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Research Article

Investigating Fatigue and Its Relationship to Quality of Life and Pruritus in Cutaneous T-Cell Lymphoma

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Cancer-related fatigue as a morbid state of physical, emotional, and mental exhaustion influencing everyday life is an important yet poorly investigated symptom in patients with cutaneous T-cell lymphomas. The aim of this study was to evaluate the prevalence of and the association between pruritus, quality of life, and fatigue in patients with cutaneous T-cell lymphomas. Mycosis fungoides and Sézary syndrome patients were invited to complete the Functional Assessment of Cancer Therapy-General (FACT-G) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) subscale questionnaire. Pruritus was assessed using the peak pruritus numeric rating scale. Half of the 38 recruited patients reported fatigue. 13 patients (34%) suffered from severe fatigue. The median (interquartile range) FACIT-Fatigue subscale score was 35.5 (25.75–43). The advanced disease stage was associated with more severe fatigue and a poorer quality of life. The FACIT-Fatigue subscale score was significantly correlated with quality of life ($r = 0.8$ and $P < 0.0001$). More than 80% of patients reported pruritus. There was no correlation between pruritus and fatigue ($r = -0.19$ and $P = 0.26$). All in all, fatigue is a common symptom of cutaneous T-cell lymphomas in early and advanced stage disease and has a strongly negative effect on cutaneous T-cell lymphoma patients' quality of life.

1. Introduction

Fatigue is one of the most common symptoms among cancer patients. It can be described as a morbid state of physical, emotional, and mental exhaustion that is not proportional to recent activities [1, 2]. Patients may experience fatigue as being exhausted, tired, weak, or slowed. Cancer-related fatigue (CRF) underlies a multifactor genesis and may be due to the cancer itself, its treatment, and/or psychosocial variables. The affected may suffer greatly and may be heavily restricted in their everyday life [3, 4]. With its diverse manifestations, CRF is often unrecognized and overlooked [5]. Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of rare malignancies characterized by the proliferation of malignant lymphocytes that primarily manifest in the skin [6]. Mycosis fungoides (MF) is the most common type of CTCL and accounts for 60% of CTCLs. Sézary syndrome (SS) represents a rare leukemic subtype of CTCL with an approximate incidence of one case per million. Clinical presentation varies from localized eczematous patches and plaques in early stages of disease to skin tumors and/or involvement of lymph nodes, blood, or solid organs in advanced disease stages of MF and SS. Early stage CTCL is typically slowly progressive and chronic

[7–9]. The manifold of clinical manifestations causes a wide range of different symptoms. Many symptoms can have a profound and severe impact on patients' psychosocial well-being, daily functioning, and perceived overall quality of life (QoL). The most frequently reported symptoms are itching, pain, and fatigue [10]. In the past, CTCL associated fatigue was mostly neglected in clinical research and remained poorly explored. Furthermore, there is only limited data on the impact of fatigue on QoL in CTCL patients. Therefore, in this study, we aimed to evaluate fatigue and its association with QoL and pruritus in patients with CTCL.

2. Materials and Methods

CTCL patients seen at the Department of Dermatology of the Johann Wolfgang Goethe-University Hospital in Frankfurt am Main between May 2017 and August 2019 were identified. Written informed consent was obtained from all patients, and the study was approved by the Ethical Committee at the University Hospital Frankfurt (project number: 365/18). Patients were eligible if they were aged over 18 years and if they did not suffer from any other tumor disease. The use of mono or combination CTCL therapies was allowed. Demographic and clinical details were obtained from the hospital notes on age, gender, stage of disease, and current medication. The subjects had to complete the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), which is an unidimensional 40-item self-report questionnaire assessing QoL and fatigue and its impact upon daily activities and function. All items are rated using a 5-point intensity rating scale. 27 of the mentioned 40 items refer to the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire measuring QoL. The remaining 13 items refer to the FACIT-Fatigue-Subscale (FS), measuring fatigue [11]. All questionnaires are easy to complete and can be used in a variety of clinical settings. The FACIT-F is translated in more than 45 different languages, including German and allowing cross-cultural comparisons. The reliability and validity of the German translation of the FACIT-F has been confirmed [12]. By scoring convention, lower scores indicate reduced QoL. Regarding the FS, lower scores imply greater levels of fatigue.

Fatigue was defined by FS ≤ 35 [13]. Severe fatigue was defined by scores ≤30 [14]. Pruritus as a common symptom of CTCL was evaluated using the peak pruritus numerical rating scale (NRS) with a 24 h recall period.

Statistical analyses were performed using GraphPad Prism 8 software for Mac. Values are expressed as median plus interquartile range (IQR) or mean ± standard deviation, as appropriate. The normal distribution of data was assessed by the Kolmogorov–Smirnov test. Statistical differences between the groups were analyzed with the Mann–Whitney U test. Correlation studies were performed using the Spearman's correlation test. A P value of <0.05 was considered statistically significant.

3. Results

During the investigation period, 38 patients with MF and SS were seen in the outpatient clinic at the department of dermatology of the Johann Wolfgang Goethe-University Hospital in Frankfurt am Main. All of these patients were eligible participants, completed all the measurements, and were included in the analysis (Supplementary Figure 1) Table 1 shows the characteristics of the study population in detail. Subjects were equally distributed by sex. The median age was 65 years (range 29–82 and IQR 56.5–74). The median disease duration was 4 years (range 0.1–25 and IQR 1–10.25). The majority of participants were patients with early stage disease (35, stages IA-IIA). Three patients were at advanced stage disease (stages IIIA-IVB) including one patient with SS. Most of the patients were treated with topical therapies (Supplementary Table 1). The overall prevalence of fatigue was 50%. The median score of the FS was 35.5 (range 14–46 and IQR 25.75–43). 13 patients suffered from severe fatigue, 6 patients from mild fatigue (Table 2). There were no significant effects of sex and age on the FS (Supplementary Figure 2). Patients with advanced stage disease reported significantly more severe fatigue than patients with early stage disease ($P = 0.026$) based on the FS (Figure 1(a)). The Cronbach's alpha of the 13-item FS was 0.87. As a measure of life quality, median FACT-G score for all patients was 86 (range 29–106, IQR 75-97.25; FACT-G subscores, and corresponding Cronbach's alpha values are depicted in Supplementary Table 2). QoL significantly decreased ($P = 0.0008$) with advanced stage of disease (Figure 1(b)). Correlation analysis revealed a significant and positive correlation ($r = 0.82$ and $P < 0.0001$) between fatigue (FS) and QoL (FACT-G; Figure 2(a)). Further analysis showed a significant correlation of FS and FACT-G subscores (physical well-being (PWB, $r = 0.75$), social well-being (SWB, $r = 0.63$), emotional well-being (EWB, $r = 0.64$), and functional well-being (FWB, $r = 0.8$), $P < 0.0001$; Figure 2(d)). We further analyzed pruritus. Most patients reported pruritus (81.6%). The mean level of pruritus was 2 (range 0–10 and IQR 1–6) based on the peak pruritus NRS. We did not find any significant difference between pruritus scores in early and advanced stage disease. ($P = 0.77$; Figure 1(c)). Further, a minimal negative correlation between pruritus and FACIT-F turned out to be not significant ($r = -0.18$, $P = 0.28$; Figure 2(b)). Pruritus was negatively and significantly correlated with QoL based on FACT-G scores ($r = -0.35$, $P = 0.03$; Figure 2(c)). As most patients suffered from SIA disease, a subanalysis for this disease stage was performed. As in the overarching analysis, we could see that almost half of the patients (43%) reported fatigue (Supplementary Table 3). Correlation analysis revealed a significant correlation between the FACIT-Fatigue subscale and quality of life ($r = 0.8$, $P < 0.0001$; Supplementary Figure 3a). We could not see any correlation between the FACIT-Fatigue subscale and pruritus ($r = -0.24$, $P = 0.21$; Supplementary Figure 3b). Pruritus was negatively and significantly correlated with QoL ($r = -0.45$, $P = 0.01$; Supplementary Figure 3c).

Table 1: Characteristics of the study population ($n = 38$) at the time of inclusion.

Variable	*n (%)*
Male	19 (50%)
Female	19 (50%)
Variable	*Median (IQR)*
Age (years)	65 (56.5–74)
Time since diagnosis (years)	4 (1–10.5)
ISCL/EORTC-staging[a]	*n (%)*
IA	30 (78.9)
IB	5 (13.1)
IIIA	1 (2.6)
IVA1	1 (2.6)
IVA2	1 (2.6)

Staging refers to the current stage of disease. [a]ISCL/EORTC-staging according to Olsen et al. [15].

Table 2: Fatigue degree based on FACIT-F questionnaire.

	n (%)
No fatigue	19 (50)
Mild fatigue	6 (16)
Severe fatigue	13 (34)

Fatigue was defined by FACIT-Fatigue subscale values ≤35. Severe fatigue was defined by scores ≤30.

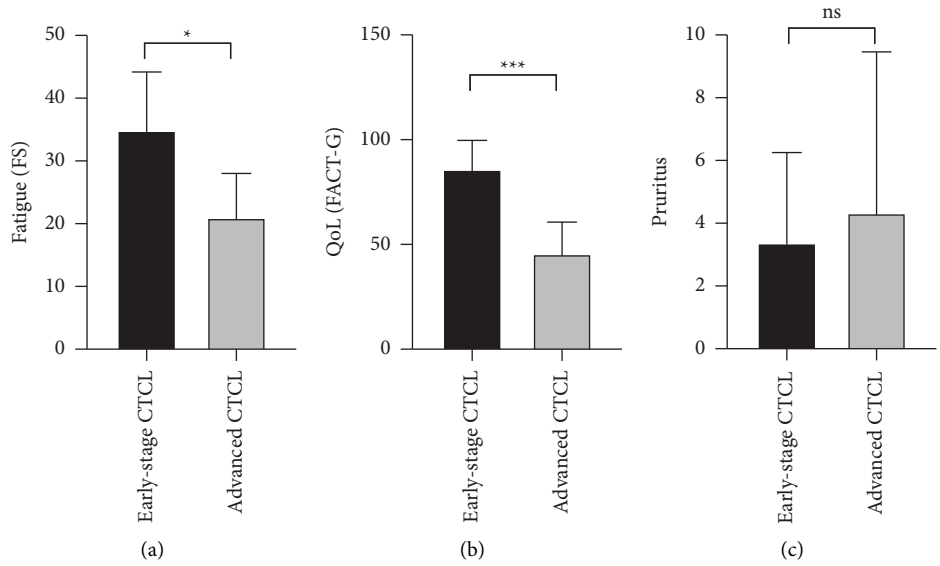

Figure 1: Comparison of early stage and advanced stage CTCL. Advanced disease stage was associated with significantly more severe fatigue and a poorer quality of life (QoL). (a) Fatigue based on FACIT-Fatigue subscale (FS) value. (b) Quality of life assessed by FACT-G questionnaire. (c) Pruritus was measured by the peak pruritus numerical rating scale (NRS). Data from 38 patients were analyzed. Statistical differences between the groups were analyzed with the Mann–Whitney (U). Note that lower fatigue scores indicate more severe fatigue. $^{*}P < 0.05$, $^{***}P < 0.001$, and ns = not significant.

4. Discussion

Fatigue is a common yet ignored concern for patients with CTCL. To our knowledge, this is the first study comprehensively investigating the association between fatigue, QoL, and pruritus in patients with CTCL, especially in early stage disease. In the present study, we were able to demonstrate that half of the CTCL patients included experienced fatigue. Fatigue was widespread in patients in all cancer stages including early stage cancer, with only small areas of skin affected. In general, fatigue was found to be associated with CTCL patients' QoL, indicating a strong negative effect of fatigue on patients' perceived QoL. Patients with advanced stage disease exhibited more severe fatigue and poorer QoL. Our population shows higher levels of fatigue than the US and German general populations of similar age [12, 16]. Our FS mean score was comparable to other studies investigating fatigue in patients with different cancer entities, thereby

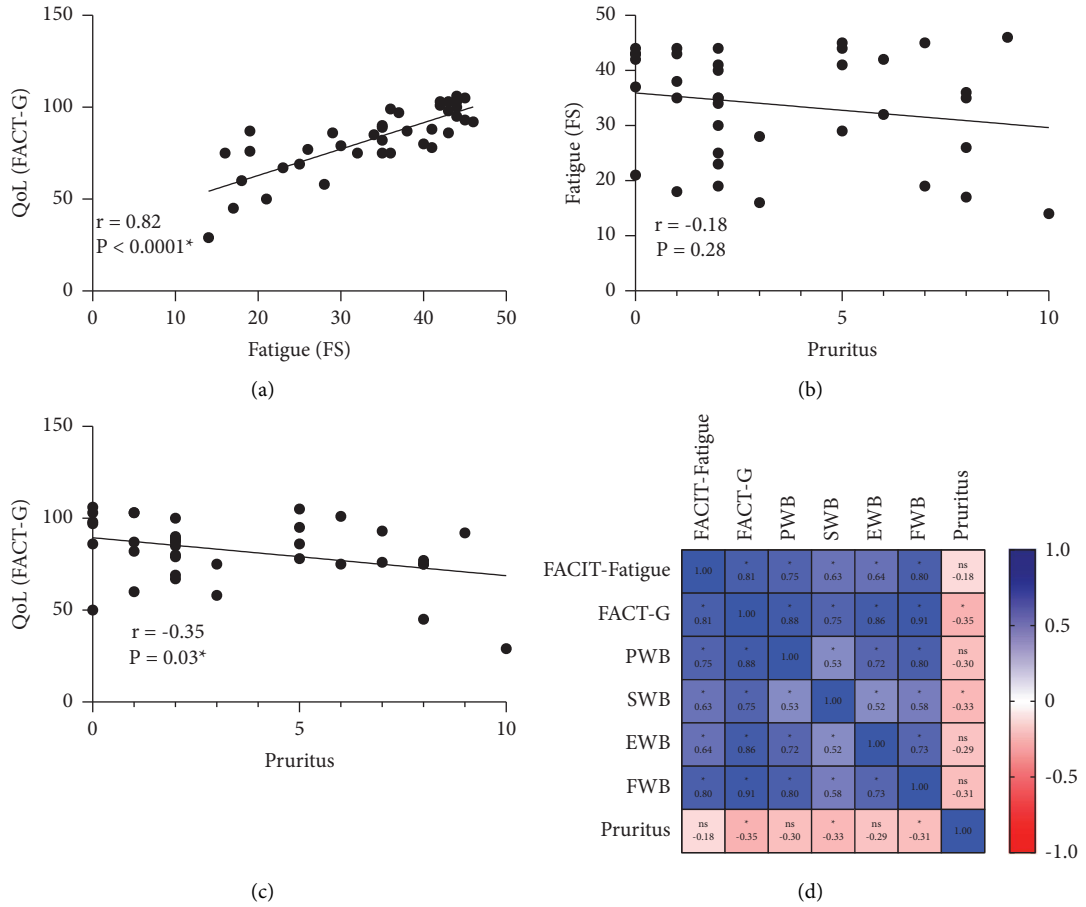

Figure 2: Correlation analysis between fatigue, quality of life, and pruritus revealed a significant correlation between fatigue and quality of life (QoL) as well as pruritus and QoL. (a) Correlation analysis between QoL and fatigue. (b) Correlation analysis between fatigue and pruritus. (c) Correlation analysis between QoL and pruritus. (d) Heatmap including fatigue, QoL, subdomains of the FACT-G, and pruritus. Fatigue based on the FACIT-Fatigue subscale (FS). Note that lower FS scores indicate more severe fatigue. QoL assessed by FACT-G questionnaire. Pruritus was measured by peak pruritus numerical rating scale (NRS). Data from 38 patients were analyzed. Correlation coefficients were determined by Spearman's correlation test. PWB: physical well-being, SWB: social well-being, EWB: emotional well-being, and FWB: functional well-being. *<0.05, **<0.01, and ***<0.001.

providing evidence for the construct validity of the FS [17, 18]. Our internal consistency of the FS with an α of 0.871 was similar to results in the German general population ($\alpha = 0.92$) [12].

CTCLs are known to be associated with significant pruritus [19]. In our study, 81.6% experienced some degree of pruritus. The mean level of pruritus reported was two. According to prior investigations, advanced stage disease is associated with significantly worse pruritus [20–22]. A similar trend was seen in our population; however, this did not turn out to be significant. One reason might be the limited number of patients with advanced stages.

As already published previously, worse pruritus significantly correlated with lower levels of QoL [22]. A minimal negative correlation between pruritus and fatigue was not significant, implicating that pruritus might only play a minor role in the genesis of fatigue in CTCL patients, especially in early stage disease. However, itch intensity was averagely low in our cohort, which was most likely based on the disproportionately larger number of patients suffering from early stage disease included. In the future, a subanalysis of a higher number of patients with advanced stage CTCL might help to investigate an association between pruritus and fatigue in patients with more severe disease that are known to suffer from more severe pruritus.

Limitations of this study include the small sample size restricted to a single academic institution. Yet, most of our findings are in concordance with previous studies conducted at other institutions for different entities [12, 17, 18]. In addition, most participants suffered from stage IA disease. Only three patients with advanced disease were included. Thus, the generalizability of our results is limited, especially for advanced stage disease and SS. We further did not include the impact of sociodemographic characteristics such as marital status, employment status, and level of education in our analysis, which are known to influence QoL and fatigue [12]. In addition, we did not account for comorbidities which are known to have an impact on patients QoL and CRF [23–25].

Based on the limited sample size and the fact that the included patients received a variety of different mono and combination therapies, treatment-related effects on QoL and fatigue could also not be adequately assessed. Recent studies comparing different novel treatment options for CTCL indicate that some therapies might have a greater influence on fatigue and QoL compared to others [26].

It should also be mentioned that the cancer-specific FACT-G and FS do not cover skin disease symptoms and are not specific for MF. The FACT-G questionnaire might therefore fail to recognize small but relevant changes in QoL in CTCL patients [27]. Yet, at the moment, the FACT-G and the skin disease-specific Skindex-29 are still one of the most established and valid tools to measure QoL in CTCL [19, 28, 29]. The FACT-G was chosen for this current research project as it can be easily complemented with a fatigue assessment tool.

5. Conclusions

In conclusion, our findings indicate that fatigue is a widespread symptom in CTCL patients, including all cancer stages. Consequently, awareness of fatigue in CTCL needs to be improved. As there are no known clinical markers for fatigue in CTCL patients explicitly screening at regular intervals for CRF is essential to identify patients in need of additional support. Currently, there is no clear recommendation for the most appropriate procedure to measure CRF. There are no tools that have been primarily developed to screen for fatigue in CTCL. In the future, there is a high need for a disease-specific tool which is suitable to measure QoL and fatigue in early and advanced stage disease.

Upcoming future studies investigating fatigue in CTCL would benefit from a multicentric setting and should consider a longitudinal approach to enable the assessment of the impact of different treatment options. Furthermore, the impact of comorbidities on QoL and CRF should be taken into account. These studies should also cover new treatment modalities such as brentuximab vedotin or mogamulizumab.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Supplementary Materials

Supplementary Table 1: current therapy at baseline. Supplementary Table 2: FACT-G subscale properties across the study population. Supplementary Table 3: fatigue degree in Stage IA disease based on the FACIT-F questionnaire. Supplementary Figure 1: CONSORT diagram describing patient selection. Supplementary Figure 2: sex and age have no impact on fatigue. Supplementary Figure 3: correlation analysis between fatigue, quality of life, and pruritus in Stage IA disease revealed a significant correlation between fatigue and quality of life (QoL) as well as pruritus and QoL. (*Supplementary Materials*)

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