Cancer-related fatigue: Identification of hallmarks to enable refined treatment approaches

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Abstract
Objective: Recommendations for fatigue management are commonly given in an undifferentiated manner without further evaluation of patient's specific symptomatology. Thus, we aimed to identify hallmarks of potential fatigue subgroups which might guide more refined treatment.

Methods: The FiX study assessed fatigue with the EORTC QLQ-FA12 in patients around 2 years after cancer diagnosis (T0) including 15 different entities. After 2 years, a follow-up survey (T1) was conducted. The analyses comprised all patients with prevalent fatigue at T0 (N = 1023). Hierarchical cluster analysis was performed using the Ward method and including the dichotomized factors emotional distress, pain, insomnia, and obesity. Emotional distress, that is, depressive symptoms and anxiety, was assessed by the PHQ-4. Pain and insomnia were based on the according symptom scores of the EORTC QLQ-C30. Analysis of covariance was conducted to investigate the association of the fatigue clusters at T0 with subsequent fatigue at T1.

Results: Four hierarchical clusters were identified. The first cluster comprised patients with moderate-to-severe distress. The remaining fatigue cases were differentiated by obesity and then by pain. Fatigue cases without any of these three symptoms formed the last cluster. Physical, emotional and cognitive fatigue were highest in the distress cluster. Additionally, this cluster was associated with higher physical, emotional and cognitive fatigue at T1 compared to the other clusters.

Conclusions: Fatigue in conjunction with emotional distress had worse impact, persisted longer, and may require other treatment approaches than fatigue in patients without emotional distress. Obesity and pain may be further distinguishing hallmarks for refined fatigue management.

Keywords
cancer, cancer-related fatigue, oncology, patient-reported outcomes, patient-tailored treatment, psycho-oncology, psychological factors, quality of life, supportive care, survivorship
1 | BACKGROUND

Cancer-related fatigue is one of the most common and burdensome symptoms during and after cancer treatment. Although its pathophysiology is still not well understood there is wide agreement that fatigue is multi-causal as well as multi-dimensional in nature. Yet, while tailoring therapies individually to patient and cancer characteristics is state-of-the-art for cancer treatment, fatigue treatment is commonly still very undifferentiated without further evaluation of the symptomatology. The existing treatment approaches for fatigue, which vary widely such as physical exercise interventions or cognitive-behavioral therapies, are usually recommended to patients in a nonspecific manner. To date, no well-determined hallmarks of potential subtypes of fatigue have been defined and established in research and cancer care. Singling out specific subtypes might enable a more adapted and individual patient treatment.

Although associations of fatigue with some biological markers, such as pro-inflammatory cytokines, cortisol dysregulations, reduced energy metabolism or neuroendocrine changes have been shown, research seems still from developing laboratory diagnostics to classify specific fatigue types. Thus, to advance better targeted treatment approaches it may be more promising to consider previously identified determinants of fatigue including psychological, physiological, socio-environmental, and cognitive-behavioral factors. Besides sex and age as components influencing the experience of fatigue, depressive symptoms, anxiety, insomnia, and pain have frequently been observed to cluster or be associated with fatigue. These symptoms might share common etiologies with fatigue, but could also be predisposing or perpetuating factors. For example, dysfunctional cognitive appraisals or illness cognitions might be components to contribute to both, the development of emotional distress (depression/anxiety) and fatigue. Depressive disorders are also a risk factor for poor psychological adjustment to the stress caused by cancer diagnosis and treatment, and thus may increase vulnerability to fatigue. Longitudinal studies have shown that depressed mood predicts elevated fatigue levels during and after treatment. Moreover, depressive symptoms and anxiety can increase inflammatory response to stress and hereby might increase the risk for fatigue or influence its severity and persistence over time. Besides, insomnia can have multiple causes, manifestations and might share common etiologies with fatigue and can also sometimes be a consequence of fatigue. The association of pain with fatigue might be just as complex. Causes of pain and insomnia might include inflammatory processes, sleep problems, stress as well as inactivity and subsequent physical deconditioning. Further determinants of fatigue comprise obesity, lack of physical activity as well as psychosocial risk factors like childhood adversity or loneliness. Obesity is thought to contribute indirectly to fatigue due to inflammatory processes in fatty tissue which weaken the immune system.

Therefore, we performed a hierarchical cluster analysis to determine which of the most common correlates of fatigue, that is, emotional distress (depressive symptoms and anxiety), pain, insomnia, and obesity, may be the most relevant hallmark of a potential fatigue subtype. Further, we explored how this subtype describes current and can predict future fatigue patterns.

2 | METHODS

2.1 | Study population

The FiX study enrolled 2508 patients about 2 years after diagnosis of cancer (T0) including 15 different cancer entities. Patients were randomly sampled from the Epidemiological Cancer Registry of Baden-Württemberg, Germany, and have been described in detail previously. After 2 years, a follow-up survey (T1) was conducted. In the cluster analysis all patients were included with prevalent fatigue at T0 (n = 1023), that is, with a total fatigue score above the age and sex specific 75% percentile of the general population in Germany. Of the 1023 survivors with fatigue at T0, 128 were deceased before T1, for 55 contact addresses were no longer valid, and 129 did not respond, resulting in 711 participants at T1 of whom 467 were apparently cancer-free survivors. For the detailed number on patient flow from T0 to T1 by cluster see Supplement 1. All patients have given written informed consent.

2.2 | Assessments

Fatigue at T0 and T1 was assessed multidimensionally with the 12-item EORTC QLQ-FA12, which addresses the physical, emotional and cognitive dimension of fatigue and also provides a total fatigue score. It was shown that it can detect clinically significant fatigue in cancer patients. Additionally, to gain insights into change of patients’ fatigue burden during the cancer continuum, patients were asked to retrospectively rate their pre-diagnostic fatigue level and their highest fatigue level since diagnosis in addition to their current fatigue level on a 0–10 scale based on items of the Brief Fatigue Inventory. Emotional distress was assessed with the PHQ-4 consisting of two items measuring depressive symptoms and two items measuring anxiety symptoms (each scale 0–3). According to the PHQ-4 scoring manual summary values ≥ 6 were classified as emotional distress. Pain and Insomnia were based on the according symptom scores assessed with the EORTC QLQ-C30 and dichotomized for the cluster analysis along the reported thresholds of clinical importance, namely pain scores >25 and insomnia scores >50. Using a self-developed questionnaire, patients were asked to rate their agreement with different statements concerning psychosocial factors and attitudes towards fatigue on a five-point Likert scale. Body-mass index (BMI) was calculated from self-reported weight and height. According to the World Health Organization, a BMI ≥ 30 kg/m² was considered as obesity.
2.3 Statistical methods

A hierarchical cluster analysis was performed based on T0 data \((n = 1023)\) using SAS PROC CLUSTER with the Ward method and included the dichotomized factors emotional distress, insomnia, pain, and obesity. The number of clusters was based on the pseudo-F-statistic. Clusters were subsequently calculated with PROC TREE. Multicollinearity was checked in advance. Fatigue and patient characteristics were compared across the identified fatigue clusters using Kruskal-Wallis tests.

Analysis of covariance (ANCOVA) was conducted to investigate the association of the baseline fatigue clusters with subsequent fatigue at T1 adjusting for baseline fatigue levels, sex, age, and cancer entity. Hereby, separate ANCOVA models were calculated for physical, emotional, and cognitive fatigue. As cancer progression may have substantial impact on fatigue, this analysis was additionally conducted within the subgroup including only survivors who were apparently cancer-free at T1. Further explorative analyses using ANCOVA models investigated the association of the fatigue clusters at T0 with different statements concerning psychosocial factors and attitudes towards fatigue.

3 RESULTS

The characteristics of the 1023 fatigue cases are summarized in Table 1. The study population had an average age of 66.0 (SD = 12.5) years and was fairly balanced regarding sex. About half of survivors had received chemotherapy.

The variables used in clustering were not or only weakly correlated with each other (all \(r < 0.23\)). Based on a maximum pseudo-t-square value, four hierarchical clusters were identified among patients with fatigue at T0. The resulting hierarchical structure is summarized in Figure 1: The first cluster (CL1, \(n = 283\)) comprises fatigue cases with moderate-to-severe emotional distress. The remaining fatigue cases were differentiated by obesity (CL2, \(n = 200\)) and then by clinically important pain (CL3, \(n = 326\)). Fatigue cases without any of these three symptoms comprised the last cluster (CL4, \(n = 214\)). Fatigue cases in CL1 had besides emotional distress (median (Q1-Q3) = 58.3 (50.0–100)) also relatively high levels of pain (50.0 (33.3–66.7)) and of insomnia (66.7 (33.3–100)). Similar levels of insomnia were also seen in CL2 and CL3, whereas fatigue cases in CL4 had reported less insomnia (33.3 (0.0–66.7)). The distribution of symptoms across the clusters are presented in detail in Supplement 3.

Fatigue patterns varied significantly (all \(p < 0.0001\)) in severity, impact and dimensions across the fatigue clusters at T0, which was about 2 years post-diagnosis (Figure 2). Hereby, CL1 showed significantly higher values compared to all other clusters (all \(p < 0.0001\)), and CL4 showed significantly lower values compared to all other clusters (all \(p < 0.001\)), whereas CL2 did not differ significantly from CL3. In contrast, retrospectively assessed ratings on pre-diagnosis fatigue differed only slightly between the clusters (\(p = 0.035\)), and median levels of these pre-diagnosis fatigue ratings were markedly lower than fatigue levels at T0.

| Table 1 Characteristics of the study population |
|------------------------------------------------|
| **Survivors with fatigue at baseline (n = 1023)** |
| Age (years) | Mean (SD) | 66.0 (12.5) |
| BMI (kg/m²) | Mean (SD) | 27.2 (6.0) |
| **N %** |
| Sex | Male | 498 | 48.7% |
| | Female | 525 | 51.3% |
| Tumor entity | Multiple primaries | 94 | 9.2% |
| | Breast | 91 | 8.9% |
| | Rectum | 87 | 8.5% |
| | Non-Hodgkin lymphoma | 87 | 8.5% |
| | Kidney | 84 | 8.2% |
| | Colon | 75 | 7.3% |
| | Endometrium | 71 | 6.9% |
| | Prostate | 67 | 6.5% |
| | Leukemia | 67 | 6.5% |
| | Ovaries | 66 | 6.5% |
| | Malignant melanoma | 65 | 6.4% |
| | Bladder | 59 | 5.8% |
| | Stomach | 56 | 5.5% |
| | Pancreas | 18 | 1.8% |
| | Lung | 15 | 1.5% |
| | Liver | 14 | 1.4% |
| | Other | 7 | 0.7% |
| Chemotherapy | Never | 524 | 51.2% |
| | In the past | 408 | 39.9% |
| | Recent/current | 82 | 8.0% |
| | Missing | 9 | 0.9% |
| Radiotherapy | Never | 723 | 70.7% |
| | In the past | 283 | 27.7% |
| | Recent/current | 11 | 1.1% |
| | Missing | 6 | 0.6% |
| Targeted therapy | Never | 784 | 76.6% |
| | In the past | 163 | 15.9% |
| | Recent/current | 68 | 6.6% |
| | Missing | 8 | 0.8% |
| Endocrine therapy | Never | 830 | 81.1% |
| | In the past | 122 | 11.9% |
| | Recent/current | 64 | 6.3% |
| | Missing | 7 | 0.7% |
Further, there were significant differences between the clusters with respect to psychosocial factors and attitudes towards fatigue such as feeling helpless in the face of fatigue (Kruskal-Wallis \( p < 0.0001 \)) and the experience that their fatigue was not taken seriously by their environment (\( p < 0.0001 \), Supplement 2). Hereby, in CL1 53.0% of respondents fully or rather agreed to feeling helpless regarding fatigue versus 34.1% (CL2), 35.6% (CL3), and 21.8% (CL4). Likewise, more respondents felt their fatigue was not taken seriously in CL1 (54.9%) compared to CL2 (38.2%), CL3 (35.6%), and CL4 (32.8%). In contrast, there were no significant differences between clusters regarding feeling well informed about fatigue (\( p = 0.86 \)), addressing fatigue openly to others (\( p = 0.79 \)), and the belief that there are ways to alleviate fatigue (\( p = 0.52 \)).

Moreover, we investigated whether the fatigue clusters may predict future fatigue patterns at T1 using ANCOVA models (Table 2). Results showed that the T0 fatigue clusters were significantly (\( p < 0.001 \)) associated with change in fatigue from T0 to T1 for all three fatigue dimensions, even when adjusting for T0 fatigue levels, sex, age and cancer entity. In the subgroup of cancer-free survivors significant associations of the clusters were still seen for physical fatigue (\( p = 0.007 \)) and somewhat weaker also for emotional fatigue (\( p = 0.046 \)). Survivors in CL1 had significantly less decrease in physical fatigue than survivors in CL3 and CL4, and significantly less decrease in emotional fatigue than survivors in CL2 and CL4.

4 | DISCUSSION

In our sample of 1023 fatigue cases a hierarchical cluster analysis revealed emotional distress, that is, depressive symptoms and anxiety, as a prominent hallmark for a subgroup with a specific fatigue phenotype. Fatigue in conjunction with moderate-to-severe
emotional distress was of higher severity, manifested in all dimensions (physical, emotional, and cognitive fatigue), had worse impact on daily life and persisted longer compared to fatigue occurring without emotional distress. Subsequent characteristics for segregating additional subgroups among the remaining fatigue cases were obesity followed by pain.

A history of depression and (trait) anxiety has been observed as an important predisposing risk factor for fatigue in previous research. Likewise, a clustering of emotional distress with fatigue has been shown in numerous studies. Our results underpin the importance of emotional distress for discrimination of fatigue cases with particularly high burden and multidimensional manifestation. Emotional distress showed not only a cross-sectional association with fatigue but also emerged as a significant predictor for longer-term persistence of fatigue, even when adjusting for baseline fatigue and other potential confounders. In general, a comprehensive model of causal relations is still missing. It remains unclear whether fatigue and emotional distress share a common etiology, for example, inflammatory processes or genetic predispositions, or whether these common problems during cancer treatment just occur in many cancer patients in parallel. Further, fatigue can be a sequela of emotional distress, or vice-versa. The associations of emotional distress with fatigue may lie also in the overlap of their characteristic symptoms, for example, the loss of energy.

Among fatigue cases without high emotional distress, the hierarchical cluster analysis distinguished fatigued survivors with obesity as a second fatigue subgroup. Among survivors without emotional distress, those who were obese had a markedly smaller decrease in physical fatigue compared to non-obese survivors. In contrast, emotional fatigue decreased significantly over time. Similar fatigue courses have been previously observed. Reasons might be inflammatory processes in fatty tissue or persistent physical impairment and reduced physical fitness due to obesity.

Finally, fatigue cases without emotional distress and without obesity were differentiated by pain. The fatigue phenotype of the pain group did not differ substantially from the obesity group, except for slightly more improvement in physical fatigue and less in emotional fatigue 2 years later. Yet, physical and emotional fatigue levels in cancer survivors with pain were higher and longer lasting than in survivors without pain supporting observations from previous research. Pain levels were similar across clusters CL1 to CL3, indicating that pain may be a less important factor to differentiate between different fatigue types than distress and obesity. It remains to note, however, that pain was measured only very generally with the single EORTC QLQ-C30 item. Interestingly, insomnia did not show up as an important distinguishing factor in our analysis. However, the measurement of insomnia was assessed by only one item of the EORTC QLQ-C30. Previous literature assumes that sleep disturbances in general (not only insomnia) play a perpetuating role in fatigue. To date there is no clear evidence for a causal role in the sleep-fatigue relationship and due to limited information about the sleep disturbances of the studied sample, our results cannot contribute to a better understanding of this relationship.

### 4.1 Clinical implications

The lack of knowledge of the exact underlying mechanisms of fatigue should not hinder translation of the observed results into clinical practice of fatigue management. The results underline the

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**TABLE 2 Adjusted mean changes in fatigue from T0 to T1 with 95% confidence intervals**

|                  | Physical fatigue | Emotional fatigue | Cognitive fatigue |
|------------------|------------------|-------------------|-------------------|
| **All respondents at T1** |                  |                   |                   |
| n                | 703              | 701               | 657               |
| CL1              | 1.6 (−2.1, 5.4)  | 3.8 (−0.8, 8.4)   | 2.4 (−1.2, 6.0)   |
| CL2              | −3.1 (−7.1, 0.9) | −4.8 (−9.5, −0.0)** | −1.8 (−5.7, 2.1) |
| CL3              | −5.5 (−9.0, −2.0)** | −3.0 (−7.2, 1.2)** | −5.9 (−9.2, −2.5)*** |
| CL4              | −11.1 (−15.0, −7.2)*** | −8.9 (−13.7, −4.1)*** | −5.9 (−9.6, −2.1)*** |
p < 0.0001

|                  |                   |                   |                   |
| **Disease-free respondents at T1** |                  |                   |                   |
| n                | 465              | 463               | 434               |
| CL1              | −0.5 (−5.4, 4.4) | 2.0 (−4.1, 8.1)   | 1.4 (−3.6, 6.4)   |
| CL2              | −4.2 (−9.0, 0.6) | −6.1 (−11.8, −0.5)* | −2.3 (−7.1, 2.6) |
| CL3              | −8.1 (−12.6, −3.6)** | −2.5 (−7.9, 3.0)  | −3.4 (−8.0, 1.2)  |
| CL4              | −10.1 (−14.9, −5.2)** | −7.6 (−13.5, −1.7)** | −3.2 (−8.1, 1.6) |
p = 0.0071

**Note:** All ANCOVA models were adjusted for baseline fatigue, sex, age, and cancer entity. Only cancer survivors who were apparently cancer-free at T1 are included to avoid confounding of results by cancer progression. \( n_{obs} \) = number of non-missing observations.

\( p < 0.05, **p < 0.01, ***p < 0.001 \): least square mean significantly different to CL1.
need to pay attention to emotional distress, when a patient shows signs of fatigue. The 4-item PHQ-4 appears to be an easy, feasibly and - based on our results - also meaningful tool for taking this important marker into fatigue management in clinical practice, but also other validated instruments might be used. An assessment of emotional distress as well as other treatable contributing factors, followed by a state-of-art symptomatic treatment is recommended in the current National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) clinical practice guidelines for fatigue. Separate NCCN guidelines on managing distress in cancer patients exist and several countries are heading for a routine distress screening.

Nevertheless, further fatigue treatment is not considered in dependence on emotional distress in the guidelines. Different fatigue treatment approaches are recommended in parallel, such as physical activity/exercise interventions and psychosocial interventions. Those approaches have shown significant benefits on fatigue in many studies and meta-analyses. However, effect sizes were rather in the small-to-medium range, demonstrating that there may not be a one-fits-all approach. Motivating people to adhere to a regular exercise training can be a challenge, and it might be even more demanding for fatigued cancer patients with emotional distress. In our study, fatigue cases with emotional distress more often felt helpless in the face of fatigue compared to the others, although this group did not feel less informed about fatigue. In addition, although a similar proportion as in the other groups addressed their fatigue openly towards family and friends, a higher proportion felt that their fatigue was not taken seriously. As previous literature pointed out, a lack of good coping strategies as well as feeling misunderstood and isolated in their fatigue can reinforce fatigue. Thus, for patients with fatigue in conjunction with emotional distress it may be insufficient to solely promote physical activity. Rather, additionally providing and applying coping strategies to deal with fatigue could counteract the feeling of helplessness. Furthermore, our results underpin that relatives should also be involved in fatigue education to prevent patients from feeling left alone with this burdensome symptom. Besides, it has been shown previously that in cancer patients with both, fatigue and depressive symptoms, treatment of the latter also partly improved fatigue. So, an individually tailored and multidimensional approach to improving patients’ symptoms can also result in the alleviation of symptom burden not directly targeted.

Additionally, obesity might be used as a further distinguishing marker for fatigue treatment. It may be hypothesized that intervention programs focusing on increasing physical activity and weight loss in combination with psychoeducational modules for a healthy lifestyle and coping with fatigue could be helpful for obese patients to alleviate their symptoms. According to the NCCN and ESMO guidelines for fatigue, within a thorough fatigue assessment, overweight as well as pain and also insomnia should be assessed and symptomatically treated in any case.

Our results underline the importance of these symptoms in relation to fatigue and show that they contribute differently to the experienced fatigue burden.

4.2 | Study limitations

First, our sample might not be fully representative as extremely fatigued patients as well as patients with major depression might not have been able to take part in the survey. Second, reverse causation concerning highest fatigue levels in the emotional distress cluster cannot be fully excluded, although longitudinal regression analyses showed a significant association of the baseline fatigue clusters with fatigue patters 2 years later. All statistical analyses were explorative in nature, and underlying causal mechanisms cannot be identified. However, we believe this does not limit the clinical impact. Optimal fatigue management involves the recommended comprehensive fatigue examinations including clarification of distress, pain and physical conditions. However, it must be realized that this has hardly been implemented in clinical practice, possibly because up to now resources as well as time for accurate fatigue diagnostics and care are limited. Thus, it might be a reasonable starting point in case of signs of fatigue to check at least for emotional distress first. Future research should investigate treatment options for fatigue specifically in the subgroup of patients with emotional distress.

Another limitation of our hierarchical cluster approach is the restriction to pre-selected determinants of fatigue. It is therefore possible that other hallmarks exist which also could guide future cancer treatment. Here, previous literature points at socio-cognitive mechanisms like illness acceptance or the amount of social support. Further, we dichotomized the factors used in the hierarchical cluster analysis because their numerical range comprised only few values, thus they were not continuously distributed. This may have led to an underestimation of the variance in the factors considered. Future studies may use continuous variables in their cluster analysis. Yet, our results provide a decision tree for possible subdivision into fatigue subgroups, which were shown to be linked with different fatigue patters.

5 | CONCLUSION

Fatigue in conjunction with emotional distress has higher severity, worse impact on daily life, and persists longer. It likely may require other treatment approaches than fatigue in patients without emotional distress, including strategies to overcome helplessness and targeting dysfunctional cognitions of anxiety and depressive symptoms.

Obesity and pain may be further distinguishing markers for the treatment of fatigue. Further research into these hallmarks of potential fatigue subtypes and correspondingly tailored treatments is warranted.

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CONFLICT OF INTEREST
Karen Steindorf received a speaker’s fee from Takeda.

ETHICS STATEMENT
This study was conducted in accordance with the ethical standards of the Helsinki Declaration. The study was approved by the Ethic Committee of the Medical Faculty of the University of Heidelberg (S654/2016). All patients have given written informed consent.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.