Predictors of Treatment Outcome in Intermittent Claudication

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Objective. To derive formulae to predict the likely 12-month health-related quality of life outcome following different treatments for intermittent claudication (IC).

Design. A prospective, randomized, controlled study.

Materials. One hundred and seventy-one unselected patients with stable IC were sequentially randomized to invasive therapy, supervised physical training or observation. Hierarchical analysis was used to identify significant predictors of outcome.

Results. The strongest outcome predictors were baseline values of the respective outcome variables in all groups. No more than two significant secondary predictors were identified for each outcome variable and no outcome variable was a predictor of any other outcome variable. Resulting prediction equations achieved between 61 and 90% concordance with improvement (75% considered adequate), with best prediction for invasive therapy and poorest for observation. Suggested cutpoints for the various endpoints in the three groups had sensitivities ranging between 65 and 100% and false positive rates between 5 and 50%.

Conclusions. The derived equations adequately predicted improvement on the various outcome variables in invasive therapy and supervised physical training, and may serve as aids in selecting patients likely to benefit most from a particular treatment strategy. The uniqueness of the outcome variables underscores the importance of implementing a comprehensive set of endpoints relevant to the impacts of the condition.

Key Words: Intermittent claudication; HRQL; Quality of life; Prediction; ROC.

Introduction

Intermittent claudication (IC) is a chronic disabling condition that affects about 5% of the elderly population1–3 and leads to significant impairment of health-related quality of life (HRQL).1–4 As few patients progress to critical limb ischaemia,15–18 the mainstay of treatment is lifestyle modification and so-called 'best medical therapy'.19–21 The role of adjuvant therapies, such as supervised exercise and angioplasty remain controversial.14,22–28 As such, it can be difficult for clinicians to decide how best to manage individual patients given limited resources. Most studies that have attempted to identify outcome predictors29–34 have focused on walking distance and not HRQL. The aims of present study were to derive formulae to predict the likely 12-month outcome following different treatments for IC.

Patients and Methods

Two hundred and fifty-three consecutive patients referred with a 6 months history of stable IC, and who did not have a contraindication to surgery and/or another disorder that would severely limit treadmill walking, were sequentially randomized to control, supervised exercise, or intervention groups, using a 21 variable algorithm.35,36 All patients were advised to stop smoking and given risk factor advice. The control group received no other treatment. The exercise group attended classes in groups of 10–12 under the supervision of a physiotherapist. There were three 30-minute sessions per week for 6 months and two sessions per week thereafter. Patients were encouraged to train at home and some patients opted for individualized programs. Patients in the intervention group underwent an endovascular or open surgical procedure depending on the results of angiography. Patients randomized to the control or training groups were allowed to undergo intervention if their ischaemia became severe.
Baseline variables comprised age, gender, weight, height, smoking habits, diabetes mellitus, creatinine, cholesterol, triglycerides, haemoglobin, blood pressure, ankle and great toe pressure, exercise ECG, dynamic spirometry, treadmill walking test and occlusion plethysmography values before and after exercise, groin pulses, symptom duration, income source and dependency on home help.

At baseline and one year follow-up patients were administered an extensive battery of generic and study-specific questionnaires covering a wide spectrum of HRQL concepts. This study reports the results from three instruments that in earlier analyses were shown to be most sensitive to change in this patient group.\textsuperscript{14} The Sickness Impact Profile IC (SIPIC) scale comprises 12 items: ambulation, home management, social interaction, mobility, alertness behavior and sleep and rest.\textsuperscript{3,37–39} The General Health Rating Index-Current Health (GHRI-CH) is a measure of perceived current health status and comprises nine items which are rated against 4-step scales from definitely false to definitely true. Ratings are summed to give a single score. Higher scores are indicative of better-perceived health status.\textsuperscript{40} The Symptoms and Complaints scale is a study-specific instrument comprising 9 items (Appendix A).

Outcome predictors, prediction equations and probabilities of outcome success associated with observed values were derived and illustrated using a six-stage hierarchical analysis.

1. Correlations between every baseline and outcome variable were calculated with Pitman’s permutation test.\textsuperscript{41} Those that were significant were selected as potential predictors.
2. Pitman correlations between potential predictor variables were calculated.
3. For variables correlating significantly with each other, their relative strength as potential predictors was elicited by partial correlations with Mantel’s test.\textsuperscript{42}
4. The resulting variables from the previous steps were entered as covariates in a multivariate regression analyses to obtain estimates of the proportion of the variance in the outcome variable accounted for by the model.
5. Logistic regression analyses were performed using the derived regression models to predict one-year outcome in variables dichotomized as improved versus no-change/deteriorated.

6. Lastly, observed values and associated probabilities of successful outcome were represented in Receiver Operating Characteristic (ROC) curves. The area under the curve (AUC) may be interpreted as a weighted average of the degree of prediction the model provides over its entire score range, where perfect prediction is indicated by an AUC value of 1.0 and no prediction by an AUC of 0.50. The criteria used for selecting cut-off points were that sensitivity exceeded 60% and that false positive rate was less than half the sensitivity.

### Results

There were no significant differences in baseline characteristics between 25 patients who declined, and those who agreed, to complete the study. At 12 months, data were available in 171 patients (66% male) of mean (SD) age 67 (8.3) years because 30 died, nine underwent amputations and 18 were lost to follow-up. These patients had significantly better SIP sleep and rest scores than the other 57 patients. There were 65, 48 and 58 patients in the control, supervised exercise and intervention groups, respectively. Results are only presented where predictors explained at least 20% of the variance in outcome and where AUCs were greater than 0.75.

Treatment success was defined as an improvement, irrespective of degree, over baseline values. No treatment achieved a 100% success in terms of any outcome variable (Table 1). The intervention group had the highest proportion of improved patients.

#### Walk symptoms

**Invasive treatment.** Analyses produced three significant predictors of change in walk symptoms: walk symptoms, exercise ECG and groin pulse (Table 2). Change in walk distance correlated negatively with baseline walk symptoms and groin pulse and positively with exercise ECG. The regression model accounted for 47% of the variance and the logistic
regression achieved 87% concordance in predicting improvement. Fig. 1(a) shows the ROC curve expressing the relationship between the true positive rate and the false positive rate for each observed value obtained from the regression equation. The optimal cut-off point for screening of candidates potentially deriving benefit in terms of walk symptoms from invasive treatment appears to be 1.89 (71% sensitivity, 9% false positive rate and 74% overall accuracy).

**Supervised physical training.** Significant baseline predictors of change in walk symptoms were walking distance and toe pressure (Table 2). A significant negative correlation was found with baseline walk symptoms and a positive correlation with toe pressure. The regression model explained 40% of the variance and the logistic regression model achieved 79% concordance. Fig. 1(b) shows the ROC curve for the regression equation. The optimal cut-off point appears to be −0.15 (67% sensitivity, 17% false positive rate and 77% accuracy).

**Rest symptoms**

**Invasive treatment.** Rest symptoms at baseline was the only significant predictor of change in rest symptoms (negative correlation) (Table 3). The regression model accounted for 43% of the variance in 1-year change in rest symptoms. The logistic regression model achieved 81% concordance. Fig. 2(a) shows the ROC curve for observed values obtained from the regression equation. The optimal appears to be −0.52 (100% sensitivity, 38% false positive rate and 76% accuracy).

**Supervised physical training.** A significant negative correlation was found for baseline rest symptoms (Table 3). The regression model explained 30% of the variance and the logistic regression model achieved 86% concordance. The optimal cutpoint shown in Fig. 2(b) appears to be 0.58 (68% sensitivity, 15% false positive rate and 77% accuracy).

**Sickness Impact Profile Intermittent Claudication scale (SIP(IC))**

**Invasive treatment.** There was one significant predictor of change in SIP(IC): baseline SIP(IC) (negative correlation) (Table 4). The regression model accounted for 35% of the variance in 1-year change in SIP(IC). The logistic regression model yielded 79% concordance. The optimal cut-off point for the obtained values (Fig. 3) appears to be 1.28 (69% sensitivity, 16% false positive rate and 74% accuracy rate).
General Health Rating Index—Current Health (GHRI-CH)

**Invasive treatment.** Three significant predictors were identified: GHRI-CH at baseline (negative correlation), creatinine (negative) and ECG (negative) (Table 5). The regression model accounted for 37% of the variance. The logistic regression model achieved 90% concordance in predicting improvement. The optimal cut-off point for observed values obtained from the regression equation (Fig. 4(a)) appears to be 2.26 (72% sensitivity, 0% false positive rate and 73% accuracy).

**Supervised physical training.** Significant baseline predictors of change in GHRI-CH were baseline GHRI-CH (negative correlation), cholesterol (positive) and ankle pressure (negative) (Table 5). The regression model explained 22% of the variance and the logistic regression model produced 77% concordance. The optimal cut-off point appears to be 0.08, with 78% sensitivity, 0% false positive rate and 73% accuracy.
Table 3. Rest symptoms. Performance of derived prediction equations in predicting one-year improvement in the invasive treatment and supervised training groups.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>% Improved</th>
<th>Predictors</th>
<th>% Variance</th>
<th>Regression equation</th>
<th>% Concordance</th>
<th>Optimal cutpoint</th>
<th>% Sensitivity, false positive, accurate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive treatment</td>
<td>53</td>
<td>Rest symptoms</td>
<td>43</td>
<td>$-2.453 + 1.682 \text{RS}$</td>
<td>83</td>
<td>$-0.52$</td>
<td>100, 38, 76</td>
</tr>
<tr>
<td>Supervised training</td>
<td>50</td>
<td>Rest symptoms</td>
<td>30</td>
<td>$-5.272 + 3.253 \text{RS}$</td>
<td>86</td>
<td>0.58</td>
<td>68, 15, 77</td>
</tr>
</tbody>
</table>

Table 4. Sickness Impact Profile Intermittent claudication. Performance of derived prediction equations in predicting one-year improvement in the invasive treatment group.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>% Improved</th>
<th>Predictors</th>
<th>% Variance</th>
<th>Regression equation</th>
<th>% Concordance</th>
<th>Optimal cutpoint</th>
<th>% Sensitivity, false positive, accurate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive treatment</td>
<td>64</td>
<td>SIP$_{IC}$</td>
<td>35</td>
<td>$-1.196 + 0.619 \text{SIP}_{IC}$</td>
<td>83</td>
<td>1.28</td>
<td>69, 16, 74</td>
</tr>
</tbody>
</table>
sensitivity, 30% false positive rate and 73% accuracy (Fig. 4(b)).

Discussion

Traditionally, conservative management was advocated for claudicants with mild-to-moderate symptoms, while interventional treatment was confined to patients with only the most severe symptoms. However, the relative effectiveness of conservative versus interventional therapy remains controversial and it can be difficult to predict how individual patients will respond. Although many previous studies have attempted to identify predictors of outcome, the present study is unique in that the patients were relatively unselected, randomized to one of three treatment strategies, followed prospectively for one year and were assessed by means of patient-focused outcomes.

Success rates were highest in the intervention group, while supervised training and conservative treatments produced similar results. However, no treatment modality achieved 100% success rate on any outcome variable at one year after treatment.

In order to identify significant baseline predictors of patient improvement at one year an hierarchical analysis procedure was used. Of these, a maximum of three of 30 baseline variables qualified as significant, independent predictors of any single outcome variable.
for each treatment. A major finding in this study was that, independent of treatment modality, the strongest predictors of treatment outcome were baseline values of the respective outcome measures used, where poorer baseline values were associated with improved outcome. The latter result is consistent with three earlier studies, but contradicts the results from another. The low response rate (63%) obtained in the last study may have biased those results. Furthermore, no baseline values of any other outcome variable explained a significant proportion of the variance in outcome variables at one year, indicating the uniqueness of the study endpoints. This uniqueness underscores the importance of implementing a comprehensive set of endpoints relevant to the impacts of the condition.

Age has previously been found to predict walking performance in training programs. However, in our study age predicted walking performance only in the invasive treatment group (data not shown) and was not a predictor of any other outcome. Given that claudicants are a relatively homogeneous group with respect to age, it is perhaps surprising that age predicts outcome at all. Further research is needed to determine the varying impacts of age on treatment outcomes.

In light of the demonstrated risks associated with smoking and benefits prescribed smoking cessation, an unexpected result in this study was that smoking cessation was not a significant predictor of outcome. A possible reason for this is that since all patients were strongly encouraged to quit smoking, those who did not comply responded in a socially desirable manner. In fact, in a sub-sample of patients for whom blood nicotine levels were available, many patients had nicotine concentrations inconsistent with self-reported smoking cessation.

The ROC curves presented here allow comparison of obtained patient values with our observed values and associated sensitivities and false positive rates. Based on such comparisons the clinician may estimate the probability of a patient achieving successful treatment outcome in a variety of areas impacted on by the disease. Such estimates may aid both in consultations with patients by providing them realistic expectations of treatment success from a patient perspective and in clinical decision making by allowing comparisons of success probabilities for any one treatment option. The suggested cut-off points have been provided only as rough guidelines for distinguishing the values above which outcome discrimination accuracy is poor (the upper extreme of the curve categorizes all cases as improved, i.e. 100% sensitivity and 100% false positive rate). The choice of a cut-off for predicting improvement is difficult because of the implicit trade-offs between sensitivity and specificity. The decision naturally depends on the implications of either missing patients who may actually improve or misclassifying patients who may not. ROC curves illustrate the trade-off for each obtained value and ideally allow the practitioner to choose the most appropriate cut-off, weighing in the

Fig. 4. General Health Rating Index - Current Health. Receiver operating curves (ROC) for GHRI-CH in the invasive therapy group and the supervised physical training group, respectively. Plotted values are derived from the regression equations shown in the figures, where \( GH = \text{General Health Rating Index-CURRENT Health} \) and \( \text{ECGrec} = \text{exercise ECG} \). Area under the curves (AUC), indicating the overall degree of prediction of the model, is given in the figures.
In summary, we suggest that the prediction of treatment outcome can be enhanced by the use of these equations in combination with the probabilities of treatment success associated with obtained values (ROC curves). Such information may be helpful in selecting patients for treatments and in patient consultations. Their predictive power can possibly be improved by adding other correlates of the outcome variables to the models than those studied as well as by collecting additional patient data.

Acknowledgements

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Appendix Symptoms and complaints scale

Patients sometimes say that they have the following problems. Please indicate to what extent you have experienced these problems during the past week. Mark the box under the response choice that best applies to you (Table A1).

Table A1.

<table>
<thead>
<tr>
<th>During the past week:</th>
<th>Not at all</th>
<th>A little</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you had difficulty sleeping?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Have you had pain in your feet while resting?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Have you had pain in your legs or ankles at night?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Have you had cramps in your calves at night?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Have you woken up at night and had to get up to relieve these pains?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Have you had pain in your feet or ankles while walking?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Have you had pain in your calves while walking?</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>8. Have you had pain in your whole leg while walking?</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Have you had pain in your hip while walking?</td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

References

10. Currie IC, Wilson YG, Baird RN, Lamont PM. Treatment of


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