

# The Relationships Among Physiologic Variables, Quality of Life, and Fatigue in Patients With Multiple Myeloma

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**F**atigue is a symptom with several possible etiologic factors related to disease and treatment, including low hemoglobin (hgb), nutritional deficiencies, cytokines, cachexia, tumor burden, anxiety, depression, sleep disturbance, physical activity, and unmanaged symptoms (Ahlberg, Ekman, Gaston-Johansson, & Mock, 2003; Morrow, Shelke, Roscoe, Hickok, & Mustian, 2005; Olson et al., 2008). Fatigue in cancer has been described as being unlike fatigue associated with normal physical or mental exertion, with distinct physical, sensory, affective, and cognitive components (Barnes & Bruera, 2002; Gutstein, 2001; Olson & Morse, 2005). A consequence of the disease and treatment, fatigue is a seemingly ubiquitous symptom that patients with multiple myeloma encounter along the illness trajectory. The purpose of the current study was to begin an investigation of factors related to disease that contribute to the development of fatigue in patients with multiple myeloma.

Although researchers have examined disease-related factors associated with cancer-related fatigue, none has expressly examined the factors in patients with multiple myeloma. Many researchers have focused on the association between hgb and fatigue (Ryan et al., 2007); however, the relationship between anemia and fatigue has not always been consistent, and the degree of anemia is not always correlated with severity of fatigue (Morrow, Andrews, Hickok, Roscoe, & Matteson, 2002; Olson et al., 2002). For example, patients who are not anemic and undergoing radiotherapy often are profoundly fatigued (Ahlberg, Ekman, & Gaston-Johansson, 2004). Furthermore, in many patients, fatigue can be a persistent symptom years beyond the completion of treatment (Bower et al., 2000; Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006).

Cancer and its treatment are associated with the release of inflammatory markers by immune and malignant cells (Schubert, Hong, Natarajan, Mills, & Dimsdale, 2007). The finding that symptoms such as fatigue, fever, depressed

**Purpose/Objectives:** To investigate the relationships among physiologic variables, fatigue, and quality of life (QOL) in patients with multiple myeloma.

**Design:** Cross-sectional, descriptive, exploratory.

**Setting:** Outpatient ambulatory care clinics at a tertiary oncology center.

**Sample:** 56 patients with multiple myeloma were accrued consecutively via nonprobability sampling strategy.

**Methods:** Study participants completed the European Organisation for Research and Treatment of Cancer QLQ-C30 and the Functional Assessment of Cancer Therapy–Fatigue. Physiologic variables and demographic data were collected from patient charts.

**Main Research Variables:** Hemoglobin (hgb), C-reactive protein (CRP), fatigue, and QOL.

**Findings:** Statistically significant correlations were found among hgb and two measures of fatigue and QOL, as well as among CRP and two measures of fatigue and QOL. Regression analysis revealed that as soon as the effect of CRP was removed, hgb was no longer a significant predictor of fatigue or QOL.

**Conclusions:** Although significant relationships between hgb and fatigue and hgb and QOL were identified, CRP made a significant contribution to predicting the variance in fatigue and QOL, whereas hgb did not. The findings suggest that higher CRP is predictive of greater fatigue and lower QOL.

**Implications for Nursing:** Nurses play an integral role in the assessment and management of cancer-related fatigue. Greater understanding of the pathophysiology of fatigue may lead to progress in assessment and intervention, with the ultimate goal of reducing cancer-related fatigue and improving QOL.

activity, and anorexia are induced by the infusion of cytokines has led clinicians and researchers to speculate about the role of cytokines in their development (Lee et al., 2004). In addition to influencing subjective symptoms, cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) have been found to interfere with red blood

cell production (Kurzrock, 2001). The contributions of cytokines to the development of fatigue may be direct or indirect as in the genesis of anemia, which then could contribute, at least in part, to fatigue. The hypothesis underlying the current study was that proinflammatory cytokines play a key role in the development of fatigue in patients with multiple myeloma and that after the effect of the cytokines was removed, the effect of hgb on fatigue would no longer be significant.

## Fatigue and Multiple Myeloma

Fatigue is one of the most commonly reported symptoms in patients with multiple myeloma. Patients with multiple myeloma have fatigue for several reasons. The most recognized theory is that fatigue is a consequence of anemia (Kyle et al., 2003). Evidence is emerging that other factors related to the inflammatory process may contribute. Mazhar, Gillmore, and Waxman (2005) discussed the role of inflammation in the pathogenesis of malignancy. Overexpression or aberrant expression of proinflammatory cytokines has been identified as an essential component of tumor progression and proliferation. Proinflammatory cytokines also may contribute to the development of cancer-related symptoms, including lean tissue loss, poor performance status, fatigue, and anemia (Brown, McMillan, & Milroy, 2005; Kurzrock, 2001).

When proinflammatory cytokines are found in the bone marrow microenvironment, they contribute to the pathogenesis of myeloma (Harousseau & Moreau, 2002). In particular, the production and secretion of certain cytokines is thought to confer proliferative and survival benefits to myeloma cells. Some cytokines also are capable of conferring drug resistance and antiapoptotic properties. Nuclear factor-kappa B (NF- $\kappa$ B) has been found to regulate adaptive and innate immune responses (Lee et al., 2004). NF- $\kappa$ B controls the activity of several cytokines, chemokines, cell-surface adhesion molecules, and certain receptors (Lee et al.). Furthermore, NF- $\kappa$ B activates expression of gene-encoding enzymes that participate in the inflammatory process. The subsequent result is inducible expression of cyclooxygenase-2 and production of prostaglandins. Lee et al. noted that prostaglandins are known to induce symptoms associated with sickness, such as fatigue, lethargy, and fever, and suggested that NF- $\kappa$ B could represent a possible link between the expression of cytokines and the production of cancer-related symptoms.

### Interleukin-6

IL-6 influences growth and survival of myeloma cells (Tripathi, Corringham, Klein, & Rossi, 2003). IL-6 is overproduced by bone marrow stromal cells, and elevated levels have been found in active and advanced disease (Hideshima, Bergsagel, Kuehl, & Anderson, 2004; van Zaanen et al., 1998). Specifically, IL-6 has been found

to influence JAK (antiapoptosis), RAF (proliferation), and PI3K (migration, antiapoptosis, and cell cycle) pathways. IL-6 inhibitors include corticosteroids, non-steroidal anti-inflammatory drugs, estrogens, and other cytokines. Dimeo et al. (2004) found that patients with chronic fatigue syndrome have increased serum IL-6.

Hepcidin, a peptide produced by hepatocytes and induced by IL-6, is an iron regulatory hormone. Hepcidin is responsible for the inflammation-induced iron dysutilization implicated in the anemia related to acute and chronic infection and chronic renal disease. Hepcidin also is hypothesized to play a role in anemia related to malignancy (Andrews, 2004; Maccio et al., 2005; Rivera et al., 2005). Nemeth et al. (2004) found that the infusion of IL-6 in humans led to increased hepcidin secretion, decreased serum iron, and decreased transferrin saturation. Hepcidin-induced altered iron use is not observed in IL-6 knockout mice that have been genetically altered to delete or "knock out" the IL-6 gene (Nemeth et al.). IL-6 induces the transcription and translation of ferritin and induces hepcidin, which ultimately leads to increased storage of iron in the reticuloendothelial system and hypoferrremia. Hypoferrremia then results in a blunted erythropoietin response and subsequent anemia (Nemeth et al.).

Sharma et al. (2008), in a study involving newly diagnosed patients with stage III myeloma (N = 44), found a significant inverse correlation between hgb and urinary hepcidin levels ( $p = 0.0014$ ). Although a trend existed toward a positive relationship between urinary hepcidin and serum IL-6, the relationship was not statistically significant ( $p = 0.06$ ). However, hepcidin levels were significantly positively correlated with serum ferritin ( $p = 0.048$ ) and C-reactive protein (CRP) ( $p = 0.0012$ ).

Evidence for the impact of IL-6 on the development of cancer-related symptoms is supported by the administration of anti-IL-6 therapy in patients with multiple myeloma. In an early trial of patients with advanced multiple myeloma receiving anti-IL-6 monoclonal antibody (mAb) therapy, Bataille et al. (1995) reported that patients experienced subjective improvement in pain and fatigue, as well as reductions in CRP levels. Patients who previously had been experiencing fever and hypercalcemia had resolution of the symptoms. When Rossi et al. (2005) infused patients with multiple myeloma with an anti-IL-6 mAb, they found that the mAb was able to block *in vivo* proliferation of myeloma cells and reduce IL-6-related symptoms such as fever and cachexia. In addition, patients treated with the mAb required fewer transfusions of red cells as compared with the control group ( $p < 0.01$ ). Thus far, the ability of anti-IL-6 mAbs to reduce cancer-related symptoms such as fever, cachexia, and pain has been tempered by the modest clinical response as far as control of myeloma. For the most part, these agents have been trialed in patients with advanced or refractory multiple myeloma (Tripathi et al., 2003; van Zaanen et al., 1998).

## C-Reactive Protein

Several inflammatory markers have been associated with fatigue or depressed mood in patients with cancer. CRP, an acute-phase protein synthesized by the liver in response to proinflammatory cytokines and released in the early phase of inflammation, is a well-established marker of systemic inflammation (Clearfield, 2005). Elevated levels of CRP have been associated with infectious states, inflammatory conditions, and various malignancies and also may contribute to the pathogenesis of cardiovascular disease (Yang et al., 2007).

Scott et al. (2002) found that elevated levels of CRP were associated with increased fatigue and poor performance status in patients with inoperable non-small cell lung carcinoma. The production of CRP is regulated by IL-6 in vitro and in vivo (Tripathi et al., 2003). Rossi et al. (2005) reported that CRP production was blocked in patients receiving an anti-IL-6 mAb. The association between CRP and IL-6 was confirmed by the lack of production of CRP in IL-6 knockout mice (Rossi et al.). Yi et al. (2007) examined the effects of CRP on myeloma cells. In vitro, CRP promoted myeloma cell proliferation and reduced primary cell death as well as dexamethasone- and melphalan-induced apoptosis. In vivo, the therapeutic effects of dexamethasone and melphalan were reduced when CRP was injected into myeloma-severe combined immunodeficiency mouse models. Yi et al. also found that CRP enhanced myeloma cell secretion of IL-6 and worked synergistically with IL-6 to protect cells from chemotherapy-induced apoptosis.

IL-6 production is dysregulated in patients with multiple myeloma. Furthermore, the production of CRP and hgb are regulated by IL-6. The hypothesis of the current study was that in the case of patients with multiple myeloma, inflammation (measured using CRP) played a significant role in the development of fatigue and reduced QOL. In addition, if the effect of inflammation was removed, hgb would not be a significant predictor of fatigue or QOL. Figure 1 depicts the hypothesized relationships among the study variables.

## Methods

### Sample and Setting

The study employed a prospective, descriptive, exploratory design. A consecutive sampling approach was used to accrue 56 patients from clinics at a cancer center in western Canada. Patients were asked to participate in the study if they had a diagnosis of multiple myeloma, were aged 18 years or older, and were able to provide consent to participate in the study. The only exclusion criterion was a diagnosis of a plasma cell dyscrasia other than myeloma.

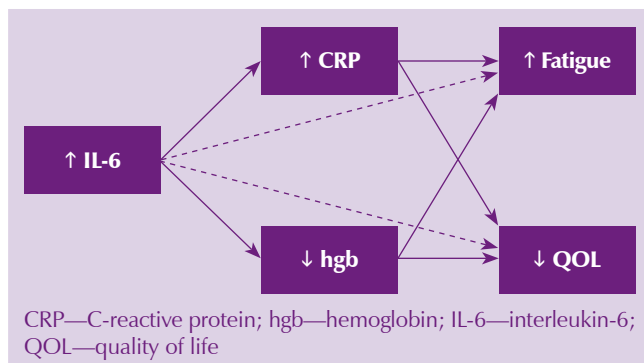


Figure 1. Relationship Among Study Variables

## Ethical Considerations

All procedures in the current study were conducted in accordance with the ethical standards outlined by the University of Alberta (2004) and the Alberta Cancer Board (2004). Approval for the study was obtained from research ethics boards of the University of Alberta and the University of Calgary Conjoint Health Research Ethics Board. Study participants were provided with a written description of the study and opportunity to ask questions about the study and participation as they arrived for their clinic appointments. Written consent was obtained from patients interested in participating in the study.

## Data Collection

When consent was obtained, participants were asked to complete the study instruments. Demographic and clinical information, including age, gender, disease stage, hgb, and CRP, were obtained from participants' charts. CRP was collected routinely for some patients; for other patients, it was an additional test. The inclusion of CRP as another test did not require any additional volume of blood to be taken. Data collection occurred at one time point: when participants came to the clinic for an outpatient hematology visit.

## Instruments

The European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) is a 30-item questionnaire that measures QOL (Aaronson et al., 1993) and is comprised of subscales that assess physical, role, emotional, social, and cognitive function as well as a number of symptoms, including fatigue, pain, emesis, distress induced by financial concerns, dyspnea, sleep disturbance, appetite, diarrhea, and constipation. Patients are asked to reflect on the prior week when completing the questionnaire. The questions on QOL and general health are each rated on a numerical rating scale (1–7), with the lower end of the scale anchored by very poor (overall health or overall QOL) and the upper end

anchored by excellent (overall health or overall QOL). The psychometric properties of the EORTC QLQ-C30 were examined in patients with cancer in Canada (N = 696) and the Netherlands (N = 485) (Osoba, Aaronson, Zee, Sprangers, & te Velde, 1997). The global QOL score was found to have satisfactory internal consistency with Cronbach alpha ranging from 0.83–0.92 (Osoba et al.). In the current study, the total score on the EORTC QLQ-C30 was used as one of the measures of QOL, noted hereafter as QOL<sub>QLQ</sub>.

The EORTC QLQ-C30 includes a three-item fatigue subscale. Questions are answered with yes or no or are rated on a 4-point numerical rating scale from 1 (not at all) to 4 (very much). In a study examining the psychometric performance of the scales of the EORTC QLQ-C30 in more than 2,000 patients with cancer, the fatigue subscale was found to have satisfactory internal consistency with a Cronbach alpha of 0.88 (Ringdal et al., 1999). The fatigue subscale score is constructed such that a high score indicates greater fatigue. The fatigue subscale of the QLQ-C30, noted hereafter as Fatigue<sub>QLQ</sub>, was used as one of the measures of fatigue in the current study.

The **Functional Assessment of Cancer Therapy–Fatigue (FACT-F)**, developed in 1994, comprises the 28 items of the FACT-General (FACT-G) as well as 13 items to assess fatigue. The FACT-G is a collection of questions that assess health-related QOL (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997). A total score is obtained by summing all items, and a high score indicates less fatigue. Scores are stable (test-retest  $r = 0.87$ ), and the scale is internally consistent (Cronbach alpha = 0.95–0.96) (Yellen et al.). The FACT-F (version 4) was used as the second measure of fatigue in the current study and is noted hereafter as Fatigue<sub>FACT</sub>. Permission to use the questionnaire was provided by David Cella, PhD, via www.facit.org.

## Data Analysis

Statistical information was computed with SPSS® version 14.0. Descriptive statistics were computed for all variables. Correlations among variables were assessed by Pearson’s  $r$  test. Linear regression was used to explore predictive relationships among inflammation, anemia, fatigue, and QOL. The correlation and regression results were confirmed with GraphPad Prism version 4.0.

## Findings

Fifty-seven patients were approached and asked to participate in the study. Of these, only one patient declined participation, citing disinterest as the reason. The resulting sample included 56 patients who attended outpatient hematology clinics from May 2006 to January 2007. Demographic information for study participants is summarized in Table 1.

## Study Variables

The means, medians, standard deviations, and minimum and maximum scores are summarized in Table 2. Although the results for hgb, QOL<sub>QLQ</sub>, Fatigue<sub>QLQ</sub>, and Fatigue<sub>FACT</sub> were distributed normally, an extreme outlier in the CRP data was identified and removed prior to data analysis. Seven values were missing for CRP and three for Fatigue<sub>FACT</sub>. Only cases for which complete data on all variables were available were included in the regression analysis ( $n = 47$ ). The cases included in the correlational analysis varied from 47–56, depending on the availability of data for variables included in each calculation.

Only 5% ( $n = 3$ ) of participants reported no fatigue at all, whereas 16% ( $n = 9$ ) reported the worst possible fatigue, with an adjusted score of 100 on the Fatigue<sub>QLQ</sub>. One patient (2%) had a score of 52, the highest possible score and one that indicates no fatigue, whereas two patients (4%) had a score of 7, indicating significant fatigue on the Fatigue<sub>FACT</sub>. The Fatigue<sub>QLQ</sub> score and the Fatigue<sub>FACT</sub> score were correlated highly with each other ( $r = -0.88$ ,  $p < 0.01$ ).

## Relationships Among Study Variables

Hgb and Fatigue<sub>QLQ</sub> were negatively correlated ( $r = -0.345$ ,  $p = 0.009$ ). Hgb and Fatigue<sub>FACT</sub> and hgb and QOL<sub>QLQ</sub> were positively correlated ( $r = 0.421$ ,  $p = 0.002$  and  $r = 0.405$ ,  $p = 0.002$ , respectively). The positive relationship between hgb and Fatigue<sub>QLQ</sub> and negative relationship between hgb and Fatigue<sub>FACT</sub> can be explained by the differences in scoring between the two instruments. A high score on the Fatigue<sub>QLQ</sub> indicates high fatigue, whereas a high score on the Fatigue<sub>FACT</sub> indicates low fatigue. CRP and Fatigue<sub>QLQ</sub> also were positively correlated ( $r = 0.495$ ,  $p < 0.00001$ ). CRP and Fatigue<sub>FACT</sub> and CRP and QOL<sub>QLQ</sub> were negatively correlated ( $r = -0.459$ ,  $p = 0.001$  and  $r = -0.480$ ,  $p = 0.001$ , respectively). As regression analysis was

**Table 1. Demographic Characteristics**

Characteristic	n	%
<b>Age (years)</b>		
$\bar{X} = 62$	–	–
Range = 41–84	–	–
<b>Months since diagnosis</b>		
$\bar{X} = 22$	–	–
Range = 1–77	–	–
<b>Gender</b>		
Male	30	54
Female	26	46
<b>Stage</b>		
I	13	23
II	12	21
III	28	50
Not available	3	5

N = 56

Note. Because of rounding, not all percentages total 100.

**Table 2. Study Variables**

Variable	Normal Range	N	$\bar{X}$	Median	Minimum	Maximum
Hemoglobin	120–160 g/l	55	118	129	81	151
C-reactive protein	0–8 mg/l	49	11	5	0.2	83
Quality of Life <sub>QLQ</sub>	1–7	56	4	4	1	7
Fatigue <sub>QLQ</sub>	0–100	56	57	56	0	100
Fatigue <sub>FACT</sub>	0–52	53	30	31	7	52

Fatigue<sub>FACT</sub>—Functional Assessment of Cancer Therapy–Fatigue; Fatigue<sub>QLQ</sub>—European Organisation for Research and Treatment of Cancer QLQ-C30 fatigue subscale; Quality of Life<sub>QLQ</sub>—European Organisation for Research and Treatment of Cancer QLQ-C30

planned, correlations among the variables to be entered as independent variables also were calculated. The correlation between hgb and CRP was  $-0.612$ ,  $p < 0.00001$ . With the standard criterion of a correlation coefficient of 0.80 (Hair, Anderson, Tatham, & Black, 1998), no evidence of multicollinearity existed between hgb and CRP. Correlations among study variables are presented in Table 3.

## Regression

For the regression model, Fatigue<sub>QLQ</sub> was the dependent variable and hgb and CRP were the independent variables. Initially, hgb was entered first in the regression model, but the model was rerun entering CRP first with no difference in results. The regression model was rerun two further times with Fatigue<sub>FACT</sub> and QOL<sub>QLQ</sub> as the dependent variables in each regression model; on both occasions, the order in which hgb and CRP were entered made no significant impact on the results.

With Fatigue<sub>QLQ</sub> as the dependent variable, a significant model emerged ( $F = 7.313$ ,  $p = 0.002$ ). CRP was significant in predicting Fatigue<sub>QLQ</sub> ( $\beta = 0.514$ ,  $p = 0.003$ ), whereas hgb was not significant ( $\beta = -0.031$ ,  $p = 0.849$ ). Similarly, with Fatigue<sub>FACT</sub> as the dependent variable, a significant model emerged ( $F = 6.800$ ,  $p = 0.003$ ). Again, CRP was a significant predictor of Fatigue<sub>FACT</sub> ( $\beta = -0.350$ ,  $p = 0.034$ ), whereas hgb was not ( $\beta = 0.192$ ,  $p = 0.237$ ). When QOL<sub>QLQ</sub> was used as the dependent variable, the model was again significant ( $F = 7.169$ ,  $p = 0.002$ ). CRP was a significant variable in predicting QOL<sub>QLQ</sub> ( $\beta = -0.396$ ,  $p = 0.020$ ), and hgb was not a significant predictor of QOL ( $\beta = 0.136$ ,  $p = 0.412$ ).

## Discussion

The current study identified negative significant correlations between hgb and fatigue and positive correlations between hgb and QOL. The findings are consistent with previous studies (Holzner et al., 2002; Lind et al., 2002; Ludwig et al., 2002; Palumbo et al., 2004; Prue, Rankin, Allen, Gracey, & Cramp, 2006). The findings of the current study differ from those of Wisloff, Gulbrandsen, Hjorth, Lenhoff, and Fayers (2005), who examined the relationship between hgb and fatigue as well as hgb

and QOL in patients with multiple myeloma. Although the authors found a positive statistically significant relationship between hgb and fatigue, their regression model suggested that the ability to predict fatigue from hgb level was low. Furthermore, when multivariate analysis was conducted on data collected at 12-month follow-up, the relationship between hgb and fatigue was only of borderline significance (Wisloff et al.).

The finding in the current study that hgb was not a significant predictor of fatigue or QOL when the effect of inflammation (measured here as CRP) was removed is novel. In addition, the finding suggests that additional factors may be involved in the development of cancer-related fatigue and that the influence of low hgb on QOL may not be as important to the prediction of QOL as originally thought in this population. Previous authors have identified elevated CRP levels in patients with cancer experiencing fatigue (Brown et al., 2005; Maccio et al., 2005; Wratten et al., 2004), though none has studied the relationship in patients with myeloma. IL-6 and CRP are implicated in inflammatory processes and have been found to be elevated or dysregulated in patients with myeloma (Durie et al., 2003; Hideshima et al., 2004; van Zaanen et al., 1998). More specifically, CRP is an IL-6–induced acute-phase protein (Illman et al., 2005), suggesting a mechanistic link between CRP-related fatigue and inflammatory cytokines.

In a review of 20 published studies on the relationships between fatigue and inflammatory markers in patients with cancer, Schubert et al. (2007) reported that although many of the individual studies failed to demonstrate a relationship between cytokines and cancer-related fatigue, pooled analysis of all correlations resulted in overall significantly positive associations between cancer-related fatigue and inflammatory markers. The studies were heterogeneous with respect to cancer and treatment type, fatigue questionnaire used, and type of inflammatory marker(s) measured. Importantly, the aberrant production or expression of cytokines varied with type of cancer diagnosis (Schubert et al.).

An advantage of the current study is its focus on a homogenous group of patients as far as diagnosis is concerned. CRP is elevated in patients with multiple myeloma (Durie et al., 2003). Studying this patient

**Table 3. Correlations Among Study Variables**

Variable	C-Reactive Protein	Fatigue <sub>FACT</sub>	Fatigue <sub>QLQ</sub>	Hemoglobin	Quality of Life <sub>QLQ</sub>
<b>C-reactive protein</b>					
Pearson	1	-0.459	0.495	-0.612	-0.48
Sig (two tailed)	–	p = 0.001	p < 0.00001	p < 0.00001	p = 0.001
N	48	47	48	48	48
<b>Fatigue<sub>FACT</sub></b>					
Pearson	-0.459	1	-0.883	0.421	0.602
Sig (two tailed)	p = 0.001	–	p < 0.00001	p = 0.002	p < 0.00001
N	47	53	53	53	53
<b>Fatigue<sub>QLQ</sub></b>					
Pearson	0.495	-0.883	1	-0.345	-0.627
Sig (two tailed)	p < 0.00001	p < 0.00001	–	p = 0.009	p < 0.00001
N	48	53	56	56	56
<b>Hemoglobin</b>					
Pearson	-0.612	0.421	-0.345	1	0.405
Sig (two tailed)	p < 0.00001	p = 0.002	p = 0.009	–	p = 0.002
N	48	53	56	56	56
<b>Quality of Life<sub>QLQ</sub></b>					
Pearson	-0.48	0.602	0.627	0.405	1
Sig (two tailed)	p = 0.001	p < 0.00001	p < 0.00001	p = 0.002	–
N	48	53	56	56	56

Fatigue<sub>FACT</sub>—Functional Assessment of Cancer Therapy–Fatigue; Fatigue<sub>QLQ</sub>—European Organisation for Research and Treatment of Cancer QLQ-C30 fatigue subscale; Quality of Life<sub>QLQ</sub>—European Organisation for Research and Treatment of Cancer QLQ-C30

population may explain why CRP was found to be a significant predictor of fatigue even though previous studies of heterogeneous patient populations have failed to identify such a relationship.

## Limitations

The nonprobability sampling strategy in the current study may have led to selection bias and influenced the study results by limiting generalizability. The study employed a cross-sectional design, only capturing patients' symptoms and clinical variables at one time point. Assessing the trends of variables over time, throughout the illness and treatment trajectories, would likely provide valuable data on patterns of fatigue and relationships with clinical parameters.

The data analysis did not account for comorbid conditions, such as anxiety or depression, or psychosocial factors, such as marital status, relationships, employment status, or financial stress, which also may influence fatigue. In addition, the variability in the sample with respect to previous and current treatment regimens might have been a confounder in the study.

## Nursing Implications

### Practice

Nurses play a pivotal role in the assessment and management of cancer-related fatigue (Wood, Nail, Gilster,

Winters, & Elsea, 2006). As a greater understanding of the mechanisms underlying fatigue emerges, potential targets for therapy also will emerge. The findings of the current study suggest that nurses should monitor markers of the inflammatory process and help patients include the information in the fatigue-management strategies they choose. Although more research clearly is needed in this area, strategies such as modest exercise may be helpful when inflammatory markers are low, but strategies such as rest that require less energy expenditure may be more appropriate when inflammatory markers are high.

### Research

Further research on the etiology of fatigue clearly is needed. Studies that seek the best markers for inflammation are particularly warranted, as are studies that aim to identify the processes that trigger increases in inflammation. In addition, long-term studies assessing correlates of fatigue in patients throughout the illness trajectory are needed. Assessing correlates of fatigue in patients with no active disease or those with stable disease who are not receiving treatment may help to clarify the role of the inflammatory process in the development of cancer-related fatigue and also help to identify other factors associated with the development of cancer-related fatigue.

### Education

The prevalence of fatigue experienced by patients in the current study highlights the importance of educating

nurses and members of the allied healthcare team about fatigue assessment and management. The findings suggest that interventions for fatigue must extend beyond the correction of low hgb. In a systematic review prepared for the Cochrane Library, Bohlius et al. (2006) showed that, although the administration of erythropoietin clearly is associated with significant increases in hgb, the evidence that it also reduces fatigue is inconclusive. The finding is in keeping with the clinical observations of the current study; the correction of anemia with transfusion of packed red cells or administration of erythropoietin given according to evidence-based practice guidelines (Turner et al., 2001) rarely ameliorates fatigue to the degree intended.

In addition to nursing education, great opportunity exists for patient education with respect to fatigue and its management. Encouraging patients to report their fatigue to members of the treatment team is an important element of patient education. Patients often are hesitant to discuss their fatigue with physicians because they fear their treatment may be altered (National Comprehensive Cancer Network, 2008). In addition, many patients do not recognize the severity of fatigue as its onset can often be insidious. Many patients expect fatigue as part of their cancer diagnosis or treatment and are not aware that anything can be done to treat it.

## Conclusions

Although much of the literature to date has focused on the role of hgb in cancer-related fatigue, the findings in the current study suggest that additional factors, such

as inflammation, may play a role in the development of fatigue in patients with multiple myeloma.

Further research exploring the pathophysiology of fatigue clearly is warranted. The management of other cancer-related symptoms, including chemotherapy-induced nausea and pain, has benefited greatly in recent years as a result of greater understanding of the pathogenic mechanisms involved in each symptom. The introduction of 5-hydroxytryptamine 3-receptor antagonists has revolutionized the management of chemotherapy-induced nausea and vomiting. Similarly, greater understanding of the pathology of pain and the distinction of various types of pain as nociceptive or neuropathic have led to dramatic improvements in pain management. Though fatigue is a complex symptom with numerous potential etiologic factors, its ubiquitous presence in the lives of patients with cancer emphasizes the need for unfailing assessment and intervention with the goal of reducing morbidity and increasing QOL in patients with cancer.

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