Prognostic Factors and Predictors of Mortality in Patients with Critical Limb Ischemia: A Current Clinical Perspective

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Abstract

Critical limb ischemia (CLI) is an end-stage of peripheral arterial disease (PAD). Mortality, limb loss, pain, and diminished health-related quality of life are affected by CLI complications. 20 to 50% CLI Mortality is intensely observed within the first six months to five years of CLI diagnosis, respectively. Prognostic treatments, including utologous bone marrow mononuclear cell implantation (BMMNCI), Low-intensity pulsed ultrasound (LIPUS) technology, and medication therapy using Cilostazol, are available. In addition, required prognostic factor such as timely access to medical care can control the death. Impaired mobility, old age, low BMI, CKD (end-stage), T2DM, COPD (oxygen-dependent), HF, smoking, high Wound, Ischemia, and Foot Infection (WIfI) are the additional predictors for CLI diagnosis. Due to the poor survival and prognosis, it is crucial to identify the prognostic factors that will lead to better clinical benefits, including amputation-free survival rate and improved quality of life. This review highlights the current clinical perspective on the prognostic factors and predictors of mortality in CLI patients.

Significance | PAD and its impact in physical impairment or mortality.

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Introduction

Peripheral Arterial Disease (PAD) in the legs or lower extremities is the narrowing or blockage of the vessels that carry blood from the heart to the legs. Circulatory impairment in the lower extremities often leads to the development of a chronic vascular condition known as peripheral arterial disease (PAD) (Duff et al., 2019). Approximately 7-8 million individuals are affected by PAD in the United States, while the global impact targets nearly 200 million people (Beckman and Creager, 2014). Although it may appear asymptomatic in the initial stages (Duff et al., 2019); however, critical limb ischemia (CLI), which is considered as the end-stage of PAD, imposes a greater risk of lower limb loss and mortality in patients (Akagi et al., 2018). In addition, the basal metabolic demands in about 2-3% of the PAD patients are not sustained due to inadequate arterial perfusion; this eventually results in the development of critical limb ischemia (Beckman and Creager, 2014).

The "Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)" described CLI through the presence of chronic ischemic pain at rest, gangrene, or ulceration, which attributes to an arterial occlusive disease (Uccioli et al., 2018). Nearly 12% of the adult population are affected by CLI, with men

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Table 1. Prognosis of critical limb ischemia based on different treatment modalities

Author & Year	Treatment Modalities	Prognosis/Outcome
Revascularization		
Akagi et al., 2018	Surgical revascularization	The prognosis did not improve after surgical revascularization. So conservative therapy should also be considered before conducting endovascular therapy or bypass surgery
Majmundar et al., 2022	Endovascular revascularization and surgical revascularization	Findings indicated that endovascular revascularization had a better safety profile than surgical revascularization, and it was associated with an 18% higher risk of major amputation at 6 months and a 17% lower risk of in-hospital safety outcomes, but there were no evident differences in mortality
Rutherford et al., 1997	Surgical technique, antecedent cardiovascular risk factors, presentation and duration of the acute episode, and the occlusion site	These prognostic factors had a major impact on surgical revascularization by thromboembolectomy or bypass
Cell Therapy		
Kondo et al., 2018	Autologous bone marrow mononuclear cell implantation (BMMNCI)	It lead to an improved rate of major amputation free survival among the CLI patients
Idei et al., 2011; Mohamad Yusoff et al., 2019	Autologous BMMNCI	It has shown promising effects in the prevention of amputation and improvement in the survival rate
Lozano Navarro et al., 2022	Mesenchymal stem cells (MSCs)	This particular cell therapy has emerged as an attractive therapeutic agent in CLI treatment, due to its role in tissue regeneration and immunomodulation
Shimizu et al., 2022	Adipose-derived stem cells (ADSCs)	Implantation of autologous ADRCs was found to be safe and effective for the achievement of therapeutic angiogenesis. It resulted in improved major amputation-free survival rate in patients with no-conventional option against CLI
Gene Therapy		
Barć et al., 2022	Two-Stage Gene Therapy (VEGF, HGF and ANG1 Plasmids)	The effectiveness of gene therapy with the growth factors was evaluated among patients with CLI in the course of complicated DM, and it showed significant wound healing with minimal side effects
Pharmacotherapy		
Furuyama et al., 2018	Medication therapy using cilostazol (selective inhibitor of phosphodiesterase-3)	It played a significant role in the ischemic ulcer healing and improving of the amputation free survival rate
Varu et al., 2010	Statins, antiplatelet drugs, and β-blockers	It has been reported that statin use was associated with improved survival in CLI patients 1 year after revascularization, while antiplatelet medication and β-blockers had no effect on the survival
Additional Factors/ Interventions		
Fagundes et al., 2005	Interval for medical care and attention	Access to medical care was found to be the most important and modifiable prognostic factor for death or amputation
Harwood et al., 2021	Heat therapy	There appears to be some potential benefit to heat therapy as either an alternative or an adjunctive therapy for patients with intermittent claudication due to PAD
Mohamad Yusoff et., al 2021	Low-intensity pulsed ultrasound (LIPUS) technology	LIPUS is a non-invasive procedure for therapeutic angiogenesis, and it has shown promising effects in reducing the incidence of major amputation rate among CLI cases
Soga et al., 2014	Age, ambulatory status, body mass index (BMI), left ventricular ejection fraction (LVEF), cerebrovascular disease, haemodialysis, and tissue loss	These were the independent prognostic factors of the 2-year life expectancy (2YLE) of CLI patients

Table 2. Predictors of mortality in patients with critical limb ischemia

Author & Year	Predictive Markers	Historical Impact
Azuma et al., 2019	Old age, impaired mobility, low BMI, renal failure, HF, and high Wound, Ischemia, Foot Infection (WIfI) grade	These risk factors were analyzed to be the independent predictors of all-cause mortality among CLI patients undergoing revascularization
Soga et al., 2014	Age, ambulatory status, body mass index (BMI), left ventricular ejection fraction (LVEF), cerebrovascular disease, haemodialysis, and tissue loss	These were the independent factors that influenced the 2-year life expectancy (2YLE) of CLI patients
Brahmanandam et al., 2009	Advancing age, African-Americans, female gender, highest income quartile, private hospital care, longer stay in hospital, and amputation or debridement	These were independent predictors for the increased utilization of healthcare services after lower extremity bypass (LEB) in CLI patients
Beckman & Creager, 2014	Nursing home residence, inability to leave the home, dementia, and ambulation inability after revascularization	It has been recommended that these important predictors should be considered before initiating the plan of treatment
Fagundes et al., 2005	Duration of occlusion >24 hours and diabetes	Both were significant factors for death or amputation within 30 days in the logistic regression model
Kobayashi et al., 2015	Non-ambulatory status and older age (>75 years)	The study reported that these can be predictors of death even after complete wound healing post endovascular therapy
Kuoppala et al., 2008	Ischemic heart diseases and foot ulcers	It resulted in higher long-term risks for amputation and mortality
Roijers et al., 2020	Age, physical impairment, staying in a nursing home, and the physical status classification by American Society of Anaesthesiologists (ASA)	These predictive markers showed the highest association with increasing mortality in CLI patients
Simons et al., 2019	Age above 80 years, end-stage chronic kidney disease, oxygen-dependent chronic obstructive pulmonary disease, and bedbound status	All these factors were the independent predictors of mortality in patients with CLI
Uccioli et al., 2018	CVDs such as coronary artery disease and cerebrovascular arterial disease	An increased rate of mortality was noted due to the accompanying cardiovascular diseases in CLI patients

women. The age-dependent prevalence indicates that almost 20% of adults above 70 are diagnosed with CLI (Davies, 2012). While the estimated annual incidence is about 500 to 1000 new cases per million people in developed nations. The number of new CLI cases is gradually rising due to the subsequent increase in cardiovascular risk factors (Duff et al., 2019).

CLI is not only associated with recurrent lower extremity rest pain, ulceration, and gangrene but is also linked to an increased amputation rate, mortality, and adverse cardiovascular events (Duff et al., 2019). Therefore, it establishes a substantial healthcare burden on the patients and clinicians (Teraa et al., 2016). Furthermore, CLI patients often suffer from multiple comorbidities and poor systemic illnesses, which leaves them with limited treatment options (Akagi et al., 2018). Percutaneous transluminal angioplasty and surgical bypass, combined with pharmacological treatment, are the common therapeutic practices for revascularization procedures and symptom management in PAD patients with chronic CLI (Chowdhury, 2017). Drug-eluting stents play a major role in the reduction of restenosis. However, the optimal correction of peripheral vasculatures cannot be performed as surgical bypass, angioplasty, and stenting are only done in the major arteries (Chowdhury et al., 2020). Surgical or peripheral endovascular therapy (EVT) helps to provide adequate blood flow to the extremities. Nevertheless, minor or major amputations are being performed when less invasive methods cannot be attempted or failed to treat patients (Duff et al., 2019). Globally, almost 90% of amputations occur due to CLI, especially in patients aged above 50 years (Chowdhury, 2017).

Unacceptably high amputation rates pose a disproportionate risk to several demographic and socioeconomic groups (Duff et al., 2019). Restrained under the poor clinical prognosis, reduced survival rate, and burdened quality of life, this study area necessitates a current review of the literature. Hence, this review concisely highlights the current clinical perspective on the prognostic factors and predictors of mortality among patients with critical limb ischemia.

Prognosis

Over the years, the prognosis regarding limb salvage and survival among PAD patients has improved (Teraa et al., 2016). Although amputation rates are declining, but are still being performed despite the current advancements in revascularization therapies. CLI patients require increased healthcare services after getting discharged from the hospital. The previous study reported that advancing age, African-Americans, female gender, highest income quartile, private hospital care, longer stay in the hospital, and amputation or debridement were some of the major independent predictors for increased utilization of healthcare services among the patients (Varu et al., 2010).

Previous literature emphasizes that patients with ischemic heart disease (IHD) and foot ulcers face higher long-term risks for amputation and death (Kuoppala et al., 2008). In Japan, Kondo et al. (2018) found that the utilization of autologous bone marrow mononuclear cell implantation (BMMNCI-I) is linked with an increased rate of major amputation free survival in CLI patients. Few other studies (Idei et al., 2011; Mohamad Yusoff et al., 2019) have also magnified the significance of autologous BMMNCI implantation in preventing the amputation and improving the

survival among CLI cases. However, some patients can experience long-term survival with conservative therapies only. Akagi et al. (2018) reported that the prognosis among CLI patients did not improve after surgical revascularization. Therefore, conservative therapy should also be considered before conducting EVTs or bypass surgery (Akagi et al., 2018). Furuyama et al. (2018) found that medication therapy using cilostazol (selective inhibitor of phosphodiesterase-3) plays a major role in ischemic ulcer healing and improving the amputation-free survival rate; while no cilostazol use and IHDs are significantly related to poorer prognosis.

Several prognostic factors, including surgical technique, antecedent cardiovascular risk factors, presentation and duration of the acute episode, and the occlusion site, may impact the surgical revascularization by thromboembolectomy or bypass (Rutherford et al., 1997). The most significant and modifiable prognostic factor for mortality or amputation in CLI patients is timely access to medical treatment (Fagundes et al., 2005). Other factors (e.g., nursing home residence, inability to leave home, and dementia) related to ambulation inability after revascularization are important predictors that should be considered before deciding the treatment plan (Beckman and Creager, 2014).

Soga et al. (2014) identified the prognostic factors of 2-year mortality among CLI patients and evaluated the 2-year life expectancy (2YLE) and the aetiology of death. In most cases, death was caused due to the presence of cardiovascular events and infections. Age, ambulatory status, body mass index (BMI), left ventricular ejection fraction (LVEF), cerebrovascular disease, haemodialysis, and tissue loss were the independent prognostic factors for 2YLE. Furthermore, a 2YLE score was calculated using the hazard ratios of these prognostic factors that helped identify the CLI patients with poor prognoses and their suitable treatment options (Soga et al., 2014). According to Khaira et al. (2017), patients presenting with both CLI and heart failure (HF) tend to show a poor 5-year survival rate, despite the extent of impairment in the left ventricular systolic function. However, there were no significant differences in 5-year freedom from major amputation or freedom from major adverse limb events among the CLI patients with or without HF (Khaira et al., 2017).

Mortality

Mortality in CLI is dramatically high as 20% of the patients die within the first 6 months of diagnosis, and only 50% surpass to 5 years (Akagi et al., 2018; Teraa et al., 2016; Uccioli et al., 2018). In contrast, the mortality rate among non-revascularizable or non-treatable CLI patients vary from 10-40% (Teraa et al., 2016). The increased mortality rate is mostly due to accompanying cardiovascular diseases, such as coronary artery disease and cerebrovascular arterial disease (Uccioli et al., 2018). In addition, the survival and prognosis of limb preservation are often poor among non-treatable CLI patients with a higher risk of lower limbs amputation in 10%-40% of cases at 6 months (Teraa et al., 2016; Uccioli et al., 2018).

A recent study by Simons et al. (2019) analyzed the independent predictors of death among a large cohort of chronic limb-threatening ischemia (CLTI) patients who underwent endovascular intervention and infrainguinal bypass. The independent predictors of mortality correlated with age above 80 years, end-stage chronic kidney disease, oxygen-dependent chronic obstructive pulmonary disease, and bedbound status (Simons et al., 2019). While another study reported that non-ambulatory status and older age (>75 years) could be the predictors of death even after complete wound healing post-endovascular therapy (Kobayashi et al., 2015). Similarly, Azuma et al. (2019) identified old age, impaired mobility, low BMI, renal failure, HF, and high Wound, Ischemia, and Foot Infection (WIfI) grade as independent risk factors for all-cause mortality in CLI patients undergoing revascularization. Their predictive model based on the preoperative risk factors further revealed that cystatin C-based estimated glomerular filtration rate, LVEF, and cholinesterase levels were additional independent risk factors, though it lacked predictive accuracy due to time-dependent receiver operating characteristics curve and requirement of net reclassification improvement (Azuma et al., 2019). Furthermore, a clinical study by Roijers et al. (2020) investigated the 6-month mortality among elderly patients and concluded that age, physical impairment, staying in a nursing home, and the physical status classification by American Society of Anaesthesiologists (ASA) have the highest association with increasing mortality. While another recent study that assessed factors impacting mortality within 1-year post endovascular revascularization found that the duration of diabetes, anaemia, and smoking were all linked to a greater risk of death in type 2 diabetes mellitus (T2DM) patients with CLI (Yunir et al., 2022). In Japan, Mohamad Yusoff et al. (2021) conducted a pilot trial to investigate the efficacy of low-intensity pulsed ultrasound (LIPUS) technology in treating CLI. Although there were no significant differences in mortality-free survival rates among the control and LIPUS groups, the overall amputation-free survival rate was significantly higher in the LIPUS group. Hence this study (Mohamad Yusoff et., al 2021) indicates that LIPUS is a non-invasive procedure for therapeutic angiogenesis and can be beneficial in mitigating the incidence of major amputations among CLI patients.

Concerns and Recommendations

Critical limb ischemia is significantly associated with high mortality, limb loss, pain, and diminished health-related quality of life; thus, contributing to a critical healthcare burden. The estimated prevalence of CLI has been reported to be the highest among the three developed regions in the world and includes USA

(2,595,676), Europe (2,551,917), and Japan (1,019,876) according to the pooled data from a meta-analysis (Biancari, 2013). Nevertheless, due to inadequate population-based statistics, it is challenging to precisely estimate the prevalence of CLI globally and take necessary measures, particularly in developing nations (Fereydooni et al., 2020). In fact, in community settings and tertiary care facilities, the incidence rates of risk factors, complications, and mortality of CLI may be overestimated due to the limitations in large clinical databases and registries (Fereydooni et al., 2020). Therefore, more systematic and well-coordinated, digitalized data repositories are required to address the CLI patients' needs and store patient-management information.

In addition, CLI patient management may vary according to ethnic origin, leading to different outcomes such as revascularization or amputation. Therefore, understanding the risks of clinical CLI among the at-risk population might help to determine the best course of treatment action (Baser et al., 2013). Thus, keeping the at-risk population in mind and specifically correlating the predictors of CLI mortality, individualized management interventions should be implemented since the outcome event risk varies from person to person.

Revascularization with surgical bypass or endovascular intervention has been considered as the cornerstone of CLI treatment. Yet optimal strategies for deciding the best CLI treatment plans, especially for individuals who favor open and percutaneous procedures, are still insufficient (Levin et al., 2020). Hence effective therapeutic measures should focus on attenuating amputation-related mortality, mitigating the cardiovascular risk parameters, preserving limb viability, and promoting favorable long-term prognosis for all CLI patients. Besides, early diagnosis and public education may also be essential for successful therapeutic outcomes (Fereydooni et al., 2020). Thus more educational resources on CLI and targeted awareness platforms should be engaged at different community levels so that early identification of PAD can be initiated.

Conclusion

Due to these patients' poor survival and prognosis, it is important to identify the prognostic factors that may lead to better clinical outcomes, including amputation-free survival rate and improved quality of life. Hence this review highlighted the importance of prognostic factors and predictive markers in relevance to CLI mortality. Treatment modalities such as BMMNCI and LIPUS that led to promising prognostic outcomes involving amputation rate reduction and therapeutic angiogenesis promotion were reported in this review. Furthermore, several clinical characteristics significantly linked to increased mortality, such as diabetes, ESRD, HF, COPD, cardiovascular diseases, low BMI, non-ambulatory status, and high WIfI grade, were mentioned. In addition, the importance of demographic factors such as increasing age, female gender, African ethnicity, smoking, and lower income quartile was also highlighted.

Using prognostic and predictive models in the decision-making process would further enable clinicians to provide better and improved treatment modalities for the CLI patients. However, the decision to evaluate who might benefit from a surgical or endovascular therapy remains on the procedural morbidity and mortality rather than on the expected survival rate. Therefore, the factors above should be considered to identify the at-risk individuals for mortality and estimate the chances of clinical success.

Author Contributions

The conceptualization process involved SH and MC. SH, MC, and SM surveyed literature. SH, MC, and SM did manuscript drafting and editing. YDS and YH performed critical review, validation, and supervision. All authors have read and agreed to the published version of this manuscript.

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The authors have no conflict of interest

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