Review: Atherosclerosis as pathogenetic substrate for Sars-Cov2

“cytokine storm”

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Abstract

Sars-CoV-2 outbreak represents a public health emergency, affecting different regions of the world. Lung is the organ more damaged due to the high presence of Sars-CoV-2 binding receptor ACE2 on epithelial alveolar cells. Severity of infection vary from absence of symptomatology to be more severe, characterized by acute respiratory distress syndrome (ARDS), multiorgan failure and sepsis requiring treatment in Intensive Care Unit (ICU).

It is not still clear why in a small percentage of patients immune system is not able to efficiently suppress viral replication.

It has been documented as predictive factors for severity and susceptibility affections of cardiovascular system such as heart failure (HF), coronary heart disease (CHD) and risk factors for atherosclerotic progression, hypertension and diabetes among others.

Atherosclerotic progression, as chronic inflammation process, is characterized by immune system dysregulation leading to pro-inflammatory pattern, including (Interleukin 6) IL-6, Tumor Necrosis Factor α (TNF-α) and IL-1β raise.

Reviewing immune system and inflammation profiles in atherosclerosis and laboratory results report in severe Sars-CoV-2 infection we have supposed a pathogenetic correlation. Atherosclerosis may be a pathogenetic ideal substrate to high viral replication ability leading to adverse outcomes, how reported in patients with cardiovascular factors. Moreover, level of atherosclerotic progression may impact on a different degree of severe infection and in a vicious circle feeding itself Sars-CoV-2 may exacerbate atherosclerotic progression due to excessive and aberrant plasmatic concentration of cytokines.
Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak is affecting different regions of the world since the end of 2019, representing a public health emergency.

Up to the date (i.e. 14 April, 2020) more than 1,681,964 cumulative cases have been confirmed by the Center for System Science and Engineering (CSSSE) at Johns Hopkins University (JHU) and the number of deaths is 102,026 until now (https://coronavirus.jhu.edu/map.html).

The incubation period of Sars-CoV-2 to develop symptomatology is of 4-5 days, extending up to 14 days [1]. Severity of infection vary from absence of symptomatology, to having fever, cough, shortness of breath, anorexia and fatigue up to most severe cases characterized by severe pneumonia, acute respiratory distress syndrome (ARDS) and sepsis [2][3][4]. Respiratory failure, shock and multiorgan system dysfunction describe a critical illness, representing approximately 5% of cases and requiring mechanical ventilations in Intensive Care Unit (ICU) [5].

Pathogenesis of COVID-19 severity is not well known [6][7].

Angiotensin Converting Enzyme 2 (ACE2) is the functional receptor of Sars-Cov-2 representing the entry site to the human cells and may be ubiquitous although more expressed by epithelial cells of lungs, myocytes and vascular endothelial cells [8]. Interestingly referring to Sars-CoV similarities of shared ACE2 structure, it may be present on macrophages, monocytes and lymphocytes triggering the immunological activation [9]. Immunological response to the viral infection results the main cause for acute organ injury due to excessive activation. Moreover, in patients recovered in ICU and severe/critical manifestation of Sars-CoV-2 the immunological pattern is more dysregulated, being characterized by pro-inflammatory pattern [9], leading to an abnormal and disproportionate activation of cytokine host cascade labeled as ‘cytokine storm’ [7].

The causes of immune response exacerbation are largely unknown and is not clear why this small percentage of patients develop a persistent and dangerous infection, potentially leading to death [9].

A meta-analysis conducted on 53,000 infected patients in Wuhan has demonstrated as risk factors for severity of COVID-19: older age, sex male, smoking and any comorbidity. Hypertension, diabetes, cardiovascular disease (CVD), cerebrovascular diseases, chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) have in fact shown a higher significative incidence in severe cases (54,9%) than in non severe ones (27,6%) [10].
Except for CKD and COPD, the other risk factors documented for severity are involved or are a direct consequence of atherosclerotic process, which is characterized by a progression strongly related with immune system dysregulation.

Our aim is to review the pathogenetic mechanism of severe COVID-19 focusing on atherosclerotic process describing it for immune system and inflammation profiles.

**Pathogenesis of COVID-19**

Sars-CoV-2, as causative agent of the novel respiratory infectious disease COVID-19, is a single-stranded Ribonucleic Acid (RNA) virus characterized by a high transmission human to human mainly trough respiratory droplets [11][12].

The virus colonizes primarily lungs after passed trough mucous membranes and causes the ‘viremia phase’ as defined by Lin et al, entering in the peripheric blood. Typically fever and cough represent the early most common symptoms detectable in this phase [6].

The high documented transmissibility of COVID-19 may be explained by the high viral load during ‘viremia phase’ and by the molecular efficient mechanism to recognize binding protein ACE2 allowing the invasion of alveolar epithelial human cells [8][12].

The immune function of patients is involved to control the virus during the ‘acute phase’, it seems in fact that acute organ damage follows the first ‘viremia phase’ occurring approximately after 7 days the onset of symptoms, when Sars-Cov-2 is not efficiently suppressed by immune system.

In the ‘acute phase’, exploiting ACE2 binding receptor, COVID-19 leads to worsening respiratory functionality causing pneumonia [6].

The severity of respiratory disease vary from a picture of mild symptoms such as cough and shortness of breath up to Acute Respiratory Distress Syndrome (ARDS), as expression of critical illness [13].

The ubiquitous presence of ACE2 and patients susceptibility may be associated besides to multiorgan failure, comprising acute myocardial causing directly myocarditis, kidney and liver injury leading to a systemic impairment [14].

The immune system, triggered by viral replication, plays a crucial role to damage organ during the ‘acute phase’ due to the excessive activation [9].
An abnormal inflammatory response leads to an exuberant amounts of cytokines and chemokines among others. The postulated pathogenetic mechanisms involved, due to the high affinity for ACE2, are associated to the massive viral replication in targeting cells such as alveolar epithelial, endothelial, macrophages and lymphocytes causing respectively apoptosis and pyroptosis in the cells of the immune system.

Moreover, basing on the pathogenesis of COVID-19, the role of viral induction on ACE2 may be involved due to downregulation and shedding of receptor leading to renin-angiotensin system dysfunction and increasing vascular permeability. Instead is controversial the role of anti-S-protein-neutralizing antibodies that it seems to facilitate acute lung injury [9].

Immune system results dysregulated showing a pro-inflammatory pattern characterizing mainly lung for a large amounts of cells infiltration.

COVID-19 increases the plasmatic secretion of IL-1β, Interferon-γ (IFN-γ), interferon γ-induced protein 10 kDa (IP-10), Monocyte Chemoattractant Protein-1 (MCP-1), IL-4, and IL-10.

In particular after severe infection, pathway of T Helper (Th) 1 lymphocytes is hyperactivated causing an excessive production of CD14++ CD16+ inflammatory monocytes, responsible of inflammatory exacerbation and increased plasmatic concentration of IL-6.

IL-6 is the key-cytokine triggering increased liver production of acute-phase proteins (APPs) such as C-reactive protein (CRP) and fibrinogen causing an hypercoagulable disease and may predict severity of infection [16][17]. Moreover, IL-6 is the target for therapy with Tocilizumab, a monoclonal antibody that has demonstrated efficacy in severe infection and actually in trial to be approved against Sars-CoV-2.

In addition to IL-6 a high plasma levels of IL-2, IL-7, IL-10, granulocyte colony stimulating factor (GCSF), IP-10, MCP-1, macrophage inflammatory protein 1-alpha (MIP-1α), and TNF-α have been documented in the host representing the well described “cytokine storm”. In ICU patients decreases the plasmatic concentration of lymphocytes due to pulmonary sequestration [7][9].

The pathogenetic mechanism to explain the different degree of immune system hyperactivation able to give a severe picture is not still clear [10].

However, analyzing statistics in Italy and China of severe infection or related death, predisposing patterns are highlighted able to confer more susceptibility to COVID-19.
In the meta-analysis conducted in Wuhan on 53,000 infected patients, severe illness and death occurred in the 20.2% and 3.2% of cases, respectively. Risk factors for severity, as reported in the introduction, were represented by old age (60 yrs), sex male and the concomitance of any comorbidity such as hypertension, diabetes and CVD among others [10].

Data about COVID-19 related-death in Italy (https://www.epicentro.iss.it/coronavirus/sars-cov-2-decessi-italia), up to this date (i.e. 14 April, 2020), reported 16,654 died patients with an average age of 78 years, 67.7% were men and only 3.5% of cases without any comorbidity. Moreover, focusing on the prevalence of pre-existing comorbidities, the most common is hypertension with approximately 75% of cases, a similar prevalence of diabetes and coronary heart disease (CHD) more than 25%, followed by CKD, atrial fibrillation (AF) and COPD.

**The role of atherosclerosis**

Atherosclerosis is the leading cause of CVD worldwide underlying many of the common causes of deaths, including stroke and CHD.

It is a chronic inflammatory disease characterized by infiltration, deposit and lipid oxidation which activates and promote a self-maintenance inflammatory state [17][18][19][20][21].

The most common risks factor are smoking, hypertension, dyslipidemia, metabolic dysregulation such as obesity and diabetes mellitus and non-modifiable factors as advanced age and gender. All these conditions represent also the main risk factors and pre-existing comorbidities in patients COVID-19 with worst clinical manifestation [3][4][10][13] suggesting a link between atherosclerosis and severity of COVID-19.

In Atherosclerosis mechanical stress and endothelium damage enable the accumulation of several plasma lipoproteins, in particular LDL, in the sub-endothelial space where they are modified into oxidized-LDL and trigger inflammation of arterial wall. Both innate and adaptive immune system play a crucial role in lesion formation and plaque characterization maintaining and promoting a pro-atherogenic state.

Oxidized-phospholipids and cholesterol crystals acquiring properties of damage-associated molecular patterns (DAMPs) are recognized by toll-like receptors (TLRs) and nod-like receptors (NLRs) and activate NLRP3 inflammasome pathway which results in proteolytic cleavage of proIL-1β and pro-IL18 to mature IL-1β and IL18 [22].
IL-1β has pro-inflammatory effects inducing expression of cytokines such as IL-6, TNF-α, IL-8, chemokines, improving the susceptibility of macrophages to lipid deposition and enhancing local inflammation and plaque instability [21][23]. L-1β, IL-6 and TNFα are also produced by CD14++ CD16+ non-classical monocytes activated in atherosclerosis disease which are strictly correlated with the disease progression [23].

In the atherosclerosis disease other inflammatory signaling pathways activated are TLR4/NF-κβ and the JAK/STAT which contributed to boost inflammatory state raising cytokines expression and consequent activation of innate and adaptive immunity cells [20].

Increasingly studies have demonstrated the link between high levels of pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β and progression and instability of atherosclerosis plaque pointing out their potential as novel target therapy [21][24][25][26]. Clinical research is focusing on agents that inhibit IL-1, IL-6 and TNFα pathways in order to reduce risk of coronary heart disease and reduce adverse outcomes after injury [20][21][25].

In the CANTOS trial Ridker et al. compared Canakinumab, a monoclonal antibody targeting IL-1β, with placebo in patients with previous myocardial infarction in order to reduce adverse clinical outcomes. This study shown a reduction in cardiovascular events in patients who received the drug although an increased incidence of fatal infections [28]. In addition Anakinra (IL-1R antagonist) proved the potential to reduce the inflammatory response in acute myocardial infarction patients [28][29].

For the causal association between IL6R-related pathways and CHD [30], targeting treatment of IL-6 receptor provided a promising therapeutic approach. In this field the impact of Tocilizumab, an IL-6R monoclonal antibody, is currently evaluating in a randomized, placebo-controlled trial [21].

Etanercept, Infliximab and Adalimumab are anti TNF-α antibodies used in rheumatoid arthritis treatment, which demonstrated in this class of patients significant increase of HDL cholesterol levels and endothelial function improvement [31][32][33][34].

Nidorf S.M. et al. performed successfully a small prospective clinical trial with low-dose colchicine treatment in order to reduce cardiovascular events in patients with stable coronary disease [35] although more research is needed.

The T-helper1 cells type have shown to be the predominant CD4+ effectors in the context of atherosclerosis promoting disease progression due to increasing expression of pro-inflammatory cytokines [36][37].
addition the B2 subsets of B-cells are the main activated in turn exacerbating the adaptive immune response [21].

Several studies suggest also an autoimmune response [38][39] in atherosclerosis with a switch in regulatory T cells from an initial protective phenotype (FoxP3+) into a pathogenic one (RORγt, T-bet, Bcl-6) [40]. This pro-inflammatory and dysregulate state may play a crucial role in increasing host susceptibility to develop “cytokine storm” and worst adverse manifestation of COVID19 due to excessive activation of immunological response. Sars-Cov-2 infection may act as a trigger in these susceptible hosts in which specific inflammation pathways are already activated (Inflammasome, JAK/STAT, NF-κβ pathways) and there is a dysregulation of autoimmune system. Although several studies are needed, this hypothesis may partly explain the severity of infection manifestation in this class of patients.

**Effects of Sars-CoV-2 on Cardiovascular System**

Bonow et al. [41] have postulated ways to explain the documented more susceptibility of patients affected by coronary artery disease (CAD) and risk factors for atherosclerotic cardiovascular disease to develop adverse outcomes and death due to COVID-19 [5][10].

As described in literature for others acute infections [42], in patients with predisposing factors for coronary events, the precarious balance is exacerbated by hyperdynamic circulation caused by COVID-19, increasing myocardial demand of oxygen and resulting in acute coronary events (ACS). Interestingly, they have speculated that ACS in infected patients may be caused by excessive cytokines raise leading to atherosclerotic plaque instability and rupture [41].

The progression and instability of atherosclerotic plaque is in fact strongly related with raise in plasmatic concentration of IL-6, TNF-α and IL-1β and protease activation leading to plaque rupture and luminal thrombosis due to direct negative effect on plaque protective fibrous cap [22].

Confirmations about the impact of Sars-CoV-2 on lipid metabolism and progression of atherosclerotic process is highlighted by an observational study conducted to analyze long-term effect of acute Sars-CoV infection [43].

Twenty-five patients were recruited 12 years after recovery due to Sars-CoV in 2003. Metabolomic analysis was performed, showing an altered lipid metabolism with a significantly increased values of free fatty acids,
lysophosphatidylcholine, lysophosphatidylethanolamine and phosphatidylglycerol. Moreover, the 44% of patients were affected by CVD.

Sars-CoV pathogenesis has shown a high similarity if compared with COVID-19, being characterized by an abnormal hyperactivation of immune system leading to excessive amounts of cytokines too [6]. Hyperactivation of pro-inflammatory pattern, mainly characterized by ‘cytokines storm’ may increase risk of restenosis in patients underwent percutaneous coronary intervention (PCI) with stent implantation due to CHD. As recently reported by Sun et al, pre-operative increased levels of IL-6, TNF-α and IL-23 may predict efficiently risk of restenosis after PCI associated to drug-eluting stents implantation [44].

Besides ACS, cardiovascular system may be involved in patients affected by heart failure, due to hemodynamic decompensation, and in little cases, without prior evidence of CVD, acute myocarditis may occur due to ACE2 presence on cardiac myocytes, leading potentially to dilated cardiomyopathy [41][45][46].

Hospitalized patients who developed myocardial injury, have been described by Shi et al. [47] and Guo et al. [48] highlighting similar characteristics. Evidence of myocardial injury was characterized by increased plasmatic levels of high-sensitivity troponin I (TnI).

Clinically, patients with elevation of TnI are older and characterized by a high prevalence of hypertension, diabetes mellitus, CAD and heart failure. A more severe systemic inflammation has been documented including higher plasmatic concentration of leucocytes and CRP among others, leading to a more complicated respiratory picture with higher incidence of ARDS requiring assisted ventilation than in patients without evidence of myocardial injury.

In particular Shi et al. [47] have documented on a total population of 416 hospitalized patients studied with confirmed diagnosis of Sars-CoV-2, 82 patients (19,7%) with evidence of myocardial injury, resulting in a mortality rate in this group of 51,2% significantly higher than in patients without elevation of TnI (4,5%). Similarly, Guo et al. [48] have studied 187 patients with confirmed laboratory diagnosis, the 27,8% with evidence of myocardial injury characterized by higher in-hospital mortality rate of 57,6% compared with patients not affected (8,9%). Moreover in this report, also patients with pre-existing CVD as comorbidity but without TnI elevation have shown a worse outcomes with mortality rate of 13,30%.

Potentially, long-term effects of cardiovascular system involvement mainly due to hemodynamic changes atherosclerotic progression and resulted increased risk of thrombosis due to COVID-19 may impact directly
on left ventricular systolic function and increasing retrograde pressure on right cardiac chambers leading to decompensation. Moreover, increased incidence of deep vein thrombosis (DVT) events due to abnormal blood clotting may cause more pulmonary embolism events and pulmonary hypertension.

**Conclusion**

The proposed pathogenetic correlation of atherosclerosis and Sars-CoV-2 infection is simplified and summarized in *Figure 1*. Atherosclerosis, as chronic inflammatory disease, may cause an ideal substrate to the high viral replication capacity of Sars-CoV-2 in human cells leading hyperactivation of pro-inflammatory pattern due to immune system dysregulated. Probably the level of atherosclerotic progression may influence severity of COVID-19 in susceptible patients, causing different degree of excessive amounts of immune system cells, cytokines among others, mainly involved in the organ damage. Moreover, the aberrant inflammatory response, as in a vicious circle feeding itself, may leads to atherosclerotic progression increasing risk of instability and rupture. These hypothesis are sustained also by novel therapeutic approach for atherosclerosis with drugs working mainly against inflammatory intermediary, of which Tocilizumab among others has demonstrated a great efficacy to reduce severe Sars-CoV-2 infection too. However, methodological studies focused on this topic are necessary to fortify these suggesting.
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References

[1] Lauer, S. A., Grantz, K. H., Bi, Q., Jones, F. K., Zheng, Q., Meredith, H. R., et al (2020). The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Annals of internal medicine.*

[2] Hu, Z., Song, C., Xu, C., Jin, G., Chen, Y., Xu, X., et al (2020). Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Science China Life Sciences,* 1-6.

[3] Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Fan, G., et al (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet,* 395(10223), 497-506.

[4] Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., et al (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine.*

[5] Wu, Z., & McGoogan, J. M. (2020). Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Jama.*

[6] Lin, L., Lu, L., Cao, W., Li, T. (2020). Hypothesis for potential pathogenesis of SARS-CoV-2 infection——a review of immune changes in patients with viral pneumonia. *Emerging Microbes & Infections,* (just-accepted), 1-14.

[7] Zhou, Y., Fu, B., Zheng, X., Wang, D., & Zhao, C. (2020). Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *National Science Review.*

[8] Zhang, H., Penninger, J. M., Li, Y., Zhong, N., & Slutsky, A. S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. *Intensive Care Medicine,* 1-5.

[9] Fu, Y., Cheng, Y., & Wu, Y. (2020). Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. *Virologica Sinica,* 1-6.

[10] Zhao, X., Zhang, B., Li, P., Ma, C., Gu, J., Hou, P., et al (2020). Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis. *medRxiv.*
[11] Wu, D., Wu, T., Liu, Q., & Yang, Z. (2020). The SARS-CoV-2 outbreak: what we know. *International Journal of Infectious Diseases*.

[12] Chen, Y., & Li, L. (2020). SARS-CoV-2: virus dynamics and host response. *The Lancet Infectious Diseases*.

[13] Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S. C., & Di Napoli, R. (2020). Features, evaluation and treatment coronavirus (COVID-19). In StatPearls [Internet]. StatPearls Publishing.

[14] Yang, X., Yu, Y., Xu, J., Shu, H., Liu, H., Wu, Y., et al. (2020). Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine*.

[15] Chen, L., Liu, H. G., Liu, W., Liu, J., Liu, K., Shang, J., et al. (2020). Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Zhonghua jie he he hu xi za zhi= Zhonghua jiehe he huxi zazhi= Chinese journal of tuberculosis and respiratory diseases, 43, E005-E005.

[16] Han, H., Yang, L., Liu, R., Liu, F., Wu, K. L., Li, J., et al. (2020). Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clinical Chemistry and Laboratory Medicine (CCLM)*, 1(ahead-of-print).

[17] Wolf, D. & Ley, K. Immunity and Inflammation in Atherosclerosis. *Circ. Res.* 124, 315–327 (2019).

[18] Taleb, S. Inflammation in atherosclerosis: L’inflammation dans l’athérosclérose. *Arch. Cardiovasc. Dis.* 109, 708–715 (2016).

[19] Abbasi, J. (2020). Cardiovascular Corner—Stable Coronary Artery Disease, An LDL “Vaccine,” and Anti-inflammatories. *JAMA*.

[20] Zhu, Y., Xian, X., Wang, Z., Bi, Y., Chen, Q., Han, X., ... & Chen, R. (2018). Research progress on the relationship between atherosclerosis and inflammation. *Biomolecules*, 8(3), 80.

[21] Li, B., Li, W., Li, X. & Zhou, H. Inflammation: A Novel Therapeutic Target/Direction in Atherosclerosis. *Curr. Pharm. Des.* 23, 1216–1227 (2017).

[22] Miteva, K., Madonna, R., De Caterina, R., Van Linthout, S. Innate and adaptive immunity in atherosclerosis. *Vascul. Pharmacol.* 107, 67–77 (2018).
[23] Wildgruber, M., Aschenbrenner, T., Wendorff, H., Czubba, M., Glinzer, A., Haller, B., et al (2016). The “intermediate” CD14++ CD16+ monocyte subset increases in severe peripheral artery disease in humans. Scientific reports, 6(1), 1-8.

[24] Cai, T., Zhang, Y., Ho, Y. L., Link, N., Sun, J., Huang, J., et al (2018). Association of interleukin 6 receptor variant with cardiovascular disease effects of interleukin 6 receptor blocking therapy: a phenome-wide association study. JAMA cardiology, 3(9), 849-857.

[25] Ridker, P. M. & Lüscher, T. F. Anti-inflammatory therapies for cardiovascular disease. Eur. Heart J. 35, 1782–91 (2014).

[26] Ridker, P. M. From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream to Identify Novel Targets for Atheroprotection. Circulation Research (2016) doi:10.1161/CIRCRESAHA.115.306656.

[27] Ridker, P. M., Everett, B. M., Thuren, T., MacFadyen, J. G., Chang, W. H., Ballantyne, C., et al (2017). Antiinflammatory therapy with canakinumab for atherosclerotic disease. New England journal of medicine, 377(12), 1119-1131.

[28] Abbate, A., Van Tassell, B. W., Biondi-Zoccai, G., Kontos, M. C., Grizzard, J. D., Spillman, D. W., et al (2013). Effects of interleukin-1 blockade with anakinra on adverse cardiac remodeling and heart failure after acute myocardial infarction [from the Virginia Commonwealth University-Anakinra Remodeling Trial (2)(VCU-ART2) pilot study]. The American journal of cardiology, 111(10), 1394-1400.

[29] Morton, A. C., Rothman, A. M., Greenwood, J. P., Gunn, J., Chase, A., Clarke, B., Hall, AS., et al (2015). The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. European heart journal, 36(6), 377-384.

[30] IL6R Genetics Consortium Emerging Risk Factors Collaboration. (2012). Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. The Lancet, 379(9822), 1205-1213.

[31] Cardillo, C., Schinzari, F., Mores, N., Mettimano, M., Melina, D., Zoli, A., et al (2006). Intravascular tumor necrosis factor α blockade reverses endothelial dysfunction in rheumatoid arthritis. Clinical Pharmacology & Therapeutics, 80(3), 275-281.

[32] Taguchi, H., Nishi, K., Suzuki, T. & Okano, Y. Anti-atherosclerotic effects of etanercept in Rheumatoid Arthritis Patients. Japanese J. Clin. Immunol. 35, 183–7 (2012)
[33] Seriolo, B., Paolino, S., Sulli, A., Fasciolo, D. & Cutolo, M. Effects of anti-TNF-α treatment on lipid profile in patients with active rheumatoid arthritis. *Ann. N. Y. Acad. Sci.* **1069**, 414–9 (2006).

[34] Tam, L. S., Kitas, G. D. & González-gay, M. A. Can suppression of inflammation by anti-TNF prevent progression of subclinical atherosclerosis in inflammatory arthritis? *Rheumatol. (United Kingdom)* **53**, 1108–1119 (2014).

[35] Nidorf, S. M., Eikelboom, J. W., Budgeon, C. A. & Thompson, P. L. Low-dose colchicine for secondary prevention of cardiovascular disease. *J. Am. Coll. Cardiol.* **61**, 404–410 (2013).

[36] Tabas, I. & Lichtman, A. H. Monocyte-Macrophages and T Cells in Atherosclerosis. *Immunity* **47**, 621–634 (2017).

[37] Hedrick, C. C. Lymphocytes in atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **35**, 253–257 (2015).

[38] Matsuura, E. *et al.* Is atherosclerosis an autoimmune disease? *BMC Medicine* (2014) doi:10.1186/1741-7015-12-47.

[39] Sima, P., Vannucci, L. & Vetvicka, V. Atherosclerosis as autoimmune disease. *Ann. Transl. Med.* **6**, (2018).

[40] Maganto-García, E., Tarrio, M. L., Grabie, N., Bu, D. X., & Lichtman, A. H. (2011). Dynamic changes in regulatory T cells are linked to levels of diet-induced hypercholesterolemia. *Circulation, 124*(2), 185-195.

[41] Bonow, R. O., Fonarow, G. C., O’Gara, P. T., & Yancy, C. W. (2020). Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. *JAMA cardiology*.

[42] Smeeth, L., Thomas, S. L., Hall, A. J., Hubbard, R., Farrington, P., & Vallance, P. (2004). Risk of myocardial infarction and stroke after acute infection or vaccination. *New England Journal of Medicine, 351*(25), 2611-2618.

[43] Wu, Q., Zhou, L., Sun, X., Yan, Z., Hu, C., Wu, J., et al (2017). Altered lipid metabolism in recovered sars patients twelve years after infection. *Scientific reports, 7*(1), 1-12.

[44] Sun, J., Yu, H., Liu, H., Pu, D., Gao, J., Jin, X., et al (2019). Correlation of pre-operative circulating inflammatory cytokines with restenosis and rapid angiographic stenotic progression risk in coronary artery
disease patients underwent percutaneous coronary intervention with drug-eluting stents. *Journal of clinical laboratory analysis*, e23108.

[45] Chen, C., Zhou, Y., & Wang, D. W. (2020). SARS-CoV-2: a potential novel etiology of fulminant myocarditis. *Herz*, 1-3.

[46] Buggey, J., & ElAmm, C. A. (2018). Myocarditis and cardiomyopathy. *Current opinion in cardiology*, 33(3), 341-346.

[47] Shi, S., Qin, M., Shen, B., Cai, Y., Liu, T., Yang, F., et al (2020). Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA cardiology*.

[48] Guo, T., Fan, Y., Chen, M., Wu, X., Zhang, L., He, T., et al (2020). Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA cardiology*.
Figures

Figure 1. Proposed pathogenetic correlation between atherosclerosis and Sars-CoV-2