Critical Limb Ischemia and Its Impact on Patient Health Preferences and Quality of Life—An International Study

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Abstract

Critical limb ischemia (CLI) has a significant impact on patients' quality of life (QoL). Despite cost utility evaluations being required by different authorities, data on patient health preferences and utilities for CLI are scarce. Hence, the objective of this study was to assess the impact of CLI on health preferences and health status of affected patients, and to generate health state utilities. In the International Study, 200 patients with CLI (stages III and IV according to Fontaine scale) were interviewed by trained interviewers with a discrete choice instrument, a standard gamble (SG), and the EuroQol-five dimension (EQ-5D) questionnaires (Marten Meesweg, Rotterdam, Netherlands). Conjoint analysis showed that a planned amputation (33%) was the most relevant health attribute followed by ambulatory function (25%) and chronic pain (15%). Non-dependence on caregiver impacted on patient health state preference considerably, whereas healing of ulcer/skin lesions had less impact. Preference values obtained from the SG were 0.84, for an amputation subpopulation arriving at 0.70. The EQ-5D index values as well as the EQ-5D visual analog scale for patients with CLI were 0.56. The QoL data of patients with CLI result in decreased QoL and preference values with a planned amputation.

Keywords

- critical limb ischemia
- peripheral artery disease
- quality of life
- utility
- discrete choice model

Some recent studies suggest the negative impact of critical limb ischemia (CLI) on a wide range of quality of life (QoL) dimensions.^{1,2} Patients with CLI reported QoL scores below the general population. Particularly, the physical functioning dimension, the role of physical functioning, and bodily pain were affected most intensively by this disorder.² Furthermore, the exclusion of a planned amputation plays a major role with regard to the health state preference as well as the ability of a patient to perform daily walking activities (without support device).

During the last decades, it has become more and more important to consider the impact on patient's QoL, and also in health economic assessment of new medical treatments—at

least if a disease affects the patient's QoL significantly. Usually this will be realized by using quality-adjusted life years (QALYs) as health economic outcome parameters. To calculate QALYs, a utility value is needed that reflects the QoL. A utility is a measure of health-related QoL (HRQoL), ranging on an interval scale between 0 for death and 1 for full complete health.³ If utility values are multiplied with life years one obtains QALYs, paying respect not only to the quantity but also quality of remaining life time.

Several different instruments are available to get information on utilities and to give a specific health state, a specific utility value.⁴ First, a direct measurement of utilities can be

performed for condition-specific health states. This could be done by interview techniques such as standard gamble (SG) or the time tradeoff method. An indirect measurement of utilities can be performed by applying utility algorithms to generic or disease-specific preference-based questionnaires, or by mapping from a disease-specific HRQoL instrument onto the utility algorithm of a generic instrument such as the EuroQoL five dimension (EQ-5D).⁵

With regard to health state preference, conjoint analysis, particularly choice-based and discrete choice designs, can be used to quantify preferences for several aspects of an intervention. Conjoint analysis methods are particularly useful for quantifying preferences for nonmarket goods and services or where market choices are severely constrained by regulatory and institutional factors, such as in health care.⁴

Aligning health care policy with patient preferences could improve the effectiveness of health care interventions by improving adoption of, satisfaction with, and adherence to clinical treatments or public health programs.⁴

So far, only few studies assessed patient-based utility values for CLI and, to our knowledge, no utility data are available for several countries. The objective of this study was to assess the impact of CLI on health preferences and the health status of affected patients, and to derive health state utilities reflecting the possible reduction in QoL.

Materials and Methods

Study Design

The study was designed as an international patient study. After giving informed consent, patients suffering from CLI (stages III and IV, i.e., with pain at rest and ulcers and/or gangrene or amputation according to Fontaine scale) were interviewed by trained and highly experienced interviewers (28 interviewers over the three countries) in health care and patient research. To ensure that all interviews were conducted with high quality and standard procedure, all interviewers have been trained by the core project team via a central telephone briefing. During this briefing, all details regarding the interview process were explained in detail, including the main interview tools used (see "Measuring Instruments" heading). The methodology used in the survey was paper and pencil and face-to-face interviews between June 14, 2010 and July 12, 2010. The average total length of interview was 30 minutes.

Measuring Instruments

The following instruments were used.

Discrete Choice Modeling, Conjoint Analysis

The application of conjoint analysis—including discrete choice experiments—in health has increased rapidly over the past decade.⁶ In this survey, patients were asked within different scenarios to choose between several health states defined by different attributes (pain, wound healing, mobility, dependency degree, planned amputation, prolonged time to amputation due to the medication) and attribute levels. These attributes and attribute levels have been determined on

the basis of preliminary literature reviews and qualitative research with CLI sufferers and clinical experts. All scenarios shown to respondents were computer generated: the number of scenarios to be shown to the respondents was generated following the guidelines of the Sawtooth Software (North Orem, UT) Technical Papers.⁷ In this case, sample size, number of attributes, and attribute levels were defined so that 15 scenarios resulted from the calculation. Furthermore, 15 different, computer-generated versions of the conjoint exercise (each containing the 15 scenarios) were used to guarantee the conjoint design is well balanced across respondents. The 15 versions of the conjoint exercise were distributed across the respondents in each country uniformly. In each scenario (15 different scenarios overall), the patient was asked to choose between three potential health states. The exact questioning used in this survey was the following:

"For the next 15 minutes, I want to do an exercise with you. Let's imagine the following situation: Three patients suffering from limb ischemia meet and talk about their disease. They talk about their current quality of life, their current medication and therapy goals. They discuss the following topics:

Degree of chronic pain they suffer from

Course of healing of ulcer/skin lesion(s) due to current treatment

Their dependency of others

Their mobility

Planned amputation

Prolonged time to amputation due to current medication

In the following I will show you 15 sheets. Each sheet describes the current situation of the three persons A, B, and C. Their current situation is primarily influenced by the current treatment of their limb ischemia. Please select the one person who is living in the best situation according to your opinion."

One scenario example, consisting of three different hypothetical patients, is shown in ► **Table 1**.

EuroQoL Five Dimension Questionnaire

The EQ-5D is a standardized instrument for use as a measure of health outcome and to derive health state utilities. The EQ-5D was developed by the EuroQoL group as a generic instrument for describing and investigating HRQoL.⁸ The EQ-5D is applicable to a wide range of health conditions and treatments, and it provides a simple descriptive profile and a single index value for health status. It is based on a descriptive system that defines health in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.⁹

The EQ-5D questionnaire was answered by respondents and the correspondent index was calculated, indicating the respondent's health status. Additionally, the respondents

Table 1 Exemplary scenario consisting of three hypothetical patients used in conjoint analysis

Patient A	Patient B	Patient C
Chronic pain Moderate pain at rest	Chronic pain Mild pain at rest	Chronic pain Extreme pain at rest
Healing of ulcer/skin lesion(s) Complete cure of skin lesion(s)	Healing of ulcer/skin lesion(s) No improvement of skin lesion	Healing of ulcer/skin lesion(s) Reduction of the number of skin lesion(s)
Dependency Need of a caregiver (e.g., a family member or a nurse) at least once weekly	Dependency 24 × 7 need of a caregiver (e.g., a family member or a nurse)	Dependency No need of a caregiver (e.g., a family member or a nurse)
Ambulatory function/mobility Confined to a chair/wheelchair	Ambulatory function/mobility Walking only inside at home (no need of support device)	Ambulatory function/mobility Daily walking activity with support device (e.g., walker)
Planned amputation Major amputation above knee	Planned amputation No amputation necessary	Planned amputation Major amputation below knee and above the ankle
Prolonged time to major amputation due to the medication Time of 6 months until major amputation		Prolonged time to major amputation due to the medication More than 12 months until major amputation

Appendix 1 Standard gamble interviewing

The following is appendix to “standard gamble interviewing”:

“Imagine there is a new treatment, which is able to cure limb ischemia completely. If the therapy succeeds, it lets them recover the next day and live in perfect health. Though, the therapy is attached to a risk: if the treatment fails, you die painlessly over night. Your physician is not able to predict for which patient the therapy will be successful and for which patient it will be not. He will support your decision for or against the therapy equally.

Would you decide for this new treatment right now if the chances of full health and dead, respectively, are distributed as follows?”

were asked to assess their own current HRQoL using the EQ-5D visual analog scale (VAS). It is important to realize that the evaluation of the EQ-5D VAS mostly differ from those of the EQ-5D index, since it is based on preferences that have been determined, for example, based on a population survey.

Standard Gamble Interviewing

Patients with diagnosis of CLI were interviewed regarding their socioeconomic status, disease status, and preferences. The already published article¹⁰ and slightly modified SG questionnaire used in our study are attached in **Appendix 1**.

Health state is described and followed by a series of 18 single SG tradeoffs. Tradeoffs are presented in descending order from 100% chance of full healing (utility = 1.0) to 10% (utility = 0.1). Health state utility values were estimated as the midpoint between the chance of cure represented by the highest value the patient would accept and the next lowest value. Tradeoff questions are focused on the upper range (above 50% probability of full healing) of the utility scale based on the observation by previous studies that QoL of patients affected by CLI would not be reduced by more than 50%.^{11,12} The SG method we have used in our study did not consider individual life expectancy of participating patients.

Statistical Analyses

For the EQ-5D as well as the SG, the overall utilities were calculated as means ± standard deviation as well as medium values (IQR, interquartile range) over (sub) groups. For comparisons on statistical significance, Mann–Whitney *U* test was used. For statistical analyses, we used PASW© statistics version 18.0.0 (SPSS Inc., Chicago, IL).

For the conjoint analysis, we used a hierarchic Bayes regression based on a mixed multinomial Logit Model to be able to estimate the individual utilities.¹³

Results

A total number of 200 eligible participants (*n* = 75 in France, *n* = 75 in the United States, and *n* = 50 in the UK) were interviewed.

Patient's Baseline Characteristics

Important characteristics of the participating patients are shown in detail in **Table 2**. Most items seem well distributed without any large country-to-country differences. However, there was a noticeable difference in frequency of open wounds at the affected limb and corresponding wound

Table 2 Baseline characteristics of participating patients

Item	Total (n = 200)	United Kingdom (n = 50)	United States (n = 75)	France (n = 75)
Proportion female	46%	48% $p = 0.751$	49% $p = 0.571$	40% $p = 0.414$
Age (mean)	68 years	72 years $p = 0.048$	61 years $p = 0.000$	71 years $p = 0.047$
Patients who had an amputation of the affected limb	9%	8% $p = 0.683$	7% $p = 0.418$	11% $p = 0.176$
Patients with planned amputation	3%	4% $p = 0.720$	1% $p = 0.436$	4% $p = 0.678$
CLI diagnosis (year)	2002	2001 $p = 0.139$	2005 $p = 0.011$	2001 $p = 0.239$
Patients who had a surgery to restore blood flow	42%	38% $p = 0.653$	20% $p = 0.001$	65% $p = 0.000$
Symptoms				
Pain when walking shorter distances	66%	67% $p = 0.870$	53% $p = 0.052$	79% $p = 0.049$
Pain while resting	67%	74% $p = 0.383$	61% $p = 0.387$	69% $p = 0.829$
Open wound/skin lesion at affected limb	73%	89% $p = 0.020$	71% $p = 0.842$	63% $p = 0.128$
Inflammation	67%	65% $p = 0.852$	74% $p = 0.244$	60% $p = 0.309$
Numbness of legs	42%	41% $p = 0.924$	33% $p = 0.181$	52% $p = 0.154$
Comorbidities				
Hypertension	71%	70% $p = 0.889$	71% $p = 0.956$	72% $p = 0.870$
Diabetes	54%	52% $p = 0.849$	55% $p = 0.863$	53% $p = 0.980$
Heart failure	23%	18% $p = 0.446$	23% $p = 0.953$	27% $p = 0.527$
Pulmonary diseases	15%	20% $p = 0.339$	13% $p = 0.805$	12% $p = 0.593$
Renal diseases	13%	16% $p = 0.514$	12% $p = 0.910$	11% $p = 0.677$
Anemia	11%	14% $p = 0.554$	11% $p = 0.937$	9% $p = 0.689$
Cancer ^a	7%	10% $p = 0.393$	8% $p = 0.663$	3% $p = 0.214$
Previous treatment				
Bypass operation/replacement of blood vessels	20%	10% $p = 0.101$	12% $p = 0.124$	35% $p = 0.011$
Mechanical dilation of blood vessels (e.g., balloon angioplasty)	27%	34% $p = 0.328$	11% $p = 0.004$	39% $p = 0.062$
Other blood vessel surgeries	13%	12% $p = 0.850$	13% $p = 0.941$	13% $p = 0.941$
Amputation of a leg or lower leg above the ankle	8%	10% $p = 0.561$	9% $p = 0.618$	4% $p = 0.297$
Amputation of the foot or parts of the foot below ankle	9%	6% $p = 0.561$	3% $p = 0.091$	16% $p = 0.072$

Table 2 (Continued)

Item	Total (n = 200)	United Kingdom (n = 50)	United States (n = 75)	France (n = 75)
Infusion of drugs restoring the blood flow	11%	4% $p = 0.157$	11% $p = 0.968$	15% $p = 0.338$
Oral drugs restoring the blood flow	61%	54% $p = 0.368$	49% $p = 0.082$	77% $p = 0.011$
Pain medication	76%	76% $p = 0.941$	83% $p = 0.207$	68% $p = 0.211$
Wound care, for example, wound dressing and/or débridement	72%	84% $p = 0.083$	72% —	64% $p = 0.199$

Abbreviations: a, currently diagnosed or diagnosis within the last 5 years; CLI, critical limb ischemia.

Note: A p values tested at a 90% confidence interval for each country versus total ($n = 200$).

care. Particularly, the rate of affected patients was comparably high in the United Kingdom, where in 89% of all patients open wounds were recorded; however, the rates in France and the United States were clearly lower (63 and 71%), respectively. Additionally, patients in the United States had a mean of 10 years younger than those in France or the United Kingdom.

Discrete Choice Modeling, Conjoint Analysis

A total of 200 patients took part at the conjoint analysis. The analysis of the relative importance of health attributes showed that a planned amputation had the largest impact on health state preferences (relative importance was 33%), followed by ambulatory function (25%) and chronic pain (15%). Results on the importance of single attributes and on the relative utilities of attribute levels are shown in ►Table 3a, b.

According to this, it can be stated that the omission of a planned amputation as well as the ability to perform daily walking activities (without support device) increase dramatically the health state preference. Regarding chronic pain, even the case of moderate pain at rest, it was accepted by patients; however, extreme pain at rest had a significant negative impact on health state preference.

Not being dependent on a caregiver had a great impact on health state preference, but healing of ulcer/skin lesions had little impact on health state preference, even in a case of complete healing. When it came to prolonged time to amputation, it had a positive influence on patient's health state preference if the time went beyond 12 months.

Table 3a Importance of health attributes (indirect importance), $n = 200$

Chronic pain	15%
Healing of ulcer/skin lesion(s)	8%
Dependency	9%
Ambulatory function/mobility	25%
Planned amputation	33%
Prolonged time to amputation due to the medication	10%

Table 3b Part-worth utility values (relative utilities), $n = 200$

Chronic pain	
No pain or discomfort	26.83
Mild pain at rest	14.16
Moderate pain at rest	8.34
Extreme pain at rest	−49.32
Healing of ulcer/skin lesion(s)	
No improvement of skin lesion	−15.53
Improvement of skin lesion in terms of size reduction	1.62
Reduction of the number of skin lesions	3.88
Complete cure of skin lesion(s)	10.04
Dependency	
No need of a caregiver	25.49
Need of a caregiver	4.8
Daily need of a caregiver	−9.4
24 × 7 need of a caregiver	−20.89
Ambulatory function/mobility	
Daily walking activity	54.44
Daily walking activity with support device	29.24
Walking only inside at home	8.99
Walking only inside at home with support device	−1.01
Confined to a chair/wheelchair	−6.15
Bedridden	−85.5
Planned amputation	
No amputation necessary	125.05
Major amputation below knee and above the ankle	−56.23
Major amputation above knee	−68.82
Prolonged time to amputation due to the medication	
Time of 3 months until major amputation	−22.28
Time of 6 months until major amputation	−9.16
Time of 12 months until major amputation	16.83
More than 12 months until major amputation	14.61

Table 4 Country specific utility results of EQ-5D and standard gamble interviews

Country	EQ-5D Index (<i>n</i> = 200; <i>n</i> _{UK} = 50; <i>n</i> _{USA} = 75; <i>n</i> _{France} = 75)		EQ-5D VAS (<i>n</i> = 200; <i>n</i> _{UK} = 50; <i>n</i> _{USA} = 75; <i>n</i> _{France} = 75)		Standard Gamble (<i>n</i> = 199; <i>n</i> _{UK} = 50; <i>n</i> _{USA} = 74; <i>n</i> _{France} = 75)	
	Mean utility ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Mean utility ± SD	Median (IQR)
All	0.555 ± 0.270	0.689 (0.480)	56 ± 20	50 (25)	0.8376 ± 0.2150	0.9250 (0.2150)
UK	0.474 ± 0.303	0.474 (0.591)	55 ± 23	60 (25)	0.8109 ± 0.2383	0.8500 (0.2075)
United States	0.573 ± 0.199	0.573 (0.364)	54 ± 18	50 (20)	0.8457 ± 0.1702	0.9000 (0.1950)
France	0.590 ± 0.301	0.701 (0.497)	58 ± 20	50 (25)	0.8473 ± 0.2384	0.9700 (0.2249)

Abbreviations: IQR, interquartile range; SD, standard deviation.

EuroQol Five Dimension Questionnaire

The EQ-5D was completed by all patients. CLI patients reported particular impairment in pain and discomfort (64% with some problems and 30% with extreme problems), mobility (84% with some problems and 4% extreme problems), and usual activities (65% with some problems and 12% with extreme problems). The less affected level of HRQoL was self-care, where 58% of all patients did not report any problems. The mean calculated EQ-5D index for CLI patients was 0.555 ± 0.270 (median 0.689, IQR 0.480), the mean EQ-5D VAS score was 56 ± 20 (median 50, IQR 25). Detailed results are also shown in ►Table 4. The investigation did not find any significant differences between countries.

Since the conjoint analysis showed the largest impact of a planned amputation status on patient's QoL, we further analyzed subgroups with regard to the amputation experience (►Table 5). If patients were already amputated respon-

dents or an amputation was planned within the next 12 months, the mean self-rating score (EQ-5D VAS) was significantly lower (mean score for amputation group [*n* = 20] 44.85 ± 22.68 vs. no amputation group [*n* = 180] 56.89 ± 19.61; *p* = 0.016).

Standard Gamble Interviewing

The SG question was answered by 199 patients. The mean overall utility was 0.8376 ± 0.2150 (median 0.9250, IQR 0.2150), a slight country-to-country variation (►Table 4).

Additionally, we measured a significant impact of amputation status on mean health state utilities. If patients were already amputated or an amputation was planned within the next 12 months, the mean utilities were lower for patients in each country compared with patients without amputation (►Table 5). This difference reached statistical significance looking at the total number of participants (mean utility

Table 5 Results on EQ-5D and standard gamble with respect to amputation status (already amputated and planned amputation)

Country	Already amputated or planned amputation within next 12 months	No amputation	<i>p</i> Value
EQ-5DVAS			
All (<i>n</i> = 199)	<i>n</i> = 20 45 ± 23	<i>n</i> = 180 57 ± 20	0.016
UK (<i>n</i> = 50)	<i>n</i> = 6 40 ± 28	<i>n</i> = 44 57 ± 22	0.119
United States (<i>n</i> = 74)	<i>n</i> = 5 46 ± 28	<i>n</i> = 70 55 ± 18	0.283
France (<i>n</i> = 75)	<i>n</i> = 9 47 ± 17	<i>n</i> = 66 59 ± 20	0.121
Standard gamble			
All (<i>n</i> = 199)	<i>n</i> = 20 0.7047 ± 0.2855	<i>n</i> = 179 0.8524 ± 0.2012	0.012
UK (<i>n</i> = 50)	<i>n</i> = 6 0.7167 ± 0.2322	<i>n</i> = 44 0.8237 ± 0.2388	0.119
USA (<i>n</i> = 74)	<i>n</i> = 5 0.7190 ± 0.2944	<i>n</i> = 69 0.8549 ± 0.1573	0.354
France (<i>n</i> = 75)	<i>n</i> = 9 0.6889 ± 0.3407	<i>n</i> = 66 0.8689 ± 0.2155	0.121

amputation group [$n = 20$] 0.7047 ± 0.2855 vs. no amputation group [$n = 179$] 0.8524 ± 0.2012 ; $p = 0.012$). No significant differences with regard to gender were detectable.

Conclusion and Discussion

We performed a preference and QoL study in patients with CLI comprising a discrete choice instrument, a SG instrument, and the EQ-5D. Conjoint analysis showed that planned amputation (33%) was the most relevant health attribute, followed by ambulatory function (25%) and chronic pain (15%). Non-dependence on caregiver impacted on health state preference considerably, whereas healing of ulcer/skin lesions was not impactful. Preference values obtained from the SG are 0.84, for an amputation subpopulation arrived at 0.70. The EQ-5D index values as well as the EQ-5D VAS for CLI patients were 0.56.

Our main SG findings are in line with previously published data. Bult et al reported a mean utility of 0.85 and medium utility of 0.93 among 68 patients with symptomatic peripheral arterial disease.¹² Michaels et al reported a mean utility of 0.79 (95% confidence interval 0.76–0.82) and a median of 0.85 for patients suffering from acute limb ischemia.¹² Also, the results of our EQ-5D questionnaires are in line with results of another recently published international study. As reported by the investigation of Sprengers et al, the largest negative impact of CLI on QoL could be found on dimension pain and discomfort (64% reported some problems + 36% with extreme problems), followed by mobility (96% reported some problems + 4% with extreme problems) and usual activities (62% reported some problems + 28% with extreme problems).² Holler et al identified for a German peripheral artery disease population in Fontaine scales III and IV severity classes corresponding values of 0.58 and 0.53, respectively.¹⁴ EQ-5D VAS values were considerably lower at 0.46 and 0.44, which might be due to the higher amputation subgroup in their population.

Comparing our conjoint analysis results with other studies is not appropriate, as to our knowledge no preference analysis in CLI patients have been reported so far. However, a study identifying treatment preferences in vascular patients identified a preference for local treatment delivery with a willingness to accept increased risks in perioperative mortality, and amputation at least in one health care setting.¹⁵ These results confirm the importance of the identified non-dependence factor.

SG values directly obtained by the patients are significantly higher than the EQ-5D index values. This phenomenon is well known: asking patients regarding their health states leads to higher values compared with interviewing healthy subjects. This is explained both by the fact that values differ by experience with patients rating health states higher than healthy members of the general population (response shift)¹⁶ as well as due to the observation that the general population focuses more on negative aspects of state of illness.¹⁷ As a consequence, the general population may also undervalue or is insensitive to small movements between severe states.¹⁸

Results from other disease areas provided evidence that systematic differences exist in preference values between countries.¹⁹ However, despite a small trend to lower values

being observed for the United Kingdom population, no significant country impact could be detected in our data.

Obtaining preferences for health states are the fundamental basis for the QALYs concept.²⁰ It is well known and accepted that QALYs can only be characterized as utilities under strong restrictive assumptions. One of these assumptions is the linearity of the time component. However, the linear QALY model is most likely to apply to mild health states only.²¹ For severe health states, such as CLI patients with amputation, the deviation is expected to be larger according to Abellán-Perpiñán et al.²¹ Hence, even the threat of amputation in the near future will have a more substantial impact compared with an amputation event being expected in more distant life years.

An interesting finding was made with regard to disease duration and QoL assessment. Patients suffering from longstanding CLI and receiving several surgical interventions are deemed to have a lower QoL than patients with a more recent diagnosis. This effect seems to be mainly driven by a continuous worsening of the disease-related symptoms. In some other diseases, a converse effect is known: a longer disease manifestation can lead to an adaptation effect, which is associated with better QoL assessment.

Our study has several strengths: the setting includes the United States and two European countries (UK and France), which allows for a country control. Furthermore, the number of interviewed patients is substantial ($n = 200$) providing for valid and robust data. Recent comparable studies applying discrete choice methodology reported the following number of patients: Fitzpatrick et al reached 75 patients' parents,²² Waltzman et al approached 111 participants,²³ Bederman et al included 164 patients,²⁴ and Hong et al in a Medicare center setting achieved 355 participants.²⁵

A limitation of our study might be the fact that the number of patients for subgroups, such as the amputated versus non-amputated patients, is unbalanced, that is, the number of amputated patients is rather low (9%). A further aspect might be the selection of only one individual preference instrument, the SG, which is considered by some authors as bearing empirical difficulties in valuing "whole lives."²⁶ Lastly, the cross-sectional nature of our study allows only for analyzing the different groups based on the corresponding variables of interest and does not provide information with regard to longitudinal individual changes, for example, due to amputation.

When considering future preference studies in the CLI setting, the impact of different stakeholders in assessing preferences should be taken into account: Bederman et al confirmed the well-known difference between different stakeholders when comparing patients, family, physicians, and surgeons.²⁴

Overall, it can be stated that the existence of CLI results in decreased QoL values. As utilities obtained from the conjoint analysis reflect the qualitative component of living with a disease, it should be considered as an additional factor in future investigations. Giving patients the outlook of no (further) amputation can impact tremendously patient's preference for a new treatment. Furthermore, the perspective of having an increased mobility (in terms of walking activity) and being quite independent from caregivers can also affect considerably patient's preference for a new treatment.

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