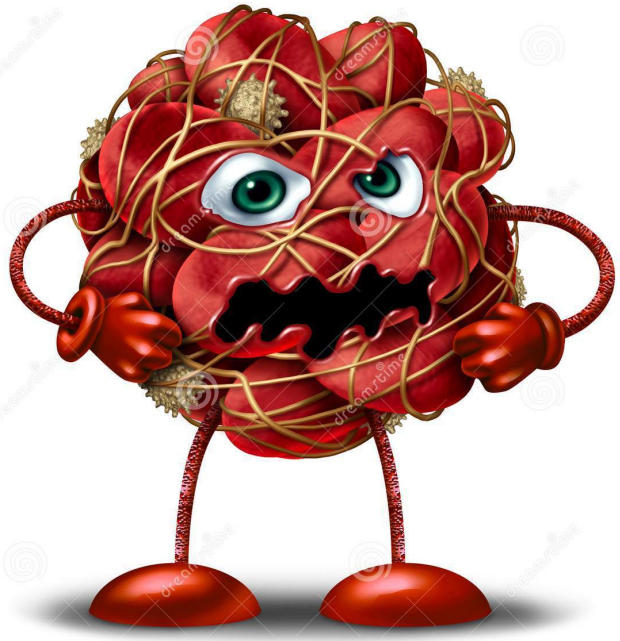
Thromboembolic Complications

- Among hospitalized patients, new thromboembolism has emerged as a important disease manifestation. Autopsy studies have demonstrated a high incidence of macro and microthrombi.
- Observational analyses have suggested potential benefit for in-hospital use anticoagulation. Yet, practice patterns vary significantly due to lack of rigorous evidence for optimal regimens. In a preliminary analysis of 2700 patients admitted to the Mount Sinai Health System, we found an association between in-hospital therapeutic anti-coagulation and improved survival compared to patients on no/prophylaxis.
- A follow-up study of ~4,500 patients, median age 65 (IQR, 53–77) years, 44% female, 25% African American and 25% Hispanic/Latino, including 1000 on therapeutic and 2000 on prophylactic and 1500 on NO anticoagulants; 1/10th were on anticoagulants (1.5%) or antiplatelets (8.5%).



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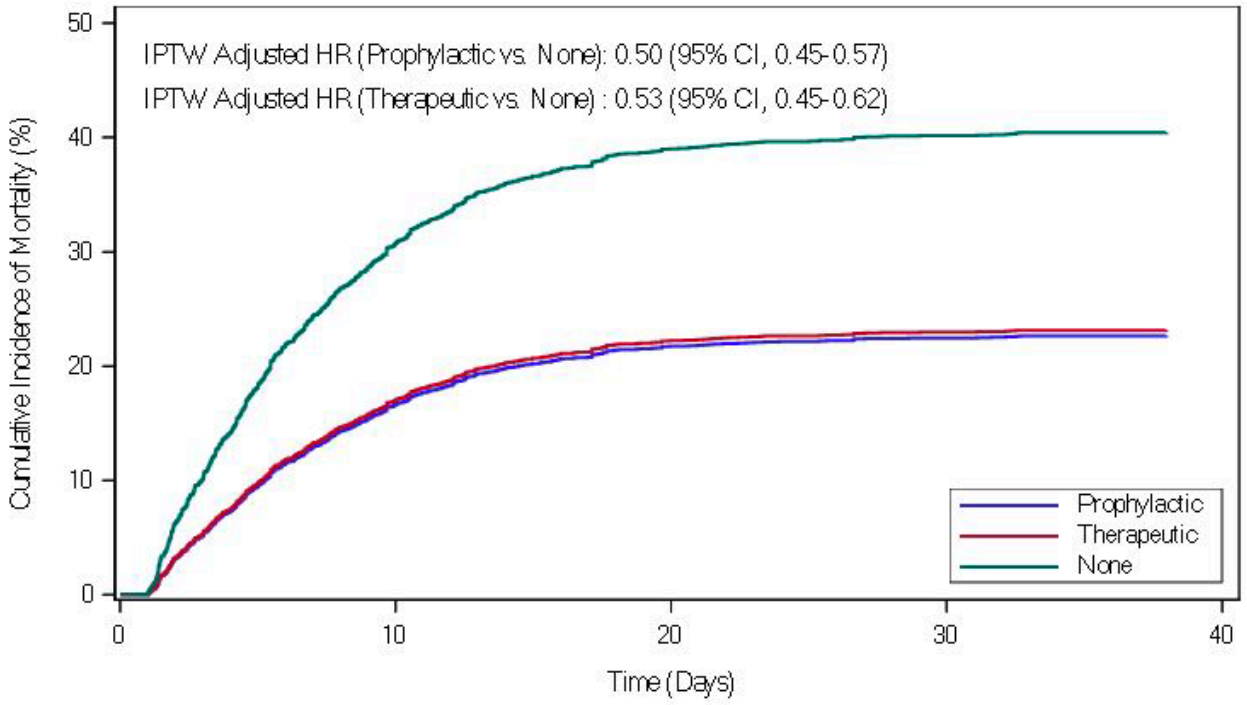

Association of Prophylactic/Therapeutic vs. No Anticoagulation for In-Hospital Mortality

25% died in-hospital during study; therapeutic/prophylactic anticoagulation vs none-adjusted hazard ratio was 50% lower

Nadkarni et al. JACC (submitted) 2020

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Myocardial Injury in COVID-19

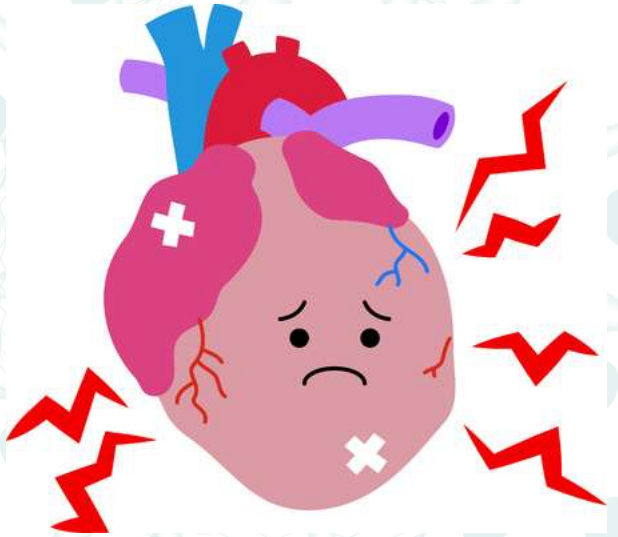
Journal of the American College of Cardiology
June 2020
DOI: 10.1016/j.jacc.2020.06.007

PDF Article

ORIGINAL INVESTIGATIONS

Just Accepted

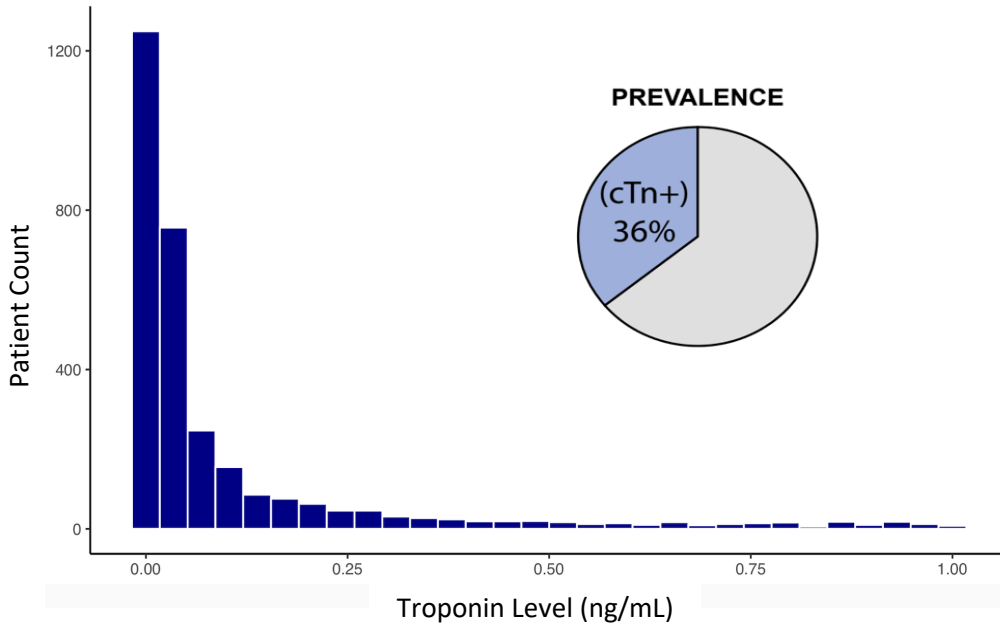
Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection

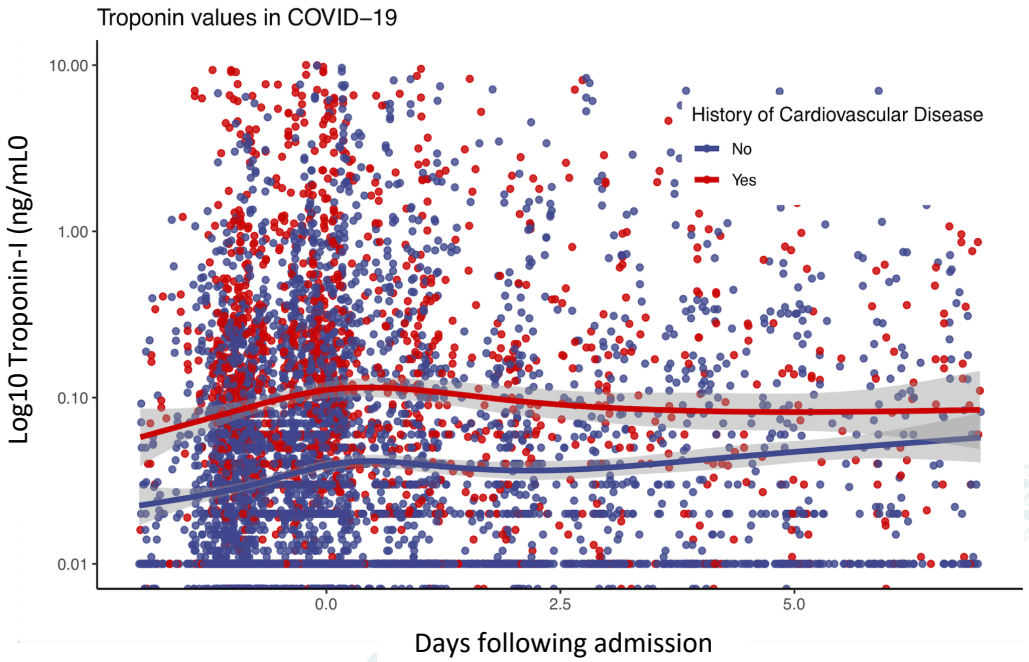


- ~3000 hospitalized patients
- 25% AA, 27% Hispanic/Latino
- 25% with CVD
  - Afib, HF, or CAD
- 25% with HTN or DM
- 22% on ACE/ARB; 36% on statins

Lala et al. JACC 2020

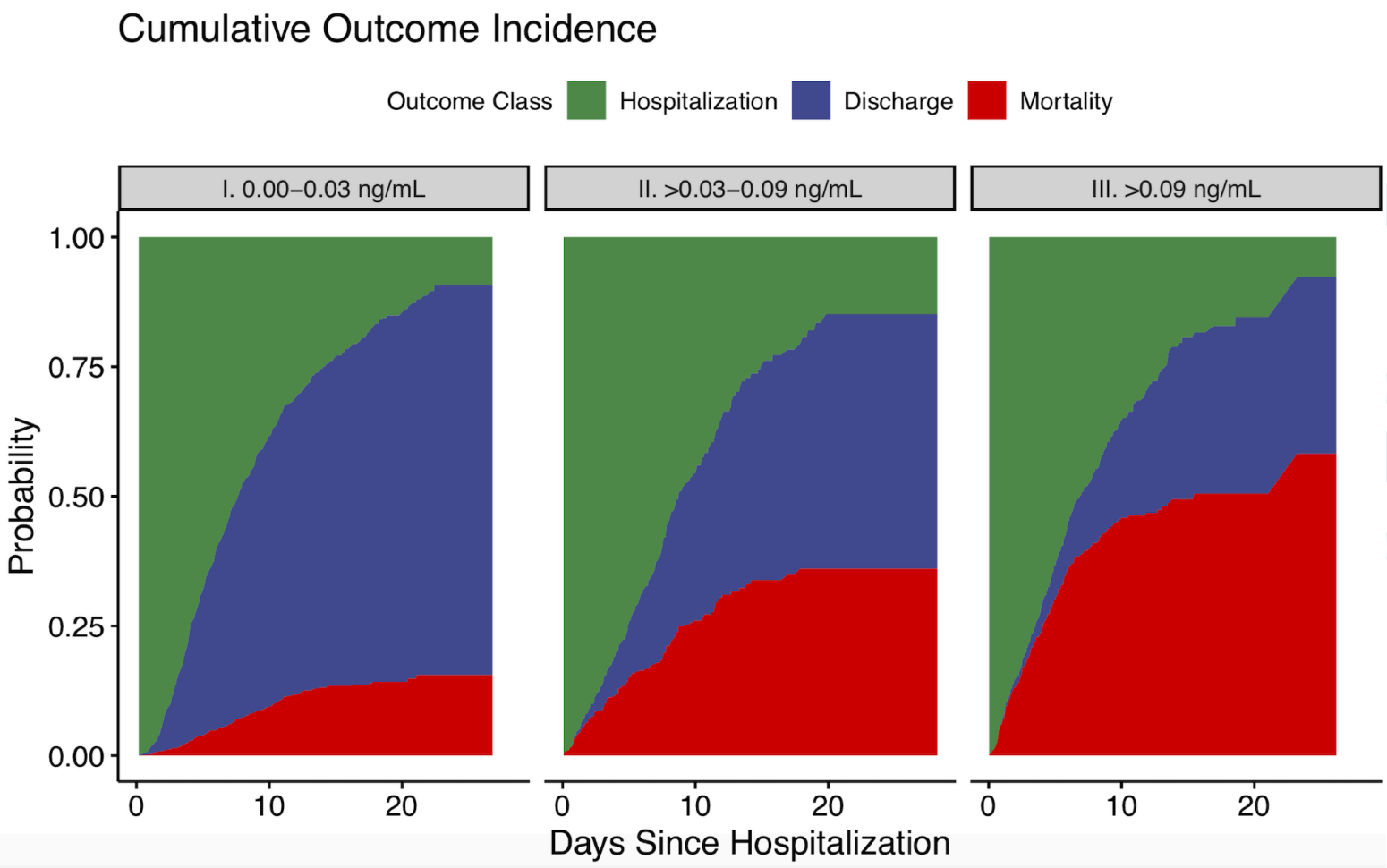
Myocardial Injury in COVID-19

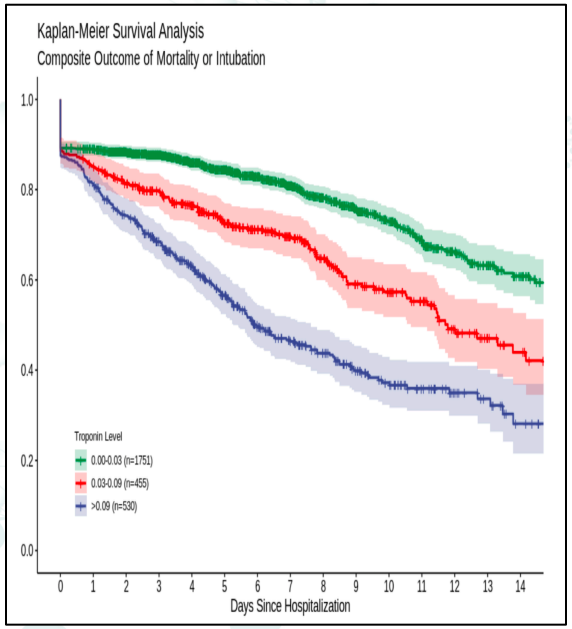




Lala et al. JACC 2020

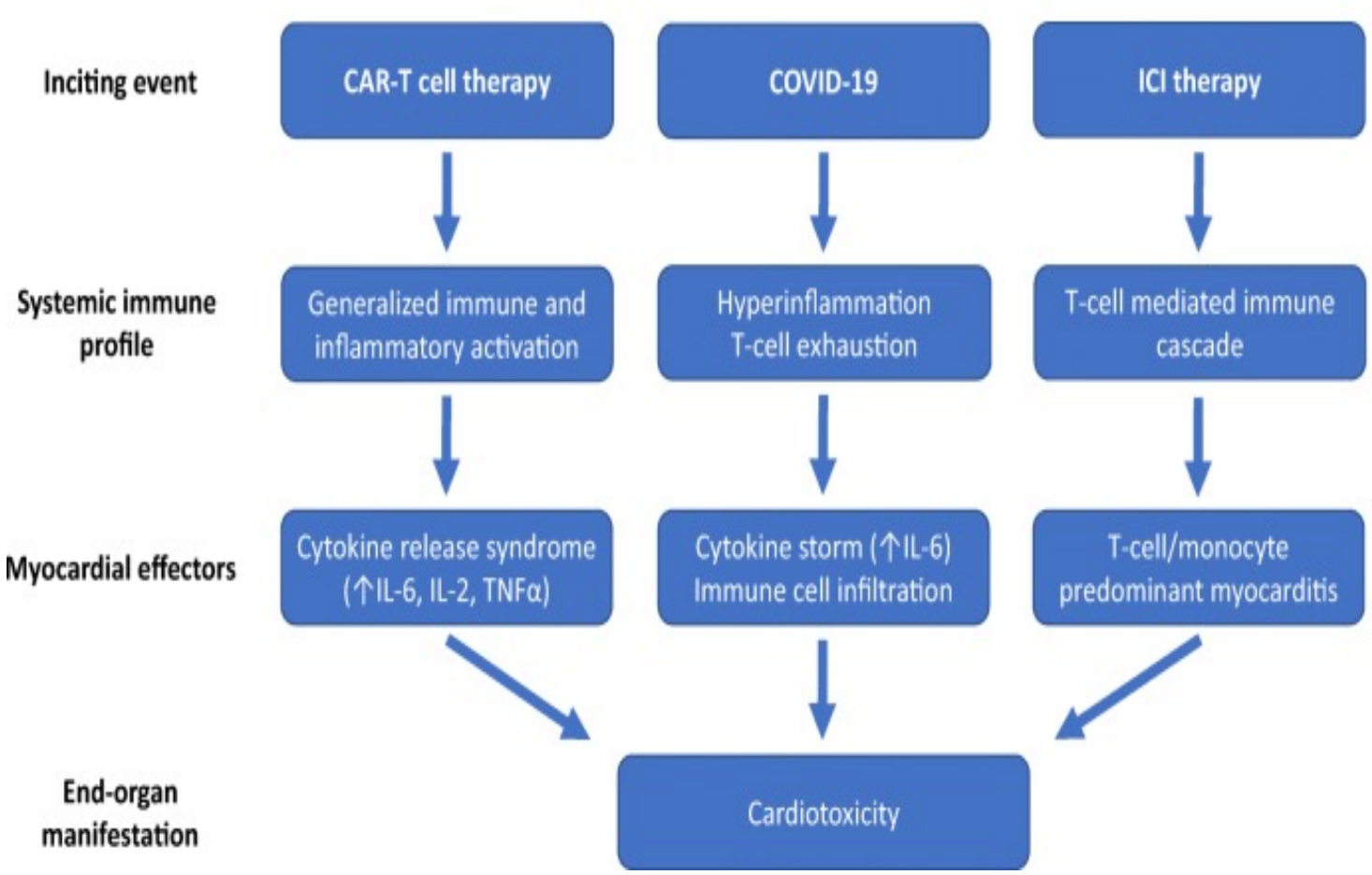
Impact: Discharge & Death by Troponin Levels





Lala et al. JACC 2020

DELAYED CV MANIFESTATIONS AFTER RESOLUTION OF INFECTIVE PHASE OF COVID-19

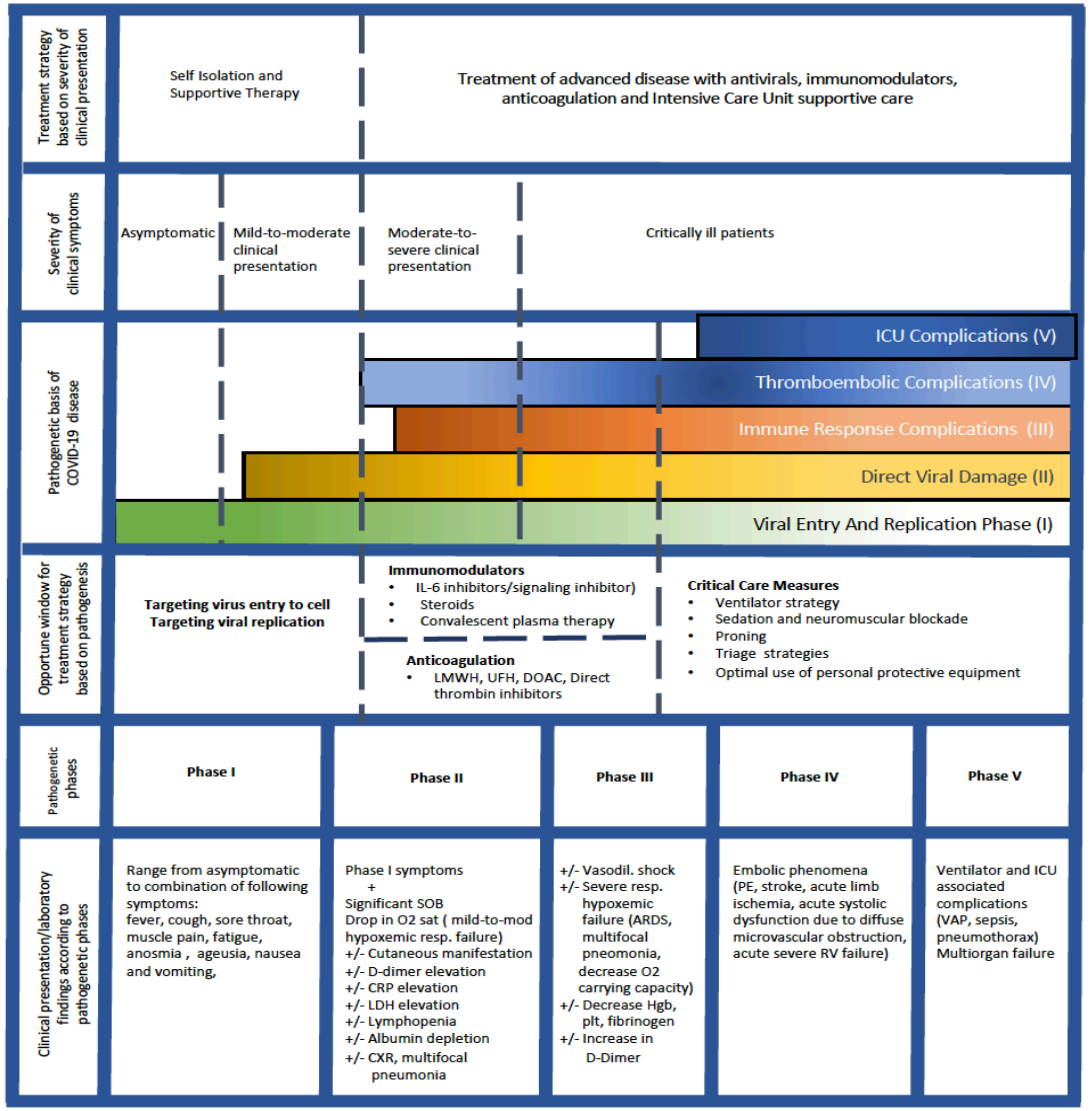


Siddiqui & Neilan. JCTR 2020

Putative mechanisms of cardiotoxicity in COVID-19:

1. Hyperimmune response analogous to contemporary anti-cancer therapies
2. Or, is it smoldering response to low dose of sequestered intracellular viral persistence in absence of obvious infection

Staging of a New Disease



Optimal window for evaluating efficacy of specific treatment strategies based on pathophysiology phases of the disease.

Ahmadi, Narula et al.
Am J Med (2020; in press)

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