

BOLETIM RAMB COVID-19

Número 6
2 de maio de 2020

Viral infections and atherothrombosis: another caution in the wake of COVID-19?

*Marcel de Paula Pereira
Eduardo Gomes Lima
Carlos Vicente Serrano Junior*

Em um momento em que há uma emergência mundial de saúde pública, é fundamental que o conhecimento científico gerado durante a pandemia chegue rapidamente à classe médica classe médica.

Dentro desta dinâmica a Revista da Associação Médica Brasileira (Ramb) está adotando uma série de medidas a fim de acelerar o processo editorial para publicação de artigos sobre a Covid-19. A partir de hoje (14/04/2020), a AMB publicará o Boletim Ramb Covid-19, que antecipará os artigos científicos selecionados pelos editores da Ramb sobre o tema.

“Os artigos foram escritos por especialistas e selecionados dentro dos critérios da Ramb para esclarecer temas fisiopatológicos, assim como oferecer orientações de prevenção e tratamento da doença. Dessa forma, esperamos colaborar com os médicos para o melhor atendimento aos seus pacientes, com a disponibilidade mais ágil desses artigos, antes de sua publicação na Ramb”, comenta Carlos Serrano Jr., editor-chefe da Ramb.

Para o diretor científico da AMB, Antonio Carlos Palandri Chagas, “neste momento ímpar vivido no mundo por conta da pandemia de Covid-19, a AMB cumpre seu papel de estar levando à comunidade científica brasileira os recentes artigos sobre os mecanismos fisiopatológicos e aspectos clínicos relevantes dessa situação que assola a saúde pública”.



Carlos Serrano Jr.



Antonio Carlos Palandri Chagas

EDITORIAL BOARD

EDITORS-IN-CHIEF

Carlos V. Serrano Jr.
José Maria Soares Jr.

CO-EDITOR

Wanderley M. Bernardo

MANAGING EDITOR

César Teixeira

ASSOCIATED EDITORS

Albert Bousso
Sérgio C. Nahas

SPECIALTY EDITORS

ACUPUNCTURE

Ari Ojeda Ocampo Moré
Pedro Cavalcante
Dirceu de Lavôr Sales
Marcia Lika Yamamura
Hildebrando Sábato
Fernando Claudio Genschow

ALLERGY AND IMMUNOLOGY

Herberto José Chong Neto
Luis Felipe Chiaverini Ensina
Pedro Francisco Giavina-Bianchi Júnior

ANAESTHESIOLOGY

Marcos Antonio Costa de Albuquerque
Maria Angela Tardelli
Maria José Carvalho Carmona
Rogean Rodrigues Nunes

ANGIOLOGY AND VASCULAR SURGERY

Marcelo Fernando Matielo
José Fernando Macedo
José Aderval Aragão
Arno Von Ristow
Daniel Mendes Pinto

CARDIOLOGY

Wolney de Andrade Martins
Olimpio Ribeiro França Neto
Otavio Rizzi Coelho Filho
Pedro Silvio Farsky
Humberto Graner Moreira

CARDIOVASCULAR

Eduardo Augusto Victor Rocha
João Carlos Ferreira Leal
Rui M. S. Almeida

CLINICAL PATHOLOGY / LABORATORY MEDICINE

Álvaro Pulchinelli Júnior
Maria Elizabete Mendes
Marinês Dalla Valle Martino
Silvana Maria Elói Santos

COLOPROCTOLOGY

Fábio G. Campos
Sergio Nahas

DERMATOLOGY

Mauro Yoshiaki Enokihara
Flávia Bittencourt

DIGESTIVE ENDOSCOPY

Adriana Safatle

DIGESTIVE SURGERY

Bruno Zilberstein
Nelson Andreollo
Oswaldo Malafaia
Carlos Eduardo Jacob

EMERGENCY MEDICINE

Hélio Penna Guimarães
Marcus Vinícius de Andrade
Júlio Marchini

ENDOCRINOLOGY AND METABOLISM

Márcio Corrêa Mancini
Manoel Ricardo Alves Martins

Auro Del Giglio

Claudia Leite

Edna Frasson de S. Montero

Eduardo F. Borba

Elias Jirjoss Ilias

Isabela Giuliano

Lucia Pellanda

Paulo Kassab

Werther B. W. de Carvalho

Linamara Batistella

Dimas Ikeoki

Anna Andrei

Maria Laura Costa do Nascimento

FAMILY AND COMMUNITY MEDICINE

Thiago Sarti
Leonardo Fontenelle

GASTROENTEROLOGY

João Galizzi Filho
André Castro Lyra
Raquel Canzi Almada de Souza

GENERAL SURGERY

Luiz Carlos Von Bahten
Pedro Eder Portari Filho
Rodrigo Felipe Ramos

GYNAECOLOGY AND OBSTETRICS

César Eduardo Fernandes
Corintio Mariani Neto
Rosiane Mattar
Edmund Chada Baracat

HAND SURGERY

João Baptista Gomes dos Santos
Samuel Ribak
Antonio Carlos da Costa

HEAD AND NECK SURGERY

Antonio Jose Gonçalves
Flávio Carneiro Hojaij
José Guilherme Vartanian
Leandro Luongo Matos

HEMATOLOGY AND HEMOTHERAPY

Fernando Ferreira Costa

HOMEOPATHY

Silvia Irene Waisse Priven

INFECTIOUS DISEASES

Helio Bacha
Alexandre Vargas Schwarzbald

INTENSIVE CARE MEDICINE

Rosane Sonia Goldwasser
Cintia Magalhães Carvalho Grion
Claudio Piras

INTERNAL MEDICINE

Fernando Sabia Tallo
Abrão José Cury Junior

LEGAL MEDICINE AND MEDICAL EXAMINATIONS

Ivan Dieb Miziara
José Jozafra B. Freite

MASTOLOGY

Gil Facina
Rene Aloisio da Costa Vieira
Ruffo de Freitas Junior

MEDICAL GENETICS

Vera Lucia Gil da Silva Lopes

NEUROSURGERY

Luis Alencar B. Borba
Jean Gonçalves de Oliveira
José Carlos Esteves Veiga
José Marcus Rotta
Eberval Gadelha Figueiredo
Benedicto Oscar Colli

NEPHROLOGY

Andrea Pio de Abreu –
Vinicius Daher Alvares Delfino
David Jose de Barros Machado

NEUROLOGY

Carlos Roberto de Mello Rieder
Marcondes Cavalcante França Jr..

NUCLEAR MEDICINE

Juliano Julio Cerci
Cristina Sebastião Matushita
George Barberio C. Filho
Rafael Willain Lopes

NUTROLOGY

Elza Daniel de Mello
Juliana Machado
Durval Ribas Filho

OCCUPATIONAL MEDICINE

Francisco Cortes Fernandes
Rosylane Nascimento das Mercês Rocha
Andrea Franco Amoras Magalhães

ONCOLOGY

Daniela Rosa
Markus Gifoni
Romualdo Barroso

OPHTHALMOLOGY

Keila Monteiro de Carvalho
Eduardo Melani Rocha

ORTHOPAEDICS AND TRAUMATOLOGY

Marco Kawamura Demange
Benno Ejinisman
Daniel Soares Baumfeld
Alex Guedes
Robinson Esteves Santos Pires

OTOLARYNGOLOGY

Marcio Nakanishi
Luciano Rodrigues Neves
Vinicius Ribas de Carvalho Duarte
Fonseca
Edson Ibrahim Mitre

PAEDIATRIC

Emanuel Savio Cavalcanti Sarinho
Debora Carla Chong e Silvia
Simone Brasil de Oliveira Iglesias

PAEDIATRIC SURGERY

Maria do Socorro Mendonça de Campos
Lisieux Eyer de Jesus
José Roberto de Souza Baratella

PATHOLOGY

Fernando Augusto Soares
Kátia Ramos Moreira Leite

PHYSICAL MEDICINE AND REHABILITATION

Silvia Verst
Eduardo Rocha
Luciana Dotta
Ligia Cattai
Marcus Yu Bin Pai

INTERNATIONAL EDITORS

Frida Leonetti
Geltrude Mingrone
Giuseppe Barbaro
Marcelo Marotti
Walter Ageno
Michael Farkouh

JUNIOR EDITORS

Matheus Belloni Torsani
Hélio Amante Miot
Rubens Zeron
Luiz de Menezes Montenegro
Gustavo K. Matsui

PLASTIC SURGERY

Ricardo Frota Boggio
Rodrigo Gouvea Rosique
Fabio Kamamoto

PREVENTIVE MEDICINE AND HEALTH ADMINISTRATION

Antonio Eduardo Fernandes D'Aguir
Milton Massayuki Osaki
Helio Komagata

PSYCHIATRY

Antônio Geraldo da Silva
Itiro Shirakawa
Francisco Baptista Assumpção Junior
Leonardo Rodrigo Baldaçara
Sérgio Tamai

PULMONOLOGY / PHTHISIOLOGY

José Miguel Chatkin
Marcelo Fouad Rabahi
Rodrigo Luis Barbosa Lima
Rosemeri Maurici Da Silva

RADIOTHERAPY

Arthur Accioly Rosa
Gustavo Nader Marta
Gustavo Viani Arruda
Mauricio Fraga da Silva

RADIOLOGY

Alair Sarmet
Valdair Muglia
Dante Luiz Escuissato
Luciana Costa Silva
Claudia Leite
Manoel Rocha

RHEUMATOLOGY

Eduardo dos Santos Paiva

SPORTS MEDICINE

André Pedrinelli;
Fernando Carmelo Torres
Marcelo Bichels Leitão.

SURGICAL ONCOLOGY

Alexandre Ferreira Oliveira
Reitan Ribeiro
Gustavo Andreazza Laporte

TRAFFIC MEDICINE

José Heverardo da Costa Montal
Arlilson de Souza Carvalho Junior
Egas Caparelli Moniz de Aragão Dáquer

THORACIC SURGERY

Darcy Pinto
Carlos Alberto Araujo
Ricardo Terra

UROLOGY

Eduardo Carvalho
Gilberto Almeida
Stênio Zequi
Lucas Teixeira A. Batista
Francisco Bretas

**ASSOCIAÇÃO MÉDICA BRASILEIRA (BRAZILIAN MEDICAL ASSOCIATION)
MANAGEMENT BOARD 2017-2020**



PRESIDENT

Lincoln Lopes Ferreira (Minas Gerais)

1ST VICE-PRESIDENT

Diogo Leite Sampaio (Mato Grosso)

2ND VICE-PRESIDENT

Robson Freitas de Moura (Bahia)

VICE-PRESIDENTS

José Luiz Dantas Mestrinho – Mid-West (Federal District)

Arno Buertiner Von Ristow – Southeast (Rio de Janeiro)

Eduardo Francisco de Assis Braga – North (Tocantins)

Mauro Cesar Viana de Oliveira – Northeast (Maranhão)

Alfredo Floro Cantalice Neto – South (Rio Grande do Sul)

GENERAL SECRETARY

Antônio Jorge Salomão (São Paulo)

1ST SECRETARY

Carmita Helena Najjar Abdo (São Paulo)

1ST TREASURER

Miguel Roberto Jorge (São Paulo)

2ND TREASURER

José Luiz Bonamigo Filho (São Paulo)

CULTURAL DIRECTOR

Fernando Antonio Gomes de Andrade (Alagoas)

DIRECTOR OF CORPORATE RELATIONS

Carlos Alfredo Lobo Jasmin (Rio de Janeiro)

DIRECTOR OF INTERNATIONAL RELATIONS

Eduardo Nagib Gaudi (Rio de Janeiro)

SCIENTIFIC DIRECTOR

Antonio Carlos Palandri Chagas (São Paulo)

ACADEMIC DIRECTOR

Maria José Martins Maldonado (Mato Grosso do Sul)

DIRECTOR OF MEMBER SUPPORT SERVICES

Marcio Silva Fortini (Minas Gerais)

DIRECTOR OF PARLIAMENTARY AFFAIRS

Débora Eugenia Braga Nóbrega Cavalcanti (Paraíba)

**RAMB - REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
(JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION)**

RAMB

EDITORS-IN-CHIEF: *Carlos V. Serrano Jr. and José Maria Soares Jr.*

CO-EDITOR: *Wanderley M. Bernardo*

MANAGING EDITOR: *César Teixeira*

E-MAIL: *ramb@amb.org.br*

WEBSITE: *www.ramb.org.br*

Address: Rua São Carlos do Pinhal, 324

Bela Vista – São Paulo

Postal Code: 01333-903

Phone no.: (+55 11) 3178-6800 Ext. 177

The RAMB, Journal of The Brazilian Medical Association, is an official publication of the Associação Médica Brasileira (AMB – Brazilian Medical Association), indexed in Medline, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B2 Capes databases, and licensed by Creative Commons®. Registered in the 1st Office of Registration of Deeds and Documents of São Paulo under n. 1.083, Book B, n. 2.

Publication norms are available on the website www.ramb.org.br

All rights reserved and protected by Law n. 9.610 – 2/19/1998. No part of this publication may be reproduced without prior written authorization of the AMB, whatever the means employed: electronic, mechanical, photocopying, recording or other.

THE RAMB IS INDEXED IN SCIELO - SCIENTIFIC ELECTRONIC LIBRARY ONLINE.



TIMBRO EDITORA

PUBLISHER: *Rodrigo Aguiar*

AUTHORIZING EDITOR: *Luciano Bauer Grohs*

EDITOR: *Celina Maria Morosino Lopes*

PRODUCER: *Maria Fortes*

EDITORIAL PRODUCER: *Helvânia Ferreira*

ENGLISH TRANSLATION OF ARTICLES: *Alpha & Omega*

REFERENCE REVIEWER: *Rosângela Monteiro*

PROOFREADING: *Hebe Ester Lucas e Alpha & Omega*


GRAPHIC DESIGN: *Angela Mendes e Murilo M. Camargo*




The advertisements and opinions published in the Ramb are the sole responsibility of the advertisers and authors. The AMB and Timbro Comunicação are not responsible for its content.

Viral infections and atherothrombosis: another caution in the wake of COVID-19?

 Marcel de Paula Pereira ¹

 Eduardo Gomes Lima ¹

 Carlos Vicente Serrano Junior ¹

1. Departamento de Aterosclerose – Instituto do Coração (InCor) – HCFMUSP, São Paulo, SP, Brasil

The COVID-19 pandemic is caused by the novel coronavirus (Sars-COV-2), with global impact and leading to numerous hospitalizations and deaths in several countries. Data from 01 April 2020 show over 887,000 infected individuals and over 44,000 deaths.

Publications ¹⁻⁴ show that the main risk factors for an unfavorable outcome are: hypertension 6-31% (SAH), diabetes 7.3-19% (DM), age, and presence of cardiovascular disease 8-15% (CVD); the main risk factor to date is age over 80 years. It should be noted, therefore, that patients with cardiovascular disease are at higher risk of complications. COVID-19 invades cells by binding to the of the angiotensin-converting enzyme (ACE-2), which has a greater expression in cardiac and pulmonary tissues ⁵.

Zhou, et al., ² has reported the clinical characteristics of 171 patients admitted with infections caused by COVID-19. Among the abnormal laboratory results found in multivariate analysis was the increase of D-dimer > 1ug/ml, which was related to worse prognosis, as were advanced age and increased SOFA score. Studies have also demonstrated that many patients can evolve with lymphopenia ¹⁻⁴. The presence of coagulopathy, evidenced by the increase of D-dimer, prothrombin time (PT), and disseminated intravascular coagulation (DIC), was also a marker of negative prognosis, regardless of its high levels during admission or at any time during hospitalization ^{2,6}. In a recent meta-analysis ⁷, high

levels of troponin were also related to a worse prognosis.

In another publication on 416 hospitalized patients ⁸, there was an association between increased troponin and mortality; whereas the higher its value, the higher was the risk. Myocardial injury was identified in 19.7% of patients. These were older, had a higher number of comorbidities (including cardiovascular), and presented other increased inflammatory parameters in relation to the control group, such as increased leukocytes, C-reactive protein, and procalcitonin, as well as greater opacity on computed tomography scans of the chest. In addition, these patients had a longer period of mechanical ventilation, renal dysfunction, and coagulation disorders. The difference in mortality was 51.2% vs. 4.5% (P<0.001). This inflammatory storm, with increased cytokines, troponin, D-dimer, among others, leads to a greater predisposition to cardiovascular events and death. In addition, data show that acute coronary events, arrhythmias, myocarditis, Takotsubo syndrome, and acute heart failure can occur related to COVID-19. In relation to acute heart complications, Wang ⁴ reported 16% of arrhythmia.

Preliminary evidence ⁹⁻¹² demonstrates that infections, viral ones included, lead to systemic inflammatory conditions, including atherosclerotic plaques. As shown in Figure 1, during the inflammatory activity triggered by the infection, there is an infiltrate of cells in the atherosclerotic

plaque (T cells, macrophages, and neutrophils), contributing to the production of cytokines, coagulation factors, oxygen radicals, and vasoactive molecules, leading to increased vascular permeability, endothelial damage, rupture of the fibrous layer, and exposure of thrombogenic elements (collagen, tissue factor, and platelet adhesion molecules), contributing to the formation of thrombus. The plaque erosion alone is not enough to cause coronary ischemic syndromes. Other important factors for the emergence of injury and ischemia are: the nature of the thrombus formation (partial vs. total), degree of stenosis, presence of vasoconstriction, distal perfusion, and an imbalance between supply and demand in the coronary bed evidenced by hypoxia, hypotension, tachycardia, and the increase of endogenous catecholamines leading to local vasoconstriction. Previous reviews ¹³⁻¹⁵ have demonstrated the role of platelets and the coagulation system in viral infections. It is suggested that platelets can bind to pathogens through receptors on their surface and help eradicate them. After the binding, there is a release of factors such as Thromboxane A2 and Adenosine Diphosphate (ADP), activating the coagulation and inflammatory cascade. There have been reports that this platelet activation results in thrombocytopenia, a common finding in viral infections (such as Influenza, Coronaviruses, and HIV). An endothelial lesion can lead to exposure of prothrombotic

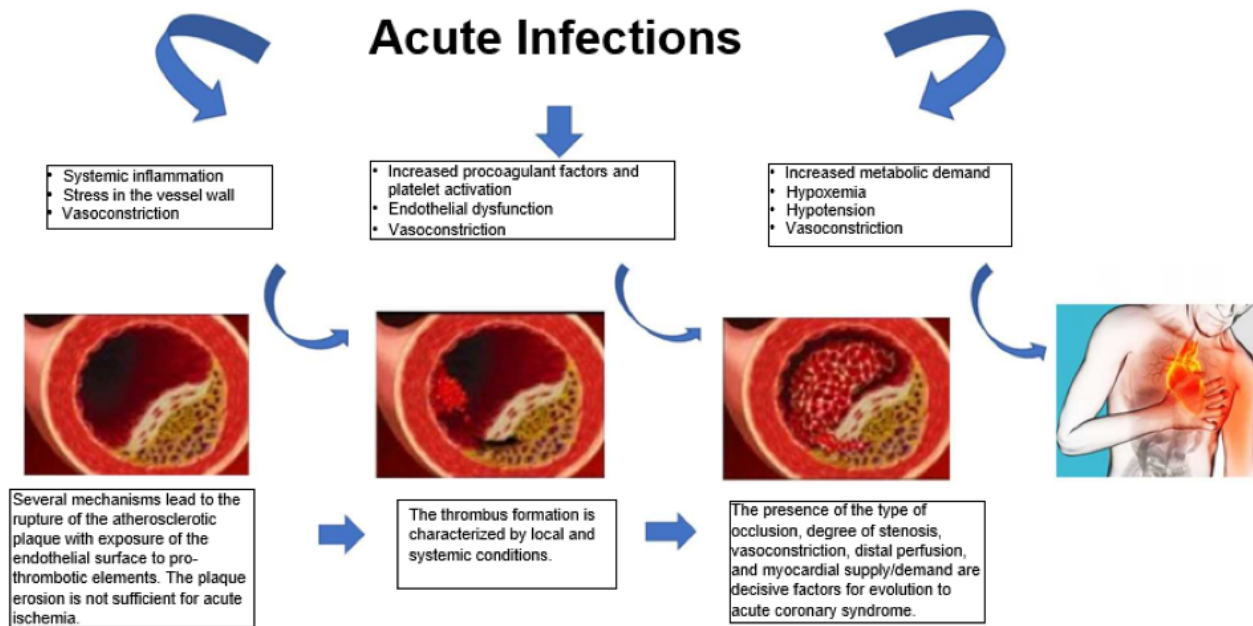


FIGURE 1. Acute infections triggering myocardial injury and acute coronary syndromes. (Adapted from Medina et, al; Role of acute infection in triggering acute coronary syndromes; Lancet Infect Dis 2010; 10: 83-92).

factors, such as the Von Willebrand factor, on the vessel wall, as well as to the decrease of endogenous anticoagulant factors, such as proteins C and S, and antithrombin. Previous data show that in infections caused by Influenza and SARS, there was an increase of thrombi and fibrin deposits in the lungs, thus suggesting local microthrombosis.

There have also been descriptions of “shock-induced Endotheliopatia in critical patients”¹², which suggests that during shock there is sympathetic -adrenal hyperactivation, with an increase of circulating catecholamines, leading to endothelial and microcirculation damage due to capillary leak, with increased local inflammatory mediators, vascular edema, and tissue hypoxia, generating a vicious cycle of endothelial lesion. Thus, the endogenous anticoagulant system would be damaged, leading to microvascular occlusion, which can justify the increased D-dimer and troponin in more severe patients. In addition, in the final shock cascade, there can be

coagulopathy and even DIC as a compensatory mechanism. Johansson et al. suggested that young people have less endotheliopathy (in patients with trauma-related shock) in comparison with the elderly. In addition, smokers, hypertensive, and diabetics patients have greater endothelial dysfunction, and the finding of endotheliopathy could be associated with the outcomes of death in the short and long term.

In a study published in 2018¹⁶, viral infections by Influenza were associated with a higher rate of acute coronary events. It evaluated the diagnoses of acute myocardial infarction (AMI) during a 1-year period before and after a positive diagnosis for Influenza. In this study, there was a higher rate of AMI in up to 7 days after the diagnosis of Influenza in relation to the control group. According to the data presented, infections, among them, viral ones included, can lead to acute coronary conditions, as well as endothelial and microvascular lesions. Increased D-dimer and troponin suggest a worse prognosis and

greater risk of mortality in COVID-19 positive patients, probably because they are associated with a greater inflammatory response, endothelial damage, and thrombotic events.

A Chinese study¹⁷ that included 449 patients admitted for COVID-19 showed that the strategy of prescribing enoxaparin 40-60mg/day or non-fractionated heparin 10,000 to 15.000U/day brought benefits in mortality after 28 days in 2 subgroups. One of them comprised patients with criteria of coagulopathy induced by sepsis ≥ 4 (which uses the criteria of increase of PT, decreased platelet count, and increased SOFA score), with a difference of 40% vs. 64.2% ($P = 0.029$). The other subgroup was composed of patients with D-dimer $> 6x$ the upper threshold of normality, with a difference of 32.8% vs. 52.4% ($P = 0.017$), demonstrating that the strategy of prescribing chemical prophylaxis for venous thromboembolism (VTE) should be considered in patients admitted with COVID-19, even if they present low/intermediate risk of VTE.

In relation to the therapeutic procedures for patients with CVD who are infected with COVID-19, the hypothesis has been raised that medications that interfere with the ACE can be harmful to the patient. Since there have been no studies demonstrating such association, most medical societies recommend not discontinuing angiotensin-converting enzyme (ACE)

inhibitors and angiotensin II receptor blockers (ARB), as well as any medications that were already in use, particularly those used with prognostic benefits^{5,18}. Pro-thrombotic events, including acute coronary events, require increased attention, and there is no evidence that recommends the routine interruption of antiplatelet and anticoagulant drugs. In addition,

the recommendations for influenza and pneumococcus vaccinations in patients with previous indications are maintained. ■

Submitted Date: 02-Abr-2020

Accepted Date: 04-Abr-2020

CORRESPONDING AUTHOR:

Marcel P. Pereira

E-mail: marcelppereira@hotmail.com

REFERENCES:

1. Guan W, Ni Z, Hu Y et al. Clinical Characteristics of Coronavirus Disease 2019 in China. DOI: 10.1056/NEJMoa2002032
2. Fei Zhou, Ting Yu, Ronghui Du, Guohui Fan, et al.; Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study; [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)
3. Bo Li1, Jing Yang, Faming Zhao, et al.; Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China; *Clinical Research in Cardiology*; <https://doi.org/10.1007/s00392-020-01626-9>
4. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. Published online February 07, 2020. doi:10.1001/jama.2020.1585
5. Clerkin et al.; COVID-19 and Cardiovascular Disease; 10.1161/CIRCULATIONAHA.120.046941
6. Tang, Ning et al.; Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia; *J Thromb Haemost*. 2020;00:1-4. _
7. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis; <https://doi.org/10.1016/j.pcad.2020.03.001>
8. Shaobo Shi, et al.; Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China; *JAMA Cardiol*. doi:10.1001/jamacardio.2020.0950
9. Braunwald's Heart Disease Review and Assessment, 11 edition, 2018
10. Vicente F Corrales-Medina, Mohammad Madjid, Daniel M Musher; Role of acute infection in triggering acute coronary syndromes; *Lancet Infect Dis* 2010; 10: 83-92
11. Higuchi et al; Mycoplasma and chlamydia in vulnerable plaques associated to AMI; *Arq Bras Cardiol*, volume 81 (nº 1), 12-22, 2003
12. Johansson et al; Shock induced endotheliopathy (SHINE) in acute critical illness - a unifying pathophysiologic mechanism; *Critical Care* (2017) 21:25
13. Seyoum et al; Human blood platelets and viruses: defense mechanism and role in the removal of viral pathogens; *Thrombosis Journal* (2018) 16:16
14. Antoniak, Silvio; The coagulation system in host defense; *Res Pract Thromb Haemost*. 2018;2:549-557
15. Goeijenbier et al; Review: Viral Infections and Mechanisms of Thrombosis and Bleeding; *Journal of Medical Virology* 84:1680-1696 (2012)
16. Jeffrey C. Kwong, M.D., Kevin L. Schwartz, M.D., Michael A. Campitelli, M.P.H, et al; Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection; *N Engl J Med* 2018;378:345-53.
17. Tang, Ning et al; Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy; doi: 10.1111/JTH.14817
18. Vaduganathan, Muthiah, Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19; DOI: 10.1056/NEJMs2005760