The need for improved risk stratification in chronic critical limb ischemia

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Vascular surgeons are well acquainted with chronic critical limb ischemia (CLI), the most severe manifestation of peripheral arterial disease, with patients presenting with ischemic rest pain or ulcerations, or both. Epidemiologic data predict a burgeoning epidemic of CLI within the United States, commensurate with the increasing incidence and prevalence of atherosclerotic risk factors, especially age and diabetes. Untreated, the risk of major amputation (above the ankle) or death, or both, ranges between 20% and 40% at 1 year. Current open and endovascular therapies have imperfect results, diverse treatment options, and recommendations that are often conflicting and confuse physicians, industry, and patients alike. The best treatment options are ideally evaluated by prospective, randomized controlled trials. However, these have proven impractical in CLI because the rapid evolution of devices and techniques has outstripped the ability to measure outcomes and compare treatment options. Alternatively, risk-stratifying models have been proposed to allow physicians, patients, and industry to objectively evaluate new therapeutics and devices as they evolve. These models are developed from prospective cohorts to identify and quantify variables that can subsequently predict outcome in individual patients. The risk stratification models can also compare CLI outcomes between physicians and institutions, supporting quality assessments, and compensation decisions within Accountable Care Organizations under the Affordable Health Care Act (ACA). Widespread adoption of risk-stratification schemes has yet to occur, despite the critical need for such a tool in CLI, because present models lack optimal predictive ability and generalizability. The passage of the ACA amplifies the importance of developing an improved risk-stratification tool to ensure equitable quality assessments and compensation. This review presents current risk-stratification models for CLI with a summary of the respective strengths and limitations of each. Future research is needed to simplify and improve the accuracy and generalizability of risk stratification in CLI. (J Vasc Surg 2014;60:1677-85.)

Chronic critical limb ischemia (CLI) is the most severe manifestation of peripheral arterial disease (PAD) and encompasses all patients with symptoms of chronic rest pain, ulcerations/gangrene, or both, with concomitant objective evidence of arterial insufficiency. This includes all patients at Fontaine stages III and IV and Rutherford classes 4 to 6.[1-3] The term CLI was initially coined in the early 1980s and was initially intended to describe patients with arterial insufficiency, rest pain, or gangrene in the absence of diabetes.[4]

Untreated, CLI portends a grim prognosis, with up to 40% of patients requiring a major amputation (either an above-the-knee or below-the-knee amputation) ≤1 year of diagnosis.[5] At 5 years, patients with symptomatic PAD have a 20% to 30% risk of myocardial infarction, stroke, or death,[1] with CLI patients at the higher end of the spectrum. Survival of CLI patients at 1 year is similar to those with stage IV malignancies, ranging between 10% and 40%.[1]

Epidemiologic data predict a burgeoning epidemic of CLI within the United States (U.S.) Current estimates of the incidence and prevalence of CLI vary, with the most consistent approximations of the incidence ranging between 500 and 1000 new cases/year/million in an American or Western European population.[1] This likely underestimates the true incidence and prevalence of disease in the U.S. due to the frequent underdiagnosis of PAD.[6]

Moreover, the population is growing, with an increasing proportion of the population aged >65 years. By 2030, an estimated 20% of the population will be aged >65 years, which is double the current proportion of people aged >65 years.[7] Combined with the increasing incidence and prevalence of atherosclerotic risk factors, especially diabetes and obesity,[8] the current and projected incidence and prevalence of CLI is likely significantly higher than published estimates.

PERSISTENT SUBOPTIMAL OUTCOMES IN CLI

Outcomes of interventions for CLI, unfortunately, remain imperfect, magnifying the significance of the looming epidemic of CLI. Summarized results of prospective randomized data of open surgical bypass for CLI show that ~25% of patients fail to survive with an intact limb at 1 year from the infrainguinal revascularization attempt (Table I).[2,9-12] Less than 15% of patients ultimately achieve the ideal surgical result of an uncomplicated bypass,

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Table I. Summarized results of open infrainguinal bypass (*IAB*) for chronic critical limb ischemia (*CLI*)[a]

First author	*Journal*	*Year*	*Design*	*No.*	*Main findings*
Adam[11]	*Lancet*	2005	PRCT comparing IAB vs angioplasty in CLI at 5.5 years	452	12-month AFS: 68% in each arm
Conte[9]	*J Vasc Surg*	2006	PRCT comparing IAB performed with ex vivo vein graft treatment vs placebo in CLI	1404	12-month AFS or intervention-free survival: 50.1% vs 48.6%
Nehler[10]	*J Vasc Surg*	2007	PRCT comparing IAB performed with adjunctive lipoecraprost vs placebo in CLI	284	6-month AFS: 80% vs 74%
Bradbury[12]	*J Vasc Surg*	2010	PRCT comparing IAB vs angioplasty in CLI at 8 years	452	Survivorship improved for IAB arm at >2 years: HR, 0.61 (95% CI, 0.5-0.75)
Conte[2]	*J Vasc Surg*	2009	Pooled data set of above trials of open autologous vein infrainguinal bypass in CLI	838[b]	Pooled AFS at 1-year: 76.5%

AFS, Amputation-free survival; *CI,* confidence interval; *HR,* hazard ratio; *PRCT,* prospective, randomized controlled trial.
[a]No trial showed a statistically significant difference between placebo and treatment arms.
[b]Used only patients in the open surgery control groups, resulting in the cohort of 838.

maintenance of ambulatory and domiciliary status, symptom relief, and freedom from reinterventions.[13]

Because of modest outcomes and significant morbidity after infrainguinal bypass for CLI, many practitioners favor endovascular interventions. Recent population-based studies show that endovascular interventions are more commonly performed for CLI compared with open procedures.[14] Results for endovascular interventions vary widely, with a broad range of primary and secondary end points evaluated; however, overall clinical success after endovascular interventions is modest as well, ranging between 31% and 74%.[15] This deficit persists despite the rapid increase in new techniques and devices to revascularize patients' limbs for CLI. The lack of clear superiority of any modality, coupled with persistent compromised outcomes and a myriad of therapeutic options, has obscured the interpretation of trials regarding the outcomes in CLI.

Patient-centric functional outcomes, such as maintenance of ambulation, wound-healing, and domiciliary status, remain incompletely evaluated end points in the CLI population, with only retrospective analyses providing insight into these end points. Considering the modest results after revascularization, limited life expectancy, and morbidity associated with revascularization attempts, these end points may ultimately be more germane when designing future comparative effectiveness trials between endovascular and open surgical reconstructions in CLI.[16-19] Available data suggest equally poor outcomes using these end points. Taylor et al[16] showed that at 5 years after revascularization, maintenance of ambulation was 70.6% and that maintenance of independent domiciliary status was 81.3%. Complete wound healing, defined as the healing of all ischemic and surgical wounds, was <50% at 6 months.[17]

Revascularization is a mainstay of therapy because nonoperative interventions for CLI are limited to investigational use only. Development of nonoperative options for CLI is significant: Up to 50% of patients are not candidates for revascularization due to medical comorbidities, lack of conduit, extensive gangrene, or vascular anatomy that cannot be reconstructed.[10] The recently completed Use of Tissue Repair Cells in Patients with Peripheral Arterial Disease to Treat Critical Limb Ischemia (RESTORE-CLI) trial[19] shows promise with Ixmyelocel-T (Aastrom Biosciences, Inc, Ann Arbor, Mich), which is used to expand the patient's own bone marrow-derived mononuclear cells, which stimulates angiogenesis and encourages the development of arterial collaterals. Powell et al[19] were able to show an increase in amputation-free survival (AFS) by 32% in the treatment arm, although this was not statistically significant. These patients represent an important comparison group when outcomes in CLI are evaluated.

Primary major amputations remain an important treatment modality in patients with CLI, although rates appear to be decreasing.[14] Although frequently considered a treatment failure, timely above-the-knee or below-the-knee amputations may be preferable in some patients. In fact, there is a segment of the CLI population whose ambulatory outcomes after major amputation appear to rival outcomes of CLI patients who undergo revascularization.[18] Patients undergoing major amputation also represent an important comparison group when outcomes in CLI are evaluated.

THE COST OF CLI

Cost analyses are increasingly salient in the U.S. as health care costs continue to spiral, currently amounting to ~18% of the U.S. gross domestic product[20]; moreover, the rate of growth is becoming unsustainable. In an attempt to curb health care expenditures, the U.S. Congress passed the Affordable Health Care Act (ACA) in 2010.[21]

For all of the aforementioned reasons, comparative effectiveness research (CER) has become particularly germane to the vascular surgery population, for whom care is often laborious, expensive, and complex due to the patients' multiple comorbidities.[13] Cost-effectiveness comparisons have been sparse in the literature, with very few having been performed in the past 20 years. Many of these studies failed to evaluate patientcentric outcomes, such ambulation and wound healing, and also failed to use more sophisticated measurement techniques, such as microcosting, activity-based accounting, or transition cost-accounting. Rather, they simply used claims data, modeling, or other proxies for estimating the costs[22]; hence, accurate comparisons between different strategies are glaringly absent in the CLI literature.

The existing data conflict, with several authors suggesting that infrainguinal bypasses or other traditional revascularization techniques are more cost-effective than primary amputation.[23] Infrainguinal bypass may be less cost-effective compared with endovascular therapies.[24] Other more recent modelling data suggest that open revascularization is the most cost-effective treatment strategy, with the caveat that if wound healing rates were >37%, or if procedural costs were decreased by 42%, then endovascular-first revascularization strategies were the most cost-effective.[25]

IMPORTANCE OF RISK STRATIFICATION IN CLI

Better risk prediction is instrumental to (1) complement patient and physician decision-making about which patients will benefit from specific vascular interventions and (2) evaluate and improve risk-adjusted outcomes and use of resources. The absence of a mechanism to accurately risk-stratify CLI patients partly explains the relative dearth of quality CER in CLI. This is especially important in light of the passage of the Affordable Health Care Act in 2010, which has led to the creation of Accountable Care Organizations (ACOs), which are designed to align physician compensation by Medicare with the quality of the outcomes of their procedures. Appropriate risk stratification is essential to ensure appropriate comparisons among interventions, practitioners, and institutions and permit equitable compensation in ACOs.[21] An example of this need is evident in articles regarding the role of specialty training and outcomes in lower extremity interventions. Although some authors argue that specialty training predicts outcomes,[26] others argue that the indication for the intervention or severity of ischemia more strongly predicts outcome.[27] Improved risk stratification could clarify these differences, thereby permitting equitable comparisons across practitioners. Moreover, the improved ability to compare different outcomes would simplify the patient consent process, which could perhaps mitigate the detrimental effects of medicolegal activity. The prototypical development of a risk prediction model is outlined in the Fig.[28-33]

CER in CLI has been hampered by two main factors. The first is study heterogeneity regarding the definition of CLI and the end points. Inclusion and exclusion criteria among CLI studies differ significantly, resulting in considerable variability in the results and hampering the interpretability and generalizability of the outcomes. This reflects the heterogeneity of conditions that present with a combination of lower limb infection, ischemia, and ulceration that ultimately result in limb loss. Moreover, multiple end points exist for study, without a definite consensus as to which are the best for study.[2]

The second factor is failure to capture differences in comorbidities and extent of disease. The initial definition of CLI failed to include diabetic patients, who currently comprise a significant proportion of patients presenting with limb-threatening ischemia.[4] Recent models fail to consistently stratify by whether the patient underwent endovascular therapies, the vascular anatomy,[32] wound

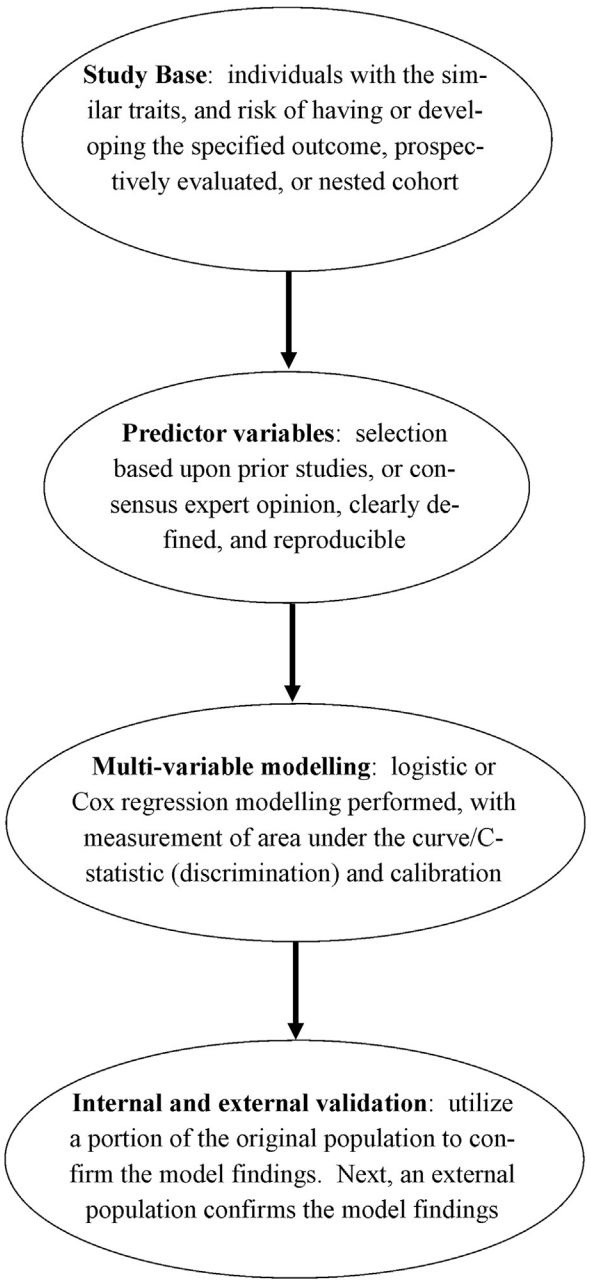

Fig. Simplified schematic representation shows the derivation and validation of a prototypical risk-prediction model.

severity,[34] and pre-existing medical adherence to atherosclerotic risk factor managment.[35] These unmeasured differences can result in treatment and control groups that are not comparable, even within prospective, randomized controlled trials (PRCTs). Although PRCTs theoretically control for unmeasured confounders, when the PRCTs show a lack of a treatment effect, determining whether the lack of an effect is due to a true lack of effect or from an unmeasured bias is difficult.[36]

Further, PRCTs provide the best evidence but pose several difficulties when studying CLI. First, PRCTs

Table II. Summary of risk-prediction models in critical limb ischemia (CLI)

First author	*Journal*	*Year*	*Study base*	*No.*	*Designed end point(s)*	*AUC*	*C statistic*
Externally validated							
Biancari[28]	*World J Surg*	2007	FINNVASC registry of open revascularizations	3925	30-day AFS	0.506	0.630
Schanzer[29]	*J Vasc Surg*	2008	Nested cohort of PIII data	1404	1-year AFS	0.582	0.634
Bradbury[32]	*J Vasc Surg*	2010	Nested cohort of BASIL data	452	2-year mortality	0.651	
No external validation							
Taylor[37]	*Ann Surg*	2003	Single-center prospective cohort	137	6-month mortality, patency, limb salvage, functional outcomes	Not performed	
Gupta[39]	*J Vasc Surg*	2012	NSQIP data 2007-2009	9556	30-day mortality	0.81	
Meltzer[40]	*J Vasc Surg*	2013	NSQIP data 2007-2009	3275	30-day M&M	0.61	0.77
Mills[34]	*J Vasc Surg*	2013	Not applicable	Not applicable	Not defined	Not applicable	

AFS, Amputation-free survival; *AUC,* area under the curve; *BASIL,* Bypass vs Angioplasty in Severe Ischaemia of the Leg; *FINNVASC,* National vascular registry in Finland; *M&M,* morbidity and mortality; *NSQIP,* National Surgical Quality Improvement Program; *PIII,* PREVENT III (Edifoligide for the Prevention of Infrainguinal Vein Graft Failure).

generally take a considerable length of time to complete. Owing to the rapid evolution of new devices, therapeutics, and techniques, the significance of results at the completion of the trial are often reduced because they may compare outdated therapies. This issue was evident in the Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL) trial, which is the only published trial to compare endovascular and open revascularization for chronic CLI.[11,12] The BASIL study, however, defined endovascular therapies as percutaneous balloon angioplasties only. By the time the study had been complete, multiple other registries had shown the lack of efficacy of balloon angioplasty alone compared with adjunctive stenting, in several of the arterial beds, such that adjunctive stenting was commonly performed in modern practices.[14] This grossly limited the generalizability of the results of the BASIL trial to modern practice.

Furthermore, enrolling patients into a placebo arm for CLI is difficult ethically and pragmatically because the outcomes of untreated CLI are already known to be markedly inferior to revascularization. Finally, PRCTs are significantly more expensive to perform than single-armed prospective evaluations of individual interventions. When considering the aforementioned difficulties, PRCTs are becoming increasingly impractical in the study of CLI and may slow the pace of innovation and eventual evolution of therapies for CLI. Therefore, many experts in the field are advocating for a common trial design that will allow physicians and industry to objectively evaluate new therapeutics and devices as they evolve.[2,36]

CURRENT EXTERNALLY VALIDATED MODELS TO RISK-STRATIFY PATIENTS AND OUTCOMES IN CLI

Biancari et al[28] were the first group to attempt to risk-stratify patients with CLI, with the development of the National vascular registry in Finland (FINNVASC) score (Table II). This score determined the risk of a patient undergoing a major amputation or dying ≤30 days of an open surgical revascularization. The authors used the FINNVASC Registry, which included details on 5709 CLI procedures between 1991 and 1999 from five university hospitals, 16 central hospitals, and four district hospitals.[28] The FINNVASC Registry is the second largest of the data sets used to develop a prediction model. They defined CLI as the presence of Fontaine stages III and IV disease. They limited their evaluation to 3925 procedures performed as an open surgical revascularization only. Approximately half of the patients were used to create a model, and the remaining patients were used to internally validate the model.

The authors identified four variables that were independently predictive of 30-day AFS: a history of diabetes mellitus, coronary artery disease, gangrene at presentation, and the need for an urgent operation. Each of these variables was assigned 1 point to develop the risk score. Patients had statistically significantly different 30-day AFS in each of the scoring strata, 0-4. The area under the curve (AUC), which is a measure of the ability of the model to predict the outcome, was 0.611 ($P < .0001$), which means that the FINNVASC score was able to predict 61.1% of the time whether patients underwent a major amputation or died at 30 days.

The results were statistically significant, but the model had several weaknesses due to the deficiencies in the data collection and unmeasured variables (Table III). The model did not include several variables that have been shown to be predictive of AFS in other studies, including a history of tobacco abuse, hyperlipidemia, and baseline ambulatory status. Also absent were data regarding the severity of the wound(s) at presentation, atherosclerotic risk factor management, and angiographic patterns of disease. Finally, the model limited their evaluation to open infrainguinal revascularizations and evaluated outcomes at 30 days only. Hence, endovascular outcomes and end points >1 month cannot be evaluated with this model.

Schanzer et al[29] followed the FINNVASC group by performing a nested-cohort study from the Edifoligide for the Prevention of Infrainguinal Vein Graft Failure (PREVENT III [PIII]) trial,[9] which consisted of 1404 infrainguinal bypass patients from >80 Canadian and

Table III. Strengths and weaknesses of current risk-stratification schema developed to compare outcomes in chronic critical limb ischemia (*CLI*)

First author	*Journal*	*Year*	*Predictive variables in the model/score*	*Strengths*	*Weaknesses*
Externally validated					
Biancari[28]	*World J Surg*	2007	• DM • CAD • Gangrene • Urgent operation	• Large number of patients • Multicenter registry of university and community hospitals	• 30-day outcomes only • Open revascularizations only • Missing significant variables • Finland only
Schanzer[29]	*J Vasc Surg*	2008	• Dialysis dependence • Tissue loss • Age ≥75 years • Hct ≤30% • CAD	• Nested, multicenter cohort of prospective randomized data	• Highly selective group of patients • Missing significant variables
Bradbury[32]	*J Vasc Surg*	2010	• Tibial angiogram scores • Severity of ischemia • Presence of pedal necrosis • BMI, age, serum Cr, tobacco abuse	• Nested, multicenter cohort of prospective randomized data • Inclusion of angioplasty subjects	• Highly selective group of patients • Missing significant variables • Evaluated survival at 2 years only
No external validation					
Taylor[37]	*Ann Surg*	2003	• Arteriographic variables • Ischemic severity (claudication or CLI) • Ambulatory status, age, obesity, CAD • Technical factors (lack of conduit, redo surgery)	• Internally validated • No indication bias, with inclusion of all PAD patients	• Not limited to CLI only • 6-month outcomes only
Gupta[39]	*J Vasc Surg*	2012	• Age • Chronic steroid use, COPD, development of SIRS, ESRD, rest pain on presentation, and dependent functional status	• Best predictive ability • Derived from large data set	• 30-day mortality only • Not externally validated • Only infrainguinal bypasses • Mix of claudicant and CLI patients
Meltzer[40]	*J Vasc Surg*	2013	• Age >75 years • Prior amputation or revascularization, tissue loss, hemodialysis, severe cardiac disease, emergency surgery • Functional and total dependence	• Excellent predictive ability • Derived from large data set	• 30-day mortality and morbidity only • Only infrainguinal bypasses
Mills[34]	*J Vasc Surg*	2013	• Location, depth, and size of the ulcer • Associated infection • Severity of ischemia	• Inclusion of wound and infectious parameters • No indication bias, with inclusion of all wounds	• Complex, especially as it needs to be combined with other risk stratification models • Not validated • No outcome specified

BMI, Body mass index; *CAD,* coronary artery disease; *COPD,* chronic obstructive pulmonary disease; *Cr,* creatinine; *DM,* diabetes mellitus; ESRD, end-stage renal disease; *Hct,* hematocrit; *PAD,* peripheral arterial disease; *SIRS,* systemic inflammatory response syndrome.

American hospitals (Table II). The model was derived from 953 of these patients, and the remaining 451 were used to internally validate the model. Subsequently, a cohort of 716 infrainguinal bypass patients from two university hospitals and one community hospital was used to externally validate the model.

The independent predictors of AFS were used to derived weighted point scores for each variable, which was used to generate a risk score for major amputation or death for each patient at 1 year. Four independent predictors of 1-year AFS were initially identified: dialysis dependence, the presence of tissue loss, age >75 years, and a

history of coronary artery disease. These were use to generate the PIII CLI risk score, ranging between 0 and 12. The PIII risk score was subsequently modified to include anemia, defined as a baseline hematocrit of <30%, and found to consistently predict AFS in external surgical outcomes data sets.[30]

However, the PIII risk score was also limited to infrainguinal bypass surgeries, which currently comprise the minority of the procedures performed for CLI in a modern vascular surgery practice.[14] Similar to the FINNVASC score, the PIII score also failed to analyze several variables that have been found to be predictive of AFS. The PIII score and FINNVASC scores were subsequently compared in an external data set of 1425 patients undergoing either endovascular revascularizations, infrainguinal bypasses, or both.[31] This study revealed both models were only modestly predictive of 30-day and 1-year AFS, with an AUC for 1-year AFS of 0.634 for the PIII risk score and an AUC of 0.630 for the FINNVASC model (Tables II and III).

The sole PRCT studying the role of endovascular vs open surgical revascularization in CLI was the BASIL trial from the United Kingdom (Table II).[11,12] This trial compared the AFS of patients randomly allocated to receive balloon angioplasty only or infrainguinal bypass surgery first, and recruited 452 patients from 27 hospitals. The data from this trial were subsequently used to develop a prediction model for 2-year survival only, given the patients' baseline characteristics.[32] The rationale for the end point was drawn from the findings of the original BASIL trial, which showed that the infrainguinal bypass arm had a statistically significant increase in AFS for patients who survived >2 years. The authors used 75% of randomly selected patients from the nested cohort and found that the baseline variables predictive of death at 2 years were the severity of ischemia (defined by the number of Doppler signals present at the ankle and the maximum ankle pressure obtained), the severity of tibial and pedal obstructions (defined as the Bollinger angiogram scores), presence of pedal necrosis, age, serum creatinine, and smoking status. A history of myocardial infraction or angina and a history of stroke or transient ischemic attack were also included in the model because they were defined a priori as significant determinants of survival.[32] With these variables, the authors found that the proportion of survivors at 6 months, 1 year, and 2 years was 85%, 77%, and 65%, respectively.[32]

The BASIL score was subsequently externally validated and compared with the FINNVASC and modified PIII scores in a retrospective cohort of 342 individuals undergoing infrainguinal bypass or angioplasty, or both. With respect to survival only at 12 months, the BASIL score was best able to predict mortality, with an AUC of 0.651. This compared with the FINNVASC and modified PIII scores, which had AUCs of 0.506 and 0.582, respectively.[33]

The BASIL score was more comprehensive than the prior scoring systems but also failed to include data on the multitude of endovascular interventions currently performed in vascular practices (Table III). It is unclear whether the BASIL results remain valid in the current era of vascular surgery in which angioplasty alone is rarely performed. Moreover, the BASIL score, although having data on a wider range of variables, still fails to include data regarding the severity of pedal necrosis at presentation, the quality of medical risk factor management at presentation, and the quality of wound care. The BASIL score is also more complex than the prior systems, limiting its applicability to daily use. Finally, the outcomes were limited to survival only, leaving practitioners to extrapolate other outcomes, such as limb salvage, from other scoring systems.

MODELS LACKING EXTERNAL VALIDATION

Mills et al[34] has also proposed a new scoring scheme, using the Delphi consensus process, that is designed to risk-stratify patients presenting with ischemic ulceration using the Wound, Ischemia, and Foot Infection (WIfI) system. This is particularly important, because the incidence and prevalence of diabetes is increasing, which may be altering the morphology and distribution of vascular insufficiency in patients presenting with ischemic ulcerations.[34] The WIfI system categorizes the variables of wound depth, location, and sepsis in conjunction with the severity of presenting ischemia, as defined by the ankle-brachial index or ankle pressures, toe pressures, or transcutaneous oxygen measurements. This system recommends that patients with diabetes be stratified by the presence or absence of neuropathy as well as by the severity of the toe pressure decrements. Wounds are recategorized also after control of infection and debridement. The intent of the WIfI system is that it is to be used in conjunction with a comorbidity stratification system and an anatomic score to aid in clinical decision making and for clinical trials. The WIfI system has yet to be validated against any data set, and the added complexity may decrease its clinical utility (Tables II and III).

The Lower Extremity Grading System (LEGS) is the only directive stratification tool developed to guide the treatment of patients presenting with PAD, including those with claudication (Table II).[37] This was initially developed as a clinical decision-making aid to determine whether the patient should undergo traditional open vs endovascular revascularization in CLI. The score included arteriographic variables, ischemic severity (claudication or CLI), ambulatory status, age, obesity, coronary artery disease, and technical factors, such as lack of conduit, and redo surgery. The score was prospectively validated within the authors' institution, showing that use of the scoring system resulted in acceptable 6-month mortality, limb salvage, and functional outcomes in the scored patients that was superior to limb salvage, patency, and ambulatory status outcomes achieved without use of the LEGS scoring mechanism.[38] The LEGS score has not been externally validated, precluding its use as a risk-stratification tool for clinical trials and outcomes assessments. Moreover, the inclusion of claudicant patients makes comparisons with CLI-only populations problematic. However, the LEGS scoring system does include all

patients that present for evaluation for revascularization or amputation, which more accurately represents the decisions required of vascular specialists (Table III).

Two groups used the American College of Surgeons National Surgical Quality Improvement Program data from 2007 through 2009 to develop CLI risk-prediction models. Gupta et al[39] (Table II) developed a model to predict 30-day mortality, using outcomes data from 9556 patients undergoing an infrainguinal bypass. Independent predictors of 30-day mortality included age, a history of chronic steroid use, chronic obstructive pulmonary disease, development of the systemic inflammatory response syndrome, dialysis dependence, rest pain on presentation, and dependent functional status. The C statistic for this model was 0.81, meaning that the model correctly identified 81% of those who died after an infrainguinal bypass. Oddly, the authors' risk calculator found that tissue loss at presentation did not independently predict death, as was seen in the BASIL model,[32] or in the subsequent model studying CLI-only patients.

This model has not been externally validated and lacks data regarding the severity of pedal necrosis, severity of arterial disease burden, and quality of baseline medical therapy. The model also included patients with claudication, clouding the ability to predict outcomes in CLI patients. Moreover, the end point for that study was limited to survival after infrainguinal bypass. However, several novel predictors of 30-day mortality, such as chronic obstructive pulmonary disease and postoperative systemic inflammatory response syndrome, which warrant further study (Table III).

The Comprehensive Risk Assessment for Bypass (CRAB) also used the American College of Surgeons National Surgical Quality Improvement Program data set to develop a risk-prediction model for 30-day morbidity and mortality (M&M) in CLI patients undergoing infrainguinal bypass (Table II).[40] A total of 3275 patients were used to derive a prediction model of the composite end point of M&M, with 1620 patients in the internal validation set used to validate the model against M&M as well as mortality and morbidity alone. This study has a smaller study base that the Gupta et al[39] study due to the inclusion only of patients with International Classification of Diseases, Ninth Revision codes consistent with CLI.

Independent predictors of 30-day M&M included age >75 years, prior amputation or revascularization, tissue loss, hemodialysis, severe cardiac disease, emergency surgery, partial functional dependence, and total functional dependence. Integer scores were assigned to each of these predictors based on the magnitude of the effect attributed to each of these variables on multivariable analysis. The C index of the model for M&M was 0.68 and was 0.61 for morbidity alone and 0.77 for mortality alone. This model has also not been externally validated and is limited only to infrainguinal bypass patients and evaluation of 30-day outcomes. However, this model has some of the best discriminatory ability in the literature and also warrants further evaluation (Table III).

SUMMARY OF CRITICAL GAPS IN KNOWLEDGE REGARDING RISK STRATIFICATION IN CLI

Risk stratification in CLI is in its infancy. The existing risk models have demonstrated modest predictive abilities. These risk-stratification systems are heterogeneous in predictor variables and outcomes assessed. For instance, the inclusion of endovascular therapies is not uniform nor is the evaluation of the severity of pedal necrosis or the adequacy medical risk-factor management and other known risk factors of AFS. Moreover, all of the scoring systems have difficulties with generalizability related to the patient population that they were derived from or to the lack of rigorous external validation from data sets outside of their institutions. Confounding by indication[41] is also a significant problem, because many of the derivation sets included only infrainguinal bypasses or angioplasties, but not both. This means that the estimates of predictor variables cannot necessarily be extrapolated to an entire population of CLI patients. Hence, only the LEGS[34] and WIfI[33] scoring systems are applicable to all patients who may present to a vascular specialist. Finally, as investigators discover novel baseline, intraoperative, and postoperative predictors of outcomes in CLI, the scoring systems become increasingly complex.

Future scoring systems may benefit from the inclusion of other variables that are variably present in prior studies or absent altogether. This may help to improve the prediction capabilities, as evidenced by Gupta et al,[39] who showed that use of previously unstudied baseline and postoperative variables improved the predictive ability of his model relative to prior models. Moreover, inclusion of patients from populations that most closely mimic that of the CLI population that presents to a vascular specialist's clinic is critical to avoid confounding by indication[41] and improve the ability of the risk-scoring systems to predict AFS. Decreasing heterogeneity in the predictive models can be improved by consensus on the optimal end points for study.[2] Information technologies may assist in decreasing the complexity entailed with the scoring systems, ultimately improving the ease of use and dissemination. Finally, future scoring mechanisms would benefit from improved external validation in large data sets that are becoming increasingly available. Although no risk stratification tool will perfectly forecast a patient's outcome, improved risk stratification certainly has the potential to greatly improve patient and physician decision making, adjudication of quality assessments, and compensation in ACOs.

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