Defining risks and predicting adverse events after lower extremity bypass for critical limb ischemia

Abstract: Successful treatment of patients with critical limb ischemia (CLI), hinges on the adequacy of revascularization. However, CLI is associated with a severe burden of systemic atherosclerosis, and patients often suffer from multiple cardiovascular comorbidities. Therefore, CLI patients in general represent a cohort at increased risk for procedural complications and adverse events. Although endovascular therapy represents a minimally invasive alternative to open surgical bypass, the durability of surgical reconstruction is superior, and it remains the “gold standard” approach to revascularization in CLI. Therefore, selection of the optimal treatment modality for individual patients requires careful consideration of the procedural risks and likelihood of adverse events associated with surgery. Individualized decision-making with regard to revascularization strategy requires a comprehensive understanding of the likelihood of adverse outcomes after major surgery. Here we review the risks of surgical bypass in patients with CLI, with particular emphasis on the identification of preoperative variables that predict poor outcome.

Keywords: critical limb ischemia, bypass, adverse events

Introduction

Peripheral vascular disease affects approximately up to 10 million Americans with approximately 1% having critical limb ischemia (CLI). Despite the increased utilization of minimally invasive endovascular interventions for CLI, surgical bypass remains the gold standard against which all minimally invasive treatments are measured. Less invasive therapies may offer a more favorable perioperative safety profile, therefore making them preferable in high risk patients, whereas the durability of endovascular interventions is superior. Therefore, optimal decision-making for an individual patient hinges on careful risk stratification and consideration of patients’ suitability for surgical reconstruction. Because patients with CLI commonly suffer from associated comorbidities, they represent a “high risk” cohort, in which adverse events are not uncommon. Multiple studies have suggested that perioperative mortality exceeds 2%, with complication rates exceeding 20% in some groups.

Furthermore, these patients are at relatively high risk for hospital readmission and increased length of stay (LOS) postoperatively. The objectives of this review are to summarize existing data regarding the risks associated with surgical bypass in this unique patient population. To accomplish this, we assess historic and contemporary outcomes data to estimate the incidence of adverse events after surgical bypass, and describe recent efforts to develop targeted risk assessment tools to improve perioperative risk stratification.
Perioperative risk assessment

Generalized risk prediction models have been developed to stratify surgical patients with respect to perioperative risk. The most widely accepted model is the American Society for Anesthesiology (ASA) Classification.9 This generalized scoring system stratifies patients into categories based on their comorbidities and the subsequent risk to their everyday life to establish how fit they are to undergo an operation. There are no specific conditions mentioned and there is room for a lot of variability. The surgical risk score and American College of Surgeons Risk Calculator represent increasingly more detailed efforts to estimate the risks of surgery for a wide range of surgical procedures across many different specialties.9,10 More specific risk assessment tools have been created to predict postoperative mortality in specific patient populations, including those undergoing pancreatic surgery, bariatric surgery, and colorectal procedures.10–12

Due to the high prevalence of cardiovascular risk factors, estimation of preoperative cardiac risk has traditionally been the focus of more specific efforts, and preoperative cardiac evaluation. The most widely accepted tool used to predict cardiac risk is the Revised Cardiac Risk Index, with patients often referred for preoperative cardiac evaluation.13 Preoperative cardiac evaluation is often obtained before major vascular surgery. However, the utility of such assessment has recently been questioned, with respect to perioperative and long-term outcomes, by Monahan et al.14 The authors identified all patients that met the American College of Cardiology and the American Heart Associations’ criteria for preoperative cardiac evaluation. These patients were divided into two groups – those who underwent preoperative cardiac evaluation and those who did not. In the group that received a workup, 13% underwent coronary revascularization; this was divided into 60% percutaneous and 40% coronary artery bypass. Patient survival at 12 months for the group without a workup compared to those who had a cardiac workup, and to those who were revascularized was 85.3%, 78.5%, and 80.0%, respectively and 73.6%, 62.9%, and 80.0%, respectively at 36 months – showing no significant difference. Median length of hospitalization was also not significantly different.14 In an effort to more specifically assess cardiac risk, members of the Vascular Study Group of New England (VSGNE) utilized multi-institutional surgical outcomes data to develop a targeted risk assessment tool for cardiac risk in patients undergoing lower extremity revascularization.15 Other efforts to predict outcome in this patient population include the PREVENT (PRoject of Ex vivo vein Graft Engineering via Transfection) III Score, which predicts the likelihood of mortality or amputation at 1 year.7

The limitations of these existing models for preoperative risk stratification are apparent. Generalized models (eg, ASA classification, surgical risk score) may have limited applicability with respect to the high risk population with CLI. Existing efforts to predict “risk” specifically in this patient population (PREVENT III Score, VSGNE), however, have tended to focus on prediction of mortality and/or adverse cardiac events, without specifically addressing the occurrence of major morbidity that is not related to cardiac disease, but certainly may negatively impact quality of life in surgical patients.

Our group has previously published a more comprehensive, targeted risk assessment tool to predict 30-day major morbidity and mortality after bypass surgery for CLI; The Comprehensive Risk Assessment for Bypass.6 A review of the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) found that the 30-day mortality rate after lower extremity bypass for CLI was 2.9%, with a major morbidity at a rate of 19.1%.6 The composite major morbidity and mortality end point was seen in 10.1% of patients. Significant predictors by multivariate analysis included age >75 years, prior amputation or revascularization, tissue loss, dialysis dependence, severe cardiac disease, emergency operation, and functional dependence. When weighed based on the odds ratio for morbidity and mortality, total functional dependence and emergent case were assigned 6 points each, recent angina/myocardial infarction and dialysis dependence were assigned 4 points, and advanced age, prior lower extremity intervention, ulceration, and partial functional dependence were given 3 points. High risk patients (>12 points) had a 25% rate of major morbidity and mortality within 30 days, medium risk (7–12) had a 13% risk, and low risk (0–6) had a 6% chance for major morbidity and mortality within 30 days.6

Not surprisingly, there is considerable overlap in these models of risk prediction (Table 1). Certain patient-level factors have repeatedly been shown to portend poor outcome in patients with CLI undergoing surgical bypass (Table 2). Several distinct patient groups warrant more in-depth discussion.

Advanced age

Elderly patients are generally at higher risk for perioperative events.16,17 However, a retrospective review of 262 lower extremity bypasses, almost all for CLI, in octogenarians showed promising results.18 The 5-year primary, assisted...
primary, and secondary graft patency rates in octogenarians were 72%, 80%, and 87%, respectively. The 5-year limb salvage rate was 92% and patient survival was 44%. On average, both residential and ambulatory statuses significantly improved postoperatively. Although advanced age is a risk factor for adverse events, lower extremity bypass can safely be performed and preserve ambulatory status and independence. Furthermore, when comparing open versus endovascular revascularization in the elderly, both groups had similar decreases in functional status post-procedure; however, the open bypass group had an advantage at 6 months compared with the endovascular group in regards to functional status.

On the other end of the age spectrum, patients younger than 40 years old are also at increased risk for poor outcomes. The majority of these patients have juvenile diabetes. Perioperative morbidity and mortality is low, however graft failure is high with 30-day graft failure being 11%, and 1-year primary patency of 71.0%, secondary patency of 82.5%, and limb salvage of 87.1%. At 5 years, these rates have been reported as 51.9%, 63.4%, and 77.2%, respectively. Overall survival at 1 year was 88.2% and at 5 years was 73.3% with patients with renal dysfunction, in particular, having poorer survival (Table 3).

### Table 2 Shared high risk groups

<table>
<thead>
<tr>
<th>Coronary artery disease</th>
<th>Dialysis dependence</th>
<th>Advanced age</th>
<th>Impaired functional status</th>
<th>Tissue loss</th>
<th>Emergency operation</th>
<th>Congestive heart failure</th>
<th>Smoking</th>
<th>Chronic obstructive pulmonary disease</th>
</tr>
</thead>
</table>

### Table 1 Perioperative risk assessment strategies

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Society of Anesthesiology (ASA)</td>
<td>Degree of systemic disease</td>
<td>Assess overall fitness for surgery</td>
</tr>
<tr>
<td>American College of Surgeons Risk Calculator</td>
<td>Age, sex, BMI, ASA class, functional status, case urgency, wound class, steroid use, asci tes, sepsis, ventilated, disseminated cancer, diabetes, hypertension, previous cardiac event, CHF, dyspnea, smoker, COPD, dialysis, ARF</td>
<td>Assess risks for perioperative mortality as well as specific complications</td>
</tr>
<tr>
<td>Surgical Risk Score</td>
<td>Case urgency, ASA class, case complexity</td>
<td>Predicts mortality and major morbidity</td>
</tr>
<tr>
<td>Revised Cardiac Risk Index</td>
<td>CAD, CHF, history of CVA/TIA, diabetes, CRI, intra-abdominal/intra-thoracic surgery</td>
<td>Risk of cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest</td>
</tr>
<tr>
<td>PREVENT III</td>
<td>Dialysis, CAD, tissue loss, anemia, age</td>
<td>Predictor of death or major amputation in 1 year</td>
</tr>
<tr>
<td>VSGNE</td>
<td>Age, smoking, beta-blocker use, COPD, CRI, CHF, CAD, diabetes</td>
<td>Risk of perioperative cardiac events</td>
</tr>
<tr>
<td>Comprehensive Risk Assessment for Bypass (CRAB)</td>
<td>Age, dialysis dependence, tissue loss, functional status, severe cardiac disease, emergency operation, prior amputation/ revascularization</td>
<td>Predictor of 30-day major morbidity and mortality</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARF, acute renal failure; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRI, chronic renal insufficiency; CVA, cerebrovascular accident; PREVENT, PRoject of Ex vivo vein Grafts Engineering via Transfection; VSGNE, Vascular Study Group of New England; TIA, transient ischemic attack.

### Sex

In our progressively aging population, women 65 years of age and older outnumber their male counterparts by >30%, and by more than twice for women aged 85 years and over. Prior studies have demonstrated sex-related differences in vascular diseases such as abdominal aortic aneurysm (AAA) and carotid disease. Hypotheses to explain these differences have ranged widely from biochemical, anatomical, and social factors. A recent study analyzing sex disparities in patients with intermittent claudication and CLI using the National Inpatient Sample (NIS) demonstrated salient differences in presentation, revascularization modality, and amputation and inpatient mortality rates based on patient sex. At presentation, women were older (by an average of 3.5 years) and more likely to have CLI than intermittent claudication compared to men. Of those patients undergoing a revascularization procedure, CLI was a more common indication for women and they were more likely to undergo endovascular interventions for both intermittent claudication and CLI. The amputation and inpatient mortality rates have been declining over the years for both sexes. Interestingly, in-hospital mortality was...
found to be persistently higher in women than men regardless of disease severity or intervention performed. Given these data, sex-based differences are apparent in lower extremity peripheral artery disease (PAD) presentation, management, and outcomes. Further studies will be required to elucidate the underlying causes for these incongruences.22

**Race**

Race has been shown to affect outcomes in many medical conditions, including in postoperative vascular surgery patients.23 A retrospective review showed that African-American patients compared to Caucasians undergoing bypass for CLI, although younger, had higher rates of diabetes, hypertension, cerebrovascular disease, congestive heart failure, dialysis dependence, and were more likely to present with gangrene.24 Vein conduit and target vessels were similar between the two groups. Overall morbidity and mortality were similar between the two groups, however patency and limb salvage outcomes were worse in the African-American group. Thirty-day graft failure was 12% in African-Americans versus 5% in Caucasians; \( P = 0.003 \). The overall 5-year primary graft patency was also significantly worse in African-American patients (52% versus 67%; \( P = 0.009 \)) as was the 5-year limb salvage rate (81% versus 90%). In multivariate analysis, African-American race was an independent predictor of primary graft failure along with young age, female sex, secondary reconstructions, tibial bypasses, and CLI (Table 3).24

### Preoperative functional status

Poor preoperative functional status has consistently been shown to be a negative predictor of outcome after lower extremity procedures. It is an independent risk factor for prolonged LOS as well as morbidity and mortality after infrainguinal lower extremity bypass. This morbidity and mortality risk in the perioperative phase is particularly pronounced in patients with dependent functional status combined with an emergency operation and/or dialysis dependence.16

Furthermore, in postoperative patients, improvements in quality of life measures were significantly better in those who had better baseline functionality than those who did not. These measures included greater improvement in activities of daily living and mental well-being. Physical symptoms such as extremity cramping and pain both when walking and at rest, and wounds, were also improved. Those who had a better subjective preoperative functionality seemed to have the most improvement.25

### End stage renal disease and renal transplant patients

End stage renal disease is a comorbidity universally associated with poor outcomes. Given the prevalence of chronic kidney dysfunction and the associated poor outcomes in bypass patients with CLI, this group warrants particular attention.6,7,15 Even though renal failure patients are at high risk for mortality after bypass for CLI, patients with a kidney transplant seemed to fair better than those who remain on dialysis.27 A retrospective single-center review showed that the overall major complication rate was 11.8% and the 30-day mortality rate was 1.3% for lower extremity bypass for CLI in renal transplant patients. At 1 year, survival was 93.3% and at 5 years it was 66.6%. Limb salvage was 87% at 1 year and 78% at 5 years. Primary graft patency was 78% at 1 year and 44% at 5 years. Those who had a well-functioning allograft, as classified by a serum creatinine of less than 2.0 mg/dL, had improved 5-year survival (73.4% versus 37.5%; \( P = 0.01 \)), but no difference in limb salvage and patency (Table 3).26

### Procedural factors

In addition to the aforementioned patient-level factors, such as demographics and comorbidities, that have been associated with poor outcome, specific procedural details may define groups at higher risk for adverse events.

### Conduit choice

The ideal conduit is the ipsilateral greater saphenous vein; however, this is not always available. One alternative autologous vein that shows good results is an arm vein. The majority of these cases were distal/tibial revascularizations that used a single vein. The source was the cephalic vein alone in 50.4% of cases, the cephalic and basilic vein in 35.6%, and the basilic vein alone in 14%. In many of these cases (39%), the contralateral saphenous vein was suitable. Vein configuration and splicing did not affect patency rates. Early patency was excellent at 94.8% at 30 days. At 1 year

### Table 3 Subgroup patency

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Patency rate</th>
<th>CLI target</th>
<th>Tibial target</th>
<th>Duration of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octogenarians</td>
<td>72%</td>
<td>96%</td>
<td>76%</td>
<td>5 years16</td>
</tr>
<tr>
<td>Younger than 40</td>
<td>52%</td>
<td>87%</td>
<td>46%</td>
<td>5 years16</td>
</tr>
<tr>
<td>African-American</td>
<td>52%</td>
<td>91%</td>
<td>67%</td>
<td>5 years12</td>
</tr>
<tr>
<td>Renal transplant</td>
<td>44%</td>
<td>95%</td>
<td>78%</td>
<td>5 years16</td>
</tr>
<tr>
<td>Arm vein conduit</td>
<td>52%</td>
<td>99%</td>
<td>84%</td>
<td>3 years17</td>
</tr>
<tr>
<td>Prosthetic conduit</td>
<td>60%</td>
<td>96%</td>
<td>100%</td>
<td>5 years18</td>
</tr>
<tr>
<td>Severely calcified target</td>
<td>60%</td>
<td>90%</td>
<td>100%</td>
<td>2 years19</td>
</tr>
</tbody>
</table>

Abbreviation: CLI, critical limb ischemia.
the primary patency rate at 1 year was 70.6%, the secondary patency rate was 76.9%, and the limb salvage rate was 88.2%. The 3-year primary patency rate was 51.9%. In 22.7% of patients, the available contralateral saphenous vein was used for distal revascularization. It was recommended that an arm vein be used as the next option when the ipsilateral greater saphenous vein is not available and even if the contralateral greater saphenous vein is available – preserving it for future bypass on the other leg or for coronary bypass.27

When no autologous conduit is available, bypasses to tibial vessels using prosthetic material (polytetrafluoroethylene) can be successfully used. In cases where prosthetic graft is used to construct a bypass primary patency rates have been reported as 87%, 87%, and 60% at 30 days, one year, and 5 years respectively.28 Limb salvage rates at 30 days, 1 year, and 5 years were 91%, 68%, and 63%, respectively. Cumulative survival rates at 3 and 5 years, however, were 53%, and 42%, respectively. The 29 grafts (64%) that were postoperatively anticoagulated with warfarin showed a trend toward improved primary patency (47% versus 19%, P=0.07), secondary patency (49% versus 20%, P=0.03), and limb salvage (67% versus 58%, P=0.06), at 3 years. There were no significant differences between diabetics and non-diabetics except in a trend toward decreased patient survival at 3 and 5 years in the diabetic population.28

As an alternative, either in cases where there is poor conduit or as primary treatment, endovascular techniques can be used. Advances such as drug eluding and covered stents have been used with good short-term results for femoral-popliteal disease. Drug eluding stents at 2 years showed a 75% primary patency.30 Heparin-bonded covered stents had a primary patency of 71% at 1 year but fared worse at 3 years (24%).31 Drug eluding balloons also have promising short-term results compared to standard balloon angioplasty.32 However, these studies contain a large percentage of claudicants. Long-term outcomes and outcomes in CLI patients remain unclear as the majority of these patients studied were claudicants.

**Distal anastomotic target**

Comparison between those arteries that were assessed as severely calcified and unclampable to those that were not, showed no significant short- and long-term differences in outcomes. Primary patency, secondary patency, and foot salvage rates at 24 months were 60%, 65%, and 77%, respectively for the severe calcification group, which did not significantly differ from the no calcification group rates of 74%, 82%, and 93%, respectively.33 Perioperative mortality (0.99% severe calcification versus 0.95% no calcification) and 24-month survival rates (84% severe calcification versus 83% no calcification) were also similar between groups. Severely calcified, unclampable outflow arteries can be bypassed with results comparable to those obtained with clampable, uncalcified vessels. This population should not be ruled out for bypass for limb salvage indications (Table 3).33

Another difficulty seen with target vessels is when there is a local infection near the area. A retrospective review discussed treatment of bad diabetic foot infections where the target vessel was the dorsalis pedis artery.34 Achieving adequate control of the infection and sepsis prior to the bypass was important to success. Bypasses were delayed by an average of almost 11 days due to the need to control the infection. Graft patency in such cases was 92% at 36 months and limb salvage was 98% at 36 months.34

In cases where the main pedal vessels are not adequate targets, plantar and tarsal vessels are options. Inframalleolar bypass can be used even when previous bypass more proximally has failed. These bypasses have acceptable patency rates; however, compared to main tibial vessel bypass, these have higher rates of graft failure and limb loss. Saphenous vein conduit had the best patency.35

**Predicting postoperative infectious complications**

Surgical site infections (SSI) are one of the most common complications after lower extremity bypass. SSI were seen in up to 11% of cases 30 days postoperatively regardless of bypass origin.37 Graft failure was also significantly associated with postoperative SSI. Independent predictors of SSI were obesity, diabetes, poor preoperative functional status, a history of smoking, and female sex.36,37

One of the most morbid complications postoperatively is a prosthetic graft infection. Graft infection, as defined by exposed graft or presence of purulent fluid around a graft, has been reported in up to 3.8% of bypasses using prosthetic graft.38 Independent predictors of graft infection have been identified as a redo bypass, active infection at the time of bypass, female sex, and diabetes mellitus. Graft infection was predictive of major lower extremity amputation along with preoperative tissue loss. However, graft infection did not predict long-term mortality whereas chronic renal insufficiency and preoperative tissue loss both did. Infected grafts were removed 79% of the time. More have been able to be salvaged in recent years with treatment with vacuum assisted device placement and in some cases
rotational muscle flaps. *Staphylococcus epidermidis* (37%) and methicillin-sensitive *Staphylococcus aureus* (26%) were the most common pathogens isolated. It was recommended in these high risk patients that autologous vein for lower extremity bypass and endovascular interventions should be considered when feasible.\(^{38}\)

### LOS and readmissions

Admissions of PAD with CLI are associated with prolonged and costly hospitalizations. This is particularly true for patients in the postoperative phase after infrainguinal bypass for CLI. Prolonged LOS and readmissions are both costly to hospitals and are seen as a measure of poor quality of care.\(^{39-41}\) This is not only due to these patients’ significant comorbidities, but also the continued wound care, additional procedures during the hospitalization, postoperative complications, and difficulty placing these patients due to functional impairment.

The average LOS after lower extremity bypass for CLI is 7.5 days with a median of 6 days. There are several variables that can be identified in the preoperative phase that predict prolonged LOS. The highest predictive variables include impaired functional status, prolonged preoperative hospitalization greater than 5 days, and emergency surgery. Impaired functional status represents an overall debilitated patient as well as some who can be difficult to place postoperatively. Prolonged preoperative hospitalization not only possibly represents more severe disease and sicker patients, but it also puts the patients at risk for nosocomial infections. Other factors associated with increased LOS include demographic factors such as advanced age and non-Caucasian race. Medical comorbidities that significantly increased LOS included obesity, dialysis dependence, cardiac and pulmonary comorbidities, and bleeding disorders/chronic anticoagulation. More severe PAD disease, as noted by distal target sites, open wounds or gangrene, and prior arterial surgery also increased LOS.\(^{17}\)

Identification of preoperative risk factors for prolonged LOS allows for the development of pathways that potentially can identify high risk patients in the preoperative phase. This would allow a multidisciplinary approach with the vascular surgeon, medical subspecialists, physical therapists, and social workers who can preemptively intervene to try and decrease LOS. However, data showing success of such efforts to decrease postoperative LOS without sacrificing health care quality are still pending.\(^{17}\)

Similar to protracted LOS, readmissions after lower extremity bypass for CLI are costly. Readmissions continue to be viewed as a quality of care indicator and are targets for decreased reimbursement to hospitals. Efforts to decrease LOS should be balanced with maintaining a low readmission rate. CLI patients are particularly at risk for early postoperative readmission due to wound complications and significant comorbidities.

In a retrospective analysis of a large multi-institutional series, the average readmission rate for CLI patients ≤30 days of discharge after lower extremity bypass was shown to be 24.4%.\(^{42}\) The most frequent reason for readmission was a wound infection in the bypassed extremity (39.8%), followed from a need for additional procedures on the affected leg, and nonvascular reasons (19%). The highest risk factor for readmission that could be identified in the preoperative phase was dialysis dependence followed by loss of graft patency during initial admission, tissue loss, current smoking, and female sex. Thirty-day readmission rates were as high as 38% for the highest risk patients. Thirty-day readmission was not associated with loss of long-term graft patency but was associated with long-term limb loss.\(^{42}\)

ACS-NSQIP analysis of readmissions showed an 18% readmission rate within 30 days. This showed similar risk factors for readmission including dependent functional status, dialysis, dyspnea, obesity, CLI, and a return to the operating room during the initial admission. The most common readmission indications included wound infection (37%) and graft failure (10%).\(^{41}\)

### Adjuncts

#### Common femoral endarterectomy

Common femoral endarterectomy with or without profundaplasty is often performed with a distal revascularization for severe concurrent obstructive lesions in the common femoral artery. This alone can also provide relief for patients with distal disease, particularly those with rest pain.\(^{44}\) A review of patients undergoing isolated elective common femoral endarterectomy showed a 30-day mortality rate of 1.5%.\(^{45}\) Wound infection was the most common postoperative complication divided into superficial (6.3%) and deep (2.0%). Other complications included septic, pulmonary, cardiac, renal, urinary tract infection, thromboembolic, and neurologic etiologies. Eight percent of patients had at least one complication postoperatively. Independent predictors of mortality included impaired preoperative functional status and dyspnea at rest. Steroid use, diabetes, and obesity predicted postoperative morbidity. Overall common femoral endarterectomy is well-tolerated.
in patients and can be the first line treatment for common femoral lesions in conjunction with bypass or alone in selected patients.45

Conclusion
Lower extremity bypass for CLI is still the predominant revascularization modality for those patients who have failed endovascular interventions and the most durable revascularization option.5 Numerous factors, both systemic and anatomical, can affect morbidity, patency, limb salvage, and mortality. Models and quality improvement projects such as with ACS-NSQIP, Surgical Care Improvement Project Vascular Quality Initiative (SCIP), and VQI have attempted to identify these risk factors to better risk stratify these patients.

Disclosure
The authors report no conflicts of interest in this work.

References


