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Review

Do inflammaging and coagul-aging play a role as conditions contributing to the co-occurrence of the severe hyper-inflammatory state and deadly coagulopathy during COVID-19 in older people?

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ABSTRACT

The coronavirus disease 2019 (COVID-19) is a new infectious respiratory disease, which has caused a pandemic that has become the world's leading public health emergency, threatening people of all ages worldwide, especially the elderly. Complications of COVID-19 are closely related to an upregulation of the inflammatory response revealed by the pro-inflammatory profile of plasma cytokines (to the point of causing a cytokine storm), which is also a contributing cause of the associated coagulation disorders with venous and arterial thromboembolisms, causing multiple organ dysfunction and failure. In severe fulminant cases of COVID-19, there is an activation of coagulation and consumption of clotting factors leading to a deadly disseminated intravascular coagulation (DIC). It is well established that human immune response changes with age, and also that the pro-inflammatory profile of plasma cytokines is upregulated in both healthy and diseased elderly people. In fact, normal aging is known to be associated with a subclinical, sterile, low-grade, systemic pro-inflammatory state linked to the chronic activation of the innate immune system, a phenomenon known as "inflammaging". Inflammaging may play a role as a condition contributing to the co-occurrence of the severe hyper-inflammatory state (cytokine storm) during COVID-19, and also in other severe infections (sepsis) in older people. Moreover, we must consider the impact of inflammation on coagulation due to the crosstalk between inflammation and coagulation. The systemic inflammatory state and coagulation disorders are closely related, a phenomenon that here we call "coagul-aging" (Giunta S.). In this review, we discuss the various degrees of inflammation in older adults after being infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the adverse effects of aging on the inflammatory response and coagulation system.

It is important to note that although there is no gender difference in susceptibility to COVID-19 infection, however, due to differences in angiotensin-converting enzyme 2 (ACE2) expression, innate immunity, and comorbidities, older men exhibit more severe disease and higher mortality than older women.

There are currently no FDA-approved specific antiviral drugs that can be used against the virus. Therapies used in patients with COVID-19 consist of remdesivir, dexamethasone, low-molecular-weight heparin, in addition to monoclonal antibodies against the spike protein of SARS-CoV-2 in the early phase of the disease. Future pharmacological research should also consider targeting the possible role of the underlying scenario of inflammaging in healthy older people to prevent or mitigate disease complications. It is worth mentioning that some specific cytokine antagonists and traditional Chinese medicine preparations can reduce the elderly's inflammatory state.

1. Introduction

COVID-19 is a new infectious respiratory disease caused by SARS-CoV-2, a highly contagious and life-threatening disease (Gorbalenya et al., 2020; Ludwig and Zarbock, 2020). The virus enters human cells by binding to the receptor angiotensin-converting enzyme 2 (ACE2)

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(Hoffmann et al., 2020; Letko et al., 2020). This virus threatens people of all ages worldwide, especially the elderly. Although there is no significant difference in the risk of infection among the various age groups (Bi et al., 2020), older people, the most vulnerable population, appear to be particularly susceptible to COVID-19 and at higher risk of disease severity, complications, and mortality, especially older males with preexisting comorbidities (Gao et al., 2020; AlGhatrif et al., 2020; Wang et al., 2020; Dang et al., 2020).

For example, in China, the case-fatality rate (CFR) was 2.3% in the early 44,672 confirmed cases, but the CFR was 8.0% in people aged 70 to 79 years and 14.8% in people over 80 years (Wu and McGoogan, 2020). In the United Kingdom, most patients hospitalized due to the SARS-CoV-2 infection were elderly ≥60 years old, accounting for 72.7% of the total hospitalizations. Compared with the age group of <50 years, the hazard ratio of death in the 70–79 years group was 8.51 (95% confidence interval 6.85 to 10.57), and that in the group ≥80 years was 11.09 (95% confidence interval 8.93 to 13.77) (Docherty et al., 2020). In Italy, the deaths were mainly elderly people. Elderly patients over 80 years old accounted for 52.3% of the total deaths, and the CFR was 20.2% (Onder et al., 2020). According to the estimates of O'Driscoll et al., the average increase in infection fatality ratio (IFR) is 0.59% (95% confidence interval 0.51% to 0.68%) for every five years of age increase (O'Driscoll et al., 2021). Especially elderly men, they have a higher rate of severity and mortality compared to women of the same age (Jin et al., 2020; Yanez et al., 2020; Pérez-López et al., 2020; Borges do Nascimento et al., 2020). For those over 80 years old, the overall IFR estimate is approximately 5.76% for women, while it is as high as 10.83% for men (O'Driscoll et al., 2021). Race is another critical factor affecting the prognosis of the elderly. In the United States, African Americans, American Indians, Hispanics/Latinos have higher rates of hospitalization and mortality relative to non-Hispanic whites. This may be related to the socio-economic status and the underlying diseases of these older people (Wilder, 2021; Garg et al., 2020).

2. Inflammaging and COVID-19

2.1. The pro-inflammatory cytokines characteristic of inflammaging are also involved in the severe hyper-inflammatory state of COVID-19

The human immune response changes with age, and the pro-inflammatory profile of cytokines is known to be upregulated in both healthy and diseased elderly. Indeed aging is known to be linked to a subclinical low-grade systemic pro-inflammatory state, known as "inflammaging" (Franceschi et al., 2000). The human innate immune system triggers inflammaging, which is recently believed that the phenomenon also includes non-immune cells, such as endothelial, adipocytes, and other senescent cells. Besides, inflammaging is in the absence of infection ("sterile" inflammation) and is one of the main "hallmarks of aging" (Franceschi et al., 2000; Giunta, 2006; Giunta, 2008; Dewan et al., 2012; Xia et al., 2016), relating to the increase in plasma levels of some cytokines, particularly of interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β) and other pro-inflammatory mediators (Franceschi and Campisi, 2014; Salminen et al., 2008; Ferrucci et al., 1999; Fabbri et al., 2015; Maggio et al., 2006). IL-6 has been defined by Ershler "A Cytokine for Gerontologists" (Maggio et al., 2006) as one of the major signaling pathways implicated in senescence, and its plasma levels are elevated with increasing age (Bhandage et al., 2019). Increased plasma levels of IL-6 in the elderly have been demonstrated to constitute a crucial risk factor and predictor of frailty, comorbidity/multimorbidity, and mortality (Franceschi and Campisi, 2014; Ferrucci et al., 1999; Fabbri et al., 2015; Maggio et al., 2006; Ma et al., 2018). Through binding with the transmembrane IL-6 receptor (mIL-6R) or soluble IL-6 receptor (sIL-6R), and the signal transduction subunit gp130, IL-6 activates the downstream JAK/STAT3 and many other signal pathways to contribute to the occurrence of inflammation (Uciechowski and Dempke, 2020). In particular, for what is concerned with pulmonary inflammaging, IL-6 strengthens the secretion of monocyte chemoattractant protein (MCP-1) by monocyte and monocytes' differentiation into macrophages, which aggravates the pulmonary inflammation and injury (Yu et al., 2002).

Another cytokine closely related to inflammaging is TNF-α (Desdin-Mico et al., 2020; Fabbri et al., 2015; Franceschi et al., 2000; Franceschi et al., 2018; Michaud et al., 2013). TNF-α can induce senescence and is involved in age-associated comorbidity, frailty, sarcopenia, insulin resistance, dementia, and other aging-related diseases (Krabbe et al., 2004; Magalhaes et al., 2018; Michaud et al., 2013; Paolisso et al., 1998). The primary receptor of TNF-α is tumor necrosis factor receptor 1 (TNFR1), which is expressed on almost all cell types so that TNF-α can widely participate in the occurrence of inflammation in the body (Aggarwal, 2003).

2.2. Cytokine storm is the major cause of poor prognosis in elderly COVID-19 patients

Older people with COVID-19 infection often suffer a severe form of interstitial pneumonia accompanied to an excessive human immune response with a hyper-inflammatory condition characterized by the increase of many plasma cytokines, including IL-6, interleukin 8 (IL-8), interferon (IFN), and tumor necrosis factor levels increase, particularly of IL-6 (the so-called "cytokine storm"), a condition associated with acute respiratory distress syndrome (ARDS) and acute respiratory failure (Channappanavar and Perlman, 2017). Therefore, dramatic forms of this pro-inflammatory condition are the predominant pathophysiologic features of COVID-19 and are more common in the elderly (AlGhatrif et al., 2020; Rossotti et al., 2020; Li et al., 2020b).

What drives such intense hyper-inflammation in COVID-19 is not yet known; however, the upregulation of IL-6 seems the pivotal pro-inflammatory function is contributing to COVID-19 severity. A meta-analysis of 1426 patients from nine studies illustrated that elevated serum IL-6 on hospital admission was connected with increased mortality, and could serve as a good indicator of the severity of COVID-19 (Aziz et al., 2020). If using the circulating IL-6 level to distinguish whether the patient can survive, the best area under the curve (AUC) is 0.901 (95% confidence interval 0.860 to 0.942) (Aziz et al., 2020). The preliminary positive results obtained in COVID-19 infection with tocilizumab therapy, a recombinant humanized monoclonal antibody against both the sIL-6R and the mIL-6R, confirms the critical role of IL-6 in SARS-CoV-2 infection in a way (Rossotti et al., 2020).

TNF-α is another important cytokine participating in the cytokine storm. Fever and malaise are common symptoms caused by elevated plasma TNF-α in COVID-19 patients. Compared with mild cases, severe cases have higher TNF-α levels (Huang et al., 2020; Chen et al., 2020; Shimabukuro-Vornhagen et al., 2018).

More importantly, TNF-α also participates in inflammaging; in SARS-CoV-2 infection, it induces T cell apoptosis through the TNFR1 receptor on T lymphocytes (Gupta et al., 2005), which leads to lower T cells (including CD4+ and CD8+ cells) in severe COVID-19 patients, as well as the ability of cell clearance in patients (Diao et al., 2020; Zheng et al., 2020). In addition, TNF-α can promote the production of IL-6, which constitutes an integral part of the cytokine storm (Uciechowski and Dempke, 2020).

There are differences in the severity of cytokine storms in older adults of different genders. Estrogen is protective for older women. It can inhibit TNF release in women, and this effect is seen even for postmenopausal women (Straub, 2007). In addition, the level of ACE2 in the lungs of men is higher than that of women (Wei et al., 2020). Elderly men have higher levels of TNF-α, IL-8, high-sensitivity C-reactive protein (hsCRP) and ferritin, and lower levels of lymphocytes (Qin et al., 2020; Takahashi et al., 2020), suggesting elderly males are prone to cytokine storm, so the severity and mortality rates of elderly male patients are higher than female patients.

Herein, we suggest that the preexisting upregulation of cytokine

expression of inflammaging may trigger, and also support, the excessive hyper-inflammatory state in older people. Indeed, the superimposed SARS-CoV-2 infection in older adults may acutely exaggerate the already present pro-inflammatory background of inflammaging, predisposing older people to greater COVID-19 disease severity and mortality. The co-occurrence of the COVID-19 infection, constituting a second-hit to the preexisting pro-inflammatory condition of inflammaging, leading to a dysregulation of inflammation, which becomes harmful, reaching a severe pathological threshold (Fig. 1).

Very recently, Eshak N. et al. (Eshak et al., 2020) and Bonafè M. et al. (Bonafè et al., 2020) suggested that some characteristics of inflammaging may lead to excessive SARS-CoV-2 mortality by Covid-19.

3. Excessive inflammation leads to abnormal coagulation

We must also consider the impact of a pro-inflammatory state on coagulation because of the crosstalk between inflammation and coagulation (Kale and Yende, 2011). It is well established that the systemic inflammatory state of elderly people and coagulation disorder are closely linked, a phenomenon which here we refer to as "coagul-aging" (Giunta S.). Physiological aging is associated with increased plasma levels of many proteins of blood coagulation together with fibrinolysis impairment; this may be of great concern in view of the known association between vascular and thromboembolic diseases and aging (Mari et al., 2008), a condition which, here we suggest, may also contribute to the co-occurrence of the high incidence of coagulopathy in older COVID-19 patients.

Elderly male patients with COVID-19 are more susceptible than females to severe cytokine storms, leading them to be more prone to coagulation abnormalities (Wang et al., 2020; Yang et al., 2020). Laboratory tests also indicate that they have longer prothrombin time (PT) and higher fibrinogen than females (Shi et al., 2021; Ten-Caten et al., 2021). The higher incidence of coagulation abnormalities is another crucial reason for the high mortality rate in elderly male patients.

Therefore, the elderly population is more susceptible to the development of both a hyper-inflammatory state "cytokine storm" and of severe coagulopathy, including thromboembolism, when suffering from COVID-19 (Danzi et al., 2020; Grasselli et al., 2020; Lei et al., 2020), and DIC (Tang et al., 2020b).

Indeed, it is now established that the risk of thrombosis increases, particularly in older patients during the COVID-19 (Ackermann et al., 2020; Bikdeli et al., 2020). For instance, Llitjos and colleagues (Llitjos et al., 2020) reported that 26 critically patients with an average age of 68 years who were treated in the ICU, and requiring mechanical ventilation, 6 of them (23%), developed pulmonary embolism even though they underwent prophylactic or therapeutic anticoagulation. Therefore, a high incidence of thrombotic complications in patients with COVID-19 sometimes occurs even when thromboprophylaxis was administered.

Most elderly patients with COVID-19 have higher levels of fibrinogen and D-dimer (Llitjos et al., 2020; Xiong et al., 2020). Both D-dimer and fibrin degradation product (FDP) were significantly higher in death cases than in survivors, and PT and activated partial thromboplastin time (APTT) were longer in dead patients (Sun et al., 2020; Tang et al., 2020b). It is now well established that elderly patients with COVID-19, especially in more severe cases, have a hypercoagulable state and an increased tendency to thrombosis and thromboembolism. The causes are several, starting from the aging-associated procoagulative-state (coagul-aging), and, subsequently to SARS-CoV-2 infection, the development of a hyper-inflammatory state with cytokine storm, activation of platelets, endothelial dysfunction, and fibrinolytic dysfunction.

First of all, after a cytokine storm occurs in these patients, high concentrations of plasma IL-6 contributes to the activation of

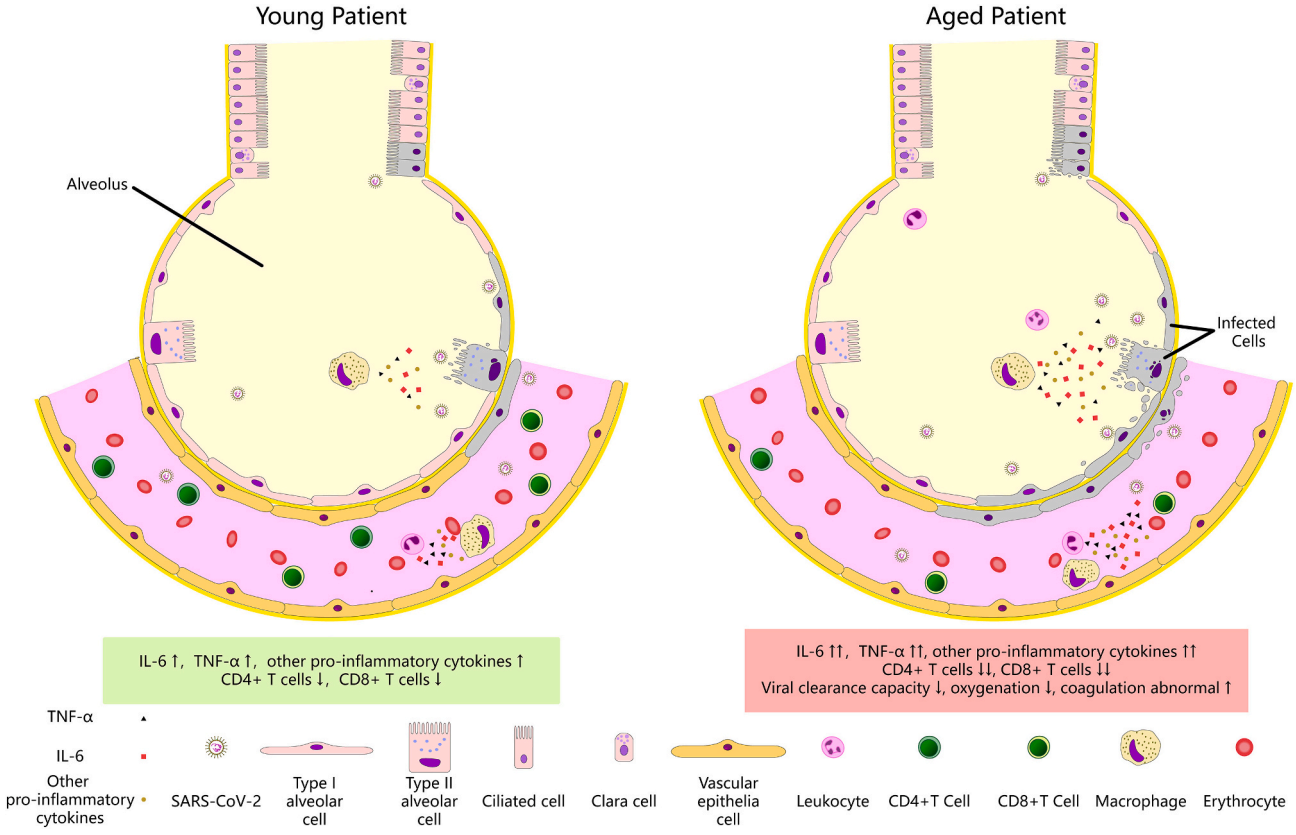

Fig. 1. Different responses of young and old COVID-19 patients. Relative to young patients, IL-6, TNF-α, and other pro-inflammatory cytokines are enormously increased in older patients; the number of CD4+, CD8+ lymphocytes is decreased, the viral clearance ability is reduced, and the coagulation function is abnormal in elderly patients.

coagulation and the formation of clotting obstacles through multiple pathways, such as stimulating the liver to synthesize more fibrinogen, upregulating vascular endothelial growth factor affecting vascular wall homeostasis. IL-6 can also promote monocytes to express more tissue factor and activate the extrinsic coagulation system. The upregulation of thrombin, in turn, induces vascular endothelial cells to produce more IL-6, forming a vicious circle (Tanaka et al., 2016). In addition, elevated TNF-α levels can increase the mass and dysfunction of mitochondria in platelets. High levels of TNF-α induce increased platelet activity and enhance platelet procoagulant ability (Davizon-Castillo et al., 2019).

The second reason is that platelets are over-activated, and more platelet-monocyte aggregates are formed in severe COVID-19 patients (Mahévas et al., 2020). In comparison with non-infected controls, asymptomatic or mild cases, P-selectin (CD62P) and CD63 on platelets of severe patients are overexpressed, with the increase of plasma Thromboxane B2 (TXB2), that may cause platelet hyper-activation, inducing monocytes to form more platelet-monocyte aggregates and monocytes to express more tissue factor (Hottz et al., 2020). The excessive activation of platelets and monocytes may exacerbate the tendency to develop thrombosis in critically ill patients.

ACE2 is expressed in vascular endothelial cells, and it has been reported that SARS-CoV-2 can also infect endothelial cells through it (Hamming et al., 2004; Hoffmann et al., 2020). Endothelial cells are subjected to viral invasion as well as immune-mediated damage, leading to endothelial dysfunction (Varga et al., 2020). Endothelial dysfunction is a characteristic of age-associated diseases such as stroke, cardiovascular diseases, and diabetes (Rajendran et al., 2013). Therefore, endothelial dysfunction can aggravate hypercoagulability and promote thrombosis in the elderly (Sepulveda et al., 2017). The SARS-CoV-2 capacity to directly infect vascular endothelial cells is the key to the high incidence of thrombosis in elderly COVID-19 patients.

Moreover, the expression of plasminogen activator inhibitor-1 (PAI-1) is upgraded in patients with COVID-19 (Tang et al., 2020a), especially in older individuals (Vaughan et al., 2017). PAI-1 inhibits the fibrinolytic system by inactivating tissue-type plasminogen activator (t-PA) (Tucker and Idell, 2013). Wright and colleagues (Wright et al., 2020) analyzed thromboelastography (TEG) in 44 patients with COVID-19, a complete lack of lysis of clot in 30 min (LY30) occurred in 25 (57%) patients, which suggested the presence of fibrinolysis shutdown. Although the increase in D-dimer concentrations in severe COVID-19 cases suggests an over-activation of the fibrinolytic system, this activity proves inadequate in relation to the rate of thrombosis. This relatively low fibrinolytic activity, associated with the state of hypercoagulability, increases the risk of thrombotic events in individuals infected with SARS-CoV-2 (Fig. 2).

Intravenous injection of t-PA was effective in severe patients, which could increase the pressure of oxygen/FiO2 (P/F) ratio and reduce mortality (Choudhury et al., 2020; Wang et al., 2020a); atomization inhalation of plasminogen could effectively treat fibrin deposition in the lung and hypoxemia during COVID-19 (Wu et al., 2020b). These findings suggest, in another way, that patients with COVID-19 have relative insufficiency of fibrinolytic activity.

4. How to help elderly COVID-19 patients

The study of the mechanisms by which elderly patients are prone to severe diseases and high mortality may help us improve the treatment for elderly COVID-19 and take targeted interventions to reduce their severity and mortality. One target is concerned with the “cytokine storm” that occurs because of the intense release of pro-inflammatory factors in seriously elderly patients with COVID-19. So inhibiting or limiting this hyper-inflammatory is a vital aspect of treatment.

Glucocorticoids (GCs) are a class of classic immunomodulatory drugs. They were widely used during the SARS epidemic in 2003, but their efficacy was controversial except for dexamethasone (Auyeung et al., 2005; Chen et al., 2006; Ho et al., 2003; Yam et al., 2007). GCs have a wide range of effects. They combine with intracellular GC receptor to form complexes, acting on the nucleus, inhibiting the expression of IL-1, IL-6, TNF-α, and other pro-inflammatory cytokines, and also the lymphocyte proliferation and monocytes-macrophages recruitment; in addition, they can inhibit the production of prostaglandins, leukotrienes and platelet activating factor through non-genomic mechanism; they also reduce the complement levels (Ericson-Neilsen and Kaye, 2014; Liu et al., 2013; Streeten, 1975). Using dexamethasone can improve patients' P/F ratio, shorten hospitalization length (Wang et al., 2020d), and decrease the mortality risk of death in patients with ARDS (Wu et al., 2020a). However, considering that GCs can inhibit B and T lymphocytes' activity, they may impair the body's capability of viral clearance; therefore, they should be used with caution (Solinas et al., 2020).

Unlike GCs, IL-6 blockers and TNF-α antagonists are more specific drugs. The use of IL-6 blockers (including tocilizumab, sarilumab, and

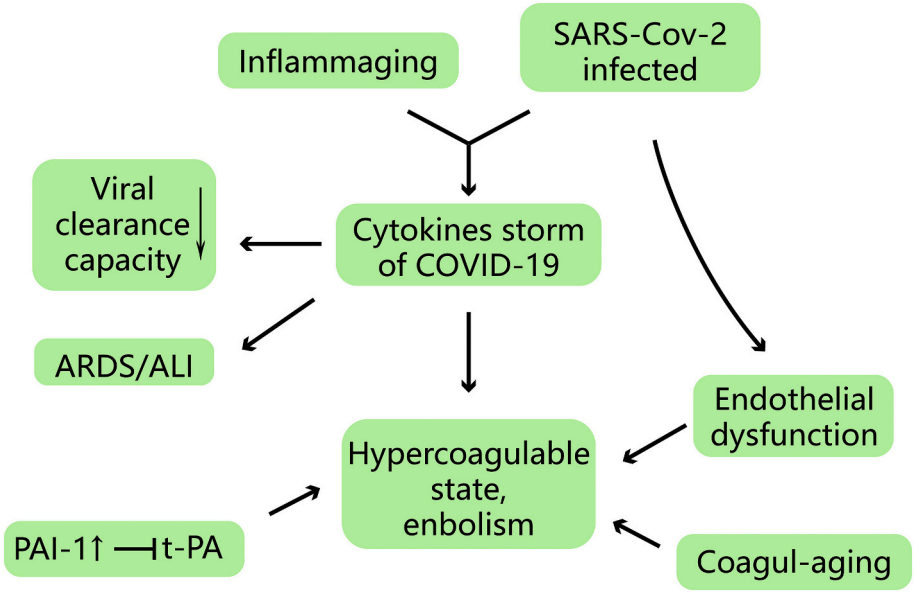

Fig. 2. Main mechanisms and effects of cytokine storm and coagulation abnormalities in elderly COVID-19 patients.

siltuximab) seems a potentially important resource for some patients with high IL-6 status (Atal and Fatima, 2020; Palanques-Pastor et al., 2020). Furthermore, clinical research on tocilizumab has shown that patients can benefit from it (Eimer et al., 2020; Moreno-Perez et al., 2020; Patel et al., 2020; Rossotti et al., 2020). For instance, an Italian research involving 222 COVID-19 hospitalized patients showed that patients using tocilizumab had significantly better overall survival than the control group, with a Hazard Ratio (HR) of 0.50 (95% confidence interval 0.26 to 0.95). Some other clinical trials have shown that tocilizumab reduces COVID-19 mortality, the use of mechanical ventilation, and increase discharge rates (Eimer et al., 2020; Moreno-Perez et al., 2020; Patel et al., 2020). However, further researches with tocilizumab are needed.

Considering that TNF-α is also a component of the "cytokine storm" in infected people, TNF-α antagonists such as infliximab and adalimumab are also potential therapeutic drugs (Duret et al., 2020; Feldmann et al., 2020). Previous research indicated anti-TNF therapy could improve mice's resistance to influenza virus and respiratory syncytial virus (Hussell et al., 2001); the therapeutic efficacy of TNF-α antagonists on COVID-19 needs further clinical research.

Moreover, for the incidence of COVID-19 coagulopathy in elderly patients because of the cytokine storm and other causes of coagulopathy, using the Caprini model, the Padua model, and the IMPROVE model, and others can be considered for the assessment first. Treatment measures may include low-molecular-weight heparin anticoagulant, and, when necessary, targeted use of t-PA or plasminogen can also help to ameliorate the condition of patients (Choudhury et al., 2020; Wang et al., 2020b; Wu et al., 2020b).

Where modernity meets tradition: targeting Inflammatory states by Traditional Chinese Medicine (TCM).

Because some TCM preparations have immune regulation, anti-inflammatory, and antiviral effects, the therapeutic effect on COVID-19 has attracted an increasing amount of attention, especially Lianhuaqingwen (LH) capsules and Xuebijing Injection (Lu, 2020; Xian et al., 2020; Zhuang et al., 2020). LH capsule is a TCM preparation consisting of Forsythia, Flos Lonicerae Japonicae, *Rheum palmatum*, Rhodiola Crenulata, and seven other herbs (Jia et al., 2015). For SARS-CoV-2, in vitro experiments illustrated that LH capsule could significantly inhibit the virus's replication and suppress cytokine storm by reducing pro-inflammatory factors (Runfeng et al., 2020).

Its mechanism is multifaceted. Forsythia, Flos Lonicerae Japonicae, and Rheum Palm have active components that can act on the spike glycoprotein and human ACE2 receptor (Ho et al., 2007; Niu et al., 2020), and Rhodiola Crenulata has protective effects on acute lung injury (Guan et al., 2012). A multicenter, randomized, prospective controlled trial conducted by Hu et al. involving 284 COVID-19 patients with a mean age of 51 years showed that taking LH capsule could significantly shorten the duration of fever, fatigue, coughing, and other symptoms, and improve the clinical cure rate (Hu et al., 2020). In China, the National Health Commission (NHC) has approved LH capsule for the therapy of COVID-19 (National Health Commission et al., 2020).

Xuebijing Injection (XBJ) is another TCM made from five herbs, including Radix Paeoniae Rubra, Flos Carthami, Radix Salviae Miltiorrhizae, Rhizoma Chuanxiong, and Radix Angelicae (Huang et al., 2011). XBJ has immunomodulation functions, anti-inflammation, anti-coagulation, vascular endothelial protection (Li et al., 2020a), and reducing pulmonary inflammatory damage (Liu et al., 2014; Sun et al., 2010). For the animal model of sepsis, XBJ can decrease the plasma levels of IL-1β, IL-6, and TNF-α (Jiang et al., 2013), and enhance the proliferation and differentiation of regulatory T cells (Chen et al., 2018). Recent clinical trials have suggested that XBJ can alleviate the diseases state of COVID-19 patients, reduce lung injury, enhance oxygenation index, decrease the partial pressure of carbon dioxide (PaCO2) and C-reactive protein (CRP) by repressing the expression of inflammatory mediators like IL-6 and TNF-α (Ma et al., 2020; Wen et al., 2020). The NHC has approved that XBJ is used for severe and critical COVID-19 patients (National Health Commission et al., 2020).

5. Conclusions

Confronted the COVID-19 pandemic, the elderly are the most vulnerable group, especially elderly male patients. Therefore protecting the elderly population and effectively treating them is the key to tackling and treating this disease.

Due to inflammaging and coagul-aging, the elderly are more prone to cytokine storm, coagulation dysfunction, and organ dysfunction. All these conditions put the elderly at a higher risk of death. In the future, we hope to carry out more studies on inflammaging and coagul-aging, which will enable us to understand the mechanism in-depth and find measures to intervene in the corresponding processes. Especially in the face of diseases such as COVID-19, which takes a high risk of critical illness and increases mortality in the elderly, more effective measures can be given.

In addition, specific cytokine antagonists, steroids, and TCM preparations showed strong potential in the fight against COVID-19 inflammatory state, which are promising directions to ameliorate the condition of elderly patients with COVID-19. With their antiviral ability, TCM preparations and extensive immune regulation function can effectively protect patients, particularly in the early COVID-19 phases. In the future, more studies on TCM preparations will not only help elderly patients with severe infections like COVID-19, but can also have the potential to intervene in the aging-associated pro-inflammatory state and the senescence process itself.

Declaration of competing interest

The authors have no competing interests to declare.

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References

Ackermann, M., Verleden, S.E., Kuehnel, M., Haverich, A., Welte, T., Laenger, F., Vanstapel, A., Werlein, C., Stark, H., Tzankov, A., Li, W.W., Li, V.W., Mentzer, S.J., Jonigk, D., 2020. Pulmonary vascular Endothelialitis, thrombosis, and angiogenesis in Covid-19. N. Engl. J. Med. 383, 120–128. https://doi.org/10.1056/NEJMoa2015432.

Aggarwal, B.B., 2003. Signalling pathways of the TNF superfamily: a double-edged sword. Nat. Rev. Immunol. 3, 745–756. https://doi.org/10.1038/nri1184.

AlGhatrif, M., Cingolani, O., Lakatta, E.G., 2020. The dilemma of coronavirus disease 2019, aging, and cardiovascular disease: insights from cardiovascular aging science. JAMA Cardiol. 5, 747–748. https://doi.org/10.1001/jamacardio.2020.1329.

Atal, S., Fatima, Z., 2020. IL-6 inhibitors in the treatment of serious COVID-19: a promising therapy? Pharm. Med. 34, 223–231. https://doi.org/10.1007/s40290-020-00342-z.

Auyeung, T.W., Lee, J.S., Lai, W.K., Choi, C.H., Lee, H.K., Lee, J.S., Li, P.C., Lok, K.H., Ng, Y.Y., Wong, W.M., Yeung, Y.M., 2005. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. J. Inf. Secur. 51, 98–102. https://doi.org/10.1016/j.jinf.2004.09.008.

Aziz, M., Fatima, R., Assaly, R., 2020. Elevated interleukin-6 and severe COVID-19: a meta-analysis. J. Med. Virol. https://doi.org/10.1002/jmv.25948.

Bhandage, A.K., Cunningham, J.L., Jin, Z., Shen, Q., Bongiovanni, S., Korol, S.V., Syk, M., Kamali-Moghaddam, M., Ekselius, L., Birnir, B., 2019. Depression, GABA, and age correlate with plasma levels of inflammatory markers. Int. J. Mol. Sci. 20 (24), 6172. https://doi.org/10.3390/ijms20246172.

Bi, Q., Wu, Y., Mei, S., Ye, C., Zou, X., Zhang, Z., Liu, X., Wei, L., Truelove, S.A., Zhang, T., Gao, W., Cheng, C., Tang, X., Wu, X., Wu, Y., Sun, B., Huang, S., Sun, Y., Zhang, J., Ma, T., Lessler, J., Feng, T., 2020. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect. Dis. 20, 911–919. https://doi.org/10.1016/s1473-3099(20)30287-5.

Bikdeli, B., Madhavan, M.V., Jimenez, D., Chuich, T., Dreyfus, I., Driggin, E., Nigoghossian, C., Ageno, W., Madjid, M., Guo, Y., Tang, L.V., Hu, Y., Giri, J., Cushman, M., Quere, I., Dimakakos, E.P., Gibson, C.M., Lippi, G., Favaloro, E.J., Fareed, J., Caprini, J.A., Tafur, A.J., Burton, J.R., Francese, D.P., Wang, E.Y., Falanga, A., McLintock, C., Hunt, B.J., Spyropoulos, A.C., Barnes, G.D., Eikelboom, J. W., Weinberg, I., Schulman, S., Carrier, M., Piazza, G., Beckman, J.A., Steg, P.G.,

Stone, G.W., Rosenkranz, S., Goldhaber, S.Z., Parikh, S.A., Monreal, M., Krumholz, H.M., Konstantinides, S.V., Weitz, J.I., Lip, G.Y.H., the Iua, S.b.t.E.S.C.W.G.o.P.C, Right Ventricular, F, Global Covid-19 Thrombosis Collaborative Group, E.b.t.I.N.E, 2020. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. J. Am. Coll. Cardiol. 75, 2950–2973. https://doi.org/10.1016/j.jacc.2020.04.031.

Bonafè, M., Prattichizzo, F., Giuliani, A., Storci, G., Sabbatinelli, J., Olivieri, F., 2020. Inflamm-aging: why older men are the most susceptible to SARS-CoV-2 complicated outcomes. Cytokine Growth Factor Rev. 53, 33–37. https://doi.org/10.1016/j.cytogfr.2020.04.005.

Borges do Nascimento, I.J., Cacic, N., Abdulazeem, H.M., von Groote, T.C., Jayarajah, U., Weerasekara, I., Esfahani, M.A., Civile, V.T., Marusic, A., Jeroncic, A., Carvas Junior, N., Pericic, T.P., Zakarija-Grkovic, I., Meirelles Guimarães, S.M., Luigi Bragazzi, N., Bjorklund, M., Sofi-Mahmudi, A., Altujjar, M., Tian, M., Arcani, D., O'Mathúna, D., Marcolino, M.S., 2020. Novel coronavirus infection (COVID-19) in humans: a scoping review and meta-analysis. J. Clin. Med. 9 (4), 941. https://doi.org/10.3390/jcm9040941.

Channappanavar, R., Perlman, S., 2017. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin. Immunopathol. 39, 529–539. https://doi.org/10.1007/s00281-017-0629-x.

Chen, R.C., Tang, X.P., Tan, S.Y., Liang, B.L., Wan, Z.Y., Fang, J.Q., Zhong, N., 2006. Treatment of severe acute respiratory syndrome with glucosteroids: the Guangzhou experience. Chest 129, 1441–1452. https://doi.org/10.1378/chest.129.6.1441.

Chen, X., Feng, Y., Shen, X., Pan, G., Fan, G., Gao, X., Han, J., Zhu, Y., 2018. Anti-sepsis protection of Xuebijing injection is mediated by differential regulation of pro- and anti-inflammatory Th17 and T regulatory cells in a murine model of polymicrobial sepsis. J. Ethnopharmacol. 211, 358–365. https://doi.org/10.1016/j.jep.2017.10.001.

Chen, L.D., Zhang, Z.Y., Wei, X.J., Cai, Y.Q., Yao, W.Z., Wang, M.H., Huang, Q.F., Zhang, X.B., 2020. Association between cytokine profiles and lung injury in COVID-19 pneumonia. Respir. Res. 21, 201 https://doi.org/10.1186/s12931-020-01465-2.

Choudhury, R., Barrett, C.D., Moore, H.B., Moore, E.E., McIntyre, R.C., Moore, P.K., Talmor, D.S., Nydam, T.L., Yaffe, M.B., 2020. Salvage use of tissue plasminogen activator (tPA) in the setting of acute respiratory distress syndrome (ARDS) due to COVID-19 in the USA: a Markov decision analysis. World J. Emerg. Surg. 15, 29 https://doi.org/10.1186/s13017-020-00305-4.

Dang, J.Z., Zhu, G.Y., Yang, Y.J., Zheng, F., 2020. Clinical characteristics of coronavirus disease 2019 in patients aged 80 years and older. J. Integr. Med. 18, 395–400. https://doi.org/10.1016/j.joim.2020.07.002.

Danzi, G.B., Loffi, M., Galeazzi, G., Gherbesi, E., 2020. Acute pulmonary embolism and COVID-19 pneumonia: a random association? Eur. Heart J. 41, 1858. https://doi.org/10.1093/eurheartj/ehaa254.

Davizon-Castillo, P., McMahon, B., Aguila, S., Bark, D., Ashworth, K., Allawzi, A., Campbell, R.A., Montenont, E., Nemkov, T., D'Alessandro, A., Clendenen, N., Shih, L., Sanders, N.A., Higa, K., Cox, A., Padilla-Romo, Z., Hernandez, G., Wartchow, E., Trahan, G.D., Nozik-Grayck, E., Jones, K., Pietras, E.M., DeGregori, J., Rondina, M.T., Di Paola, J., 2019. TNF-alpha-driven inflammation and mitochondrial dysfunction define the platelet hyperreactivity of aging. Blood 134, 727–740. https://doi.org/10.1182/blood.2019000200.

Desdin-Mico, G., Soto-Heredero, G., Aranda, J.F., Oller, J., Carrasco, E., Gabande-Rodriguez, E., Blanco, E.M., Alfranca, A., Cusso, L., Desco, M., Ibanez, B., Gortazar, A.R., Fernandez-Marcos, P., Navarro, M.N., Hernaez, B., Alcami, A., Baixauli, F., Mittelbrunn, M., 2020. T cells with dysfunctional mitochondria induce multimorbidity and premature senescence. Science 368, 1371–1376. https://doi.org/10.1126/science.aax0860.

Dewan, S.K., Zheng, S.B., Xia, S.J., Bill, K., 2012. Senescent remodeling of the immune system and its contribution to the predisposition of the elderly to infections. Chin. Med. J. 125, 3325–3331.

Diao, B., Wang, C., Tan, Y., Chen, X., Liu, Y., Ning, L., Chen, L., Li, M., Liu, Y., Wang, G., Yuan, Z., Feng, Z., Zhang, Y., Wu, Y., Chen, Y., 2020. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). Front. Immunol. 11, 827. https://doi.org/10.3389/fimmu.2020.00827.

Docherty, A.B., Harrison, E.M., Green, C.A., Hardwick, H.E., Pius, R., Norman, L., Holden, K.A., Read, J.M., Dondelinger, F., Carson, G., Merson, L., Lee, J., Plotkin, D., Sigfrid, L., Halpin, S., Jackson, C., Gamble, C., Horby, P.W., Nguyen-Van-Tam, J.S., Ho, A., Russell, C.D., Dunning, J., Openshaw, P.J.M., Baillie, J.K., Semple, M.G., 2020. Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. BMJ 369, m1985. https://doi.org/10.1136/bmj.m1985.

Duret, P.-M., Sebbag, E., Mallick, A., Gravier, S., Spielmann, L., Messer, L., 2020. Recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept. Ann. Rheum. Dis. 79, 1251–1252. https://doi.org/10.1136/annrheumdis-2020-217362.

Eimer, J., Vesterbacka, J., Svensson, A.K., Stojanovic, B., Wagrell, C., Sonnerborg, A., Nowak, P., 2020. Tocilizumab shortens time on mechanical ventilation and length of hospital stay in patients with severe COVID-19: a retrospective cohort study. J. Intern. Med. https://doi.org/10.1111/joim.13162.

Ericson-Neilsen, W., Kaye, A.D., 2014. Steroids: pharmacology, complications, and practice delivery issues. Ochsner J. 14, 203–207.

Eshak, N., Abdelnabi, M., Beltagy, A., 2020. Inflamm-aging: the missing link to COVID-19 age-related mortality? Southwest Respir. Crit. Care Chronicles 8, 66–67. https://doi.org/10.12746/swrccc.v8i34.701.

Fabbri, E., An, Y., Zoli, M., Simonsick, E.M., Guralnik, J.M., Bandinelli, S., Boyd, C.M., Ferrucci, L., 2015. Aging and the burden of multimorbidity: associations with inflammatory and anabolic hormonal biomarkers. J. Gerontol. A Biol. Sci. Med. Sci. 70, 63–70. https://doi.org/10.1093/gerona/glu127.

Feldmann, M., Maini, R.N., Woody, J.N., Holgate, S.T., Winter, G., Rowland, M., Richards, D., Hussell, T., 2020. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet 395, 1407–1409. https://doi.org/10.1016/s0140-6736(20)30858-8.

Ferrucci, L., Harris, T.B., Guralnik, J.M., Tracy, R.P., Corti, M.C., Cohen, H.J., Penninx, B., Pahor, M., Wallace, R., Havlik, R.J., 1999. Serum IL-6 level and the development of disability in older persons. J. Am. Geriatr. Soc. 47, 639–646. https://doi.org/10.1111/j.1532-5415.1999.tb01583.x.

Franceschi, C., Campisi, J., 2014. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J. Gerontol. A Biol. Sci. Med. Sci. 69, S4–S9. https://doi.org/10.1093/gerona/glu057.

Franceschi, C., Bonafe, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., De Benedictis, G., 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908, 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x.

Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., Santoro, A., 2018. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat. Rev. Endocrinol. 14, 576–590. https://doi.org/10.1038/s41574-018-0059-4.

Gao, S., Jiang, F., Jin, W., Shi, Y., Yang, L., Xia, Y., Jia, L., Wang, B., Lin, H., Cai, Y., Xia, Z., Peng, J., 2020. Risk factors influencing the prognosis of elderly patients infected with COVID-19: a clinical retrospective study in Wuhan, China. Aging (Albany N. Y.) 12, 12504–12516. https://doi.org/10.18632/aging.103631.

Garg, S., Kim, L., Whitaker, M., O'Halloran, A., Cummings, C., Holstein, R., Prill, M., Chai, S.J., Kirley, P.D., Alden, N.B., Kawasaki, B., Yousey-Hindes, K., Niccolai, L., Anderson, E.J., Openo, K.P., Weigel, A., Monroe, M.L., Ryan, P., Henderson, J., Kim, S., Como-Sabetti, K., Lynfield, R., Sosin, D., Torres, S., Muse, A., Bennett, N.M., Billing, L., Sutton, M., West, N., Schaffner, W., Talbot, H.K., Aquino, C., George, A., Budd, A., Brammer, L., Langley, G., Hall, A.J., Fry, A., 2020. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 states, march 1-30, 2020. Morb. Mortal. Wkly Rep. 69 (15), 458–464. https://doi.org/10.15585/mmwr.mm6915e3.

Giunta, S., 2006. Is inflammaging an auto[innate]immunity subclinical syndrome? Immun. Ageing 3, 12. https://doi.org/10.1186/1742-4933-3-12.

Giunta, S., 2008. Exploring the complex relations between inflammation and aging (inflamm-aging): anti-inflamm-aging remodelling of inflamm- aging, from robustness to frailty. Inflamm. Res. 57, 558–563. https://doi.org/10.1007/s00011-008-7243-2.

Gorbalenya, A.E., Baker, S.C., Baric, R.S., de Groot, R.J., Drosten, C., Gulyaeva, A.A., Haagmans, B.L., Lauber, C., Leontovich, A.M., Neuman, B.W., Penzar, D., Perlman, S., Poon, L.L.M., Samborskiy, D.V., Sidorov, I.A., Sola, I., Ziebuhr, J., 2020. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat. Microbiol. 5, 536–544. https://doi.org/10.1038/s41564-020-0695-z.

Grasselli, G., Tonetti, T., Protti, A., Langer, T., Girardis, M., Bellani, G., Laffey, J., Carrafiello, G., Carsana, L., Rizzuto, C., Zanella, A., Scaravilli, V., Pizzilli, G., Grieco, D.L., Di Meglio, L., de Pascale, G., Lanza, E., Monteduro, F., Zompatori, M., Filippini, C., Locatelli, F., Cecconi, M., Fumagalli, R., Nava, S., Vincent, J.-L., Antonelli, M., Slutsky, A.S., Pesenti, A., Ranieri, V.M., Lissoni, A., Rossi, N., Guzzardella, A., Valsecchi, C., Madotto, F., Bevilacqua, F., Di Laudo, M., Querci, L., Seccafico, C., 2020. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir. Med. S2213-2600, 30370–30372. https://doi.org/10.1016/s2213-2600(20)30370-2.

Guan, S., Xiong, Y., Song, B., Song, Y., Wang, D., Chu, X., Chen, N., Huo, M., Deng, X., Lu, J., 2012. Protective effects of salidroside from Rhodiola rosea on LPS-induced acute lung injury in mice. Immunopharmacol. Immunotoxicol. 34, 667–672. https://doi.org/10.3109/08923973.2011.650175.

Gupta, S., Bi, R., Kim, C., Chiplunkar, S., Yel, L., Gollapudi, S., 2005. Role of NF-kappaB signaling pathway in increased tumor necrosis factor-alpha-induced apoptosis of lymphocytes in aged humans. Cell Death Differ. 12, 177–183. https://doi.org/10.1038/sj.cdd.4401557.

Hamming, I., Timens, W., Bulthuis, M.L., Lely, A.T., Navis, G., van Goor, H., 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J. Pathol. 203, 631–637. https://doi.org/10.1002/path.1570.

Ho, J.C., Ooi, G.C., Mok, T.Y., Chan, J.W., Hung, I., Lam, B., Wong, P.C., Li, P.C., Ho, P.L., Lam, W.K., Ng, C.K., Ip, M.S., Lai, K.N., Chan-Yeung, M., Tsang, K.W., 2003. High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome. Am. J. Respir. Crit. Care Med. 168, 1449–1456. https://doi.org/10.1164/rccm.200306-766OC.

Ho, T.Y., Wu, S.L., Chen, J.C., Li, C.C., Hsiang, C.Y., 2007. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antivir. Res. 74, 92–101. https://doi.org/10.1016/j.antiviral.2006.04.014.

Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.-H., Nitsche, A., Müller, M.A., Drosten, C., Pöhlmann, S., 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181, 271–280.e8. https://doi.org/10.1016/j.cell.2020.02.052.

Hottz, E.D., Azevedo-Quintanilha, I.G., Palhinha, L., Teixeira, L., Barreto, E.A., Pao, C.R.R., Righy, C., Franco, S., Souza, T.M.L., Kurtz, P., Bozza, F.A., Bozza, P.T., 2020. Platelet activation and platelet-monocyte aggregates formation trigger tissue factor expression in severe COVID-19 patients. Blood 136, 1330–1341. https://doi.org/10.1182/blood.2020007252.

Hu, K., Guan, W.J., Bi, Y., Zhang, W., Li, L., Zhang, B., Liu, Q., Song, Y., Li, X., Duan, Z., Zheng, Q., Yang, Z., Liang, J., Han, M., Ruan, L., Wu, C., Zhang, Y., Jia, Z.H., Zhong, N.S., 2020. Efficacy and safety of Lianhuaqingwen capsules, a repurposed

Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. Phytomedicine, 153242. https://doi.org/10.1016/j.phymed.2020.153242.
Huang, H., Ji, L., Song, S., Wang, J., Wei, N., Jiang, M., Bai, G., Luo, G., 2011. Identification of the major constituents in Xuebijing injection by HPLC-ESI-MS. Phytochem. Anal. 22, 330–338. https://doi.org/10.1002/pca.1284.
Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506. https://doi.org/10.1016/s0140-6736(20)30183-5.
Hussell, T., Pennycook, A., Openshaw, P.J., 2001. Inhibition of tumor necrosis factor reduces the severity of virus-specific lung immunopathology. Eur. J. Immunol. 31, 2566–2573. https://doi.org/10.1002/1521-4141(200109)31:9<2566::AID-IMMU2566>3.0.CO;2-L.
Jia, W., Wang, C., Wang, Y., Pan, G., Jiang, M., Li, Z., Zhu, Y., 2015. Qualitative and quantitative analysis of the major constituents in Chinese medical preparation Lianhua-Qingwen capsule by UPLC-DAD-QTOF-MS. Sci. World J. 2015, 1–19. https://doi.org/10.1155/2015/731765.
Jiang, M., Zhou, M., Han, Y., Xing, L., Zhao, H., Dong, L., Bai, G., Luo, G., 2013. Identification of NF-kappaB inhibitors in Xuebijing injection for sepsis treatment based on bioactivity-integrated UPLC-Q/TOF. J. Ethnopharmacol. 147, 426–433. https://doi.org/10.1016/j.jep.2013.03.032.
Jin, J.M., Bai, P., He, W., Wu, F., Liu, X.F., Han, D.M., Liu, S., Yang, J.K., 2020. Gender differences in patients with COVID-19: focus on severity and mortality. Front. Public Health 8, 152. https://doi.org/10.3389/fpubh.2020.00152.
Kale, S.S., Yende, S., 2011. Effects of aging on inflammation and hemostasis through the continuum of critical illness. Aging Dis. 2, 501–511.
Krabbe, K.S., Pedersen, M., Bruunsgaard, H., 2004. Inflammatory mediators in the elderly. Exp. Gerontol. 39, 687–699. https://doi.org/10.1016/j.exger.2004.01.009.
Lei, J., Li, J., Li, X., Qi, X., 2020. CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. Radiology 295, 18. https://doi.org/10.1148/radiol.2020200236.
Letko, M., Marzi, A., Munster, V., 2020. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat. Microbiol. 5, 562–569. https://doi.org/10.1038/s41564-020-0688-y.
Li, C., Wang, P., Li, M., Zheng, R., Chen, S., Liu, S., Feng, Z., Yao, Y., Shang, H., 2020a. The current evidence for the treatment of Sepsis with Xuebijing injection: bioactive constituents, findings of clinical studies and potential mechanisms. J. Ethnopharmacol. 265, 113301 https://doi.org/10.1016/j.jep.2020.113301.
Li, X., Xu, S., Yu, M., Wang, K., Tao, Y., Zhou, Y., Shi, J., Zhou, M., Wu, B., Yang, Z., Zhang, C., Yue, J., Zhang, Z., Renz, H., Liu, X., Xie, J., Xie, M., Zhao, J., 2020b. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J. Allergy Clin. Immunol. 146, 110–118. https://doi.org/10.1016/j.jaci.2020.04.006.
Liu, D., Ahmet, A., Ward, L., Krishnamoorthy, P., Mandelcorn, E.D., Leigh, R., Brown, J. P., Cohen, A., Kim, H., 2013. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy, Asthma Clin. Immunol. 9, 30. https://doi.org/10.1186/1710-1492-9-30.
Liu, M.W., Su, M.X., Zhang, W., Wang, Y.Q., Chen, M., Wang, L., Qian, C.Y., 2014. Protective effect of Xuebijing injection on paraquat-induced pulmonary injury via down-regulating the expression of p38 MAPK in rats. BMC Complement. Altern. Med. 14, 498 https://doi.org/10.1186/1472-6882-14-498.
Llitjos, J.F., Leclerc, M., Chochois, C., Monsallier, J.M., Ramakers, M., Auvray, M., Merouani, K., 2020. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J. Thromb. Haemost. 18, 1743–1746. https://doi.org/10.1111/jth.14869.
Lu, H., 2020. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci. Trends 14, 69–71. https://doi.org/10.5582/bst.2020.01020.
Ludwig, S., Zarbock, A., 2020. Coronaviruses and SARS-CoV-2: a brief overview. Anesth. Analg. 131, 93–96. https://doi.org/10.1213/ANE.0000000000004845.
Ma, L., Sha, G., Zhang, Y., Li, Y., 2018. Elevated serum IL-6 and adiponectin levels are associated with frailty and physical function in Chinese older adults. Clin. Interv. Aging 13, 2013–2020. https://doi.org/10.2147/CIA.S180934.
Ma, Q., Qiu, M., Zhou, H., Chen, J., Yang, X., Deng, Z., Chen, L., Zhou, J., Liao, Y., Chen, Q., Zheng, Q., Cai, L., Shen, L., Yang, Z., 2020. The study on the treatment of Xuebijing injection (XBJ) in adults with severe or critical Corona virus disease 2019 and the inhibitory effect of XBJ against SARS-CoV-2. Pharmacol. Res. 160, 105073 https://doi.org/10.1016/j.phrs.2020.105073.
Magalhaes, C.A., Ferreira, C.N., Loures, C.M.G., Fraga, V.G., Chaves, A.C., Oliveira, A.C. R., de Souza, L.C., Resende, E.P.F., Carmona, K.C., Guimaraes, H.C., Cintra, M.T.G., Lanna, I.N., Zauli, D.A.G., Bicalho, M.A., Carvalho, M.G., Sousa, L.P., Caramelli, P., Gomes, K.B., 2018. Leptin, hsCRP, TNF-alpha and IL-6 levels from normal aging to dementia: relationship with cognitive and functional status. J. Clin. Neurosci. 56, 150–155. https://doi.org/10.1016/j.jocn.2018.08.027.
Maggio, M., Guralnik, J.M., Longo, D.L., Ferrucci, L., 2006. Interleukin-6 in aging and chronic disease: a magnificent pathway. J. Gerontol. A Biol. Sci. Med. Sci. 61, 575–584. https://doi.org/10.1093/gerona/61.6.575.
Mahévas, M., Moulis, G., Andres, E., Riviere, E., Garzaro, M., Crickx, E., Guillotin, V., Malphettes, M., Galicier, L., Noel, N., Darnige, L., Terriou, L., Guerveno, C., Sanchis-Borja, M., Moulinet, T., Meunier, B., Ebbo, M., Michel, M., Godeau, B., 2020. Clinical characteristics, management and outcome of Covid-19-associated immune thrombocytopenia. A French multicenter series. Br. J. Haematol. 190, e224-e229 https://doi.org/10.1111/bjh.17024.
Mari, D., Ogliari, G., Castaldi, D., Vitale, G., Bollini, E.M., Lio, D., 2008. Hemostasis and ageing. Immun. Ageing 5, 12. https://doi.org/10.1186/1742-4933-5-12.
Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B., Cesari, M., Nourhashemi, F., 2013. Proinflammatory cytokines, aging, and age-related diseases. J. Am. Med. Dir. Assoc. 14, 877–882. https://doi.org/10.1016/j.jamda.2013.05.009.
Moreno-Perez, O., Andres, M., Leon-Ramirez, J.M., Sanchez-Paya, J., Rodriguez, J.C., Sanchez, R., Garcia-Sevila, R., Boix, V., Gil, J., Merino, E., 2020. Experience with tocilizumab in severe COVID-19 pneumonia after 80 days of follow-up: a retrospective cohort study. J. Autoimmun. 102523. https://doi.org/10.1016/j.jaut.2020.102523.
National Health Commission, State Administration of Traditional Chinese Medicine, 2020. Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7). Chin. Med. J. 133, 1087–1095. https://doi.org/10.1097/cm9.0000000000000819.
Niu, M., Wang, R.L., Wang, Z.X., Zhang, P., Bai, Z.F., Jing, J., Guo, Y.M., Zhao, X., Zhan, X.Y., Zhang, Z.T., Song, X.A., Qin, E.Q., Wang, J.B., Xiao, X.H., 2020. Rapid establishment of traditional Chinese medicine prevention and treatment of 2019-nCoV based on clinical experience and molecular docking. Zhongguo Zhong Yao Za Zhi 45, 1213–1218. https://doi.org/10.19540/j.cnki.cjcmm.20200206.501.
O'Driscoll, M., Ribeiro Dos Santos, G., Wang, L., Cummings, D., Azman, A.S., Paireau, J., Fontanet, A., Cauchemez, S., Salje, H., 2021. Age-specific mortality and immunity patterns of SARS-CoV-2. Nature 590 (7844), 140–145. https://doi.org/10.1038/s41586-020-2918-0.
Onder, G., Rezza, G., Brusaferro, S., 2020. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 323, 1775–1776. https://doi.org/10.1001/jama.2020.4683.
Palanques-Pastor, T., López-Briz, E., Poveda Andrés, J.L., 2020. Involvement of interleukin 6 in SARS-CoV-2 infection: siltuximab as a therapeutic option against COVID-19. Eur. J. Hosp. Pharm. 27, 297–298. https://doi.org/10.1136/ejhpharm-2020-002322.
Paolisso, G., Rizzo, M.R., Mazziotti, G., Tagliamonte, M.R., Gambardella, A., Rotondi, M., Carella, C., Giugliano, D., Varricchio, M., D'Onofrio, F., 1998. Advancing age and insulin resistance: role of plasma tumor necrosis factor-alpha. Am. J. Phys. 275, E294–E299. https://doi.org/10.1152/ajpendo.1998.275.2.E294.
Patel, K., Gooley, T.A., Bailey, N., Bailey, M., Hegerova, L., Batchelder, A., Holdread, H., Dunleavy, V., Downey, T., Frisvold, J., Megrath, S., Pagarigan, K., Szeto, J., Rueda, J., Islam, A., Maree, C., Nyatsatsang, S., Bork, S.E., Lipke, A., O'Mahony, D. S., Wagner, T., Pulido, J., Mignone, J., Youssef, S., Hartman, M., Goldman, J.D., Pagel, J.M., 2020. Use of the IL-6R antagonist tocilizumab in hospitalized COVID-19 patients. J. Intern. Med. https://doi.org/10.1111/joim.13163.
Pérez-López, F.R., Tajada, M., Savirón-Cornudella, R., Sánchez-Prieto, M., Chedraui, P., Terán, E., 2020. Coronavirus disease 2019 and gender-related mortality in European countries: a meta-analysis. Maturitas 141, 59–62. https://doi.org/10.1016/j.maturitas.2020.06.017.
Qin, L., Li, X., Shi, J., Yu, M., Wang, K., Tao, Y., Zhou, Y., Zhou, M., Xu, S., Wu, B., Yang, Z., Zhang, C., Yue, J., Cheng, C., Liu, X., Xie, M., 2020. Gendered effects on inflammation reaction and outcome of COVID-19 patients in Wuhan. J. Med. Virol. 92 (11), 2684–2692. https://doi.org/10.1002/jmv.26137.
Rajendran, P., Rengarajan, T., Thangavel, J., Nishigaki, Y., Sakthisekaran, D., Sethi, G., Nishigaki, I., 2013. The vascular endothelium and human diseases. Int. J. Biol. Sci. 9, 1057–1069. https://doi.org/10.7150/ijbs.7502.
Rossotti, R., Travi, G., Ughi, N., Corradin, M., Baiguera, C., Fumagalli, R., Bottiroli, M., Mondino, M., Merli, M., Bellone, A., Basile, A., Ruggeri, R., Colombo, F., Moreno, M., Pastori, S., Perno, C.F., Tarsia, P., Epis, O.M., Puoti, M., 2020. Safety and efficacy of anti-Il6-receptor tocilizumab use in severe and critical patients affected by coronavirus disease 2019: a comparative analysis. J. Inf. Secur. https://doi.org/10.1016/j.jinf.2020.07.008.
Runfeng, L., Yunlong, H., Jicheng, H., Weiqi, P., Qinhai, M., Yongxia, S., Chufang, L., Jin, Z., Zhenhua, J., Haiming, J., Kui, Z., Shuxiang, H., Jun, D., Xiaobo, L., Xiaotao, H., Lin, W., Nanshan, Z., Zifeng, Y., 2020. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). Pharmacol. Res. 156, 104761 https://doi.org/10.1016/j.phrs.2020.104761.
Salminen, A., Huuskonen, J., Ojala, J., Kauppinen, A., Kaarniranta, K., Suuronen, T., 2008. Activation of innate immunity system during aging: NF-kB signaling is the molecular culprit of inflamm-aging. Ageing Res. Rev. 7, 83–105. https://doi.org/10.1016/j.arr.2007.09.002.
Sepulveda, C., Palomo, I., Fuentes, E., 2017. Mechanisms of endothelial dysfunction during aging: predisposition to thrombosis. Mech. Ageing Dev. 164, 91–99. https://doi.org/10.1016/j.mad.2017.04.011.
Shi, M.J., Lv, J.G., Lin, L., Guo, J.Y., 2021. Trends in coronavirus disease 2019 hospitalization and prognosis: gender effect. Curr. Med. Sci. 41 (2), 312–317. https://doi.org/10.1007/s11596-021-2348-8.
Shimabukuro-Vornhagen, A., Godel, P., Subklewe, M., Stemmler, H.J., Schlosser, H.A., Schlaak, M., Kochanek, M., Boll, B., von Bergwelt-Baildon, M.S., 2018. Cytokine release syndrome. J. Immunother. Cancer 6, 56. https://doi.org/10.1186/s40425-018-0343-9.
Solinas, C., Perra, L., Aiello, M., Migliori, E., Petrosillo, N., 2020. A critical evaluation of glucocorticoids in the management of severe COVID-19. Cytokine Growth Factor Rev. S1359-6101, 30161. https://doi.org/10.1016/j.cytogfr.2020.06.012.
Straub, R.H., 2007. The complex role of estrogens in inflammation. Endocr. Rev. 28 (5), 521–574. https://doi.org/10.1210/er.2007-0001.
Streeten, D.H., 1975. Corticosteroid therapy. I. Pharmacological properties and principles of corticosteroid use. JAMA 232, 944–947. https://doi.org/10.1001/jama.232.9.944.
Sun, J., Xue, Q., Guo, L., Cui, L., Wang, J., 2010. Xuebijing protects against lipopolysaccharide-induced lung injury in rabbits. Exp. Lung Res. 36, 211–218. https://doi.org/10.3109/01902140903312123.

Sun, H., Ning, R., Tao, Y., Yu, C., Deng, X., Zhao, C., Meng, S., Tang, F., Xu, D., 2020. Risk factors for mortality in 244 older adults with COVID-19 in Wuhan, China: a retrospective study. J. Am. Geriatr. Soc. 68, E19–E23. https://doi.org/10.1111/jgs.16533.

Takahashi, T., Ellingson, M.K., Wong, P., Israelow, B., Lucas, C., Klein, J., Silva, J., Mao, T., Oh, J.E., Tokuyama, M., Lu, P., Venkataraman, A., Park, A., Liu, F., Meir, A., Sun, J., Wang, E.Y., Casanovas-Massana, A., Wyllie, A.L., Vogels, C., Earnest, R., Lapidus, S., Ott, I.M., Moore, A.J., Yale IMPACT Research Team, Shaw, A., Fournier, J.B., Odio, C.D., Farhadian, S., Dela Cruz, C., Grubaugh, N.D., Schulz, W.L., Ring, A.M., Ko, A.I., Omer, S.B., Iwasaki, A., 2020. Sex differences in immune responses that underlie COVID-19 disease outcomes. Nature 588 (7837), 315–320. https://doi.org/10.1038/s41586-020-2700-3.

Tanaka, T., Narazaki, M., Kishimoto, T., 2016. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy 8, 959–970. https://doi.org/10.2217/imt-2016-0020.

Tang, N., Bai, H., Xiong, D., Sun, Z., 2020a. Specific coagulation markers may provide more therapeutic targets in COVID-19 patients receiving prophylactic anticoagulant. J. Thromb. Haemost. https://doi.org/10.1111/jth.14988.

Tang, N., Li, D., Wang, X., Sun, Z., 2020b. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J. Thromb. Haemost. 18, 844–847. https://doi.org/10.1111/jth.14768.

Ten-Caten, F., Gonzalez-Dias, P., Castro, Í., Ogava, R., Giddaluru, J., Silva, J., Martins, F., Gonçalves, A., Costa-Martins, A.G., Araujo, J.D., Viegas, A.C., Cunha, F.Q., Farsky, S., Bozza, F.A., Levin, A.S., Pannaraj, P.S., de Silva, T.I., Minoprio, P., Pinheiro da Silva, F., Andrade, B.B., Nakaya, H.I., 2021. In-depth analysis of laboratory parameters reveals the interplay between sex, age, and systemic inflammation in individuals with COVID-19. Int. J. Infect. Dis. 105, 579–587. https://doi.org/10.1016/j.ijid.2021.03.016.

Tucker, T., Idell, S., 2013. Plasminogen-plasmin system in the pathogenesis and treatment of lung and pleural injury. Semin. Thromb. Hemost. 39, 373–381. https://doi.org/10.1055/s-0033-1334486.

Uciechowski, P., Dempke, W.C.M., 2020. Interleukin-6: a Masterplayer in the cytokine network. Oncology 98, 131–137. https://doi.org/10.1159/000505099.

Varga, Z., Flammer, A.J., Steiger, P., Haberecker, M., Andermatt, R., Zinkernagel, A.S., Mehra, M.R., Schuepbach, R.A., Ruschitzka, F., Moch, H., 2020. Endothelial cell infection and endotheliitis in COVID-19. Lancet 395, 1417–1418. https://doi.org/10.1016/s0140-6736(20)30937-5.

Vaughan, D.E., Rai, R., Khan, S.S., Eren, M., Ghosh, A.K., 2017. Plasminogen activator Inhibitor-1 is a marker and a mediator of senescence. Arterioscler. Thromb. Vasc. Biol. 37, 1446–1452. https://doi.org/10.1161/ATVBAHA.117.309451.

Wang, Y., Jiang, W., He, Q., Wang, C., Wang, B., Zhou, P., Dong, N., Tong, Q., 2020. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Signal Transduct. Target. Ther. 5, 57 https://doi.org/10.1038/s41392-020-0158-2.

Wang, J., Hajizadeh, N., Moore, E.E., McIntyre, R.C., Moore, P.K., Veress, L.A., Yaffe, M. B., Moore, H.B., Barrett, C.D., 2020b. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. J. Thromb. Haemost. 18, 1752–1755. https://doi.org/10.1111/jth.14828.

Wang, L., He, W., Yu, X., Hu, D., Bao, M., Liu, H., Zhou, J., Jiang, H., 2020d. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J. Inf. Secur. 80, 639–645. https://doi.org/10.1016/j.jinf.2020.03.019.

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Wang, B., Xiang, H., Cheng, Z., Xiong, Y., Zhao, Y., Li, Y., Wang, X., Peng, Z., 2020e. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 323 (11), 1061–1069. https://doi.org/10.1001/jama.2020.1585.

Wei, X., Xiao, Y., Wang, J., Chen, R., Zhang, W., Yang, Y., Lv, D., Qin, C., Gu, D., Zhang, B., Chen, W., Hou, J., Song, N., Zeng, G., Ren, S., 2020. Sex differences in severity and mortality among patients with COVID-19: evidence from pooled literature analysis and insights from integrated Bioinformatic analysis. arXiv 13547v1, 2003. https://arxiv.org/abs/2003.13547.

Wen, L., Zhou, Z., Jiang, D., Huang, K., 2020. Effect of Xuebijing injection on inflammatory markers and disease outcome of coronavirus disease 2019. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 32, 426–429. https://doi.org/10.3760/cma.j.cn121430-20200406-00386.

Wilder, J.M., 2021. The disproportionate impact of COVID-19 on racial and ethnic minorities in the United States. Clin. Infect. Dis. 72 (4), 707–709. https://doi.org/10.1093/cid/ciaa959.

Wright, F.L., Vogler, T.O., Moore, E.E., Moore, H.B., Wohlauer, M.V., Urban, S., Nydam, T.L., Moore, P.K., McIntyre Jr., R.C., 2020. Fibrinolysis shutdown correlation with thromboembolic events in severe COVID-19 infection. J. Am. Coll. Surg. 231, 193–203 e1. https://doi.org/10.1016/j.jamcollsurg.2020.05.007.

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 323, 1239–1242. https://doi.org/10.1001/jama.2020.2648.

Wu, C., Chen, X., Cai, Y., Xia, J., Zhou, X., Xu, S., Huang, H., Zhang, L., Zhou, X., Du, C., Zhang, Y., Song, J., Wang, S., Chao, Y., Yang, Z., Xu, J., Zhou, X., Chen, D., Xiong, W., Xu, L., Zhou, F., Jiang, J., Bai, C., Zheng, J., Song, Y., 2020a. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern. Med. 180, 934–943. https://doi.org/10.1001/jamainternmed.2020.0994.

Wu, Y., Wang, T., Guo, C., Zhang, D., Ge, X., Huang, Z., Zhou, X., Li, Y., Peng, Q., Li, J., 2020b. Plasminogen improves lung lesions and hypoxemia in patients with COVID-19. QJM 113, 539–545. https://doi.org/10.1093/qjmed/hcaa121.

Xia, S., Zhang, X., Zheng, S., Khanabdali, R., Kalionis, B., Wu, J., Wan, W., Tai, X., 2016. An update on inflamm-aging: mechanisms, prevention, and treatment. J Immunol Res 2016, 8426874. https://doi.org/10.1155/2016/8426874.

Xian, Y., Zhang, J., Bian, Z., Zhou, H., Zhang, Z., Lin, Z., Xu, H., 2020. Bioactive natural compounds against human coronaviruses: a review and perspective. Acta Pharm. Sin. B 10, 1163–1174. https://doi.org/10.1016/j.apsb.2020.06.002.

Xiong, M., Liang, X., Wei, Y.D., 2020. Changes in blood coagulation in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. Br. J. Haematol. 189, 1050–1052. https://doi.org/10.1111/bjh.16725.

Yam, L.Y., Lau, A.C., Lai, F.Y., Shung, E., Chan, J., Wong, V., 2007. Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong. J. Inf. Secur. 54, 28–39. https://doi.org/10.1016/j.jinf.2006.01.005.

Yanez, N.D., Weiss, N.S., Romand, J.A., Treggiari, M.M., 2020. COVID-19 mortality risk for older men and women. BMC Public Health 20 (1), 1742. https://doi.org/10.1186/s12889-020-09826-8.

Yang, X., Yang, Q., Wang, Y., Wu, Y., Xu, J., Yu, Y., Shang, Y., 2020. Thrombocytopenia and its association with mortality in patients with COVID-19. J. Thromb. Haemost. 18 (6), 1469–1472. https://doi.org/10.1111/jth.14848.

Yu, M., Zheng, X., Witschi, H., Pinkerton, K.E., 2002. The role of interleukin-6 in pulmonary inflammation and injury induced by exposure to environmental air pollutants. Toxicol. Sci. 68, 488–497. https://doi.org/10.1093/toxsci/68.2.488.

Zheng, Y., Liu, X., Le, W., Xie, L., Li, H., Wen, W., Wang, S., Ma, S., Huang, Z., Ye, J., Shi, W., Ye, Y., Liu, Z., Song, M., Zhang, W., Han, J.-D.J., Belmonte, J.C.I., Xiao, C., Qu, J., Wang, H., Liu, G.-H., Su, W., 2020. A human circulating immune cell landscape in aging and COVID-19. Protein Cell 1–31. https://doi.org/10.1007/s13238-020-00762-2.

Zhuang, W., Fan, Z., Chu, Y., Wang, H., Yang, Y., Wu, L., Sun, N., Sun, G., Shen, Y., Lin, X., Guo, G., Xi, S., 2020. Chinese patent medicines in the treatment of coronavirus disease 2019 (COVID-19) in China. Front. Pharmacol. 11, 1066. https://doi.org/10.3389/fphar.2020.01066.