To assess the Prevalence and Predictors of Cancer-related Fatigue and its Impact on Quality of Life in Advanced Cancer Patients Receiving Palliative Care in a Tertiary Care Hospital: A Cross-sectional Descriptive Study

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Abstract

Introduction: Cancer-related fatigue (CRF) is one of the adverse outcomes of cancer and its treatment. Despite its high prevalence; the data are scarce from the Indian population on the prevalence of CRF and its predictors in advanced cancer patients. Hence, we aim to find the prevalence of the fatigue, its impact of fatigue on quality of life (QOL), and possible predictors. **Methods:** This study was conducted after approval of the ethical committee in adult patients of advanced cancer receiving palliative care. The data collected included demographic details, nutritional status, any comorbidities involving cardiorespiratory, renal, pulmonary, and neurological system, type and stage of cancer, site of metastasis, any previous or ongoing chemotherapy or radiotherapy, history of drug intake, hemoglobin, and albumin. The study parameters included assessment of fatigue, QOL, and symptom assessment as per the validated tools. The primary objective of the study was to find the prevalence of fatigue in advanced cancer patients receiving palliative care. The secondary objectives were to find predictive factors of fatigue, its impact on QOL of patients, and the relation between the fatigue and QOL receiving palliative care. The correlation between fatigue score and QOL was analyzed using Pearson's correlation coefficient. Multiple linear regression analysis was performed for identifying the predictors of CRF. **Results:** The fatigue was observed in all 110 patients in this study. Of these, severe fatigue was seen in 97 patients (Functional Assessment of Chronic Illness Therapy [FACIT]-F < 30). The median (interquartile range [IQR]) FACIT-F score was 14 (8–23). The median (IQR) of the overall QOL was 16.66 (16.6–50).The correlation between the fatigue (FACIT-F) and QOL was + 0.64 (*P* < 0.001). The predictors of fatigue included pain, physical functioning, Eastern Cooperative Oncology Group, tiredness, and the level of albumin. **Conclusion:** We conclude that the prevalence of fatigue in Indian patients with advanced cancer receiving palliative care was high and it has a negative impact on QOL. Pain, physical functioning, performance status, and albumin were found to be independent predictors of CRF.

Keywords: Albumin, cancer, fatigue, pain, palliative care, predictors, quality of life

INTRODUCTION

Cancer-related fatigue (CRF) is one of the adverse outcomes of cancer and its treatment. It has been defined as "a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[1] CRF can occur not only during the start of cancer treatment but may also occur later during the course of treatment. It may continue to persist even after completion of cancer-related treatment.

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The pathophysiology of CRF may be due to a dysregulation of the neuroimmunoendocrine system.[2] It includes interaction among various factors such as cytokines and neurotransmitters and modifies hypothalamic–pituitary–adrenal axis and circadian rhythms.[2] CRF has been observed to negatively affect the patients' quality of life (QOL) and activities of daily living.[3] Severe fatigue impairs the QOL physically, mentally, emotionally, socially, and spiritually.[4-6] There can be many contributing factors of fatigue in cancer patients such as patient demographic characteristics, comorbid conditions, performance status of patients, primary malignancy, intensity and type of treatment, nutritional status, patient reported symptoms such as pain, depression and anxiety, sleep disturbances, nausea, abnormal laboratory values such as anemia, low albumin, electrolyte disturbances, and medications.[7-9]

The prevalence of CRF in cancer patients receiving treatment varies from 60% to 96%.[10] Despite its high prevalence; the data are scarce from the Indian population on the prevalence of CRF and its predictors in advanced cancer patients. Although various studies have been done in the past to evaluate the fatigue among patients with cancers receiving treatment, very few studies have been done in patients receiving the palliative care. This study might fill up the knowledge gap, and appropriate interventions can be given in the early stage of diagnosis of CRF by identifying its prevalence, the predictors, and thus timely appropriate management which, in turn, would improve the QOL. Hence, we aim to find the prevalence of the fatigue, its impact of fatigue on QOL, and possible predictors of fatigue in patients with advanced cancer receiving palliative care at a tertiary care center.

METHODS

This cross-sectional descriptive study was conducted at the palliative care unit of a tertiary care institute after approval of the institutional ethical committee (IEC) (vide ref no. IEC-666/01.12.2017, RP-25/2017 dated December 19, 2017). The protocol was registered at Clinical Trials Registry-India (CTRI)/2018/01/011189 at CTRI. The study was conducted in compliance with the Declaration of Helsinki and its amendments and was conducted according to the principles of Good Clinical Practice. All patients of >18 years of age with advanced cancer receiving palliative treatment and have been denied curative treatment (medical, surgical, or radiotherapy) with the Eastern Cooperative Oncology Group (ECOG) Performance Status score ranging from 0 to 3 and predicted survival of >4 weeks presenting to the palliative care unit were included in the study. Patients having a history of any psychiatric disorder or inability to communicate were excluded from the study. Patients were explained about the study protocol and written informed consent was obtained.

The data were collected on a standard pro forma which included demographic details; nutritional status; any comorbidities involving cardiorespiratory, renal, pulmonary, and neurological system; type and stage of cancer; site of metastasis; any previous or ongoing chemotherapy or radiotherapy and its details; any history of drug intake such as steroids and analgesics; and blood investigations such as hemoglobin (Hb) and albumin. The data were collected from the patients' history and also from the hospital manual and electronic records. The study parameters included assessment of fatigue, QOL, and symptom assessment as per the following validated tools:

- Edmonton Symptom Assessment Scale Revised: Assessed the patients symptom including pain, nausea, loss of appetite, dyspnea, sleep disturbances, depression, and anxiety
- EORTC Quality of Life Questionnaire (QLQ)-Core 15-Palliative module (EORTC QLQ-C15-PAL): Assessed the QOL of the patient. This tool consists of 15 items including a global health status/QOL item, a 5-item functioning subscale (assessing physical, role, emotional, cognitive, and social functioning), and a 9-item symptom subscale (assessing fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties)
- Functional Assessment of Chronic Illness Therapy (FACIT)-F: Assessed the patient fatigue. This tool is a short, 13-item and easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a 5-point Likert scale (4 = not at all fatigued to 0 = very much fatigued). By scoring convention, after appropriate reverse scoring of 11 items, lower scores on the FACIT-F subscale indicate greater levels of fatigue. The score ranges from 0 to 52. A score of <30 indicates severe fatigue. The higher the score on FACIT-F scale, the better is the QOL.

The patients were provided sets of a questionnaire which contains both English and Hindi version of the questionnaire (which are already validated in either language) as per the understanding of the patient. The patient record sheet was filled with the assistance of the researcher.

The primary objective of the study was to find the prevalence of fatigue in advanced cancer patients receiving palliative care. The secondary objectives were to find the predictive factors of fatigue, its impact on QOL of patients, and the relation between the fatigue and QOL receiving palliative care.

Statistical analysis

In a study by Kapoor A *et al.*, they evaluated CRF using FACIT F scale and reported that the mean ± standard deviation (SD) fatigue score was 36 ± 3.84. Based on these data and assuming the precision of 2% of the fatigue score, the sample size calculated was 108. Thus, we recruited 110 patients for our study.

A statistical analysis was done using IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. (Armonk, NY: IBM Corp.). Mean ± SD and other descriptive analysis of parameters including study tools scores were calculated. The correlation between fatigue score and QOL was analyzed using Pearson's correlation coefficient. Multiple linear regression analysis was performed for identifying the predictors of CRF. Variables with significance levels $P < 0.05$ continued in the regression model.

RESULTS

We assessed 132 patients for inclusion, but 22 patients were not meeting the inclusion/exclusion criteria. Finally, a total of 110 patients were recruited in the study and demographic profile [Table 1], clinical parameters [Table 2], and Edmonton Symptom Assessment Scale -symptoms [Table 3] was noted. The most common malignancy was gastrointestinal (22.7%) followed by genitourinary (20%). The most common modality of treatment received was chemotherapy (59%).

The median (interquartile range [IQR]) of daily morphine consumption was 30 (15–90) mg. Of the 110 patients, 92 patients were on opioids and the rest were on nonopioid analgesics.

The fatigue was observed in all 110 patients in this study. Of these, severe fatigue was seen in 97 patients (FACIT-F <30). The median (IQR) FACIT-F score was 14 (8–23). The median (IQR) of overall QOL was 16.66 (16.6–50) and other variables of QOL are shown in Table 4.

The correlation between fatigue (FACIT-F) and QOL was + 0.64 ($P < 0.001$). Similarly, there was a highly significant ($P < 0.001$) positive correlation between FACIT-F and physical (+0.70) and emotional scores (+0.45) of QOL. The symptom scores (as assessed from EORTC QLQ-C15-PAL) had a highly significant ($P < 0.001$) negative correlation with FACIT-F except for dyspnea [Table 5]. Among other factors, FACTI-F was found to have significant positive correlation with body mass index (BMI) ($P = 0.0008$), Hb ($P = 0.0002$), albumin ($P < 0.0001$), and negative correlation with ECOG score (<0.0001).

A linear regression model was constructed with fatigue as dependent variable and QOL variables and other demographic characteristics (age, BMI, comorbidities, and treatment received) and clinical variables (ECOG, Hb, and albumin) as independent variables. The predictors of fatigue included pain, physical functioning, ECOG, tiredness, and level of albumin [Table 6]. On further subgroup analysis, it was found that there was no statistically significant difference between mean FACIT-F scores of different age groups ($P > 0.05$). The mean FACIT-F scores of group with BMI 25–29.9 (25 ± 8.57) were significantly ($P < 0.001$) higher as compared to group with BMI <18.5 (13.3 ± 7.78) and those with BMI 18.5–24.9 (15 ± 10.4). The mean FACIT F scores were significantly ($P < 0.001$) lower in patients with ECOG 3 (10.3 ± 6.4) as compared to ECOG 1 (27.5 ± 7.7) and ECOG 2 (21.6 ± 9.8) patients. Patients with Hb <10 g/dL had significantly ($P < 0.001$) lower mean FACIT-F scores (12.8 ± 8.5) as compared to those with Hb >10 g/dL (19.4 ± 10.6). The mean FACIT F

Table 1: Demographic characteristics

Variable	*n*
Gender (male:female)	47:63
Age (years), mean±SD	46.8±13.77
<20	4
21-40	33
41-60	49
61-80	24
BMI (mg/m²), mean±SD	20.83±4.76
<18.5	33
18.5-24.9	58
25-29.9	12
30-39.9	7
Comorbidities	
Hypertension	19
Diabetes mellitus	14
Coronary artery disease	3
COPD	2
Chronic renal failure	2
Chronic liver disease	2
Endocrine	3
Seizure disorder	1
Site of primary cancer	
Head and neck	13
Gastrointestinal	25
Genitourinary	22
Thoracic	3
Breast	12
Lung	15
Hematological	6
Bone and soft tissue	3
PNET	1
Melanoma	1
CUP	1
Miscellaneous	7
Treatment received	
Chemotherapy	65
Radiotherapy	42
Chemotherapy + radiotherapy	26
Surgery	18

COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, SD: Standard deviation, PNET: Primitive neuroectodermal tumor, CUP: Cancer of unknown primary

Table 2: Clinical parameters

Variable	*n*
ECOG, mean±SD	2.4±0.60
ECOG (1:2:3)	6:46:58
Hb, mean±SD (g/dL)	10±2.2
Hb (<10)	57
Hb (>10)	53
Albumin, mean±SD (g/dl)	3.32±0.66
Albumin (<3.5)	69
Albumin (>3.5)	41
Daily morphine consumption (mg)	
<30	61
30-60	15
60-120	17
>120	17

Hb: Hemoglobin, SD: Standard deviation, ECOG: Eastern Cooperative Oncology Group

Table 3: Edmonton Symptom Assessment Scale - symptoms

	None	Mild (1-3)	Moderate (4-6)	Severe (7-10)
Pain	5	27	42	36
Dyspnea	48	28	12	22
Tiredness	1	14	28	67
Nausea/vomiting	38	41	10	20
Lack of appetite	8	20	23	59
Drowsiness	25	46	22	17
Depression	24	25	27	33
Anxiety	17	29	25	39
Well-being	2	9	26	47
Constipation	70	6	12	22

Table 4: Quality of life

Variable	Median (IQR)
Overall QOL	16.66 (16.66-50)
Functional scales	
Physical function	34 (16.66-66.66)
Emotional function	34 (33.33-67)
Symptom scales	
Dyspnea score	33.33 (0-66.66)
Pain score	66.66 (50-100)
Insomnia score	63.66 (33.33-100)
Fatigue score	66.66 (66.66-100)
Appetite score	66.66 (33.33-100)
Nausea/vomiting score	33.33 (0-66.66)
Constipation score	33.33 (0-66.66)

QOL: Quality of life, IQR: Interquartile range

scores were significantly lower ($P < 0.001$) in patients with albumin <3.5 g/dL (13.13 ± 8.80) as compared to those with albumin >3.5 g/dL (20.82 ± 10.47).

Discussion

In our study, we observed a prevalence of 100% among patients of advanced cancer receiving palliative care. Of these, severe fatigue was found in 88.18% of the patients. CRF has a negative impact on QOL. Pain, physical functioning, performance status, and albumin were found to be independent predictors of CRF. These findings could be explained as CRF can carry on for months or even years after the termination of cancer treatment and the patients also had advanced cancer.

CRF is among the most distressing and prevalent symptoms among patients of advanced cancer receiving treatment.[11,12] CRF leads to poor QOL and activities of daily living. This leads to poor social interaction and poor job attendance. In our study, FACIT-F had a significant positive correlation with overall QOL, i.e., if FACIT-F decreased (severity of fatigue increased), then QOL also decreased. Fatigue (FACIT-F) also had a significant positive correlation with other variables of EORTC QLQ-C15-PAL such as physical and emotional functioning and negative correlation with symptoms scores

Table 5: Correlation between fatigue (Functional Assessment of Chronic Illness Therapy-F) and quality of life

Variable	P	P
Overall QOL	+0.64	<0.0001
Functional scales		
Physical function	+0.70	<0.0001
Emotional function	+0.45	<0.0001
Symptom scales		
Fatigue score	−0.72	<0.0001
Nausea/vomiting score	−0.36	0.0001
Pain score	−0.53	<0.0001
Dyspnea score	−0.00	0.95
Insomnia score	−0.44	<0.0001
Appetite score	−0.58	<0.0001
Constipation score	−0.25	0.006

QOL: Quality of life

Table 6: Linear regression model for predictors of fatigue

Variable	Coefficient	SE	P	95% CI
Pain	−0.07	0.02	0.001	−0.12-0.03
Physical function	0.08	0.02	0.002	0.03-0.14
ECOG	−2.37	1.12	0.03	−4.61-0.13
Tiredness	−0.13	0.03	0.000	−0.19-0.07
Albumin	2.15	0.85	0.014	0.45-3.85

SE: Standard error, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group

of EORTC QLQ-C15-PAL such as pain, lack of appetite, lack of sleep, tiredness, nausea vomiting, and constipation except for dyspnea. Previous studies have also shown that fatigue significantly affects the QOL.[13-17] In our study, fatigue had a significant correlation with other factors such as BMI, Hb, albumin, and ECOG score. In few studies, anemia has shown to be the predictor of fatigue.[18]

We also found that the independent predictors of CRF were pain ($P = 0.001$), physical functioning ($P = 0.002$), ECOG ($P = 0.03$), tiredness ($P < 0.001$), and albumin ($P = 0.014$). Pain has been shown as an important predictor of fatigue in many other studies.[19-22] Low albumin level has been associated with the severity of fatigue in some studies.[13,23,24] Poor performance status has been associated with increasing severity of fatigue in the previous studies.[12,25] We found physical functioning as an important predictor of CRF. It has been observed that patients with more fatigue have lesser physical activities which may subsequently lead to physical deconditioning, and this further exacerbates persistence of fatigue.[26-28]

Our study found few predictors of CRF, and thus, certain interventions if done will reduce the severity of fatigue. Management of fatigue includes symptom control such as pain, nausea, appetite, dyspnea, and nutritional supplements to improve Hb and albumin and exercises to improve physical functioning. It has been reported that pain leads to increased

occurrence of CRF, and the authors concluded that the optimal analgesic management would mitigate CRF.[29] A recent meta-analysis reported that exercise decreases the occurrence of CRF in cancer survivors and more so in person with high adherence to exercise protocol.[30,31] It has also been observed that improvement in biochemical parameters such as Hb and albumin leads to amelioration in fatigue.[13] The combination of physical training and increased protein intake has been found to be beneficial, more so in patients with early stage of cachexia as compared to refractory cachexia.[32]

Our study is limited by the fact for evaluation of various interventions to prevent the occurrence of CRF. Although the factors responsible for CRF have been elucidated from our study, the relevant interventions and their outcomes need to be further studied.

CONCLUSION

The prevalence of fatigue in Indian patients with advanced cancer receiving palliative care was high and it has a negative impact on QOL. Pain, physical functioning, performance status, and albumin were found to be independent predictors of CRF.

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Conflicts of interest
There are no conflicts of interest.

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