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Clinical Research: Analysis

## Translation, Cross-Cultural Adaptation, and Validation of the Lee Chronic Graft-versus-Host Disease Symptom Scale in a Brazilian Population



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### A B S T R A C T

The Lee Chronic Graft-versus-Host Disease (GVHD) Symptom Scale is a patient-reported instrument developed and validated in English to measure the symptoms and functional impact of cGVHD. This tool has not yet been validated in a Latin American population, however. The Brazil-Seattle Chronic GVHD Consortium conducted a multicenter study at 5 Brazilian institutions to validate the Lee cGVHD Symptom Scale in adults with cGVHD. Study objectives included the translation and validation of the instrument in Brazilian Portuguese and evaluation of the correlation with other quality of life (QoL) tools, including the Medical Outcomes Study Short Form 36 (SF-36) and Functional Assessment of Chronic Illness Therapy with Bone Marrow Transplant subscale (FACT-BMT). Translation and validation were done according to the American Association of Orthopedic Surgeons Outcome Committee guidelines. Spearman's correlation coefficient was used to measure construct validity. Reliability was assessed using Cronbach's  $\alpha$  and intraclass correlation coefficients. Between April 2011 and August 2012, 47 patients with cGVHD based on the 2005 National Institutes of Health criteria (29 males [62%], 18 females [38%]; median age, 48 years; range, 23 to 69 years) were enrolled in this study. The reliability of the Lee cGVHD Symptom Scale was adequate (Cronbach's  $\alpha = 0.62$  to 0.83). The correlations between similar domains of the Lee cGVHD Symptom Scale, SF-36, and FACT-BMT were moderate to high. Our data indicate that the Brazilian Portuguese version of the Lee cGVHD Symptom Scale is valid and reliable and can be used in clinical trials of cGVHD in Brazil.

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### INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a common late complication of allogeneic hematopoietic stem cell transplantation (HSCT), and is associated with increased

morbidity and mortality among HSCT survivors [1]. The incidence of cGVHD varies from 30% to 70% of allogeneic HSCTs depending on various factors, including recipient and donor ages, previous acute graft-versus-host disease, donor type, patient/recipient sex match, stem cell source, graft manipulation, post-transplantation use of cyclophosphamide, use of post-transplantation donor lymphocyte infusion, and the clinical diagnostic criteria used [1,2]. Clinical manifestations of cGVHD often affect multiple systems, including mucocutaneous, ocular, gastrointestinal, hepatic,

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and musculoskeletal, and cGVHD is associated with immunologic impairment [1]. cGVHD is also associated with a graft-versus-tumor effect, resulting in a higher disease-free survival rate compared with that in patients with no previous history of cGVHD [1].

Although the pathophysiology of cGVHD is better understood and new treatments are emerging, the management of severe cGVHD remains a challenge. Quality of life (QoL) studies in survivors of allogeneic HSCT suggest that cGVHD is associated with a decrease in functional status resulting not only from disease-related impairments, but also from adverse effects of treatment [3,4]. Patients with cGVHD are known to have lower physical, sexual, and social functioning, and show impaired physical and psychosocial recovery at 1 year after transplantation and beyond compared with patients without cGVHD [3]. In addition, patients with active cGVHD are at increased risk for developing a life-threatening clinical condition and somatic distress compared with patients with no or inactive cGVHD even 10 years after HSCT [4]. Indeed, many physical dimensions and emotional functions may be impaired by cGVHD over the lifespan. Data on QoL associated with clinical manifestations provide an indicator of health for use in clinical trials as well as for counseling patients and guiding treatment [4,5]. Moreover, higher functional levels are related to good health and longevity and should be considered when assessing disease processes [4].

Numerous QoL instruments have been developed for assessing distinct populations and their specific needs. The Lee Chronic GVHD Symptom Scale was developed and validated in English by Lee et al. [6] as a patient-reported instrument to measure symptoms and specific functional losses in cGVHD. The scale provides a simple, sensitive assessment of cGVHD manifestations. It includes 30 questions with 7 subscales containing 2 to 7 symptom items representing domains of skin, eye, mouth, respiratory system, gastrointestinal system, energy, and psychological status [6], with responses collected on a Likert scale. Completion takes less than 5 minutes.

The Lee Chronic GVHD Symptom Scale remains a broadly used patient-reported measure, recommended by the 2005 and 2014 National Institutes of Health (NIH) Chronic GVHD Consensus Response Criteria Working Group [7,8]. Several reports have validated the scale as a sensitive tool for evaluating cutaneous, fascia, joint, and ocular manifestations of cGVHD [9–11].

The Brazil-Seattle Chronic GVHD Consortium was established to facilitate collaborative studies, initially in cGVHD [12–14]. This consortium was recently adopted by the Brazilian Bone Marrow Transplantation Society as one of the first working groups focused on cGVHD and other late effects of HSCT, the Grupo de Estudos da Doença do Enxerto e Outras Complicações do TMO (GEDECO). The present multicenter study was conducted by the GEDECO at 5 Brazilian institutions. The purpose of the study was to translate, adapt, and validate the Lee Chronic GVHD Symptom Scale in a Brazilian cohort of adult patients with cGVHD, including its correlation with other QoL tools, including the Medical Outcomes Study Short Form 36 (SF-36) and the Functional Assessment of Chronic Illness Therapy with Bone Marrow Transplant subscale (FACT-BMT). Validation of the Lee Chronic GVHD Symptom Scale in different cultures and languages will support its relevance as a QoL instrument in cGVHD studies, and is necessary for its use in Brazil.

## PATIENTS AND METHODS

This was a cross-sectional multicenter GEDECO study conducted at 5 participating centers between April 2011 and August 2012. Criteria for study inclusion were adult patients (aged  $\geq 18$  years) with active cGVHD diagnosed according to the 2005 NIH consensus criteria. Exclusion criteria included an inability to complete the questionnaires and less than 6 months of life expectancy owing to comorbidity or relapse of primary disease. The study was approved by the Institutional Review Boards of the participating centers, and all participants provided written informed consent.

### Study Procedure

This study was initially registered in the national ethical information system for research studies (SISNEP no. 05070.0146.000-10) and later in the Plataforma Brasil Registry (no. 01782412.1.1001.0071). Appropriate patients were identified by individual physicians at the time of clinical visits. Potentially eligible patients were approached for the study and invited to participate. Study participants were asked to complete the Portuguese Lee Chronic GVHD Symptom Scale (Appendix), along with the validated Portuguese versions of the SF-36 and FACT-BMT [15,16]. All study surveys were completed at a single patient visit. All study participants at each center met with the study coordinator before and after completing the surveys. Participants were instructed to ask for clarification if they had any questions while finishing the surveys. All cGVHD assessment forms completed by the patient and the physician were obtained at study entry. Electronic data from each center were assembled in a centralized data base by the coordinating center, the Universidade de Campinas (UNICAMP).

### Translation and Application

The translation into Portuguese and validation of the Lee Chronic GVHD Symptom Scale were done in accordance with American Association of Orthopedic Surgeons Outcome Committee guidelines, as reported previously [17]. The Translation Committee was composed of 2 psychiatrists, 1 hematologist, 1 oral surgeon, 1 biostatistician, and 1 linguistic professional. Two questions regarding discrepancies on the back translation version 1 and version 2 were raised by the Translation Committee and were addressed by e-mail communication with Stephanie Lee, MD, MPH, the creator of the Lee Chronic GVHD Symptom Scale. The suggested correct terms were then considered for the final Portuguese version of the scale (Appendix).

The Lee Chronic GVHD Symptom Scale uses 5-point Likert scales to evaluate symptoms that reflect multiorgan manifestations of cGVHD. It is composed of 30 questions in 7 domains: skin, eyes, mouth, nutrition, lung, energy, and psychological functioning [6]. The “bother” scale is graduated from “not at all” to “slightly,” “moderately,” “quite a bit,” and “extremely,” with corresponding scores of 0 to 4. The SF-36 is a broadly used multidimensional QoL instrument with 36 questions distributed in 8 domains: physical functioning, social functioning, role limitations related to physical problems, role limitations related to emotional problems, mental health, vitality, pain, and general health state [18–20]. Two summary scores, physical and mental, may be calculated from the SF-36. The FACT-BMT is a specific HSCT scale composed of 47 questions distributed in 6 domains: physical well-being, family/social well-being, relationship with the doctor, emotional well-being, functional well-being, and additional worries. The FACT-BMT responses are captured on a Likert scale and scored according to domain as the sum of scores for responses [20].

Patients and physicians also were asked to grade cGVHD severity at the study evaluation. For the patient self-evaluation, severity was assessed by a single multiple-choice question in which the patient classified his or her disease: “Overall, do you think your chronic GVHD is mild, moderate, or severe?” Physicians were asked to score the patients’ cGVHD severity as none, mild, moderate, or severe (scale A) and also on a numerical scale ranging from 0 (as mild as cGVHD symptoms can be) to 10 (as severe as cGVHD symptoms can be) (scale B). Global severity was based on the single-item clinician assessment of mild, moderate, or severe disease.

### Statistical Analysis

Descriptive analyses were performed for demographic and disease data. Construct validity was assessed comparing the Lee Chronic GVHD Symptom Scale with the already validated Portuguese versions of the SF-36 and FACT-BMT. Spearman’s correlation coefficient was used to assess the correlations among domains of the FACT-BMT, SF-36, and Lee scales and between clinical and demographic data and the QoL instruments. The associations between the QoL instruments and patients’ self-evaluation and physicians’ severity scores of cGVHD were tested. Reliability was assessed using Cronbach’s  $\alpha$  coefficients and intraclass correlation coefficients measuring internal consistency. The statistical analyses were performed using SPSS version 15.0 (SPSS Chicago, IL).

## RESULTS

The final Portuguese version of the Lee Chronic GVHD Symptom Scale used in this study is provided in the [Appendix](#). A total of 47 patients from 5 Brazilian institutions participated in this study. Twenty-nine of the patients (61.7%) were male, and the median patients age was 48 years (range, 23 to 69 years). Demographic data and disease characteristics are summarized in [Table 1](#).

**Table 1**  
Characteristics of the Study Cohort (n = 47)

Variable	Value
Patient sex, n (%)	
Male	29 (62)
Female	18 (38)
Donor/recipient sex, n (%)	
Female/male	13 (28)
Others	34 (72)
Age at study enrollment, yr, median (range)	48 (23–69)
White race, n (%)	17 (70)
Level of education at enrollment, n (%)	
Elementary school	21 (45)
High school	14 (30)
College	12 (25)
Karnofsky Performance Scale score at study enrollment, n (%)	
70%	6 (13)
80%	10 (21)
90%	10 (21)
100%	21 (45)
Diagnosis at HSCT, n (%)	
Acute myelogenous leukemia	19 (41)
Chronic myelogenous leukemia	10 (22)
Acute lymphocytic leukemia	6 (13)
Myelodysplastic syndrome	4 (8)
Myelofibrosis	3 (6)
Lymphoma	3 (6)
Others*	2 (4)
Intensity of conditioning regimen, n (%)	
Myeloablative	33 (70)
Nonmyeloablative	14 (30)
Donor type, n (%)	
Related	43 (91)
Unrelated	4 (9)
Graft type	
Peripheral blood stem cells	36 (76)
Bone marrow	11 (24)
cGVHD severity at study enrollment, n (%)	
Mild	16 (34)
Moderate	18 (38)
Severe	13 (28)
cGVHD subtypes at diagnosis of cGVHD, n (%)	
Overlap	21 (45)
Classic	26 (55)
Type of onset of initial cGVHD, n (%)	
De novo	20 (43)
Quiescent	9 (19)
Progressive	18 (38)
Number of cGVHD-involved sites at study enrollment, n (%)	
One	2 (4)
Two	16 (34)
Three	16 (34)
Four	8 (17)
Five	5 (11)
Patients enrolled per centers, n (%)	
University of Campinas	20 (43)
Hospital Amaral Carvalho	12 (26)
National Institute of Cancer in Rio de Janeiro	10 (21)
Hospital Israelita Albert Einstein	3 (6)
Irmandade da Santa Casa de Misericórdia de São Paulo	2 (4)
Time from cGVHD diagnosis to study enrollment, mo, median (range)	12 (0–52)

\* Includes chronic lymphocytic leukemia and paroxysmal nocturnal hemoglobinuria.

Patients' self-evaluation of cGVHD severity was not correlated with any of the parameters analyzed (Karnofsky, Physician's severity evaluation [A and B scales], SF-36, FACT-BMT, and Lee Chronic GVHD Symptom Scale).

There were consistent correlations between the physicians' evaluation of mild, moderate, and severe on the physical domain of SF-36 ( $P = .03$ ) and between the physicians' evaluation of 0 to 10 on the Lee Chronic GVHD Symptom Scale summary ( $P < .0001$ ), FACT-BMT summary ( $P = .008$ ), SF-36 physical domain ( $P = .002$ ), and SF-36 emotional domain ( $P = .01$ ).

The Lee Lung subscale was correlated with age, number of cGVHD sites involved, and type of onset ( $P = .02$ ,  $.01$ , and  $.02$ , respectively). The physicians' mild, moderate, and severe scale was correlated with the Lee eye domain subscale ( $P = .04$ ), and the physicians' 0 to 10 scale was correlated with the Lee subscales of eyes, mouth and nutrition domains subscales ( $P = .02$ ,  $.01$ , and  $.02$ , respectively).

The Lee Chronic GVHD Symptom Scale reliability was adequate (Cronbach's  $\alpha = 0.62$  to  $0.83$ ). Spearman's correlations among similar domains of the Lee Chronic GVHD Symptom Scale, SF-36, and FACT-BMT were moderate to high. [Tables 2 and 3](#) show the intercorrelations among the variables of the Lee cGVHD Symptom Scale and the correlations between Lee cGVHD Symptom Scale and the SF-36 and FACT-BMT QoL instruments, respectively.

## DISCUSSION

The Lee Chronic GVHD Symptom Scale is a patient self-reported instrument validated in English to assess specific symptom bother and correlate with clinical and treatment parameters for purpose of clinical trials [6–8,21]. This study provides a transcultural validation of the Lee scale in Brazilian Portuguese to determine its appropriateness for this patient population, as well as to determine its correlation with 2 other QoL instruments commonly used in HSCT recipients, the SF-36 and FACT-BMT, which have been previously validated in Brazilian Portuguese speakers [15,16].

Since the 2006 Response Criteria Working Group from the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic GVHD recommendation of the Lee Chronic GVHD Symptom Scale as a patient-reported instrument [7], numerous clinical trials have successfully used this instrument to measure the severity of and impairments due to cGVHD and have supported its validity, reliability, and sensitivity [3,21,22]. When our Portuguese version was completed by native speakers, there were no significant criticisms related to the translation or comprehension of the scale. Most questions for clarification were related to the SF-36 and FACT-BMT. The Lee cGVHD Symptom Scale was readily comprehended by the Brazilian patients.

In general, we found weaker correlations between the Portuguese version of the Lee Chronic GVHD Symptom Scale and the SF-36 and FACT-BMT compared with the English version. In addition, the Portuguese version was more strongly correlated with the emotional and mental subscales compared with the English version, which was most strongly correlated with the physical, functional, and vitality subscales. In both the Portuguese and English versions, the relationships among the different subscales of the Lee cGVHD Symptom Scale were similar, and the eyes, mouth, and lung subscales were less closely correlated than the other subscales with the SF-36 and FACT-BMT.

Although the physicians' severity ratings correlated with the questionnaires, the patients' self-assessments did not

**Table 2**  
Score Distribution and Intercorrelation for the Lee Chronic GVHD Symptom Scale

	Energy	Skin	Nutrition	Lung	Psychological	Eye	Mouth	Summary
Items, n	7	5	5	5	3	3	2	30
Mean	24	21	10	11	26	46	22	23
SD	18	21	13	12	22	30	26	13
Median	21	15	5	10	16	41	12	21
Range	0-64	0-80	0-65	0-50	0-75	0-100	0-100	0-57
Cronbach's $\alpha$	0.81	0.77	0.62	0.65	0.71	0.83	0.71	0.86
Floor, %	6	19	34	27	21	6	36	2
Ceiling, %	2	2	2	2	6	4	2	2
Intercorrelation								
Energy		0.25	0.33 <sup>†</sup>	0.33 <sup>†</sup>	0.58 <sup>*</sup>	0.25 <sup>†</sup>	0.36 <sup>†</sup>	0.65 <sup>*</sup>
Skin			0.33 <sup>†</sup>	0.25	0.32 <sup>†</sup>	0.01	0.40 <sup>‡</sup>	0.55 <sup>*</sup>
Nutrition				0.17	0.04	0.24	0.52 <sup>*</sup>	0.48 <sup>*</sup>
Lung					0.35 <sup>†</sup>	0.27	0.28 <sup>†</sup>	0.54 <sup>*</sup>
Psychological						0.27	0.26	0.69 <sup>*</sup>
Eye							0.19	0.59 <sup>*</sup>
Mouth								0.63 <sup>*</sup>

SD indicates standard deviation.

\*  $P \leq .0001$ .

†  $P \leq .05$ .

‡  $P \leq .001$ .

correlate well with most parameters analyzed. We hypothesize that patients' self-assessment of their cGVHD severity is a broad question that addresses the clinical aspect of cGVHD generally. Patients' understanding of their disease and its severity along the spectrum of possible illness is likely less accurate than their ability to report their symptoms. Other studies have also verified that patients tend to classify themselves differently from clinicians regarding skin involvement and joint status, and the concordance between clinicians and patients was considered moderate when rated only as improved, stable, or worse [9,11]. Thus, we can

assume that discrepancies may be expected when patients are asked about their perception of clinical conditions rather than symptoms. Furthermore, a single-item response, such as patients' self-assessment, can lead to bias, misinterpretation, and increased measurement error [23].

In contrast to 59% of the original population with a bachelor or higher degree reported by Lee et al. [6], only 25% of the present study population had a college degree, which is representative of the Brazilian population. This difference could have impacted our results for patients' severity self-assessment when compared with the original study, in

**Table 3**  
Correlation Between the Lee Chronic GVHD Symptom Scale and the SF-36 and FACT-BMT

	Lee Chronic GVHD Symptom Scale							
	Skin	Eye	Mouth	Lung	Nutrition	Energy	Psychological	Summary
SF36								
Physical	•	•	•	•	•	•	•	•
Role physical	•	•	•	•	•	•	•	•
Pain	•	•	•	•	•	•	•	•
General health	•	•	•	•	•	•	•	•
Vitality	•	•	•	•	•	•	•	•
Social functioning	•	•	•	•	•	•	•	•
Role emotional	•	•	•	•	•	•	•	•
Mental health	•	•	•	•	•	•	•	•
Summary physical	•	•	•	•	•	•	•	•
Summary mental	•	•	•	•	•	•	•	•
FACT								
Physical	•	•	•	•	•	•	•	•
Social functioning	•	•	•	•	•	•	•	•
Emotional	•	•	•	•	•	•	•	•
Functional	•	•	•	•	•	•	•	•
BMT module	•	•	•	•	•	•	•	•
Summary FACT-BMT	•	•	•	•	•	•	•	•

SF-36 indicates Short-Form Health Survey; FACT, Functional Assessment of Cancer Therapy; FACT-BMT, Functional Assessment of Cancer Therapy—Bone Marrow Transplant.

•,  $0.0 < r \leq 0.2$ ; •,  $0.2 < r \leq 0.4$ ; •,  $0.4 < r \leq 0.6$ ; •,  $0.6 > r$ .

which the patients' self-assessment correlated with most of parameters related to patients' self-report of other aspects of health. We can surmise that information on clinical aspects tends to be clearer when obtained from a highly educated population. Given that in the process of cross-cultural adaptation, the patients' responses in the Brazilian Portuguese version of the Lee Chronic GVHD Symptom Scale correlated with the SF-36 and FACT-BMT for similar domains and some domains correlated with the physicians' scale, we conclude that our patients were able to understand the scale, and that the scale is a valid measure of cGVHD symptoms in this population.

The lack of correlations between some of the SF-36 domains with the physician scales could be explained by the fact that SF-36 is a general instrument of QoL and is not specific to HSCT or cGVHD. However, the correlation with the Lee cGVHD Symptom Scale was moderate to high, indicating adequacy in construct validity. Similar domains of the FACT-BMT, SF-36 and Lee Chronic GVHD Symptom Scale had moderate to high correlation, and reliability was adequate (Cronbach's  $\alpha = 0.62$  to  $0.83$ ).

In summary, the Lee Chronic GVHD Severity Scale has been successfully validated in Brazilian Portuguese patients and is now available for use in clinical trials in Brazil. Future studies are needed to evaluate the added value of this instrument for assessing treatment response and QoL in clinical trials of patients with cGVHD in Brazil.

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**APPENDIX**

Portuguese Version of the Lee Chronic GVHD Symptoms Scale

Escala de Sintomas da Doença do Enxerto contra o Hospedeiro Crônica.

Circulando um (1) número por linha, por favor, indique quanto os problemas abaixo o incomodaram durante o último mês.

	Nem um pouco	Um pouco	Moderadamente	Bastante	Extremamente
<b>PELE</b>					
1. Cor anormal da pele	0	1	2	3	4
2. Vermelhidão	0	1	2	3	4
3. Pele endurecida/grossa	0	1	2	3	4
4. Feridas na pele	0	1	2	3	4
5. Coceira na pele	0	1	2	3	4
<b>OLHOS E BOCA</b>					
6. Olhos secos	0	1	2	3	4
7. Precisa usar colírio frequentemente	0	1	2	3	4
8. Dificuldade para enxergar claramente	0	1	2	3	4
9. Precisa evitar alguns alimentos em razão de dores na boca	0	1	2	3	4
10. Feridas na boca	0	1	2	3	4
11. Recebendo alimentação pela veia ou por sonda	0	1	2	3	4
<b>RESPIRAÇÃO</b>					
12. Tosse freqüente	0	1	2	3	4
13. Alteração na cor do catarro	0	1	2	3	4
14. Falta de ar quando faz esforço	0	1	2	3	4
15. Falta de ar em repouso	0	1	2	3	4
16. Necessita de oxigênio	0	1	2	3	4
<b>ALIMENTAÇÃO E DIGESTÃO</b>					
17. Dificuldade de engolir alimentos sólidos	0	1	2	3	4
18. Dificuldade de engolir líquidos	0	1	2	3	4
19. Vômitos	0	1	2	3	4
20. Perda de peso	0	1	2	3	4
<b>MÚSCULOS E ARTICULAÇÕES</b>					
21. Dor nas juntas e nos músculos	0	1	2	3	4
22. Movimentos limitados nas juntas	0	1	2	3	4
23. Câimbras	0	1	2	3	4
24. Fraqueza nos músculos	0	1	2	3	4
<b>ENERGIA</b>					
25. Perda de energia/fraqueza	0	1	2	3	4
26. Precisa dormir mais/cochilar	0	1	2	3	4
27. Febre	0	1	2	3	4
<b>MENTAL E EMOCIONAL</b>					
28. Depressão	0	1	2	3	4
29. Ansiedade	0	1	2	3	4
30. Dificuldade para dormir	0	1	2	3	4