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Chronic limb ischemia manifestation in COVID-19 infection: awareness and treatment in primary care

Sidhi Laksono[1,2*], Reynaldo Halomoan Siregar[3], and Hillary Kusharsamita[4]

ABSTRACT

Chronic limb ischemia (CLI) is a type of peripheral arterial disease (PAD) that is still underdiagnosed and undertreated despite the increasing incidence, thus becoming a global health burden. And CLI reflects the local manifestations of a lethal systemic disease — atherosclerosis. If left untreated, chronic limb ischemia can result in major limb loss. In this pandemic era, limb ischemia has become one of several clinical manifestations that occur in patients with COVID-19 infection. Systemic inflammation in COVID-19 infection, direct viral infection, hypercoagulable state, and hyperinflammatory response are responsible for damage to the arterial system, causing endothelial dysfunction. Diagnosing PAD has become a challenge especially in the early stage and in the asymptomatic phase. The untreated condition could lead to the development of CLI. The primary physicians in the primary health facilities hold an important role in the early diagnosis and management of patients with CLI symptoms or with risk factors of CLI, especially in patients who have experienced COVID-19 infection. Due to the limitation of diagnostic testing modalities at primary health facilities, the physician can assess the ankle-brachial index (ABI) to determine the presence of CLI. Management of the disease is different for every patient and is customized based on the other comorbidities. Risk factors should be controlled in order to achieve a better outcome. A good management strategy will improve the quality of life of the patient. This review will discuss the occurrence of CLI in COVID-19 infection.

Keywords: COVID-19, ankle-brachial index, chronic limb ischemia, management

[1]Head of Cardiac Catheterization laboratory, Department of Cardiology and Vascular Medicine,
RSUD Pasar Rebo, East Jakarta
[2]Faculty of Medicine, Universitas Muhammadiyah Prof. DR. Hamka, Tangerang
[3] Faculty of Medicine of Universitas Katolik Indonesia Atma Jaya
[4] Faculty of Medicine, Universitas Diponegoro, Semarang

***Correspondence:**
Sidhi Laksono
Faculty of Medicine,
Universitas Muhammadiyah Prof. DR. Hamka
Jl. Raden Patah No.01, RT.002/ RW.006, Parung Serab, Kec. Ciledug, Kota Tangerang, Banten 13460
Phone number: +622127564161
Email: sidhilaksono@uhamka.ac.id
ORCID ID: 0000-0002-2959-8937

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INTRODUCTION

Peripheral arterial disease (PAD) is becoming a burden for the health system globally. PAD is closely related to atherosclerotic disease. The disease has affected more than 200 million people around the world and causes 12-15% mortality in Europe.[1,2] In the United States, the disease affects 1.3% of men and 1.7% of women (ages 40-49 years). The prevalence was significantly increased in the older population with 29.5% of men and 24.7% of women older than 80 years.[3] Chronic limb ischemia (CLI) is a type of PAD that is underdiagnosed and undertreated because about 20-50% of the patients may be asymptomatic at the beginning.[4,5] The burden is even higher due to unawareness of the physicians (≥70%) that the diagnosis had already been established during PAD screening.[6] However, during the progression of the disease, CLI would manifest in several symptoms that are related to the impairment of the quality of life. CLI is mainly associated with the presence of diabetes mellitus, dyslipidemia, hypertension, smoking, and also older age. These risk factors would damage the arterial system, reducing the blood flow causing poor perfusion to the tissues.[7] Although the patient may experience mild symptoms, the prevention of further progression is crucial. The well-known severe form of CLI is critical limb ischemia. This manifestation could put someone at a higher risk of limb loss and cardiovascular disease.[8] Critical limb ischemia affects 12% of the adult population and is related to a quite high mortality rate, 25% at 1 year, and 60% at 5 years. The prognosis may become poorer for patients with critical limb ischemia, thus there is a need for establishing a rapid diagnosis and early management.[9] Critical limb ischemia is also more common in the older population.[10]

The ongoing spread of severe acute respiratory coronavirus syndrome-2 (SARS-CoV-2) has resulted in a coronavirus disease (COVID-19) pandemic, raising major challenges in all medical specialties. Limb and digit ischemia have recently been linked to COVID-19 infection. Systemic inflammation in COVID-19 infection may play a role in developing limb ischemia due to endothelial dysfunction related to the ACE2 receptor.[11] Moreover, critical limb ischemia remains a life-threatening disease that necessitates prompt treatment to prevent mortality and limb loss.[12] Diagnostic modalities and management strategies in the hospital are able to treat the patient thoroughly.[4] However, patients may come to the primary health facilities at the beginning to treat the symptoms. Due to the limited modalities in the primary health facilities, necessarily the physician should be able to perform the simple yet reliable examination that is needed to establish the diagnosis of CLI. A literature search was conducted from PubMed on topic-related articles from 2011 to 2020 using the keywords "COVID-19", "SARS-CoV-2", "coronavirus", and "chronic limb ischemia". All types of article such as observational studies, systematic reviews and meta-analyses, guidelines, and other narrative reviews were included. The present review will highlight the current knowledge on COVID-19 pathophysiology, with a focus on CLI.

DEFINITION OF CHRONIC LIMB ISCHEMIA

Chronic limb ischemia (CLI) is often also defined as critical limb ischemia, thus both share a common definition. The American Heart Association/American College of Cardiology (AHA/ACC) Guideline defines this disease as a chronic condition (≥14 days) with the characteristics of ischemic pain at rest, non-healing ulcers, and the presence of gangrene. These characteristics may occur in 1 or both legs with the presence of arterial occlusive disease objectively proven.[13] These symptoms are the result of poor peripheral perfusion caused by the chronic pathological process in the arterial system. Critical limb ischemia is also defined as a chronic limb-threatening ischemia (CLTI) by another guideline.[14] It affects 11.08% of the PAD population annually.[15]

PATHOPHYSIOLOGY OF LIMB ISCHEMIA IN COVID-19 INFECTION

The mechanisms underlying thrombosis in COVID-19 infection are not fully understood yet, although various mechanisms have been proposed, including direct infection of the virus to the vascular system, hyperinflammatory responses, and coagulation abnormalities.[16] In patients with COVID-19, there are higher levels of some hypercoagulability biomarkers such as D-dimer, fibrinogen, factor VIII, and antiphospolipid antibodies and lower protein C, protein S, and antithrombin levels. These abnormalities are related to peripheral arterial ischemia.[17] Along with an increased pro-inflammatory cytokine production (interleukin, tumor necrosis factor, interferon), these mechanisms will lead to the formation of microthrombi. COVID-19 infection result in higher levels of helper T lymphocytes, triggering interleukin-6 (IL-6) production, which is responsible for the production of acute-phase reactants such as C-reactive protein (CRP) and fibrinogen. Both CRP and fibrinogen cause hypercoagulopathy, leading to thrombosis.[18,19] Direct infection of SARS-CoV-2 through the ACE2 receptor (which is expressed in endothelial cells) and inflammatory cells induce endothelitis, which is characterized by disruption of the circulation.[20] Another well-known endothelial dysfunction-based mechanism is oxidative stress-mediated endothelial dysfunction (Figure 1), [21] Endothelial cells (ECs) are found mostly in the inner layer of blood vessels and are covered by pericytes, which help to maintain the vessel structure.[22] Depending on the tissues and muscles, ECs have various functions and structures. Controlling vascular permeability and regulating vascular tone are two widely known roles of ECs in body physiology homeostasis.[22] ECs can produce and release endothelial-derived relaxing factors such as nitric oxide (NO) and prostaglandin (PG), as well as contractile factors such as endothelin (ET), thromboxane A2 (TXA2), reactive oxygen species (ROS), and angiotensin II (Ang II), all of which play important roles in the control of vascular tone.[23] When activated, ECs secrete chemoattractants, cytokines, and adhesion molecules, resulting in increased blood vessel permeability.[22] In resting ECs, NO can suppress the synthesis of these molecules. NO has a direct effect on leukocytes, inhibiting them from activating into motile forms capable of penetrating tissues.[24] A dysfunctional endothelial response to damage or infection, on the other hand, cannot produce sufficient NO.[25] COVID-19 patients have been shown to have a nitric oxide deficiency.[26] As a result, a decrease in NO bioavailability always indicates endothelial dysfunction. Reduced endothelial nitric oxide synthase (eNOS) production, a loss of eNOS substrates, eNOS inactivation, and accelerated NO degradation are thought to induce a decrease in NO bioavailability.[27] As previously mentioned, the serum level of NO in COVID-19 patients is reduced, suggesting oxidative stress (OxS).[26] Oxidative stress plays an important role in the development of a variety of arterial diseases. According to several studies of OxS in PAD, there is a series of reactive oxygen species (ROS) formation, mitochondrial injury, endothelial dysfunction, and selective damage to muscle myofibers. Thus, OxS functions as a critical mechanism in both the creation and progression of PAD.[24]

RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF CHRONIC LIMB ISCHEMIA

The presence of CLI is highly associated with the atherosclerotic process which is related to several risk factors such as smoking, diabetes mellitus, dyslipidemia, and hypertension. A study by Joosten et al. [28] showed that smoking is one of the leading risk factors for CLI, affecting 44% of the population. An active smoker has a 4.3 times higher risk for developing symptomatic PAD (including CLI) while a former smoker has a 2.3 times higher risk.[29] While it is clear that an active smoker has an increased risk of developing

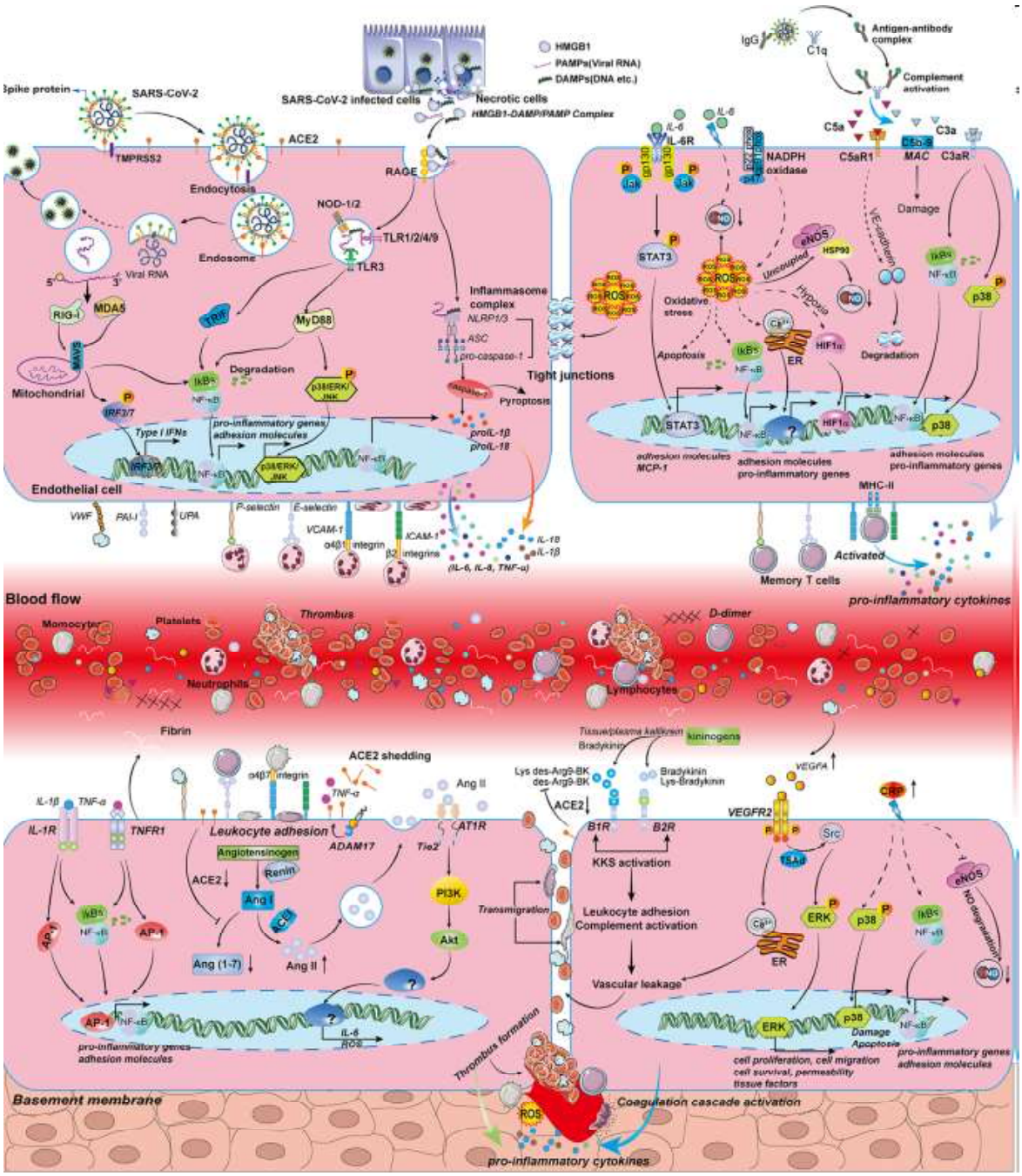

Figure 1. Mechanisms of endothelial activation and dysfunction during COVID-19. [21]

PAD, studies on the passive smoker are lacking. However, two studies showed a similar association between passive smoking and PAD. The first study showed that 2.4% (134 of 5686) of the population who never smokes, had PAD.[30] The second study showed that 3.2% of the population had intermittent claudication.[31] Diabetes mellitus increases the risk of PAD. Increased HbA1c level in diabetic patients also accounts for a 26% risk for PAD. [2] Diabetic patients with PAD are also at a 5-times higher risk of amputation.[32] Infection rates are higher in the diabetic patients and this can increase the possibility of amputation in the patients.[33]

Hypertension is an important risk factor after smoking and diabetes. Itoga et al. [34] found that a systolic blood pressure of ≥160 mmHg was related to a 21% higher risk of PAD. However, this study

also found a relation between lower systolic blood pressure (< 120 mmHg) and PAD. The result of the Itoga study is different from other cohort studies that found an association of a higher but not a lower systolic blood pressure with the risk of PAD.[35,36] The difference might come from the fact that Itoga et al.[34] conducted their study on a population that had hypertension and other cardiovascular risk factors, while the other two studies were conducted in healthy populations.

Dyslipidemia is associated with the progression of PAD and its complication. The increased ratio between total cholesterol and high-density lipoprotein cholesterol (HDL-C), triglyceride-rich lipoprotein, and also a decreased HDL level are associated with the incidence of PAD. [37]

DIAGNOSTIC CONFIRMATION OF CHRONIC LIMB ISCHEMIA IN PRIMARY CARE

Chronic limb ischemia is diagnosed based on the clinical condition, and supporting investigations. While some cases might need advanced imaging modalities, the initial examination is important and can be done by the primary physician at the primary health care facility.

History taking

The primary physician must address the related signs and symptoms and also risk factors. The patient may have symptoms of claudication, pain at rest, walking impairment, and even ulcers. Claudication is defined as pain that occurs with activity or exercise and resolves after 10 minutes of rest. It usually includes pain in the hip, buttock, calf, thigh, and foot. [39] The ischemic rest pain is usually felt in the forefoot and metatarsal area.[4]

Physical examination

In the CLI suspected patient, assessment of the arterial system of the limb is very important. The physician must palpate and address any abnormal pulses of the arteries (femoral, popliteal, dorsalis pedis, and posterior tibialis).[4] The absence of dorsalis pedis pulsation might happen in 12% of patients, but the absence of a posterior tibial pulse is always abnormal. Other physical findings are audible bruits, nonhealing wounds or ulcers, gangrenous tissue, pallor at elevation, delayed capillary refill, and cool limbs. [4,9] Besides the examination of the affected limb, we must also examine the blood pressure on both arms to evaluate if there is subclavian artery disease. A 20 mmHg difference between both arms is suggestive for subclavian disease.[40,41]

Diagnostic testing

Suspicion of CLI must be supported with the presence of occlusive disease. However, there are limitations in the primary health care facilities to perform a more advanced examination such as treadmill test, duplex ultrasound, computed tomography angiography/magnetic resonance angiography (CTA/MRA). The resting ankle-brachial index (ABI) is an initial diagnostic test that can be done to confirm CLI in primary health facilities. ABI is the highest systolic blood pressure of the foot (dorsalis pedis or posterior tibial) divided by the highest systolic pressure of the arm.[42] The resting ABI is defined as abnormal (≤0.90), borderline (0.91-0.99), normal (1.00-1.40), and noncompressible (>1.40).[43,44]

Table 1. Risk factors of CLI[38]

Age ≥ 65 years old
Age 50-64 years old along with risk factors of atherosclerosis: diabetes mellitus, hypertension, cigarette smoking, or dyslipidemia.
Age < 50 years old with diabetes mellitus and an additional risk factor for atherosclerosis
Atherosclerotic disease in other vascular beds

An ABI score of ≤0.90 shows reduced peripheral blood flow and is suggestive for the diagnosis with 95% sensitivity and 99% specificity. ABI <0.4 is indicative of severe ischemia. A lower ABI indicates a more severe ischemia.[45] However, an ABI of more than 1.40 may be associated with calcified, rigid, and non-compressible arterial walls; a risk of having cardiovascular events, and impairment of quality of life.[46,47] It is recommended to measure ABI in patients with a history and physical examination suggestive of CLI and in patients with an increased risk for CLI without features in the history and physical examination.

MANAGEMENT STRATEGY OF CHRONIC LIMB ISCHEMIA

Once the diagnosis of CLI is established, the management strategy should be initiated to prevent complications, reduce the risk of cardiovascular events, and improve the functional capacity. The early management strategy in primary health care includes pharmacological therapy and lifestyle modification.

Pharmacological therapy

The treatment using pharmacological agents in patients with CLI is customized, based on the comorbidities (hypertension, dyslipidemia, diabetes mellitus). Antiplatelet therapy using aspirin (75-325 mg/day) or clopidogrel (75 mg/day) can be given in symptomatic patients. (Class: I, Level of evidence: A). Antiplatelet therapy is indicated as secondary prevention in patients at high risk of cardiovascular events.[13] In PAD patients who are asymptomatic, the use of aspirin may reduce the risk of cardiovascular events even though a systematic review conducted by Schmit et al.[48] showed no benefit of aspirin in asymptomatic PAD patients. The use of clopidogrel is highlighted in a study by Katsanos et al.[49] where clopidogrel was able to reduce the risk of major adverse cardiovascular events (MACE). Clopidogrel can be used as a single therapy for PAD patients to prevent the risk of bleeding if combined with aspirin. In COVID-19 infection, early medical therapy to revascularize can be done by administering anticoagulants with therapeutic doses of heparin or enoxaparin. However, patients should be referred to hospitals with availability of tissue plasminogen activator (thrombolytic therapy) and interventional facilities if needed.[11]

Other comorbidities must be treated according to the guidelines. Statin therapy is indicated in all patients with PAD (asymptomatic and symptomatic) and it is associated with reduced cardiovascular events and mortality. This is supported by the data from the Reduction of Atherothrombosis for Continued Health (REACH) registry which showed a 17% reduction of the adverse cardiovascular events. In CLI patients, the low-density lipoprotein cholesterol (LDL-C) should be maintained at <70mg/dL or ≥50% from the initial LDL-C levels (if baseline: 70-135 mg/dL).[14,50,51] For the hypertensive condition, administration of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) are also associated with a decreased cardiovascular events with the goal to maintain the blood pressure at <140/90 mmHg.[14] In diabetic patients, the HbA1C levels should be maintained at <7% to prevent further complication.[52]

Symptomatic treatment for pain is also important to improve the quality of life. Physician could prescribe paracetamol or non-steroidal anti-inflammatory drugs (NSAID) to eliminate the pain, although those medications might not be sufficient.[47,53] However, we have to be aware giving the NSAID because it can disrupt the wound healing process.[54,55]

Lifestyle modification

Smoking has been a major risk factor in CLI development. Smoking cessation must be advised to the patient. Smoking cessation is associated with smoking abstinence and therefore decreases the risk of CLI.[56] Stopping of smoking will lower the mortality of the patient and also will increase amputation-free survival.[57] Some additional therapy could be given to help the smoking

cessation program, such as varenicline, bupropion, and nicotine replacement therapy.[13] Physical activity is important for CLI patients because it reduces the role of risk factors in the progression of the disease. It is recommended for patients to do structured exercise therapy, which is also able to reduce the claudication symptoms. Several studies were able to show the beneficial effect of exercise on claudication.[58,59] Structured exercise therapy (SET) can be done in a health facility or at home. The SET program at the health facility (Class: I, Level of evidence: A) includes an intermittent walking exercise which is supervised by the healthcare provider. The exercise is performed with a minimum duration of 30-45 minutes/session, with 3 sessions/ week for a minimum of 12 weeks. The patient can do the self-directed SET program at home or the SET can be community-based (Class: IIa, level of evidence: A) with the guidance and exercise regimen prescription from the healthcare provider.[13] Patients who do not have improvements after therapy and even experience limb-threatening conditions should be referred to the advanced health facilities to undergo revascularization therapy and wound management by the wound specialist team.[60-62]

Patients with chronic limb-threatening ischemia (CLTI) need a more adequate approach with a multi-specialist team. The goals are: to control the symptoms, increase the quality of life, and prevent any complications (medical goals); revascularization to preserve the limb (interventional goal); and proper monitoring after treatment (surveillance goal). Primary care physicians have an important role and should be able to give care to achieve the medical goals.[63]

PREVENTIVE STRATEGY OF CLI

Reducing the risk of CLI progression is the goal especially in the vulnerable population. Physical activity can prevent the development of the disease. It is related to its effect on controlling the atherosclerotic factor in the patient. The benefit of physical activity is also related to its function on increasing nitric oxide, thus preventing endothelial dysfunction.[64] Other preventive strategies include the maintenance or control of lipid level, blood pressure, and also blood glucose level.[65]

CONCLUSION

Endothelial dysfunction due to COVID-19 infection puts patients at higher risk for developing CLI. Resting ABI is a reliable diagnostic test for patients with suspected CLI. An ABI of ≤0.90 is suggestive of the presence of ischemia. The management includes pharmacological therapy and lifestyle modification to reduce cardiovascular risks and prevent further complications.

CONFLICT OF INTEREST

There is no potential conflict of interest

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CONTRIBUTORS

SB contributed significantly in writing the review. RH and HK all wrote the revision. All authors participated in identifying the relevant studies for inclusion. manuscript. All authors read and approved the final draft.

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