

Editorial

Cancer-related fatigue: A burden unreported by patients, undiagnosed by physicians, and unaddressed in research

Fatigue is a feeling of extreme tiredness and/or lack of energy, usually described as being exhausted. Fatigue in healthy persons differs from that in patients with cancer in the fact that the latter is not resolved or improved by rest or sleep and is usually more severe and distressing. Cancer-related fatigue (CRF) is described 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 the recent activity and interferes with the usual functioning."^[1] Studies have shown that the prevalence of CRF can be as high as 90% in patients with cancer. The most concerning aspect is that CRF is neither recognized/reported by patients nor adequately diagnosed by the physicians; this pertinent issue that can have a profound effect on the quality of life (QOL) of the patients is largely unaddressed in the clinical trials.^[2] In the Indian scenario, this issue had not been addressed in studies before the year 2000, and even after that, there have been very few institutional reports about CRF. In this context, the study by Singh *et al.* that assessed the impact of CRF on the QOL of patients with central nervous system (CNS) tumors should be appreciated for bringing this most underreported yet significant issue into the limelight.^[3]

In this study, Singh *et al.*^[3] estimated the CRF cross-sectionally in patients who had biopsy-proven primary or recurrent CNS tumors and who visited the Neuro Medical Oncology department of the Tata Memorial Hospital in Mumbai, India, during the period between May and August 2019. The information was captured by administering one of the validated questionnaires for fatigue assessment in patients with chronic illnesses including cancer called the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F). The primary objective was to estimate the CRF scores in patients with CNS tumors, while elucidating the factors affecting the CRF scores. FACIT-F is a classical tool for fatigue measurement in chronic illnesses, particularly in cancer. It is derived from the original Functional Assessment of Cancer Therapy (FACT) system. FACIT-F is a combination of 28 items from the FACT-General (FACT-G) and 13 fatigue items from the FACT-Fatigue (FACT-F) questionnaires. Thus, the FACIT-F is a set of 41 questions, of which 7 questions each are on physical well-being (PWB) and functional well-being (FWB), 6 are on emotional well-being (EWB), and

8 are on social/family well-being (SWB).^[4] The FACT-G score is obtained from a combination of EWB, PWB, FWB, and SWB; the score can range from 0 to 108 points, with a higher score indicating a higher QOL. The fatigue score is defined by a set of 13 questions related to fatigue and ranges from 0 to 52, with any score <30 indicating severe fatigue. Due to the unavailability of any large studies on CRF in the Indian population, the authors did not perform a sample size calculation and enrolled a total of 100 patients.

The mean age of the patients enrolled in this study was 40 years, with 28% of the patients being women. Patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 3 were also included in the study and accounted for 20% of the study population. The most common histology was low-grade glioma (42%) followed by glioblastoma multiforme. One-third of all patients were receiving treatment for recurrence, and three-fourths of the patients received temozolomide as chemotherapy in any setting. The median fatigue score was 36, and one-third of the patients had a score of <30, indicating severe fatigue. The authors found that all the four subsets of the FACT-G scale, PWB, EWB, SWB, and FWB were significantly associated with the severity of fatigue score. Furthermore, fatigue and PS were found to be significantly associated. Patients with an ECOG PS of 2–3 were found to have more severe fatigue scores compared to those with an ECOG PS of 0–1. Age of the patient, active treatment status, and disease recurrence were found to have a significant association with the severity of fatigue. An additional factor that the authors tried to correlate was the category under which the patient sought treatment, which indicates the financial status and is a surrogate marker for the waiting period and the ability to choose the best options for treatment. This factor has not been addressed in any of the previous studies, even the ones from the Western countries where the majority of health-care is state-sponsored or covered under universal health benefit schemes. In India, in about 65% of the general population, the majority of cancer treatment expenditure comprises out-of-pocket expenses, except in case of those who have access to state-sponsored schemes or private insurance.^[5]

While assessing for qualitative parameters like fatigue, it is especially important to take into consideration all the factors

that can result in CRF along with cancer and its treatment. A scale that measures all these factors and which is adequately validated is necessary to get real-world data. Therefore, studies that assessed the fatigue by asking a simple, single-line question, “are you feeling tired?” might have fallaciously estimated the prevalence of CRF to be as high as 90%. Fatigue Coalition, a patient advocacy group, surveyed patients with cancer in the United States of America using such a single-line questionnaire. Nevertheless, some important findings were reported by this retrospective study, which showed that three-fourths of the patients perceived that they were suffering from fatigue, but only one-third of them reported it to the physicians, with the rest accepting that fatigue was a consequence of cancer and cancer treatment. A second survey by the same group revealed that three-fourths of the patients who were on treatment or had completed treatment had to change their place of work due to CRF. An average loss of 4.5 workdays for patients and families was reported in that study.^[6,7] Except for a handful of studies in the Indian setting, this aspect has not been reported on despite its impact on the lives of patients with cancer and their families.^[8,9]

A major limitation of Singh *et al.*'s study is that the factors that may be responsible for CRF were studied cross-sectionally at a single point of time, and the preceding and later effects of such factors were not taken into consideration. These factors may vary with time, and therefore, may affect the occurrence of CRF. Fatigue is a multidimensional symptom that has cognitive, affective, behavioral, sensory, and physiologic components.^[10] Using scales that can help assess all the factors that may lead to CRF in a patient can be more helpful in ruling out factors [Figure 1] that are amenable to modification or treatment such as poor sleep, poor appetite, or depression, and will be helpful when used along with fatigue assessment scales. Some examples of such global assessment scales are, the Edmonton Symptom and Assessment System, MD Anderson Symptom Inventory, Rotterdam Symptom Checklist, etc. We suggest the use of fatigue screening tools such as the visual analog scale and verbal rating scale along with elucidating the need for in-depth evaluation.^[11] There are several unique societal and cultural factors in India that can affect CRF, which are different from those in the western countries. Therefore, it is important to develop an indigenous scale to assess CRF. A good example of such an invention is the Brief Fatigue Inventory– Greek, a scale that was validated in Greek patients with cancer.^[12]

Singh *et al.* through their study have attempted to fulfill an unmet need in the Indian scenario, by assessing the burden of CRF, an issue least addressed in the clinical setting, both due to under-reporting and under-diagnosis. The data are

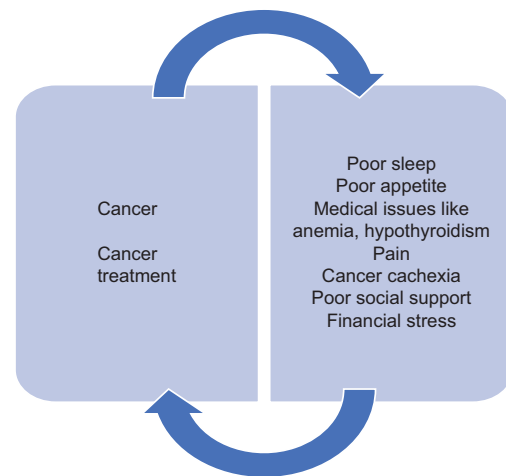


Figure 1: Factors affecting cancer related fatigue

sparse, especially in patients with CNS tumors. Some of the factors that were found to be significantly associated with CRF were age, active treatment status, disease recurrence, and category under which treatment was availed.

Similar to the limited reporting and understanding of CRF, there is no standard of care established for the treatment of CRF due to a lack of sufficient and efficient trials that have studied interventions and outcomes in CRF. With the data available from small randomized controlled trials (RCTs) and meta-analysis, it appears that non-pharmacologic interventions such as cognitive behavioral therapy and psycho-social interventions are beneficial. However, this benefit was seen only in patients who were receiving active cancer treatment, in those with curable malignancies, and cancer survivors. Similar benefits from these interventions were not seen in patients with incurable malignancies and those being treated with palliative intent. Unless contraindicated due to issues like severe thrombocytopenia, extensive skeletal metastasis, or active infection, moderate exercise is recommended for the prevention and treatment of CRF in patients with cancers of all stages, both by the American Society of Clinical Oncology and the European Society of Medical Oncology (ESMO).^[11,13] Limited evidence from RCTs suggests the benefit of mindfulness based approaches and yoga in relieving stress, although the role of acupuncture is less compelling.^[14] When these non-pharmacological agents are not helpful and other reversible factors have been ruled out as the cause of CRF, pharmacologic intervention using psychostimulants such as methylphenidate, dexamethylphenidate, and modafinil can be used on case-by-case basis. Steroids may be useful in very advanced stages or terminally ill patients with CRF and should be used based on clinical discretion.^[11,13]

Although this was a cross-sectional study with a limited sample size, it addressed a very pertinent issue in patients

with CNS tumors, which has not been addressed adequately to date. It is an appreciable effort that will turn the heads and thoughts of researchers toward the burden borne by the patients and their families and will help to design studies aimed at measuring and mitigating CRF. An important step toward addressing the problem of CRF in patients with brain tumors is the recognition and acceptance of fatigue by the patients and physicians. It is important for cancer physicians to recognize, discuss, and evaluate fatigue in the patients. Creating awareness among patients that several factors causing fatigue can be addressed using simple techniques of coping, energy conservation, rest, stress management, dietary modifications, positive self-care, and hydration or treatments that can reverse the causative factors will give them confidence to discuss fatigue and its effects on the various aspects of their lives.

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