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Cancer related fatigue-Analysing its causes to find the road map to its treatment- in the Indian scenario

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ABSTRACT

Introduction: *Cancer-related fatigue profoundly affects the physical, psychosocial, and occupational aspects of both patients and their families, thereby it results in marked deterioration of the patient's quality of life (QOL)[1]. The prevalence of CRF has been estimated to be occurring in 50% to 90% of cancer patients. This symptom has been found to be associated with sleep disorders, anemia, low performance status etc, due to its multifactorial associations many a times it is under-diagnosed, But if properly screened & treated it can drastically improve the quality of life in cancer patients.*

Purpose: ***This study was designed to evaluate:***

- *The overall prevalence of fatigue in cancer patients in our tertiary care centre &*
- *To find out the co-relation of fatigue with age, gender, cancer stage, cancer site anemia, performance status, sleep disorders so that in future we can tailor the treatment of fatigue as per the underlying cause.*

Results: *Fatigue was strongly related to sleeplessness ($P < 0.0001$) reduced performance status and anemia with Hb< 9gm/dl ($p< 0.02$). However, CRF was not found to affiliated to any one gender or any particular age group.*

Conclusions: *Prevalance of CANCER RELATED FATIGUE is around 66% in our centre Highly co-related with sleep disturbance.*

Anemia as per Indian standards (Hb<9gm) is associated with CRF, Higher stage of disease portends higher CRF values, No gender or age bias was noted.

Keywords: *Checklist individual strength (CIS), cancer related fatigue (CRF), sleeplessness, anemia.*

Introduction

Cancer-related fatigue profoundly affects the physical, psychosocial, and occupational aspects of both patients and their families, thereby it results in marked deterioration of the patient's quality of life (QOL)[1]. Prevalence have been estimated to range from 50% to 90% of cancer patients overall.

Many a times it is overlooked as patients consider it an unavoidable & untreatable side effect of cancer, hence it is largely under-diagnosed, but if properly screened & treated it can drastically improve the quality of life in cancer patients.

Although technologic advances and insights into the mechanisms of cancer have resulted in hope of increased survival and even cure in many cancer populations, but simultaneous efforts to promote quality of life through a commitment to rehabilitation and aggressive palliation have lagged considerably.

Studies have demonstrated that FATIGUE to be the most distressing phenomenon experienced by cancer patients.

How serious is the issue of cancer relate fatigue? Do we really need to bother?

The answer to the above question is a emphatic yes, as per the survey conducted by several oncological services, Fatigue was ranked number as the number one symptom among cancer patients worldwide[2]. 60% of cancer patients found fatigue to be the most distressing symptom they faced due to cancer ,even pain nausea & depression took a back seat here, similarly 54% of cancer patients felt fatigue to be the longest lasting symptom worrying them, hence treatment of cancer is complete only if we address and treat fatigue, so its high time we do an extensive study about the variables closely associated with fatigue, in doing so we can tailor the cure for fatigue at the earliest and thereby we can improve the quality of life of the cancer patients.

This study was designed to evaluate

1) The overall prevalence of fatigue in cancer patients
2) How multiple patient variables are associated with Cancer Related Fatigue and how strongly these variables predict the occurrence of fatigue in them
    a) Age of the patient
    b) Gender
    c) Stage
    d) Sleep disorders
    e) Hemoglobin status
    f) Performance status

Inclusion criteria

Biopsy proven malignancy
Undergoing treatment (RT/CT)
Age >18 yrs
ECOG 1,2,3
Able to read tamil language

Exclusion criteria

Age < 18 yrs
Brain tumours
ECOG IV

The study used the fatigue subscale of CIS (checklist individual strength) scores for assessing fatigue & the severity was scored as
Severe fatigue >= 35
Heightened fatigue 27-35

Material and Methods

Cancer patients receiving treatment at our tertiary care centre at Chennai, where we receive patients from almost all the 42 districts of tamilnadu as well as from other neighbouring states of andhrapradesh & karnataka,.

we screened a total of 78 patients who were presently undergoing radiotherapy treatment for the presence of fatigue using CIS (checklist individual strength) scores, and those in whom the total score was >= 27 were categorised as patients with fatigue.

The multidimensional checklist individual strength questionnaire (CIS) [3–7] was used to measure chronic fatigue (see appendix). The CIS was designed to measure several aspects of fatigue which is in line with our definition of fatigue. It consists of four dimensions: the subjective experience of fatigue and reduction in motivation, reduction in activity, and reduction in concentration. The CIS was tested thoroughly in the clinical setting among patients with chronic fatigue syndrome and other chronic diseases and healthy controls.[3-7] The internal consistency of the CIS seemed to be good: Chronbach's α for the total CIS was 0.90 and for the scales the α ranged from 0.83 to 0.92. The CIS was able to discriminate between patients with chronic fatigue syndrome, patients with multiple sclerosis, and healthy controls and the convergent validity was also satisfying.

In addition, the strength of other patient variables listed above which were suspected to have an impact over CRF were studied using univariate regressional analysis

Sleep disturbances was scored using The Groningen Sleep Quality Score (GSQS, 17)

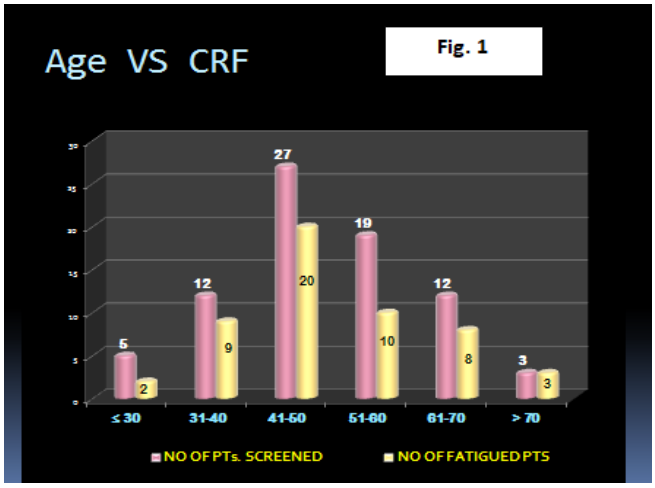
The sleep disturbances was noted as and when CIS was performed to assess the relationship

between sleep disturbances to Cancer Related Fatigue. Similarly parallel note was made about the haemoglobin level, age, gender, stage of cancer and the performance status of the cancer patients.

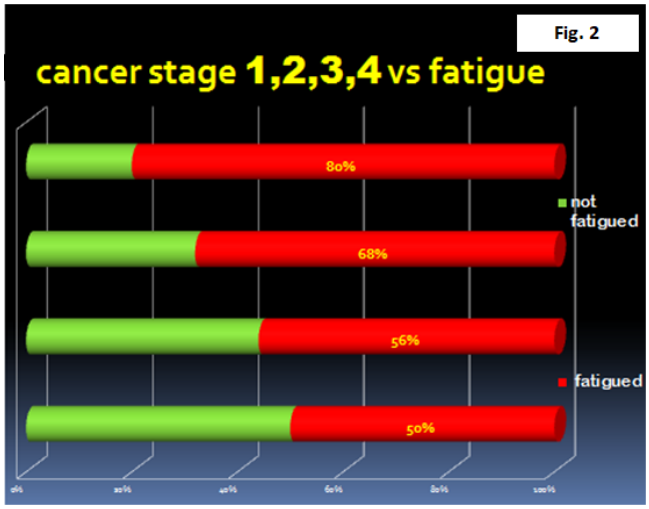
Results

CRF vs GENDER {ref fig 1}

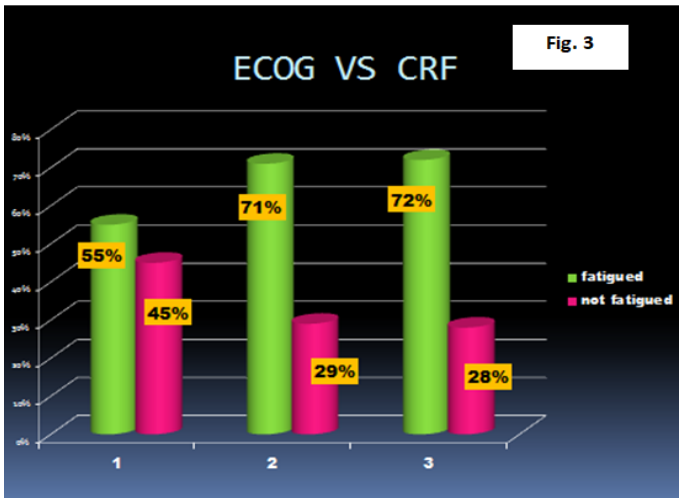
The occurrence of cancer related fatigue did not differ much between males &females, of the male cancer patients 68% had experienced fatigue, while 65% of female patients had fatigue. Both of them experienced fatigue equally.



Though numerically patients within the 40-50&50-60 age group experienced more fatigue, the association was not significant.



As expected higher stage of disease portended higher frequency of CRF {fig. 2}, almost 70%of stage III cancer patients &80% of stage IV patients were suffering from fatigue in our study and as expected patients with lower performance status had higher frequency of CRF{fig. 3}.



Discussion

Causes of Fatigue

The specific mechanisms involved in the development of cancer related fatigue are not completely known. Various factors play a part in the development of Fatigue.

Several studies have reported different mechanisms and causes of Fatigue but only few of them are proven.

Though the prevalence of fatigue in patients diagnosed with cancer is well-documented, cancer related fatigue (CRF) remains a widely under-treated and even under-reported phenomenon. If advances in health care provision are to be successful in minimizing the suffering and distress caused by cancer-related fatigue and understanding of how people communicate its impact to family, friends, and healthcare professionals is essential. Although the scientific community have a set definition for fatigue ,it is unclear whether patients will spontaneously ascribe their feeling of lack of energy, weakness, lack of motivation, desire for rest, etc. as "being fatigued." The purpose of this study was to draw a qualitative research to explore how patients with cancer-related fatigue describe it.

In most of the studies of CRF, the most salient finding that was reported was that this fatgue was of greater intensity than previously experienced tiredness and this fatigue was experienced even after adequate rest,

Since it is at least clear that this CRF is a peculiar type of fatigue, a number of studies have been conucted, but since the etiology of this CRF is sum product of a host of factors, there are certain grey areas which has been elduing the research workers and clinicians, there are some variables which have been found to be straightforwardly positively associated with CRF, but the correlation of certain variables are controversial like sleep disturbances, anaemia etc which needs further deeper understanding, hence. we shall discuss the more controversial variables which had differing results of association and how our study has tried to shed light to find answers to these controversies especially in the Indian scenario.

Anemia

Anemia (Hb level<12 g/dl) occurs due to neoplastic disease per se or as a consequence of cancer treatment. It is stated by the National Comprehensive Cancer Network as one of the treatable factors that may lead to CRF[8]. Although fatigue occurs more frequently than anemia, On an average, more than one third of patients become anemic after 3 cycles of chemo-therapy[10]. The other causes of anemia associated with cancer are nutritional deficiencies, bleeding, hemolysis and bone marrow involvement. Moreover, inflammatory cytokines, such as IL-1, IL-6, TNF-α and IFN-γ affect erythropoiesis, thereby causing anemia and fatigue [11–13].

Anemia and cancer relate fatigue- Is the association significant?- Indian scenario

Many studies have shown the relationship of anemia with fatigue[10]. Hemoglobin level may be affected in response to neoplastic disease or chemotherapy by altering erythrocytic membrane ion fluxes of potassium, chloride and magnesium. This hypothesis is supported by the fact that the lifespan of erythrocytes is diminished in anemia following cancer diagnosis[14] and from the finding that erythrocyte magnesium levels of RBCs plays a role in chronic fatigue syndrome[15]. Although how anemia is instrumental in causing fatigue in cancer patients unknown; some propose that, hypoxia-related impairment of organ function might be a cause [16].

We were curious to find out why should there be contradictory results connecting anemia and fatigue. Some study refuting the association between anemia & fatigue [17-19] and some stating that there is a positive association[10].

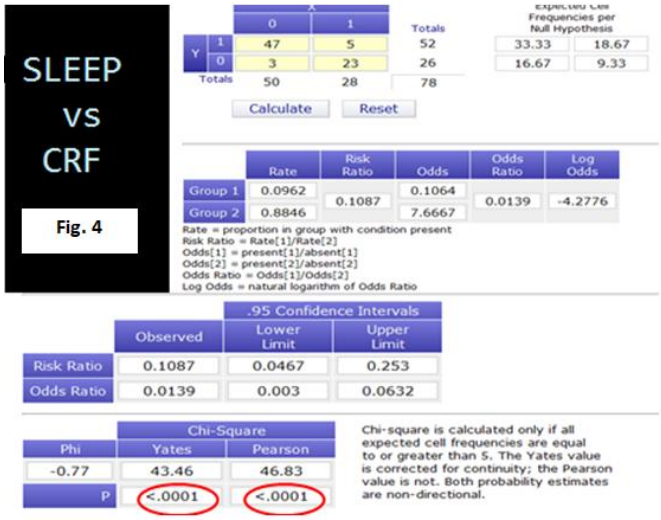
One reason might be the different yardstick that has been used to qualify anaemia. For eg Julie et al[20] describes anemia as any Hb value <12gm/dl as the yardstick and in the same article they support the positive association between anemia and CRF, where as in India its customary for normal subjects to with stand Hb upto 10gm/dl, hence hb>=10gm/dl is considered to be non-anemic level, due to this difference, may be applying western levels for anemia in indian patients might lead to false negative association, Hence we decided to run the tests of association tabulating the association of CRF vsanemia under 3 categories a) Hb<9gm/dl b)Hb<10gm/dl c) Hb<11gm/dl.{ref table no.1,2 & 3}

We found that if we fix the level for anemia as Hb< 9 gm/dl, there was asignificant association, whereas when we run the same tests keeping (b) and (c) as the yardstick for qualifying anemia, then association was not significant., implying that anemia is significantly associated as the cause of anemia in our tertiary care cancer center, and the exact qualification of anemia in indian subjects ought to be anHb< 9gm/dl.

Table-1	Anaemia Hb< 11 gm/dl		
fatigue	yes	no	
yes	40	12	52
no	16	10	26
P < 0.24			T=78

Table-2	Anaemia Hb< 10 gm/dl		
fatigue	yes	no	
yes	28	24	52
no	8	18	26
P < 0.09			T=78

Table -3	Anaemia Hb< 9gm/dl			
fatigue		yes	no	
	yes	20	32	52
	no	3	23	26
P < 0.02				T=78



Sleep Disorders- Is it anetiolgy of CRF? or a by-product of CRF? Or is it both?

It has been previously reported that fatigue and sleep disorders in patients with cancer are strongly co-related. Several mechanisms have been proposed to be behind the occurrence of sleep disturbances like the disruption of HPA-axis and circadian rhythm, alterations in serotonin metabolism and changes in cytokine expression. Sleep is highly under the control of the HPA axis. Similarly, Cortisol Releasing hormone (CRH) has been found to affect several components of sleep like slow-wave sleep, depth of sleep ,rapid eye movement (REM) sleep, and also waking too. The 24 hour circadian rhythm is mostly regulated by the suprachiasmatic nucleus (SCN), SCN is a part of hypothalamus which controls the circadian rhythm by the release of melatonin and cortisol.

Interestingly the same cortisol which the SCN uses to regulate the circadian rhythm by a complex feedback loop controls the SCN activity. Bower et al found that the CRF patients unlike normal patients have a cortisol levels which does not peak at the morning but contrarily peaks up at the evening, while during the rest of the day the cortisol levels stay subdued. Other factors which distrupt the normal sleep pattern are tumour derived peptides such as EGFR, serotonin etc. The above interlinked mechanism of sleep regulation, got unveiled in our study, our study revealed that the sleep disturbance was both a etiological factor as well as a product of CRF.

Conclusions

Prevalance of CANCER RELATED FATIGUE is around 66% at our tertiary cancer care centre

Highly co-related with sleep disturbance both as a causative as well as resultant variable

Anemia at lower levels (Hb<9gm)is associated with CRF, however when higher parameters were fixed for anemia, the association turned out to be non significant.

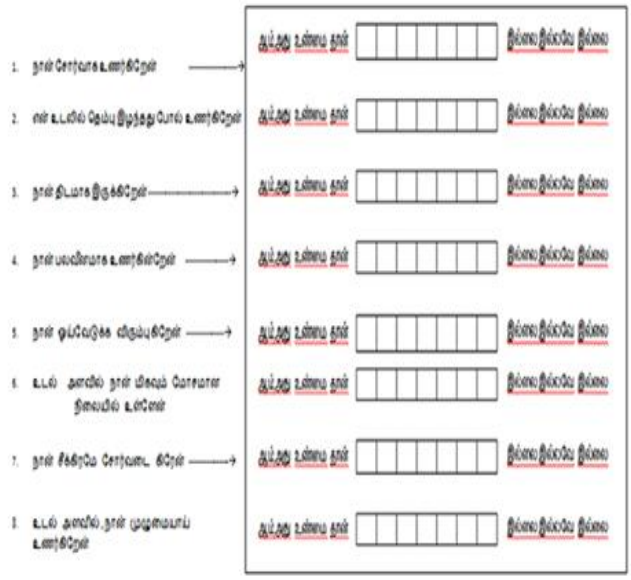
Higher stage of disease portends higher CRF values

No gender or age bias.

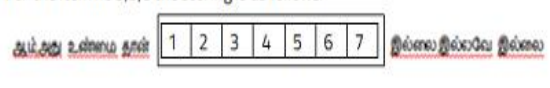
Appendix

Software package used :http://vassarstats.net/tab2x2.html

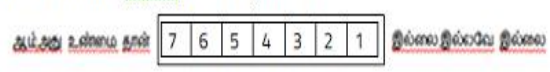
Questionnaire used:



For the item no 3,5,8 the scoring is as follows:



For the item no 1,2,4,6,7 the scoring is as follows:



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