Predicting Trends in Dyspnea and Fatigue in Heart Failure Patients' Outcomes

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Background: Dyspnea and fatigue are distressing symptoms commonly seen in heart failure (HF) patients, and are closely related to patients' disease trajectory of contributes. Identifying the effect of symptom trends on disease outcomes is important to develop effective symptom management interventions in HF patients.

Methods: One hundred and twenty-two patients were recruited. Dyspnea, fatigue, clinical characteristics, and disease outcomes were measured at the baseline assessment, three months, and 12 months. Latent class growth model and Kaplan-Meier survival analysis were used on dyspnea and fatigue to examine the relationship of disease trajectories and effects on disease outcomes.

***Results*:** A total of 122 patients were examined (mean age 62.8 ± 13.0 yrs; 79% male; 39% NYHA III/IV; 48% preserved systolic function HF). Three groups based on HF patients' dyspnea-fatigue trends were identified as "constant good," "recovery," and "getting worse." The cumulative incidence of a first cardiac event in both dyspnea and fatigue groups yielded similar results. The quality of life score for the getting worse group was significantly higher than that of the constant good and recovery groups. The result of the log-rank test was significant (χ^2 = 8.11, p = 0.017). Post hoc comparison showed that the prognosis status of the constant good group was better than that of the getting worse (p = 0.046) and recovery groups (p = 0.020), while getting worse and recovery groups did not differ in prognosis status (p = 0.30).

Conclusions: The results demonstrate the value of tracking symptoms over time to determine symptom trajectories as well as severe baseline (even with improvements at follow-ups) or increased fatigue over time were related to a worse event-free survival as compared with low but stable fatigue.

Key Words: Disease outcome • Kaplan-Meier survival analysis • Symptom trajectory

BACKGROUND

Heart failure (HF) is a worldwide health problem and social burden, affecting both developed and developing countries. An estimated 5.8 million people have HF and an additional 550,000 are diagnosed annually in the United States, accounting for about $33.2 billion spent on both direct and indirect costs in the care of HF patients in 2006.[1] Similar situations were found in other countries.[2,3] Dyspnea and fatigue are distressing symptoms commonly reported by HF patients despite improvements made in pharmacological treatments over the past few decades. The prevalence of high levels of fatigue was reported in more than half of HF patients regardless of sex.[4] Dyspnea and fatigue are caused by pathophysiological changes and are closely related to patients' disease trajectory. Therefore, HF patients' symptom status of dyspnea and fatigue may fluc-

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tuate with their disease condition.

Dyspnea is defined as the subjective experience of breathing difficulty, which could provoke high intense symptom burden and life-threatening distress forcing HF patients to seek emergency care from the hospital.[5] However, up to 51.2% of patients in Taiwan were unable to identify it as an important symptom of worsening HF.[6] Dyspnea has been described as a mixed sensation, like thirst or hunger, which is the result of the complex interaction of signals arising from the central nervous system and from a variety of receptors in the upper airways, lungs, and chest wall as well.[5,7] Variant effect impact is conceptualized as multidimensional in nature with components that include frequency, severity and distress related to experiencing the symptom.[8] In fact, dyspnea was correlated with health-related quality of life, which was the patient's perception of the overall effect of a health condition on his or her daily life. Fatigue in patients with HF is defined as persistent exhaustion and the perception of difficulty to perform daily activities.[9] In fact, the value of assessment on fatigue was commonly underestimated by patients and health care providers because of its vagueness. According to previous investigations, as many as one-third of patients with HF viewed fatigue as an unimportant symptom and up to 50% report having difficulty recognizing it as a symptom of worsening HF.[8]

A cross-sectional research design for the measurement of symptoms in this population is inadequate in evaluating the meaning of dyspnea and fatigue in HF. The development of effective symptom management interventions necessitates the identification of the effect of dyspnea symptom trends on disease outcomes in patients with HF. However, symptoms are not stationary; fully understanding the nature of the symptoms will be beneficial in looking for better solutions in symptom management. The specific aim of the study is to determine the effect of dyspnea and fatigue trends (3 time points over 12 months) on HF patients' disease outcomes [mortality, emergency room visits, hospitalization, and health-related quality of life (HRQOL)].

METHODS

Design, participants, measures, and procedure

A prospective longitudinal study was designed to determine the individual symptom trajectory effects of dyspnea and fatigue on disease outcome in patients with HF. Adult patients with HF at outpatient clinics from several medical centers in Taiwan were recruited for the study. Administrative and institutional review board approvals for the study were obtained from each site's Human Subject Review Committee. Informed consent was obtained from each patient after a comprehensive explanation by trained investigators. Patients with heart failure were eligible if they were able to communicate in Mandarin or Taiwanese, were free of dementia or active psychiatric diseases, and had access to a phone during the 12-month follow-up period. The exclusion criteria were patients who were younger than 18, lived in an extended care facility, hospice, prison, or other institutional setting, had comorbidities limiting physical function, such as stroke, amputation of limbs, cancer, or renal failure. Dyspnea, fatigue, clinical characteristics, and disease outcomes were measured at the baseline assessment, three months, and 12 months. Modified Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ-M)[10] were used to measure HF patients' exertion dyspnea and fatigue, and Minnesota Living with Heart Failure Questionnaire (MLHFQ)[11] were used to measure HF patients' HRQOL correspondingly. The PFSDQ-M is a 40-item, self-report, disease-specific measure of symptom severity for dyspnea and fatigue, including 3 dimensions, namely activity, dyspnea, and fatigue. The total possible PFSDQ-M score ranges from 0 to 10, with a higher score indicating more severe symptoms. The cardiac events of emergency department visits, hospitalization, and mortality for cardiac reasons were measured using monthly phone interviews with the patient or family members.

Statistical analysis

To examine the relationship of functional trajectories, a latent class growth model (LCGM) using the SAS program was conducted.[12] Individuals were classified into subpopulations or classes based on the trend of their dyspnea scores and fatigue scores at baseline, 3 months, and 12 months. To determine the optimal number of trajectories, the Bayesian information criteria (BIC) was used, with a lower BIC value indicating a better fit; besides, a difference on the value of $2 \times \Delta$BIC greater than ten will favor the least complex model.[12]

For comparison of demographical and clinical variables at baseline between classes, Fisher's exact test for categorical variables and one-way ANOVA test were adopted. For comparison of QOL between classes, one-way ANOVA test followed by Bonferroni post-hoc procedure was used. Kaplan-Meier survival curve and log-rank tests were used to assess whether dyspnea and fatigue trajectories were associated with mortality beyond the 12-month follow-up. The LCGM analysis was performed with SAS 8.0 and SPSS 15.0 for Windows.

RESULTS

Trajectories of exertion dyspnea

Figure 1 displays the three distinct developmental trajectories for dyspnea. The BIC improved from one class of exertion fatigue (BIC = -512.81) to three classes of exertion fatigue (BIC = -473.13), whereas a relative decline was observed in the four-class model (BIC = -475.23). Compared with two-class model (BIC = -483.24), the three-class model achieved a significant improvement in model fit.

The first group (n = 102, 83.6% of the sample) which was characterized by a good health status at baseline (intercept B_0 = 0.448, p < 0.001) and remained stable in 12 months (linear slope B_1 = -0.008, p = 0.61) was named "constant good." The second group (n = 12, 9.8% of the sample) which was characterized by a good health status at baseline (B_0 = 1.338, p < 0.001) with a significantly positive linear slope (B_1 = 0.181, p < 0.001) was named "getting worse." The third group (n = 8, 6.6% of the sample) which was characterized by a poor health status at baseline (B_0 = 4.728, p < 0.001) with a significantly negative linear slope (B_1 = -0.387, p < 0.001) was named "recovery" (Figure 1).

Trajectories of exertion fatigue

Figure 2 displays the three distinct developmental trajectories for fatigue. Similar to the results for dyspnea, the three-class model (BIC = -454.71) significantly outperformed the one-class and two-class models in model fit. The four-class and five-class models did not achieve a significant improvement in fit when compared with the three-class model. Therefore, the three-class model was again adopted for further analysis.

The first group (n = 94, 77.0% of the sample) which was characterized by a good health status at baseline (intercept B_0 = 0.178, p = 0.08) and remained stable in 12 months (linear slope B_1 = -0.005) was named "constant good." The second group (n = 21, 17.2% of the sample) which was characterized by a good health status at baseline (B_0 = 1.444, p < 0.001) with a significantly positive linear slope (B_1 = 0.077, p = 0.012) was named "getting worse." The third group (n = 7, 5.7% of the sample) which was characterized by a poor state of health at baseline (B_0 = 5.847, p < 0.001) with a significantly negative linear slope (B_1 = -1.409, p < 0.001) was named "recovery" (Figure 2).

Baseline characteristics stratified by dyspnea and fatigue class

There were few differences in demographic and clinical characteristics at baseline in the dyspnea class (Table 1) and fatigue class (Table 2). In the dyspnea class, years of education in the getting worse group (11.43 ± 5.57, p = 0.035) was higher than both that in the constant good (7.59 ± 4.98) and recovery groups

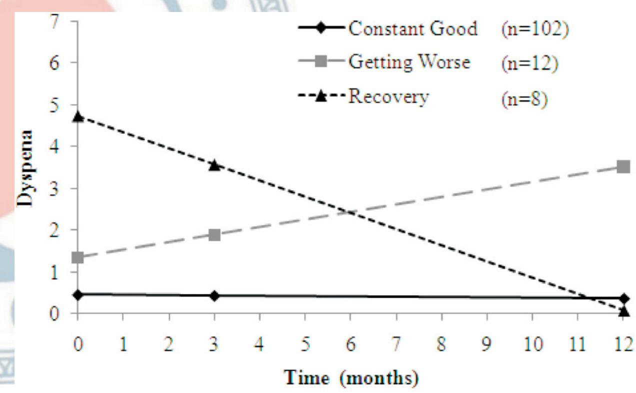

Figure 1. *Observed trajectories of dyspnea.*

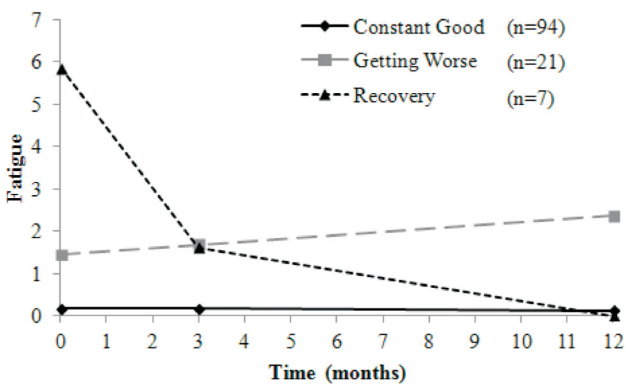

Figure 2. *Observed trajectories of fatigue.*

Table 1. Baseline characteristics stratified by dyspnea class

Variables	Dyspnea class (*N* = 122)			p value
	Constant good	Getting worse	Recovery	
Number of cases	102	12	8	
Female gender	22 (21.6)	2 (16.7)	2 (25.0)	1.00
Age (years)	62.90 ± 12.38	64.42 ± 17.42	58.25 ± 13.65	0.56
BMI (Kg/m^2)	24.92 ± 4.04	24.90 ± 4.09	22.42 ± 5.23	0.26
Without spouse	19 (18.6)	1 (8.3)	2 (25.0)	0.63
Living alone	8 (7.8)	1 (8.3)	0 (0.0)	1.00
Years of education	7.59 ± 4.98	11.42 ± 5.57	9.75 ± 6.11	0.035
LV EF < 40%	46 (47.4)	5 (41.7)	7 (87.5)	0.08
NYHA Fc. III/IV	34 (33.3)	7 (58.3)	7 (87.5)	0.003
Co-morbidities				
Diabetes mellitus	31 (30.4)	4 (33.3)	3 (37.5)	0.86
Hypertension	61 (59.8)	9 (75.0)	1 (12.5)	0.013
Ischemic etiology	63 (61.8)	10 (83.3)	5 (62.5)	0.38
Medication				
ACEI/ARB	71 (69.6)	9 (75.0)	5 (62.5)	0.85
Beta-blocker	62 (60.8)	10 (83.3)	3 (37.5)	0.13
Diuretics	47 (46.1)	7 (58.3)	5 (62.5)	0.54
Aldosterone antagonist	7 (6.9)	1 (8.3)	3 (37.5)	0.044

Categorical data were presented as *N* (%) and comparisons were made by using Fisher's exact test; continuous data were expressed as mean ± SD and comparisons were made by using one-way ANOVA following Bonferroni post hoc procedure.

Table 2. Baseline characteristics stratified by fatigue class

Variables	Fatigue class (*N* = 122)			p value
	Constant good	Getting worse	Recovery	
Number of cases	94	21	7	
Female gender	19 (20.2)	6 (28.6)	1 (14.3)	0.65
Age (years)	62.97 ± 12.38	64.43 ± 14.51	54.71 ± 15.05	0.22
BMI (Kg/m^2)	25.23 ± 3.96	23.35 ± 4.37	22.52 ± 4.69	0.06
Without spouse	17 (18.1)	3 (14.3)	2 (28.6)	0.75
Living alone	8 (8.5)	1 (4.8)	0 (0.0)	1.00
Years of education	7.84 ± 5.10	8.43 ± 5.49	10.71 ± 5.91	0.36
LV EF < 40%	41 (46.1)	11 (52.4)	6 (85.7)	0.13
NYHA Fc. III/IV	30 (31.9)	12 (57.1)	6 (85.7)	0.004
Co-morbidities				
Diabetes mellitus	29 (30.9)	6 (28.6)	3 (42.9)	0.82
Hypertension	56 (59.6)	13 (61.9)	2 (28.6)	0.27
Ischemic etiology	61 (64.9)	13 (61.9)	4 (57.1)	0.83
Medication				
ACEI/ARB	66 (70.2)	14 (66.7)	5 (71.4)	0.93
Beta-blocker	56 (59.6)	16 (76.2)	3 (42.9)	0.22
Diuretics	42 (44.7)	13 (61.9)	4 (57.1)	0.35
Aldosterone antagonist	6 (6.5)	3 (14.3)	2 (28.6)	0.08

Categorical data were presented as *N* (%) and comparisons were made by using Fisher's exact test; Continuous data were expressed as mean ± SD and comparisons were made by using one-way ANOVA following Bonferroni post hoc procedure.

(9.75 ± 6.11). Patients with hypertension were more likely to be in the getting worse groups than the other two groups (p = 0.013) and the use of aldosterone antagonist was higher in the recover group (p = 0.044) than the other two groups in the dyspnea class. Besides, patients with NYHA class III/IV were more likely to be in the recovery group than the other two groups in both the dyspnea and fatigue classes.

Trajectories of dyspnea and fatigue and QOL

The comparison of QOL among trajectory groups is shown in Table 3. The health related QOL score in the getting worse group was significantly higher than that of the constant good and recovery groups among both the dyspnea class and fatigue class.

Trajectories of dyspnea and fatigue and chronic heart failure prognosis

In a further survival analysis, the group effect of cumulative incidence of first event (mortality, emergency room visit, or hospitalization) was investigated using a log-rank test. The mean follow-up period was 388 days (*SD* = 15). During this period, 27 patients (22.1%) expired. The dyspnea class had the following event rates and survival times: constant good group (20.6%, *n* = 21; *M* = 400 days, *SD* = 15), getting worse group (33.3%, *n* = 4; *M* = 301 days, *SD* = 44), and recovery group (25%, *n* = 2; *M* = 310 days, *SD* = 59). However the result of the log-rank test was not significant (χ^2 = 2.19, p = 0.34) (Figure 3A), showing that the prognosis status did not differ among the three dyspnea groups.

The fatigue class had the following event rates and survival times: constant good group (18.1%, *n* = 17; *M* = 409 days, *SD* = 15), getting worse group (33.3%, *n* = 7; *M* = 285 days, *SD* = 27), and recovery group (42.9%, *n* = 3; *M* = 242 days, *SD* = 71). The result of the log-rank test reached significance (χ^2 = 8.11, p = 0.017) in the fatigue class (Figure 3B). Post-hoc comparison showed that the prognosis status in the constant good group was better than that of the getting worse group (p = 0.046) and recovery group (p = 0.020), while the getting worse and recovery groups did not differ in prognosis status (p = 0.30). Due to a significant difference in baseline NYHA class III/IV between the fatigue trajectories, Cox-proportional hazards regression was performed. After adjusting for NYHA class III/IV, the difference among groups became insignificant.

DISCUSSION

Fatigue and dyspnea are prominent symptoms in patients with HF, which limit their daily activities and reduce quality of life. The current study reveals the value of tracking these two major symptoms over time to determine HF patients' subjective disease outcomes. The results of this study support previous findings that poor quality of life and worse cardiac prognoses are related to higher levels of dyspnea and fatigue in HF patients. We also demonstrate that severe baseline fatigue or increased fatigue over time were related to worse event-free survival as compared with low but stable fatigue even though after adjusting for NYHA class III/IV, the difference among groups became insignificant. Compared with fatigue, dyspnea was usually the more dramatic presenting symptom due to pulmonary congestion and edema and it resulted in more emergencies for hospitalization and involvement of patients, family, and health care providers. Pulmonary congestion and

Table 3. Comparison of QOL among the three groups in dyspnea and fatigue classes

	Class			p (ANOVA)
	Constant good	Getting worse	Recovery	
Dyspnea class	15.04 ± 14.41	37.89 ± 10.81*†	7.50 ± 6.36	< 0.001
Number of cases	57	9	2	
Fatigue class	14.43 ± 14.07	34.92 ± 13.55*†	7.50 ± 6.36	< 0.001
Number of cases	54	12	2	

Data were presented as mean ± SD and comparisons among classes were made by one-way ANOVA following Bonferroni post hoc procedure.
* p < 0.05 vs. constant good; † p < 0.05 vs. recovery.

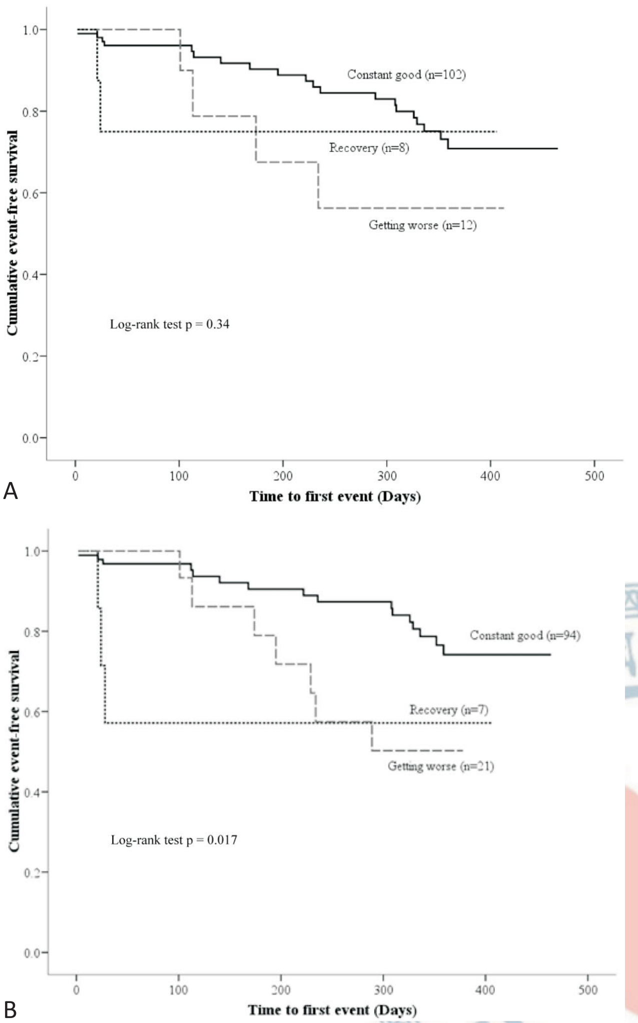

Figure 3. *Event-free survival stratified by dyspnea class (A) and fatigue class (B). The result of post hoc comparison of fatigue class: constant good vs. recovery, p = 0.020; constant good vs. getting worse, p = 0.046; recovery vs. getting worse, p = 0.30.*

respiratory muscle dysfunction caused by cardiac functional de-compensation produced dyspnea in patients with HF.[13] Dyspnea was thought to be a transient and changeable symptom under appropriate regimens. Some researchers concluded that the sensation of dyspnea was closely related to fluid retention; therefore intense fluid volume monitoring could successfully maintain circulation volume balance to alleviate dyspnea and improve functional status in HF.[5] In our study, years of education were higher in the getting worse group when compared with the other two groups. It was thought that patients with higher education level might have more awareness of the relationship between the presenting symptom and disease exacerbations, therefore would have more expectation on the disease prognosis.

The symptom of fatigue might reflect disease severity more than dyspnea but the underlying mechanisms remain unknown. The most popular theories include: 1) impaired cardiac output limiting the blood flow in peripheral circulation; 2) reduced oxygen delivery causing anaerobic metabolism; 3) endothelial dysfunction and altered availability of nitric oxide on skeletal muscle; and 4) abnormal skeletal muscle such as shunting or fiber type altering oxygen uptake.[14] Smith et al.[15] showed that increased exertion fatigue was an independent predictor for increased cardiac re-admission rate and mortality. The fatigue trend in our study showed that HF patients with low and stable fatigue could have a longer cardiac event-free survival. Contrast to our study, a previous follow-up study of 310 HF patients examining the course of fatigue, which identified six distinct trajectories for "exertion fatigue" and four trajectories for "general fatigue" showed that persistent severe fatigue could predict poor prognosis.[16]

Both dyspnea and fatigue trends could predict HRQOL of patients with HF in the current study. The results showed that patients in the getting worse group perceived worse HRQOL when compared with the other two groups in both the dyspnea and fatigue classes. Previous studies also demonstrated similar results that HF patients with more severe physical symptoms had worse HRQOL and physical symptom status, which was the strongest predictor of HRQOL.[17] Nevertheless, physical symptom status was a subjective sensation that varied with different situations and psychosocial status of individuals. The current study demonstrates that grouping by the trends of physical symptoms can also reflect the impacts of a disease accurately. Worsening symptoms make HF patients feel more negative about their HRQOL.

Patients in NYHA class III/IV were less likely to be in the constant good group, which is consistent with the study conducted by Smith et al. where they are rated as low and mild exertion fatigue groups.[15] It is reasonable to suggest that a lower degree of disease condition might reduce the stress in a patient's perception of fatigue. On the contrary, in the same study where the group had the highest proportion of NYHA class III/IV, these patients expressed severe exertion across all assessment points whereas the recovery group in our study had the highest rate of NYHA class III/IV and showed poor health at baseline but a significantly linear slope across the follow-ups. The reason for this may owe to the relatively low cost in more frequent clinic visits and medications provided by The National Health Insurance program in Taiwan when compared with the same costs in the USA. Patients with severe HF in Taiwan could suffer from the symptoms at the baseline assessment but after a series of close follow-ups (i.e. once a week) and an effective treatment regimen to adjust the disease condition more efficiently, they might feel greater improvements in terms of reduced fatigue. Given these reasons, the relatively stable symptom trajectories and cardiac event-free survival time of HF patients in Taiwan were unexpected but somewhat understandable. It was thought that these patients recruited from medical centers with easy access to specialized HF services were able to monitor their symptoms more efficiently. The value of tracking symptoms over time to determine symptom trajectories is reported in this study. We also showed that severe baseline fatigue (even with improvements at follow-ups) or increased fatigue over time were related to worse event-free survival as compared with low but stable fatigue.

Limitations of the study

Several limitations should be mentioned regarding the current study. Firstly, three time-point measures may not be sufficient for confirming symptom trajectory. It is possible that a longer follow-up period would change the inference conclusion. More time points and longer follow-up periods for HF patients' symptom trajectories are needed for identifying different symptom groups. Secondly, biomarkers for measuring symptoms of dyspnea and fatigue are not used in the current study, which, were they employed, could help strengthen its findings. More variables, such as nutritional indicators, muscle metabolism, and physiological parameters, which can elucidate the nature of fatigue and dyspnea, are also needed in future studies. Thirdly, we were not able to objectively examine the activity level or muscle strength and the coping response as references to facilitate the symptom management in the future. Fourthly, the case numbers in groups getting worse and recovery were relatively small which might have result in less reliable representative. Finally, the HRQOL scores were analyzed by 68 patients in the study because in total, fifty-four who had missing questionnaire data on one or two measurement point were excluded, therefore it should be taken into consideration of the representative.

CONCLUSIONS

The results demonstrate the value of tracking symptom trajectories over time. Therefore, different trajectories of fatigue and severe baseline fatigue or increased fatigue should not be ignored or underestimated by health care providers and tailored strategies of fatigue management are important.

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