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Review Article

Lung Fibrosis after Coronavirus Disease (COVID)-19: Is there Any Potential Treatment?

Fanny Fachrucha*, Adityo Wibowo, Mia Elhidsi and Galoeh Adyasiwi

Department Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Indonesia

***Corresponding Author:** Fanny Fachrucha, Department Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Indonesia.

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Abstract

Coronavirus Disease 2019 (Covid-19) become a health problem worldwide since its outbreak in December 2019. In the course of its pathogenesis, Covid-19 provides sequelae, especially in the lungs in the form of pulmonary fibrosis. The challenge currently being faced is in the management and prevention of sequelae due to Severe Acute Respiratory Syndrome Corona Virus 2 (SARS Cov2) virus infection. Lung sequelae affects high morbidity to post Covid-19 patient. Therapy and proper management are needed to prevent lung sequelae due to SARS Cov2 virus infection. Potential treatments to reduce lung fibrosis is still become a question among clinicians and need more research.

Keywords: *Antifibrotic; Covid-19; Lung Fibrosis; Lung Sequelae*

Introduction

Since the pandemic outbreak in December 2019, lung radiology imaging is recommended as one of the supporting examinations for coronavirus disease 2019 (COVID-19) diagnosis. The change in lung profile showed the inflammation process and exudation of the lung tissue manifested as ground-glass opacity (GGO), consolidation, air bronchogram, paving pattern, and fibrotic lesions [1]. Previous study reported that twenty-one patients post COVID-19 still showed lung fibrosis after 9 months from hospital admission [2]. Progressivity of lung lesions in COVID-19 patients will increase as much as 50% in 24 - 48 hours [3].

The pathogenesis of SARS CoV-2 started with the acute condition since day 7 - 10 after the onset of symptoms, including widespread oedema, the formation of hyaline membrane, fluid exudation, the collapse of the alveolus, and desquamation of alveolus epithelial cells. In this phase, fibrosis is already presented in some parts of the alveolus. Day 10 - 14 is known as the proliferative phase, and lung improvement showed fibrosis tissue formation in the interstitial and airway, type 2 pneumocyte hyperplasia, and cell repair by forming fibroblasts. The end phase is called the fibrotic phase (2 - 3 weeks after the onset of symptoms), showing septum thickening and widespread fibrosis in the alveolus [3]. Lung fibrosis post COVID-19 causes morbidity in some survivor patients. Until now, there is no strong evidence that prove the efficacy in improving prognosis or preventing lung fibrosis in COVID-19 patients. Several studies suggested that pulmonary sequelae could be prevented from the early stage of infection [4]. This review would explain about lung fibrosis developed from COVID-19 infection and any potential therapy could be used to reduce or prevent lung fibrosis in Covid-19 patients.

Pathogenesis of lung fibrosis in SARS COV-2 infection

Severe inflammation response due to SARS CoV-2 infection caused a cytokine storm that can damage the lung tissue or alveolus [5]. The alveolus damage triggered fibroblast migration from the interstitial to the damaged area. This fibroblast migration process is stimu-

lated by fibroblast growth factor (FGF), platelet derived growth factor (PDGF), transforming growth factor (TGF)-*β* and chemokines [6]. Basically, lung fibrosis occurred due to repair process failure of the damaged alveolar epithelial, activation of persistent fibroblasts, collagen and extracellular matrix (ECM) component deposition [4]. Over accumulation of ECM can be caused by increased synthesis of ECM or disrupted degradation process. There is an increase in collagen deposition, such as type collagen I, III and VI, which was often found in the fibrotic lesion in the lungs [7]. The ECM degradation was disrupted by inhibition of plasminogen activator (PAI-1), which was apparent in COVID-19 patients causing widespread fibrosis [8].

Cytopathological effects in epithelial cells caused by the SARS-CoV-2 virus can cause activation of the innate immune system, intra-cell stress pathway, lysosome damage, and autophagy system to maintain cell life. The fibrosis process from SARS CoV-2 can be multifactorial, including massive immune system regulation with an imperfect resolution process. The increase of inflammation and formation of fibroblast tissue is also worsened by damage of lung blood vessels from the increased angiogenic cytokine production such as macrophage inflammatory protein-2, angiopoietin-2, and vascular endothelial growth factor (VEGF) [9]. Inflammation from SARS CoV-2 infection can cause lung damage and increase the cytokine production monocyte-1 chemoattractant protein (MCP-1), transforming growth factor-β1 (TGF-β1), tumor necrosis factor α (TNF-α), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), interleukin-1b (IL-1b), and interleukin-6 (IL-6), largely produced by the damaged cells [8].

Transforming growth factor-β (TGF β) and IL-6 were known as some of the triggers of fibrosis. Both cytokines were dominant in fibroblast activation into becoming micro fibroblasts, and the process was assisted by reactive oxygen species (ROS) that appeared during cell damage. Infection of coronavirus in the acute phase is known to increase TGF-β1 in the lung, whether infected or not. Transforming growth factor-β will induce fibroblast into micro fibroblast known as EMT and started fibrogenesis. The formed fibroblast will not experience apoptosis hence making the cell sustainable and increasing in number [10]. The role of TGF-β, produced in the most inflammation process, is pro-fibrotic cytokine and reduces anti-oxidant enzyme, causing an increase in ROS production, which also stimulates fibrosis [4]. TGF-β also stimulate the production of ECM protein, increases the secretion of protease inhibitor (PAI-1), and reduces the secretion of protease (plasminogen activator) [7].

Interleukin-6 is a pleiotropic cytokine that functions as a pro-inflammatory and pro-fibrotic mediator. The signals produced by IL-6/gp130/STAT 3 are known to have an important role in fibrosis other than TGF-β/SMAD 3 [11]. In the early fibrosis process, IL-6 will be produced by macrophages and fibroblasts then the production process is continued by the damaged type 2 pneumocytes. Therapy using anti-IL-6 in the acute phase will cause important effects in inhibiting fibrosis [12,13]. Fibrosis occurred as the final result of the inflammation repair process related to immune response, whether acute or chronic. The inhibition of IL-6 after day 8 (early fibrosis phase) can reduce fibrosis significantly [14].

Monocyte-1 chemoattractant protein (MCP-1) is found in corona infection starting from week 2 after disease onset. MCP-1 pathway comes from chemokine C-C and is a potent chemotactic factor to invite monocytes/macrophages. Macrophage works as the regulator of T memory and NK cell. Macrophage is one of the main producers of MCP-1 [10,15]. MCP-1 function are essential in pro-apoptosis molecule accumulation produced by macrophage and lymphocyte, which also induces the fibrosis process. MCP-1 effect in T cell differentiation is by working as T helper 2 (Th-2), and the produced cytokines are IL-4, IL-5, IL-10 and IL-13, which can cause fibrosis [16,17].

Angiotensin Converting Enzyme (ACE)-2 has a protective role in fibrosis. In the renin-angiotensin system, angiotensin I (Ang I) is changed into angiotensin II (Ang II) with the help of ACE. ACE-2, a homolog of ACE, plays a role in the degradation of AngII to reduce the level of AngII. Angiotensin II works on 2 receptors: Angiotensin receptor 1 (AT1R) and angiotensin receptor 2 (AT2R). Through AT2R, AngII can increase the production of TGF-*β* and stimulates fibroblast activity. SARS-Cov2 will binds with ACE-2 receptor and reduced number of ACE-2, resulting increase level of Ang II. AngII enzyme also has a role in increasing TGF-β by regulating connective tissue disease growth

factor (CTGF) in deposits ECM and the fibrosis process through mitogen-activated protein kinase (MAPK). SARS CoV2 is known to bind with ACE2 receptors in the airway and therefore decrease the number of ACE2, which causes an imbalance of AngII level and increase in TGF-β, hastening the lung fibrosis process [4,7,18]. Schematic pathogenesis of lung fibrotic in SARS Cov2 infection describe in figure 1.

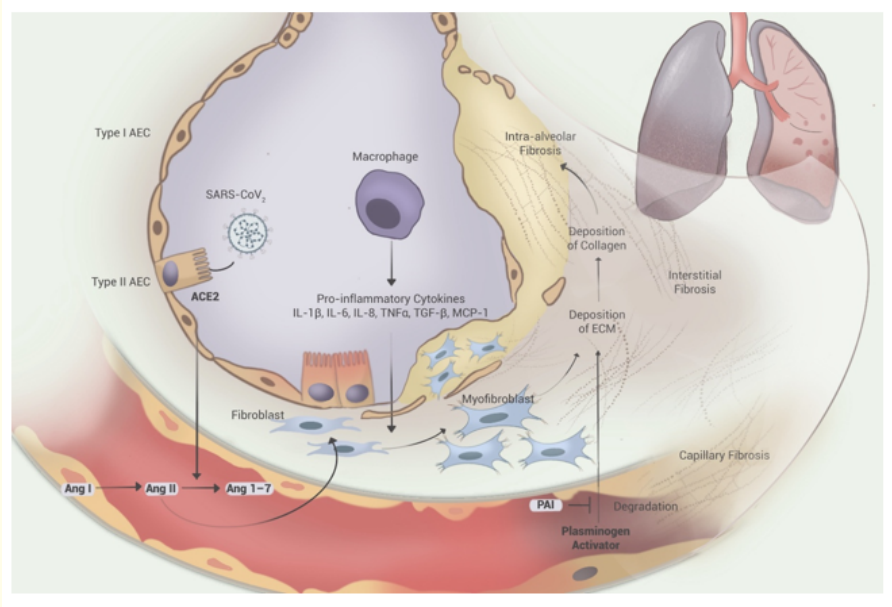

Figure 1: *Schematic pathogenesis of lung fibrosis after SARS Cov2 infection.*
ACE2: Angiotensin Converting Enzyme-2; Ang I: Angiotensin I; Ang II: Angiotensin II; Ang 1-7: Angiotensin 1-7; ECM: Extracellular Matrix; IL-1β: Interleukin-1β; IL-6: Interleukin-6; IL-8: Interleukin-8; MCP-1: Monocyte-1 chemoattractant protein; PAI: Plasminogen Activator Inhibitor; SARS-Cov2: Severe Acute Respiratory Syndrome Corona Virus 2; TGF-β: Transforming Growth Factor-β; TNF-β: Tumour Necrosing Factor-β; Type 1 AEC: Type I Alveolar Epithelial Cell; Type II AEC: Type II Alveolar Epithelial Cell.

Potential therapy reduced lung fibrotic post Covid-19

Pirfenidone and nintedanib

Pirfenidone is an anti-fibrotic known as therapy for Idiopathic Pulmonary Fibrosis (IPF). Pirfenidone effects impact several types of a cytokine such as TGF-β1, CTGF, PDGF, and TNF-α. Pirfenidone works directly to prevent excessive ROS production and decrease the expression of ACE receptors in the lungs. The anti-fibrotic and anti-apoptotic mechanism is by preventing TGF-β1 to not synthesize fibronectin-1 (FN1) and to reduce FN1 at the mRNA level but not at the protein level. Pirfenidone also decreases pro-fibrotic gene and fibril I collagen secretion, regulation of damage and tissue repair by affecting hyaluronan from the ECM and increase the regulation of regulator of G protein signalling 2 (RGS2) [19,20]. Anti-inflammation effect of pirfenidone works by reducing the secretion of TNF-α and the number of inflammation cytokines produced. The anti-apoptosis effect, which was produced by pirfenidone, works specifically towards alveolus epithelial cell damage. Pirfenidone is also known to have a role in preventing the binding of coronavirus with ACE receptors by inhibiting angiotensin II type 1 receptor (AT1R)/p38 the mitogen-activated protein kinase (MAPK) pathway and reducing the synthesis of ACE2 so that the ACE receptor cannot bind with the virus [19].

Nintedanib works by reducing the TGF-β1 level induced by collagen I, collagen III, collagen V, FN1, and PAI-1. TGF-β directly produces the PAI-1 gene, and its number is significantly reduced by nintedanib. Nintedanib works directly on collagen 1 endogen basal fibroblast and TGF-β gene target. Receptors for Platelet-derived growth factor (PDGF) and FGF are the targets in inhibiting tyrosine kinase from nintedanib to affect the collagen gene. The most produced collagens from fibroblast formation are collagen I, III, and V. Nintedanib is known to have superior work on these 3 types of collagen compared to pirfenidone only has minimal effect on collagen I and not at all on collagen III. Pirfenidone and nintedanib affect collagen production in 2 ways, first by increasing the secretion of MMP2 and ECM metalloprotease, which provides a gap in the collagen. Thus, it cannot function and the second way is by inhibiting the work of metalloproteinase 2, which is an MMP2 antagonist. To date, the administration of nintedanib and pirfenidone for fibrosis prevention for COVID-19 is still being researched [20].

Fibrinolytic and anti-thrombotic agents

One of SARS CoV-2 infection effects is the massive inflammation in the lung parenchyma, which caused fibrin deposition in the airway and lung parenchyma along with thrombocyte clots, which blocks the lung blood vessels. The damage caused by the coagulation system is due to increased activation and mobilization of blood clots with inhibition of fibrinolysis process, causing endothelial dysfunction. Plasminogen activators such as urokinase and streptokinase inhibited collagen deposition and ECM without causing a bleeding disorder. The experiment in animals found that administration through trachea and intravenous are more effective compared to aerosol. Administration of 25 mg dosage of plasminogen activator within 2 hours is continued with the next 25 mg within 22 hours, allowing no more than 0.9 mg/kgBW [4,21].

Anticoagulant therapy is one of the objectives in managing COVID-19 known for thrombosis and lung embolism. The use of unfractionated heparin in intensive patients is common because of its fast onset and unknown interaction with other COVID-19 drugs. aPTT monitoring is needed during heparin and low molecular weight heparin (LMWH) administration, which can also be considered as subcutaneous administration once or twice daily. The administration of oral anticoagulants such as warfarin, dabigatran (thrombin inhibitor), apixaban, rivaroxaban, edoxaban, and betrixaban is only recommended if the patient does not receive any antivirus due to the possibility of a high drug interaction. A COVID-19 study on acute respiratory disease syndrome (ARDS) given tissue plasminogen activator (tPA) showed poor results from parameters such as lung embolism presence, so we know that microthrombus and the prothrombotic process did not occur [22-24].

COVID-19 patients are advised to be given prophylactic anticoagulant with LMWH to prevent the presence of thrombosis and permanent organ damage such as lung fibrosis. The patient who has 3 - 4 times d-dimer increase must be admitted and given prophylactic heparin. A study by Tang in Wuhan found death cases (71%) with disseminated intravascular coagulation (DIC) compared to the surviving 0.4% [25]. Another study was on 449 patients with severe COVID-19 with heparin administration to 99 patients for at least 7 days. We found that the death rate in 28 days in patients who were given heparin was lower than those who were not given, shown from the coagulopathy induced sepsis parameter, and on patients with increased d-dimer more than 6 times [26]. A study on LMWH was also known to affect anti-inflammation in COVID-19 patients, showing a final low IL-6 level and increased lymphocyte post-administration tendency. The administered and increased dosage was only given empirically based on the increase of d-dimer [27,28].

Transforming growth factor-β Inhibitor

Inhibition of TGF-β synthesis can have an antioxidant, anti-inflammation, and anti-fibrotic effects. Based on animal study, monoclonal antibody of TGF-β can reduce the fibrosis effect caused by giving bleomycin in lab rats. Some groups of anti-TGF-β have the mechanism to inhibit fibrosis. The first group is a small molecule of TGF-β inhibitor affecting the binding of TGF-β and its receptors. Galunisertib is the drug for this group, which has shown optimum results in the phase 2 trial. Studies on patients with pancreatic cancer reported that

Galunisertib could reduce TGF-β1 level to < 4.224 pg/ml. Another study on the administration of Durvalumab combined with Galunisertib on 109 patients of liver cancer reported a reduction of TGF-β level to < 20% [29].

The next group is a monoclonal antibody called fresolimumab, which is originally known as a therapy for IPF. This drug is useful to reduce TGF-β1, TGF-β2 levels but not affecting TGF-β3. Vaccination strategy is also being developed by affecting TGF-β2 antisense and suppressing the expression of TGF-β1 dan TGF-β2 altogether. The role of TGF-β in immunomodulation and mutation on receptor 1 and 2 can be used simultaneously with immunotherapy. The delay between therapy and reduction of disease biomarkers are the correct time points in the management of TGF-β inhibitor administration. The benefits of TGF-β inhibitor still needs further research to be able to prevent fibrosis caused by SARS-CoV-2 infection [29].

Interleukin-6 inhibitor

A study found that COVID-19 can cause overexpression of IL-6, so we need a neutralizing antibody therapy that works right on the cytokine syndrome response. A study on 21 patients who received therapy with tocilizumab showed optimum results with 90% quick recovery [30]. Tocilizumab mechanism is by binding to IL-6 receptors whether from cis or trans binding. It will inhibit the binding between T cell receptor with antigen causing the cell's inability to produce interferon-γ (IFN-γ) and TNF-α which activates innate immunity to produce inflammation mediator. Tocilizumab showed useful activity after the initial dosage, and around 69% of patients showed good response in 14 days [12,31]. A study in China on 15 patients showed the effectivity tocilizumab at a dosage of 80 mg to 600 mg. Another study in Italy reported good clinical values in patients with severe pneumonia by giving 400 mg twice a day on the first day and continued with 200 mg twice a day until day 5. The intravenous dosage given to patients must reach 8 mg/kgBW with a maximum of 800 mg twice daily. Tocilizumab can also be given subcutaneously with 324 mg dosage divided into 162 mg for left and right injection of the body [32].

ACE inhibitor and angiotensin receptor blocker

ACE2 has a role in regulating the angiotensin signal through the liver angiotensinogen mechanism. ACE-2 works as enzyme that converts Ang II become Ang 1-7. The decrease in ACE2 function due to SARS CoV-2 infection is related to lung damage and acute inflammation. Effects of Ang1-7 will inhibit the work of IL-6, TNF alpha, macrophage, and increase the release of nitrite oxide, cause protective effect and inhibit fibrosis. ACE inhibitor and angiotensin receptor blocker (ARB), although not binding directly to ACE2, their mechanisms can affect ACE 2 and Ang1-7 activity [33].

A large-scale study in China recorded data for 28 days reporting hypertensive patients who received ACE inhibitor/ARB had a lower death rate than those who were not given. The recommendation stated that this therapy could be continued in COVID-19 patients and did not worsen the clinical condition. In another study on 6,272 patients, Mancia found that there was no relation between the possibility of COVID-19 disease evolution with the administration of ACE inhibitors. Gao., *et al*. found patients receiving renin-angiotensin inhibitor revealed a lower risk mortality than those who did not receive the therapy. Further studies on the effect of the renin-angiotensin inhibitor on fibrosis were not found [33].

Conclusion

Lung fibrosis occurred due to inflammation induced by SARS CoV2 and causing a particular imbalance in immunology mechanism. The pro-fibrosis factor is more dominant compared to the factors that prevent fibrosis formation. The known immunology mechanism of fibrosis formation then becomes the foundation to study pharmacology therapy to prevent fibrosis. Based on previous studies, there is no strong evidence of therapy could be used for lung fibrotic after SARS-Cov2 infection.

Conflict of Interest

There is no conflict of interest.

Bibliography

1. Zhou S., *et al*. "Imaging features and evolution on CT in 100 COVID-19 pneumonia patients in Wuhan, China". *European Radiology* 4 (2020): 1-9.

2. Pan F., *et al*. "Time course of lung changes at chest CT during recovery from coronavirus disease 2019 (COVID-19)". *Radiology* 295.3 (2020): 715-721.

3. Ding X., *et al*. "Chest CT findings of COVID-19 pneumonia by duration of symptoms". *European Journal of Radiology* 127 (2020): 1-6.

4. Lechowicz K., *et al*. "COVID-19: the potential treatment of pulmonary fibrosis associated with SARS-CoV-2 infection". *Journal of Clinical Medicine* 9.6 (2020): 1-20.

5. Wigen J., *et al*. "Converging pathways in pulmonary fibrosis and Covid-19 – the fibrosis link to disease severity". *Respiratory Medicine* (2020): 1-5.

6. Ojo AS., *et al*. "Pulmonary fibrosis in Covid-19 survivors: Predictive Factors and Risk Reduction Strategies". *Pulmonary Medicine* (2020): 1-10.

7. Zuo W., *et al*. "SARS coronavirus and lung fibrosis". *Molecular Biology of the SARS-Coronavirus* (2009): 247-258.

8. Derynck R., *et al*. "Differentiation plasticity regulated by TGF-beta family proteins in development and disease". *Nature Cell Biology* 9 (2007): 1000-1004.

9. Delpino MV., *et al*. "SARS-CoV-2 pathogenesis: imbalance in the renin-angiotensin system favors lung fibrosis". *Frontier in Cellular and Infection Microbiology* 10 (2020): 1-5.

10. Kobayashi T., *et al*. "Bidirectional role of IL-6 signal in pathogenesis of lung fibrosis". *Respiratory Research* 16.1 (2015): 1-14.

11. García LF. "Immune response, inflammation, and the clinical spectrum of COVID-19". *Frontiers in Immunology* 11 (2020): 1-13.

12. Dufour AM., *et al*. "Interleukin-6 and type-I collagen production by systemic sclerosis fibroblass are differentially regulated by interleukin-17a in the presence of transforming growth factor-beta 1". *Frontiers in Immunology* 9 (2018): 1-13.

13. Miao Y., *et al*. "Potential treatments for COVID-19 related cytokine storm - beyond corticosteroids". *Frontiers in Immunology* 11 (2020): 1-3.

14. Gubernatorova EO., *et al*. "IL-6: relevance for immunopathology of SARS-CoV-2". *Cytokine and Growth Factor Review* 53 (2020): 13-24.

15. McGonagle D., *et al*. "The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease". *Autoimmunity Review* 6 (2020): 1-7.

16. Kolahian S., *et al*. "Immune mechanisms in pulmonary fibrosis". *American Journal of Respiratory Cell and Molecular Biology* 55.3 (2016): 309-322.

17. Inoshima I., *et al*. "Anti-monocyte chemoattractant protein-1 gene therapy attenuates pulmonary fibrosis in mice". *American Journal of Physiology Lung Cellular and Molecular Physiology* 286 (2004): 1038-1044.

18. Ni W., *et al*. "Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19". *Critical Care* 24 (2020): 1-10.

19. Seifirad S. "Pirfenidone: A novel hypothetical treatment for COVID-19". *Medical Hypotheses* 144 (2020): 1-5.

20. Knüppel L., *et al*. "A Novel antifibrotic mechanism of nintedanib and pirfenidone: inhibition of collagen fibril assembly". *The American Journal of Respiratory Cell and Molecular Biology* 57.1 (2017): 77-90.

21. Wu Y., *et al*. "Plasminogen improves lung lesions and hypoxemia in patients with COVID-19". *QJM: An International Journal of Medicine* 113.8 (2020): 539-545.

22. Bikdeli B., *et al*. "COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up". *Journal of The American College of Cardiology* 75.23 (2020): 2950-2973.

23. Wang J., *et al*. "Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series". *Journal of Thrombosis and Haemostasis* 18.7 (2020): 1752-1755.

24. Whyte CS., *et al*. "Fibrinolytic abnormalities in acute respiratory distress syndrome (ARDS) and versatility of thrombolytic drugs to treat COVID-19". *Journal of Thrombosis and Haemostasis* 18.7 (2020): 1548-1555.

25. Tang N.,*et al*. "Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia". *Journal of Thrombosis and Haemostasis* 18.4 (2020): 844-847.

26. Tang N., *et al*. "Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy". *Journal of Thrombosis and Haemostasis* 18.5 (2020):1094-1099.

27. Shi C., *et al*. "The potential of low molecular weight heparin to mitigate cytokine storm in severe COVID-19 patients: a retrospective clinical study". *Medxrix* (2020).

28. Miesbach W., *et al*. "COVID-19: coagulopathy, risk of thrombosis, and the rationale for anticoagulation". *Clinical Applied Thrombosis/ Hemostasis* 26 (2020): 1-7.

29. Jeong JH., *et al*. "Novel TGF-β1 inhibitor antagonizes TGF-β1-induced epithelial-mesenchymal transition in human A549 lung cancer cells". *Journal of Cellular Biochemistry* 120.1 (2019): 977-987.

30. X Xu., *et al*. "Effective treatment of severe COVID-19 patients with tocilizumab". *Proceedings of the National Academy of Science of the United States of America* 117.20 (2020): 10970-10975.

31. Gubernatorova EO., *et al*. "IL-6: relevance for immunopathology of SARS-CoV-2". *Cytokine and Growth Factor Review* 53 (2020): 13-24.

32. Guaraldi G., *et al*. "Tocilizumab in patients with severe COVID-19: a retrospective cohort study". *Lancet Rheumatology* 2.8 (2020):474-484.

33. Wang JJ., *et al*. "Good or bad: Application of RAAS inhibitors in COVID-19 patients with cardiovascular comorbidities". *Pharmacology and Therapeutics* 215 (2020): 1-9.

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