Molecular Mechanism of Acute Sarcopenia in Elderly Patient with COVID - 19

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Case fatality rate has been on the rise among older adults. Muscle loss is a consequence of several chronic diseases (chronic sarcopenia) and recent theory also suggested that acute sarcopenia may caused by acute significant stressor such as an acute illness, surgery, infections, trauma or burns including COVID-19 infection leading to further muscle loss in elderly. Cytokine storm, the hallmark of COVID-19 pathogenesis will induce various pro-inflammatory cytokine such as IL-1 and IL-6 causing acute sarcopenia by activating negative regulators like NF-κB, atrogin-1, MURF-1. Long standing chronic inflammation also known as inflammaging along with acute inflammation during COVID-19 in elderly will cause reticulum endoplasmic and mitochondria stress activating caspase and finally increase both cytosolic and nuclear levels of AIF and EndoG to induce acute sarcopenia. Several precipitating factors shared same molecular pathway like physical inactivity and hormonal dysregulation which act through IGF-1-AKT-mTOR pathway. Physical inactivity during COVID-19 infection also induced myostatin and Atrogin-1/ MaFbx/ MuRF pathway. This review provides recent research advances dealing with molecular pathway modulating muscle mass in acute sarcopenia during COVID-19 infection.

Keywords**:** *COVID-19, acute sarcopenia, inflammation, aging.*

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2). It was first reported in December 2019 in Wuhan, China and has spread quickly to all over the world.[1] The number of confirmed COVID-19 cases has reach more than 233 million worldwide and currently has mortality rate 1.71%. [2] Indonesia has 4.2 million confirmed cases up to October 2021 including 142.115 total death.[3] COVID-19 has high mortality and morbidity in elderly patients with 38.6% death case among elderly patients in Indonesia. Men have higher proportion of both confirmed and death cases compared to women in elderly population.[4] Case fatality rate has been on the rise among older adults. According to statistical data, up to 80-

90% of deaths was mostly happened in elderly patients (≥60 years old).[5]

Globally, elderly population is growing faster than the number of people in all younger age groups each year. In 2019, aging population have reached 703 million worldwide.[6] Indonesia is one of the most populated countries and its elderly population is estimated to be 25.64 million in 2019. Elderly people will experience decrease of organ function such as loss of muscle strength. Decrease of muscle mass and muscle function will lead to sarcopenia in elderly. Sarcopenia is a syndrome characterized by loss of skeletal muscle mass and function.[7] Acute sarcopenia is defined as changes in muscle mass and muscle function less than 6 months due to significant stressor such as an acute illness, surgery, infections, trauma or burns.[8] In COVID-19 cases, acute sarcopenia was associated with increased mortality risk, longer ICU admission and risk of higher mechanical ventilator.[9,10,11,12,13] The combination of high inflammation, malnutrition, and immobilization in critically ill COVID-19 will increase the probability of elderly developing acute sarcopenia.[14] The underlying mechanism of acute sarcopenia in elderly with COVID-19 is a complex process but several cellular mechanisms are thought to be involved in the acute sarcopenia pathogenesis. This review aims to understand further about the complexity of acute sarcopenia molecular pathway in elderly with COVID -19, identify the contributing factors and the implications so that clinicians can try the best measures to prevent and treat this acute and long-term, disabling condition.

AGING, COVID-19 INFECTION, AND ACUTE SARCOPENIA

Aging is accompanied by remodeling of the immune system including decreasing immune system capability to induce antibody and cellular response to fight against infection. This phenomenon is known as *imunosenescence*, a multifactorial condition which influences innate and adaptive immunity, especially T-Lymphocyte cells. The hallmark of immunosenescence is the reduced ability to respond to new antigens, the accumulation of memory T cells, and long standing low-grade inflammation termed as inflammaging.[15] Aging has been associated with chronic inflammation and increase of inflammation markers such as *C-reactive protein* (CRP) and interleukin-6 (IL-6).[16] Aging is also risk factor for poor outcome in COVID – 19 infection. Aging will cause decrease of inhaled particle clearance in respiratory tract due to diminished ciliary amount in respiratory tract. Moreover aging also affects upper respiratory tract size which reduces its size especially in men and finally increase the risk of upper respiratory tract collapse.[17] SARS-CoV-2 S spike protein plays a crucial role in binding the human cell receptor ACE2 as entry point of the virus. In lung cells, by cleaving residues of AngII, ACE2 produces Ang I-VII which reduces the inflammatory effect of AngII. The spike protein of the SARS-CoV-2 virus causes internalization and degradation of ACE2 which exacerbates lung damage. New study found that younger subjects are prone to have higher probability for COVID-19 infection, whereas in elderly who has lower amount of ACE2 was associated with more severe symptoms in COVID-19 infection. Lower expression of ACE 2 does not protect against viral invasion because SARS-CoV-2 has a high intrinsic affinity for the ACE 2 receptor. ACE 2 deficiency is accompanied by viral downregulation of ACE 2 causing imbalance between ACE/Ang II/AT1R receptors and ACE 2/ Angiotensin 1-7 receptors. At the lung level, such dysregulation will greatly facilitate the development of the inflammatory process and hypercoagulation resulting from the hyperactivity of Ang II.[18] These phenomenon is associated with more severe alveolar damage and mechanical ventilator support.[19]

Age is not the only factor that affects the increase of disease severity. Epidemiological studies also show differences of higher incidence and mortality of COVID-19 infection in men compared to women. The number of T cells and B cells decrease significantly in elderly men and there was an increase in CD8 memory effector T cells compare to women. Elderly men showed an inverse CD4/CD8 ratio compared to women. The proliferative and secretory capacity of T cell cytokines also decreases more rapidly in male.[17] Sex hormones also play a role and explained why

men are more susceptible compared to women. Research on mice have showed differences in ACE2 expression according to sex. One study also reported higher expression of ACE2 in female mice in comparison to male mice. SARS-CoV-2 uses the cell surface enzyme ACE2 and the transmembrane serine protease 2 (TMPRSS2) for providing virus cell entry and priming. Estrogen seems play as protective factor in women. Estrogen receptor alpha (ERα) has an effect on T cells such as Th1, Th2, Th17, and T regulatory cells, as well as follicular helper T (TFH) cells. Therefore, estrogen, stands out as a key biological factor making women's immune system more active against the virus. Estrogen also has anti inflammatory and antioxidative effect on the effectors of the renin-angiotensin system.[20] On the other hand, male sex hormone might contribute to severity of COVID-19 in men compared to women. TMPRSS2 is an androgen-mediated protein that plays a critical role in priming the virus spike proteins for entry into the host cell as one of the first steps involved in infection and its activation is dependent on androgens.[21]

Sarcopenia is a syndrome characterized by progressive loss of muscle mass and muscle strength.[7,22] The definition of sarcopenia based on the European Working Group on Sarcopenia in Older People (EWGSOP) 2 is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with increasing risks such as physical disability, poor quality of life and death. Acute sarcopenia based on EWGSOP2 is defined as incident sarcopenia within six months, normally following a stressor event and if sarcopenia persists for more than six months it will be described as chronic.[22] In order to diagnose acute sarcopenia, we must obtained measurements of muscle mass and muscle function either pre-illness or during early stages of an illness.[8] **Figure 1** shows how acute sarcopenia secondary to hospitalization can lead to worsening chronic sarcopenia and this is often seen in elderly patients infected with COVID-19. Sarcopenia in elderly patients has implications not only when the patient is hospitalized, but also functional and physical decline after COVID-19 recovery.[23]

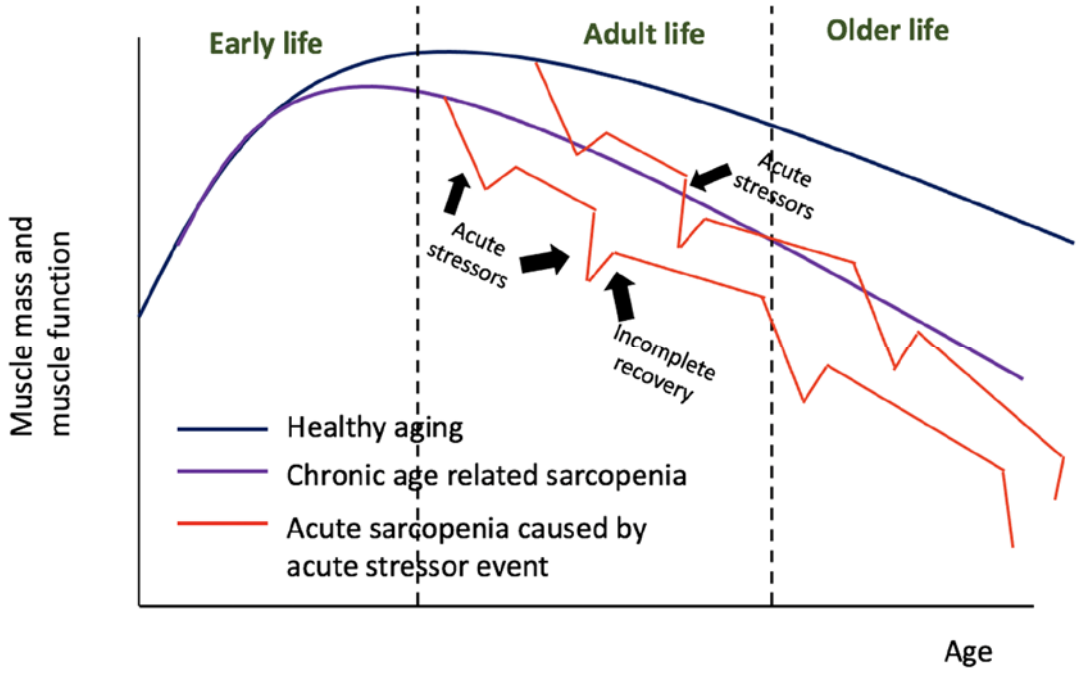

Figure 1. Acute sarcopenia, chronic sarcopenia, healthy aging illustration.[8,22]

ACUTE SARCOPENIA IN ELDERLY WITH COVID-19 INFECTION: PREDISPOSING AND PRECIPITATING FACTORS

In order to effectively prevent the development of acute sarcopenia, it is important to know predisposing and precipitation factors. Some predisposing factors play a major role on determining the outcome of acute sarcopenia in elderly with COVID – 19 infection even after recovering from COVID – 19 infection. Predisposing factors for acute sarcopenia is a complex process in which many factors can contribute. Aging is the main predisposing factor of sarcopenia, but other factors also contribute to the loss of muscle mass such as reactive oxygen species (ROS). In the context of aging, increased activity of ROS has been implicated in the processes underlying aging and, in all species, tissues (including skeletal muscle) of aged organisms contain increased amounts of oxidative damage to lipids, DNA and proteins. Aberrant ROS generation and oxidative damage have been associated with many aspects of mitochondrial dysfunction in skeletal muscle aging.[24] Sarcopenia is an example of impaired physical function that is thought to have complex relationships with individual long-term conditions and multimorbidity, including bidirectional effects. Many studies proved that elderly who developed sarcopenia often has multimorbidity. Study conducted by Richard et al, found that almost half of the sample (44.5%) had multimorbidity (two or more categories of long-term conditions). This was more common in those with sarcopenia (64.8%) than those without (43.4%).[25]

Since elderly are often at risk for both the development of sarcopenia and obesity, a double burden exists. Obesity remains one of predisposing factors that might cause elderly prone to develop sarcopenia and makes it not very surprising that the two conditions often coexist which is known as sarcopenic obesity. An important risk factor for both sarcopenia and obesity is the lower rate of energy expenditure with age, which is a result of lower physical activity, as well as a fat free mass related-lower basal metabolic rate, which is often seen with older age. Obesity may create resistance towards anabolic stimuli, such as, growth factors, hormones, amino acids, and exercise, a phenomenon called anabolic resistance. Finally, obesity is responsible for causing systemic low-grade inflammation, particularly by visceral fat, which excretes several different pro-inflammatory cytokines, such as IL-6)and TNF-α and inflammation is also one of predisposing factor for sarcopenia as well.[26] Besides obesity, malnutrition was one of the remaining problem in elderly and found to be associated with sarcopenia in several populations, including hospitalized patients. The association between malnutrition and severe sarcopenia could be explained by a lower intake of key nutrients such

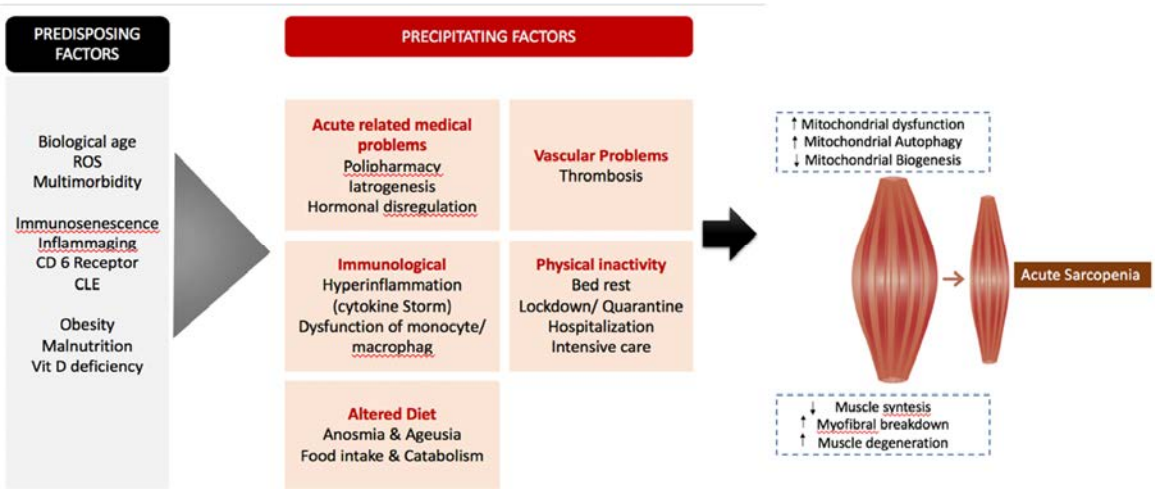

Figure 2. Predisposing and precipitating factors of acute sarcopenia in elderly with COVID-19 infection.[22-27]

as protein, vitamin D and calcium, amongst other factors, which affects preservation of muscle mass and subsequently muscle strength and physical performance. [22,27]

Acute sarcopenia is usually related to an acute illness or injury, while chronic sarcopenia is likely to be associated with chronic and progressive conditions and increases the risk of mortality. Long before elderly experienced critical illness, they often have chronic sarcopenia as consequence of aging. At one point, acute illnesses could worsen the degree of sarcopenia and this condition could be termed as an acute-on-chronic sarcopenia phenotype.[28] Some precipitating factors are playing crucial role in the accelerated development of acute on chronic sarcopenia in elderly infected with COVID-19, such as altered diet during hospitalization including anosmia and ageusia, acute medical problems including COVID -19 itself, immunological events such as cytokine storm which is the hallmark of COVID-19 pathogenesis, vascular problems, and physical inactivity.

Immobilization that occurs due to COVID-19 is very different from immobilization due to other diseases such as fractures, CHF FC IV or severe pneumonia. Elderly with COVID-19 will be more susceptible to suffering from acute sarcopenia. Study conducted by Mayer et al found that prolonged bed rest in the elderly with COVID-19 who used high-flow oxygen therapy or was treated in the ICU for COVID-19 reduced rectus femoris muscle mass by 18.5% on day 7 of treatment compared to the first day of hospital admission. Other effects include post intensive care syndrome (PICS) with symptoms of muscle weakness and some conditions, including fatigue, anxiety, depression, and sleep disturbances.[29] Immobilization during hospitalization and due to government policy to restrict mobilization will increase the probability of elderly getting a thrombotic event and longer bedrest. Loss of muscle mass does not only start as early as the second decade of life, but it is exacerbated by muscle inactivity.

The complex interaction between predisposing and precipitating factors would lead to mitochondrial dysfunction, mitochondrial autophagy and mitochondrial biogenesis and finally causing decrease of muscle syntesis, increase of myofibral breakdown and muscle degeneration. **Figure 2** showed some of predisposing and precipitating factors that might contributed in elderly with acute sarcopenia.

MOLECULAR MECHANISM OF ACUTE SARCOPENIA IN ELDERLY WITH COVID-19 INFECTION

Elderly are known to be particularly vulnerable to the effects of the illness, with age being associated with not only mortality but may cause more severe clinical presentation leading to development of acute sarcopenia. It has now become clear that survivors of COVID-19 are still at increased risk of acute sarcopenia.

Biological Age and ROS

Aging has many effects towards our body, including endoplasmic reticulum (ER) stress caused by ROS and harmful protein accumulation. Mitochondria induces apoptosis via both caspase-mediated or caspase-independent pathways. Initiator caspases such as caspase-8, caspase-9, caspase-12 will be activated if there is stimuli and leading to the activation of effector caspases (caspase-3, caspase-6, caspase-7) which is responsible for cellular degradation and DNA fragmentation via a caspase-activated DNase (CAD). The stimuli to activate pro caspase to become caspase can divided into two pathways, firstly the extrinsic apoptotic signaling that is initiated by death receptors located on the cell surface, such as the tumor necrosis factor receptor (TNF-R) and the Fas receptor and intrinsic pathways of caspase activation include those triggered by the endoplasmic reticulum (ER) and the mitochondrion. Recently, higher Fas expression on CD4 + T and CD8 + Tcells has been reported in COVID-19 patients than in healthy controls but it needs further study. Under ER stress conditions, ER-specific procaspase-12 can be activated by m-calpain, leading to caspase-3 activation. Along with aging, the caspase-independent apoptotic pathways are expressed more compare to younger age leading to sarcopenia.[30]

Immunosenescence

Aging has been associated with chronic inflammation and increase of inflammation markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) which is well known as a phenotype predictive factor for body composition change, homeostasis and immunosenescence.[16] As humans age, the presence of systemic basal inflammatory mediators increases independently of acute immune challenges in a phenomenon known as inflammaging. Long standing chronic inflammation has been speculated to be main contributor to immunosenescence, a term defined as overall changes to the immune system in elderly, including a reduced ability to combat new infections.[31] Primary goals of the innate immune system in response to a SARS-CoV-2 infection are (1) to initiate a local inflammatory response to activate and recruit immune cells, (2) to directly eliminate virally infected cells and (3) to prime the adaptive immune response. As in elderly, those abilities are either diminished or dysregulated.

Mitochondria plays a central role in the induction and regulation of programmed cell death. A study in experimental animal models has showed a proapoptotic shift in the expression pattern of Bcl-2 proteins (increased Bax and decreased Bcl-2 levels) that was observed in muscles of aged rodents. The release of mitochondria-specific apoptotic mediators is the process of mitochondrial outer membrane permeabilization (MOMP). Once MOMP has occurred, the release of apoptogenic factors stored in the mitochondrial intermembrane space ensues, initiating the series of events that result in cell death. Several studies also showed that caspase-independent apoptotic pathways are activated in elderly. Translocation of mitochondrial EndoG to the nucleus was increased in the soleus muscle of old mice. In addition, aging will increase both cytosolic and nuclear levels of AIF and EndoG and this was was observed in the rat gastrocnemius muscle. Moreover, AIF gene expression progressively increased during aging in the rat plantaris muscle, and was correlated with the progression of sarcopenia. The aforementioned findings support the role of mitochondrial caspase-independent pathway of apoptosis in the pathophysiology of sarcopenia.[32]

Hyperinflammation (Cytokine Storm)

COVID-19 is an infectious disease characterized by an increase in inflammatory cytokines known as cytokine storms. Hyperactivation of the nuclear factor kappa-light-chain- enhancer of activated B cells (NF-κB) pathway has been implicated in the pathogenesis of the severe/critical COVID- 19 infection. NF-κB activation plays major role to the acute respiratory RNA virus-induced cytokine storm. In humans, SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor and with the help of the cellular serine protease TMPRSS2 will trigger endocytosis into the host cell. Within the endosomes, RNA from single-stranded RNA virus is known to activate the Toll-like receptors TLR7 and TLR8. However, as a second major effect the activation of the TLRs can trigger—via various intermediates—the activation of IKK (IκB kinases) resulting in phosphorylation of the cytoplasmic inhibitor factor IκBα triggering its ubiquitination followed by degradation by the 26S proteasome, thereby NF-κB (a heterodimer complex consisting of protein subunits p50 and p65) is released from IκBα.NF-κB transcription factors activation promotes the gene expression of wide variety of cytokines such as IL-1, IL-6, IL-12, TNF-α, LT- α, chemokines, adhesion molecules, acute phase proteins, and inducible effector enzymes. Activation of NF-κB will induce the upregulation of Muscle Ring Finger 1 (MuRF1), a mediator of muscle atrophy and finally result in acute sarcopenia condition.[8]

On the other hand, Caspase-8 which was previously viewed exclusively as an apoptotic caspase, has now emerged as a master regulator of the three major cell death pathways, including apoptosis, pyroptosis, and necroptosis. Some studies found that SARS-CoV-2 induces caspase-8 activation to trigger cell apoptosis and directly activates some inflammatory factors such as pro-IL-1β. The IL-1β is then secreted through the SARS-CoV-2-triggered necroptosis pathway. The caspase-8-mediated apoptosis activation and inflammatory responses

in infected lung epithelial cells may induce downstream immune pathogenesis in the lung tissue. In line with the phenomenon, massive infiltration of inflammatory cells, necrotic cell debris, and pulmonary interstitial fibrosis were observed in the postmortem lung sections of fatal COVID-19 patients.[33] The caspase-8 is an initiator caspases that will activate the effector caspase-3 which are responsible for the cellular degradation and DNA fragmentation via a caspase-activated DNase (CAD) and will cause acute sarcopenia.

Physical Inactivity

Regional quarantine policies and activity restrictions for the purpose of reducing infection transmission also affect the mobility of patients, especially the elderly.[34] Bed rest is associated with decreased muscle quantity, strength and endurance. Bed rest reduces muscle protein synthesis by altering expression of ubiquitin ligases (MuRF-1 and MAFbx).[27] Kortebein et al. found that in 10 days of immobilization in elderly aged 67 ± 5 years, lower extremity mass was decreased by 6.3%, isokinetic strength decreased by 15.6%, ability to climb stairs decreased by 14%, and VO2 max decreased by 2%.[35] The molecular mechanisms that have been implicated in the development of disuse muscle atrophy are Atrogin-1/ Muscle atrophy F-Box (MaFbx)/ Muscle ring finger 1 (MuRF1) pathway, the IGF-1-AKT-mTOR pathway and the Myostatin pathway.[8]

MuRF1 is the only family member shown to be associated with muscle atrophy and to result in the attenuation of muscle loss when deleted. Similar to MuRF1, MAFbx expression is selective to striated muscle. Regulation of MuRF1 and MAFbx expression in skeletal muscle. Skeletal muscle atrophy is induced by a number of stressors. These stressors can lead to the increase in the expression of a number of transcription factors, including the forkhead transcription factors (FOXO1 and FOX03a), NF-κB transcription factors (p65, c-Rel, RelB, p52, and p50), CCAAT/enhancer-binding protein-β (C/EBPβ), kruppel-like factor-15 (KLF-15), and/or activation of the glucocorticoid receptor. These transcriptional mediators can bind to the promoter regions of either the MuRF1 or MAFbx genes, leading to an increase in their expression levels within the muscle. MaFbx and MuRF1 mRNA levels rise in rodent models of immobilisation and associated with increases in proteolysis but not inhibition of protein synthesis.[8]

Some studies has proved the importance of IGF-1 expression in the maintenance of muscle mass. When binding to IGF-1, IGF-1 receptor (IGF-1R) phosphorylates an intracellular adaptor protein insulin receptor substrate-1 (IRS-1), which recruits and phosphorylates phosphoinositide 3-kinase (PI3K) followed by Akt phosphorylation. The PI3K/Akt pathway plays a critical role in myotube hypertrophy, and activation of Akt in rat muscle prevents denervation-induced atrophy. Mammalian target of rapamycin (mTOR) is a downstream target of Akt. The IGF-1/Akt/mTOR pathway has been shown to be play major role in promoting muscle hypertrophy.[36] Immobilization is a negative regulator in IGF-1/Akt/mTOR pathway which inhibited during disuse (unloading)-induced atrophy. IGF-1 also affects protein synthesis via myostatin signalling.

Myostatin is a member of TGF-β family, its expression mainly from skeletal muscle, and negatively regulates muscle mass. IGF-1 and myostatin counteract each other. Myostatin signalling is activated by activin type II receptors (ActRIIA and ActRIIB) and activin type I receptors (ALK4 and ALK5), leading to phosphorylation of Smad proteins (Smad2 and -3). Smad2/3 form a complex with Smad4, which is also a co-mediator of the bone morphogenic protein (BMP) signalling pathway. When myostatin expression is downregulated, Smad4 becomes more available to BMP signalling and will cause muscle hypertrophy. Akt activation is downregulated by ActRIIB and balancing the activation of IGF-1, myostatin, and BMP pathways are critical to maintain muscle mass.[36]

Hormonal Dysregulation

After the age of 60 years, a variety of hormones that promote the growth of muscle cells, such as testosterone, growth hormone (GH), and Insulin-like growth factor 1 (IGF-1) are decreasing. Sex steroids such as estrogen and testosterone decline with aging and contribute to

muscle loss. Testosterone blocks the production of myostatin and ROS, inhibit apoptosis, potentiate myosatellite stem cells, accelerating muscle insulin growth factor-1 (IGF-1) expression, regulate skeletal muscle metabolism and increase muscle protein synthesis rate and muscle mass in elderly man. IGF-1 decrease by 50% by the age of 60. Growth hormone (GH) decrease in aging will also lower muscle mass.[37] Low expression of GH/IGF-1 level in elderly will cause a decrease of protein anabolism in skeletal muscle cells, which ultimately leads to changes in the structure and function of skeletal muscle cells. Study conducted by Ioannis Ilias et al (2021) found that IGF-1 was higher in Covid-19 survivors compared to non-survivors (-0.96 ± 1.89 vs -2.05 ± 2.48, respectively, p=0.030) but no significant differences were noted in GH between the groups. These results suggest that there might be an association between low IGF1 (and possibly GH) and poor outcome in patients with COVID-19.[38]

IGF-1 receptor (IGF-1R) binds to IGF-1and phosphorylates an intracellular adaptor protein insulin receptor substrate-1 (IRS-1), which recruits and phosphorylates phosphoinositide 3-kinase (PI3K) followed by Akt phosphorylation. The PI3K/Akt pathway will induce myotube hypertrophy and activation of Akt in rat muscle prevents denervation-induced atrophy. Activation of Akt activates mammalian target of rapamycin (mTOR) and its activity is tightly regulated by amino acid availability to the cells. Amino acids are necessary to build proteins, nucleic acid, glucose, and ATP in the body, mTOR activity is highly correlated with the anabolic or catabolic balance. The effect of Akt on mTOR is indirect, Akt inhibits the tuberous sclerosis complex (TSC) proteins 1 and 2, which act as a GTPase activating protein (GAP) to inhibit the small G protein Ras homolog enriched in brain (Rheb) which activates mTOR signaling. mTOR consist of two different protein complexes, the rapamycin-sensitive mTORC1 and the rapamycin-insensitive mTORC2. TORC2 is necessary for Akt phosphorylation and activation. mTORC1 phosphorylates S6 kinase (S6K), which in turn phosphorylates the ribosomal protein S6 and other factors involved in translation initiation and elongation, thus stimulating protein synthesis. The IGF-1/Akt/mTOR pathway is very important in promoting muscle hypertrophy. Therefore, decreased level of GH/ IGF-1 plays a key role in the loss of skeletal muscle mass.[39]

ROS, reactive oxygen species; CAD, caspase-activated DNase; DNA, deoxyribonucleic acid; Endo G. endonuclease G; AIF, Apoptosis-inducing factor; TNF, Tumor necrosis factor;

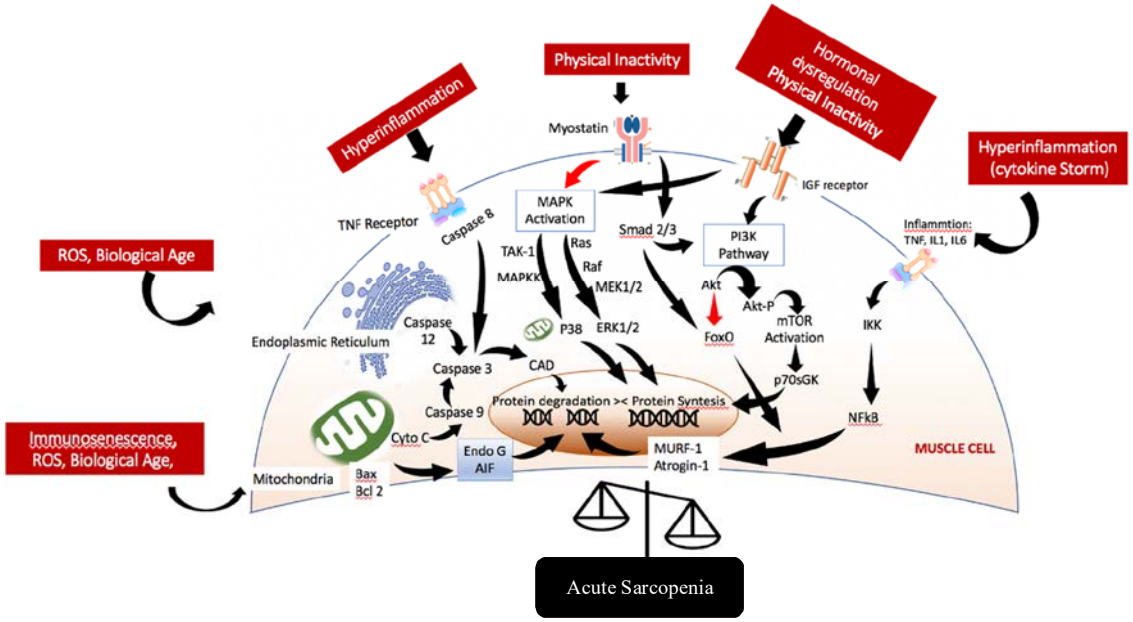

Figure 3. Proposed model of molecular mechanism of acute sarcopenia in elderly with COVID-19 infection.[8,16,30-32,36-39]

TAK-1, transforming growth factor-β-activated kinase 1; MAPKK, Mitogen-activated protein kinase kinase; MEK 1/2, Mitogen-activated protein kinase; ERK1/2, extracellular signal-regulated kinases; PI3K, Phosphoinositide 3-kinases; FoxO, The forkhead box O; Akt-P, Phosphorylated Akt; mTOR, mammalian target of rapamycin; IL, Interleukine; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; MURF-1, muscle RING-finger protein-1.

IMPLICATION OF ACUTE SARCOPENIA IN ELDERLY WITH COVID – 19

Decreased quality of skeletal muscles is the main cause of poor quality of life, immobilization, disability, falls, fractures, hospitalization, length of stay, hospital readmission, morbidity and mortality in the elderly. Hospitalization, even for a short period of time, is associated with an increased risk of nosocomial infection in sarcopenia patients and a significant decrease in muscle strength and functional capacity.[37]

ICU Admission

Acute sarcopenia is associated with an increased risk of ICU admission and mechanical ventilation. A study conducted by Giraudo et al., (2021) found muscle mass loss was a predictor of patients admitted to the ICU. Patients who lost muscle mass were significantly older (73.4±10 years) and with higher CRP values (71.5±71).[12] Low muscle mass on CT scan results is associated with higher risk of ICU admission and mortality.[40,11] Acute sarcopenia also consider as one of risk factors for difficulty in ventilator weaning.[11] Intensive Care Unit-Acquired Weakness (ICUAW) is a well-known complication following admission to the Intensive Care Unit (ICU). Most relevant risk factors that associated with ICUAW is the severity of underlying critical illness and inflammation. Both of these factor was present in elderly with COVID – 19.[8]

Length of Stay

Research conducted by Sousa et al., (2016) found that acute sarcopenia patients had a longer length of stay. Patients with sarcopenia are less likely to return home and also have longer time in bed.[31] The study by Martone et al., (2017) in hospitalized patients showed that the mean time of acute sarcopenia patients in bed was 5.1 days compared to 3.2 days in non-sarcopenia patients. Muscle protein synthesis is also impaired due to lack of nutrition and physical exercise.[41]

Frailty

Sarcopenia and frailty are two conditions that often coexist. Frailty is a multisystem organ decline characterized by an increase in the patient's susceptibility to stressors.[42] In frailty, there is a decline in the immune, metabolic, and neuromuscular systems. COVID-19 virus binds to ACE2 receptors present in various organs such as the lungs, heart, liver, kidneys, and intestines to enter human cells. COVID-19 patients experienced organ damage where 14% had respiratory failure, 15% had heart damage, 15.7% had liver damage, and 13.7% had kidney problems. Because of this organ damage, COVID-19 patients are prone to becoming frail, especially in elderly patients. Woolford et al., reported that COVID-19 patients had a 1.4 times higher risk in becoming frail.[43] Frailty was significantly associated with an increase in poor outcomes, mortality and morbidity, severity of COVID-19, likelihood of being admitted to the ICU, mechanical ventilation, and length of stay.[44] Research by Zhang et al., (2021) found that frailty was a predictor of mortality in COVID-19 patients. The prevalence of frailty is 51%, with HR 1.99 and OR 2.48.[42] Hewitt et al., (2020) studied frailty in COVID-19 patients and they found that frailty was detected in 49.4% of patients. The 7-day mortality rate increased in frailty patients with an OR of 1.22. Frailty is also associated with longer treatment.[45]

Malnutrition

COVID-19 affects patients of all ages, but has more severe clinical consequences in elderly patients. Some factors might be associated why the elderly with COVID-19 has higher chance to become malnourished. Morphine that is administered to relieve pain associated with breathing and to facilitate respiration will slow gastro-intestinal transit inducing nutritional related complaints like nausea and constipation. Dexamethasone in COVID-patients who require oxygen therapy to improve outcome, often

increase plasma glucose levels necessitating tailored nutrition and insulin therapy which can be a challenge in patients who are already diabetic. COVID-19 has a profound negative impact on nutritional status already before admission. This is proven in several studies showing that in 22% of the patients, mainly ICU patients, lost more than 5 kg extra body weight during hospital stay. It has been demonstrated that in-hospital malnutrition is associated with hospital length of stay (LOS), in-hospital mortality, and re-admission rate.[46] COVID-19 itself results in multiple nutrition-related problems such as changes in appetite, taste and energy expenditure and changes in taste that might further worsen the level of malnutrition.

Malnutrition and sarcopenia often coexist and develop clinically through a combination of decreased nutritional intake, weight loss, then decreased mass, muscle strength, and physical function. This syndrome is called Malnutrition-Sarcopenia Syndrome (MSS). Both conditions are independently associated with morbidity, mortality, decreased quality of life, rehospitalization, length of stay, and costs.[47] A study by Cederholm et al. found a significant difference in mortality after discharge from home between malnourished patients compared to good nutrition at 44% versus 18% respectively.[48] Community studies in patients with unexpected weight loss and low body mass index (BMI) had an increased risk of death at 3 years by 1.67 times.[49] A study by Newman et al. found that even 5% weight loss was a significant predictor of mortality in the elderly in the community.[50] Malnutrition is associated with a decrease in the functional capacity of treated patients based on Mini-Nutritional Assessment (MNA) values <24.[51] Malnourished elderly patients were more likely to continue treatment in nursing homes compared to returning home. This condition is also accompanied by disability, use of assistive devices, loss of muscle mass, risk of metabolic disease, and increased risk of falls and fractures.[47]

CONCLUSION

COVID-19 infection causes acute sarcopenia with various predisposing and precipitating factors such as inflammation, biological age, ROS, altered diet, physical inactivity, hormonal dysregulation and many more. Molecular mechanism of acute sarcopenia in elderly infected with COVID-19 is a complex process involving various molecular pathways. Immunosenescence, ROS, and biological age cause acute sarcopenia through endoplasmic reticulum and mitochondria stress and via caspase pathway. Hyperinflammation and cytokine storm requires IL-6, IL-1, NFkB and MURF-1 to induce acute sarcopenia. IGF-1 is the main pathway involved in acute sarcopenia due to hormonal dysregulation whereas physical inactivity has three different pathways to induce acute sarcopenia, they are Atrogin-1/ MaFbx/ MuRF1 pathway, the IGF-1-AKT-mTOR pathway and the Myostatin pathway. Sarcopenia conditions can also worsening COVID-19 infection and vice versa and leading to longer length of stay including treatment in the ICU, immune dysregulation, frailty conditions, and the occurrence of malnutrition.

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