Assessment of fatigue using the Identity-Consequence Fatigue Scale in patients with lung cancer

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INTRODUCTION

Fatigue is a subjective complaint of patients with various chronic illnesses and can affect work performance and activities of daily living, as well as social and family responsibilities.\textsuperscript{(1)} Cancer-related fatigue is reportedly in the range of 70-80\%.\textsuperscript{(1-3)} The most severe fatigue is reported among lung cancer (LC) patients and persists for several months or years after treatment completion, having a great negative impact on the quality of life of those patients.\textsuperscript{(4-7)}

The pathogenesis of cancer-related fatigue is poorly understood. In attempts to explain fatigue, models have been developed based on both physiological and psychological aspects. The mechanisms involve effects of cancer or of its treatment on the central nervous system, muscle energy metabolism, sleep/circadian rhythms,\textsuperscript{(8,9)} mediators of inflammation,\textsuperscript{(10)} stress,\textsuperscript{(10)} immune activation,\textsuperscript{(11)} and hormonal changes related to effects on the hypothalamic-pituitary axis.\textsuperscript{(12-14)} Immune activation has been associated with fatigue and depression in patients with cancer or other chronic diseases.\textsuperscript{(15,16)} Therefore, a better understanding of LC-related fatigue and its correlation with biomarkers, physical function, and psychological parameters is important to enable more personalized interventions.

Fatigue is also one of the most commonly reported symptoms by patients with chronic heart disease (CHD). Causes of fatigue in heart failure include low cardiac output, poor tissue perfusion, muscle metabolic abnormalities, autonomic nervous system abnormalities, deconditioning effects, and endothelial dysfunction.\textsuperscript{(17,18)}

Fatigue has been most commonly assessed by self-report questionnaires.\textsuperscript{(2-5)} The Identity-Consequence Fatigue Scale (ICFS) is a validated comprehensive questionnaire that identifies the energy levels of patients and is appropriate to identify both mental and behavioral consequences of cancer-related fatigue.\textsuperscript{(19,20)} The objective of this study was to evaluate the measurement properties of the ICFS, as well as the intensity of fatigue and the associated factors, in LC patients. To our knowledge, this is the first

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Financial support: This study received partial financial support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazilian National Council for Scientific and Technological Development).
study to evaluate fatigue using the ICFS in LC patients. Because ICFS is a generic fatigue questionnaire, it allows for comparisons to be made among different patient populations.

**METHODS**

This was a cross-sectional study involving 50 consecutive patients previously diagnosed with non-small cell LC (LC group) and referred to an outpatient clinic at a teaching hospital in the city of Fortaleza, Brazil, for staging and potential surgical treatment. Patients who were incapable of understanding the scale were excluded, as were those who had neurologic, vascular, or musculoskeletal diseases that limited their ability to perform the six-minute walk test (6MWT). In addition, two other groups, matched for age and gender, were studied for comparison: 50 patients with CHD recruited from the cardiology outpatient clinic in the same teaching hospital (CHD group); and 50 healthy volunteers from a local community senior center (control group).

All LC cancer participants were initially assessed in order to determine relevant demographic and clinical parameters. LC staging was obtained from the medical records of the patients. All LC patients underwent spirometry, were submitted to the 6MWT, completed questionnaires/scales (anxiety and depression, fatigue, daytime somnolence, and health-related quality of life), and had their serum C-reactive protein (CRP) levels measured. Specific questionnaires were completed in a face-to-face interview by two medical investigators. A metabolic equivalent of CRP was established in order to determine the validity of ICFS, because we hypothesized that fatigue was associated with inflammation. The participants in the CHD and control groups completed the ICFS once only.

**Research tool**

The ICFS is a 31-item self-report tool that assesses five domains of fatigue (feelings of fatigue, feelings of vigor, impacts on concentration, impacts on energy, and impacts on daily activities) and provides two summary scores: fatigue experiences and fatigue impacts.\(^{(19)}\)

The “fatigue experiences” score is the average of “feelings of fatigue,” “feelings of vigor,” and “impacts on concentration” subscale scores. The “fatigue impacts” score is the average of “impacts on energy” and “impacts on daily activities” subscale scores. For the items in the “feelings of fatigue,” “feelings of vigor,” “impacts on energy,” and “impacts on concentration” domains, the anchors are “not at all” (score = 0); and “almost never,” “some of the time,” “fairly often,” “very often,” and “all of the time” (score = 5). For the items in the “daily activity” domain, the anchors are “not at all” (score = 0); and “only occasionally,” “some of the time but less than usual,” “nearly as often as usual,” and “as often as usual” (score = 4). For two items in the “impacts on energy” subscale (“I have achieved very little with the day” and “I lack the energy to do things that I normally do”), the scores are rated as follows: 0 = “I strongly agree”; 1 = “I agree”; 2 = “neutral”; 3 = “I disagree”; and 4 = “I strongly disagree.” The scores are reported as a percentage of the maximum possible score available for each participant. In this study we used the Brazilian-Portuguese version of the ICFS.

**Translation process**

First, the English-language version of the ICFS was independently translated into Brazilian Portuguese by two of the investigators. The two translations were compared until a consensus version was agreed upon. That version was administered to a small sample of five patients with LC in order to evaluate clarity and to ensure that no terms or situations in the questionnaire were considered obscure or difficult to understand. This Brazilian Portuguese-language version was then back-translated into English by a translator who had no prior knowledge of the original scale. The author of the original scale assessed the back-translation, which was discussed with the investigators, and a final version was then obtained. The final version (Appendix) was administered to the participants in the present study. The Appendix is available online at http://jornaldepneumologia.com.br/detalhe_anexo.asp?id=50

**Measurements**

In order to test the inter-rater reliability of the Brazilian Portuguese-language version of the ICFS, the instrument was administered to the LC patients twice by two observers, 30 minutes apart, during the first visit (V1). The second visit (V2) occurred 7 days after V1, and the ICFS was again administered to the same patients by only one of the observers in order to test intra-rater reliability. We chose a 7-day interval because it was more practical for the participants who lived outside the city of Fortaleza and for those who had started receiving chemotherapy. A 7-day interval between visits has also been used in other intra-observer reliability studies.\(^{(21)}\) All other assessments were carried out at V1.

The Fatigue Severity Scale (FSS)\(^{(22)}\) is a seven-point Likert scale in which 1 means “I strongly disagree,” and 7 means “I strongly agree.” Higher scores indicate more severe fatigue. In the present study, we used the Portuguese-language version of the FSS validated for use in Brazil.\(^{(23)}\)

Symptoms of depression and anxiety states were assessed using the Hospital Anxiety and Depression Scale (HADS). This scale consists of 14 items, of which 7 focus on the assessment of anxiety (HADS-A subscale), and 7 focus on the assessment of depression (HADS-D subscale). Each item can be scored from 0 to 3, the maximum score on each subscale being 21 points. This scale was selected because it was specifically developed to assess anxiety and depression in medically ill patients; therefore, it excludes items that are related to somatic symptoms.\(^{(24)}\) We used the Portuguese-language version of the HADS validated for use in Brazil.\(^{(25)}\)

The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) is a patient-reported survey...
The sample size (50 subjects) was calculated on the type I error. The level of significance was set at 5%.

The Epworth Sleepiness Scale (ESS) is a simple and reliable instrument that has been widely used in order to measure daytime sleepiness; we used the ESS version that had been translated to Portuguese and adapted for use in Brazil. The subjects are required to rate their likelihood of falling asleep on a scale of increasing probability (from 0 to 3) for eight different situations in which most people find themselves during their activities of daily living. The scores for the eight questions are added together to obtain a single number.

Spirometry was performed in accordance with Miller et al. Measurements included FEV$_1$, FVC, and the FEV$_1$/FVC ratio. The results were compared with reference values established by Pereira et al.

The 6MWT is a simple and practical standardized test for the evaluation of exercise capacity. The six-minute walk distance (6MWD) is defined as the distance a patient can quickly walk on a flat, hard surface in a period of six minutes. The test was carried out indoors along a flat, straight, 30-m corridor. Patients were asked to walk at their fastest pace from one end of the corridor to the other end as many times as possible. The 6MWD was then measured.

Statistics

Data were statistically analyzed with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA). We used descriptive analysis and frequencies in order to assess the characteristics of the sample. Kruskal-Wallis H test was used in order to compare the fatigue scores in the three groups. We used the intraclass correlation coefficient (ICC) for the analysis of reproducibility of the application and reapplication of the ICFS (V1 vs. V2). The Wilcoxon test was used in order to compare the scores obtained from the administration of the ICFS by the same observer in V1 and V2. Bland-Altman plots were used in order to improve the visualization of the test-retest reliability obtained from the various administrations of the ICFS. The ICFS was tested for internal consistency by Cronbach’s alpha coefficient. In order to validate the ICFS, we used Spearman’s correlation test to assess the strength of the correlations between its scores and those obtained on the FSS, HADS, SF-36, and ESS, as well as the 6MWD, spirometry values, and CRP levels. Bonferroni correction was used for multiple comparisons to alter the p value to a more stringent value in order to reduce the likelihood of a type I error. The level of significance was set at 5%. The sample size (50 subjects) was calculated on the basis of the hypothesis of a moderate correlation ($r = 0.5$) between the degree of fatigue measured by the ICFS and that measured by other instruments. That level was set at two-sided $\alpha = 0.05$ and $\beta = 0.20$.

Ethical aspects

This study was conducted in accordance with Brazilian National Health Council Resolution 196/96, which established ethical principles for human research, and was approved by the local research ethics committee. All patients gave written informed consent prior to their inclusion in the study.

RESULTS

The study sample comprised 150 patients, 50 in each group (LC, CHD, and control). The major characteristics of the patients in the LC group are summarized in Table 1. A Kruskal-Wallis H test showed that there was a statistically significant difference in the “fatigue experiences” scores among the three groups—$\chi^2(2) = 23.63; p = 0.001$—with a mean rank score of 80.2 in the LC group, 92.2 in the CHD group, and 51.6 in the control group (Table 2). A post hoc test showed that there was no difference between the LC and CHD groups regarding the ICFS summary variable “fatigue experiences”; both groups presented with a higher level of fatigue when compared with the control group. There was a progressive increase in the mean rank of the ICFS summary variable “fatigue impacts” scores ($\chi^2(2) = 41.74; p = 0.001$). A post hoc test showed that there was a significant difference when the control group was compared with the LC and CHD groups (p < 0.001 for both), and when the LC group was compared with the CHD group (p < 0.001). No differences in the ICFS summary variables “fatigue experiences” and “fatigue impacts” were observed in regard to gender, age (≤ 65 years vs. > 65 years), LC staging (stages I/II vs. III/IV), or chemotherapy.

There were no significant differences between the ICFS summary variables “fatigue experiences” and “fatigue impacts” scores obtained by the same observer in different visits (V1 = 30.9 ± 18.4; V2 = 31.8 ± 17.1; p = 0.8; and V1 = 28.1 ± 15.0; V2 = 25.3 ± 12.9; p = 0.3; respectively). The ICCs for intra-rater reliability (V1 vs. V2) regarding the same summary variables were 0.94 (95% CI: 0.90-0.97) and 0.76 (95% CI: 0.57-0.86), respectively. Neither were there significant differences between the two observers of the study for the same summary variables scores (30.9 ± 18.4 vs. 32.5 ± 19.8; p = 0.6; and 28.1 ± 15.0 vs. 28.2 ± 10.0; p = 1.0; respectively). The ICCs for inter-rater reliability on the ICFS summary variables “fatigue experiences” and “fatigue impacts” were 0.94 (95% CI: 0.90-0.96) and 0.79 (95% CI: 0.64-0.88), respectively. Excellent inter-rater and intra-rater reliability were also identified in the Bland-Altman plots (Figures 1 and 2). The Cronbach’s alpha coefficient for the ICFS was 0.88 (95% CI: 0.82-0.92), indicating excellent internal consistency.

There were significant correlations of the FSS scores with the ICFS summary variables “fatigue experiences”
and “fatigue impacts” scores (r = 0.60 and r = 0.52, respectively). Anxiety and depression scales were significantly correlated with the summary variables

Table 1. Characteristics of the patients with lung cancer in the study (N = 50).+

| Variable                  | Result         |
|---------------------------|----------------|
| Age, years               | 60 ± 12.2      |
| Male                      | 27 (54)        |
| Female                    | 23 (46)        |
| Cancer stage              |                |
| I or II                   | 24 (48)        |
| III or IV                 | 26 (52)        |
| Chemotherapy              | Yes            |
|                           | 6 (12)         |
|                           | No             |
| FEV1, % of predicteda    | 86.3 ± 19.8    |
| FVC, % of predicteda     | 86.9 ± 17.8    |
| 6MWD, m4                  | 478.4 ± 104.6  |
| BMI, kg/m2                | 25.9 ± 3.5     |
| ICFS5                     |                |
| Feelings of fatigue      | 32 (12-44)     |
| Feelings of vigor        | 45 (5-60)      |
| Impacts on energy        | 35.7 (28.5-50.0)|
| Impacts on concentration | 22 (8-40)      |
| Impacts on daily activities | 14.3 (1.0-27.0) |
| ICFS summary variable    |                |
| Fatigue impacts          | 24.3 (17.6-38.0)|
| Fatigue experiences      | 31.9 ± 18.6    |
| Epworth Sleepiness Scale | 7.1 ± 3.8      |
| SF-36 MCSd               | 47.7 ± 13.3    |
| SF-36 PCSd               | 45.6 ± 8.4     |
| Fatigue Severity Scale   | 23 (12-33)     |
| HADS-Ae                  | 5 (3-8)        |
| HADS-Dd                  | 4.5 (2.0-7.0)  |
| CRP, mg/Lf               | 2.9 (1.1-6.1)  |

6MWD: six-minute walk distance; ICFS: Identity-Consequence Fatigue Scale; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; MCS: mental component summary; PCS: physical component summary; HADS-A: Hospital Anxiety and Depression Scale-anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-depression subscale; and CRP: C-reactive protein. +Values are expressed as mean ± SD. *Values are expressed as median (interquartile range).**Values are expressed as mean ± SD. "fatigue experiences” (r = 0.43; p = < 0.01; and r = 0.60; p = < 0.01; respectively) and “fatigue impacts” (r = 0.62; p = < 0.01; and r = 0.63; p = < 0.01; respectively). The same summary variables correlated negatively with the mental component summary of SF-36 (r = −0.55; p < 0.01; and r = −0.48; p = < 0.01; respectively). After the Bonferroni correction for multiple comparisons, serum CRP levels showed a positive correlation with the summary variable “fatigue impacts”. However, no significant correlations were found with the ESS score (Table 3).

**DISCUSSION**

The present study shows that the Brazilian Portuguese-language version of the ICFS has excellent inter-rater/intra-rater reliability, high internal consistency, and good correlations with clinical and psychological parameters. The ICFS clearly distinguished among different patient populations.

One issue for clinicians and researchers is the choice of the fatigue scale to be used. Certainly, there is still work to be undertaken in understanding the phenomenon of fatigue and how it should be measured. The ICFS was chosen by the investigators because it is a multidimensional instrument that captures multiple characteristics and manifestations of fatigue.

In the present study, the ICFS correlated with a wide range of variables. The strong correlation between the FSS and ICFS is remarkable, considering the fact that they were developed using different samples of patients, as well as that they present different structures, layouts, and response formats.

The mental component summary of the SF-36 correlated negatively with both of the ICFS summary variables. The reason is that the SF-36 mental component summary comprises the vitality subscale, which addresses energy level and fatigue. Tang et al.(32) showed an association between SF-36 and fatigue measured by FSS. The magnitude of the correlation was highest for the vitality domain.

Both ICFS summary variables correlated with anxiety and depression. Our results are consistent with those of previous reports that showed a strong correlation between depression and fatigue.(14,33) One hallmark of depression is a decreased motivation to do things that the patient once enjoyed. This is addressed by the ICFS items (e.g., “It has been hard for me to get motivated to do my regular activities.”)

Table 2. Comparisons among the three groups studied (N = 50 in all).

| Variable                  | Control | Lung cancer | Chronic heart disease | p     |
|---------------------------|---------|-------------|-----------------------|-------|
| Male, n (%)               | 27 (54) | 27 (54)     | 24 (50)               | 0.8   |
| Age, years                | 60.5 ± 12.2 | 60.4 ± 12.0 | 60.3 ± 12.2 | 0.9   |
| ICFS-fatigue experiences† | 51.6    | 80.2        | 92.2                  | 0.001*|
| ICFS-fatigue impacts‡     | 47.5    | 73.7        | 103.7                 | 0.001**|

ICFS: Identity-Consequence Fatigue Scale. †Value is expressed as mean ± SD. ‡Values are expressed as mean rank score. *Control group vs. lung cancer and chronic heart disease groups. **Control group vs. lung cancer and chronic heart disease groups; and lung cancer group vs. chronic heart disease group.
A remarkable correlation was found between fatigue and anxiety. This could be explained by the fact that people with anxiety are prone to panic, fear, and other high-stress responses which cause fatigue, increasing the levels of stress hormones.\(^\text{(34)}\)

Previously, correlations between fatigue and sleep disorders have been noted in patients undergoing radiotherapy and surgery, as well as in those with a variety of cancer types, including LC.\(^\text{(35)}\) In our study, under the criterion of Bonferroni correction for multiple comparisons, fatigue did not correlate with excessive daytime sleepiness. A possible explanation could be the fact that only a few patients (only 10%) presented with excessive daytime sleepiness.

In the present study, we measured fatigue in a multidimensional way and found a correlation between CRP levels and fatigue impacts. Previous studies measured fatigue in a unidimensional way and could not find significant correlations with inflammatory markers.\(^\text{(38,39)}\) Those studies are controversial, and further research is warranted in order to investigate the relationship between elevated serum concentrations of inflammatory markers and subjective complaints of fatigue.

In contrast with our results, fatigue has been previously reported to be correlated with LC stage and the use of chemotherapy.\(^\text{(6,12)}\) Because only 12% of our patients were on chemotherapy on the assessment day, it is possible that our study lacked statistical power to detect this association. A similar effect may be present in regard to cancer staging.

Our sample of LC patients reported higher intensity of fatigue than did the control group patients. By comparing the LC group with that with another chronic disease (CHD group), we found that the scores for “fatigue experiences” were similar, although those for “fatigue impacts” were lower in the former group. Patients with heart disease present with restrictions on their activities of daily living (as measured by the

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Figure 1. Bland-Altman plots. In A, intra-rater analysis of fatigue experiences: mean = −0.98; UL = 15.24; LL = −17.00. In B, intra-rater analysis of fatigue impacts: mean = 2.78; UL = 25.15; LL = −19.58. UL: upper limit; and LL: lower limit.

Figure 2. Bland-Altman plots. In A, inter-rater analysis of fatigue experiences: mean = −1.61; UL = 14.95; and LL = −18.18. In B, inter-rater analysis of fatigue impacts: mean = −0.04; UL = 22.38; and LL = −22.46. UL: upper limit; and LL: lower limit.
summary variable "fatigue impacts"); one explanation for this could be that patients with heart disease have impaired peripheral circulatory perfusion and, consequently, reduced oxygen delivery and impaired muscle strength.

One limitation of this study is that it had a cross-sectional design; therefore, it provides no indication of the responsiveness of the ICF scale over time. Another limitation is that subjects were recruited from a single center and might differ from LC patients under treatment elsewhere. Overall, more research is needed in order to understand the clinical significance attributable to patient reports of fatigue.

The strength of the study is the use of a more comprehensive measure of fatigue. The ICF scale provides a general assessment for use in a variety of medical situations in which a complete evaluation of fatigue is desired. It is important to measure fatigue in LC patients in order to develop effective, patient-centered management strategies, as well as to improve the physical functioning, quality of life, and psychological health of these patients.

In conclusion, the present study presents evidence that the Brazilian Portuguese-language version of the ICF scale is a reliable tool for measuring fatigue in LC patients.

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Table 3. Correlations of fatigue, as measured by the scores of the Identity-Consequence Fatigue Scale summary variables (fatigue experiences and fatigue impacts), with other variables studied.

| Variable | Fatigue experiences | | | Fatigue impacts | | |
|----------|----------------------|---|---|-----------------|---|---|
|          | r                    | p | p* | r               | p | p* |
| Fatigue Severity Scale | 0.60 | < 0.001 | 0.007 | 0.52 | < 0.001 | 0.007 |
| FEV₁, % of predicted | 0.14 | 0.313 | 2.171 | 0.12 | 0.376 | 2.591 |
| 6MWD | −0.16 | 0.261 | 1.827 | −0.09 | 0.950 | 6.651 |
| HADS-A | 0.43 | 0.002 | 0.014 | 0.62 | < 0.001 | 0.007 |
| HADS-D | 0.60 | < 0.001 | 0.007 | 0.63 | < 0.001 | 0.007 |
| SF-36 MCS | −0.55 | < 0.001 | 0.007 | −0.48 | < 0.001 | 0.007 |
| SF-36 PCS | 0.29 | 0.239 | 0.16 | 0.102 | 0.714 |
| Epworth Sleepiness Scale | 0.19 | 0.181 | 1.267 | 0.32 | 0.021 | 0.147 |
| CRP, mg/L | 0.28 | 0.048 | 0.336 | 0.50 | < 0.001 | 0.007 |

6MWD: six-minute walk distance; HADS-A: Hospital Anxiety and Depression Scale—anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale—depression subscale; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; MCS: mental component summary; PCS: physical component summary; and CRP: C-reactive protein. *After Bonferroni correction: α critical = 0.048.
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