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Original Research Article

Correlation of Cancer-Related Fatigue with Respiratory Muscle Strength in Breast Cancer Patients Undergoing Radiotherapy at Tertiary Health Care Hospital

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ABSTRACT

Background: Cancer-related fatigue (CRF) is a common and distressing symptom experienced by breast cancer patients undergoing radiotherapy. Respiratory muscle strength (RMS) plays a crucial role in maintaining physical function and quality of life. Understanding the relationship between CRF and Respiratory muscle strength could offer insights into the comprehensive management of breast cancer patients undergoing radiotherapy.
Objective: This observational, prospective study aimed to investigate the correlation between CRF and Respiratory muscle strength in breast cancer patients undergoing radiotherapy.
Methods: A convenient sample of 33 female breast cancer patients undergoing radiotherapy was recruited from a tertiary healthcare hospital. CRF was assessed using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale, while Respiratory muscle strength was measured using a Respiratory Pressure Meter (MicroRPM). Data were collected pre- and post-radiotherapy sessions. Statistical analysis, including Pearson correlation and paired t-tests, was conducted using SPSS version 22.0.
Results: The mean age of participants was 46.53 years. Pre-radiotherapy, the mean FACIT-F score was 29.27, indicating moderate fatigue, which decreased significantly to 25.60 post-radiotherapy ($p < 0.001$). Similarly, pre-radiotherapy, the mean Maximum Inspiratory Pressure (MIP) was 41.80 cm H_2O, and the mean Maximum Expiratory Pressure (MEP) was 45.20 cm H_2O, both of which decreased significantly post-radiotherapy ($p < 0.001$). However, Pearson correlation analysis did not reveal a significant correlation between CRF and RMS pre- or post-radiotherapy.
Conclusion: Breast cancer patients undergoing radiotherapy experience a significant reduction in CRF and Respiratory muscle strength post-treatment. However, no significant correlation was found between CRF and Respiratory muscle strength suggesting that other factors may contribute to CRF in this population. Further research is needed to explore additional variables influencing CRF in breast cancer patients undergoing radiotherapy.

Keywords: *Cancer-Related fatigue, Radiotherapy, Breast cancer*

INTRODUCTION

Cancer-related fatigue (CRF), a common and multifactorial symptom, is conventionally defined as "a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning." [2] The prevalence of CRF is extremely high, with most studies reporting rates above 60% and some reporting rates as high as 90%. [3]

Contrary to normal fatigue, CRF is disproportionate to the level of exertion and is not alleviated by rest or sleep. Even more so than pain, nausea, or vomiting, CRF is frequently cited as the most upsetting symptom related to cancer and its treatment. Thus, this symptom has the potential to drastically impair a patient's quality of life and ability to go about their daily business. [4]

CRF is frequently diagnosed even though its exact cause is still largely unknown., it is frequently associated with a wide variety of psychosocial factors (e.g., clinical depression, anxiety, and coping with chronic illness), and exacerbating symptoms (e.g., chronic pain, dyspnoea, insomnia, nausea, and weight loss) as well as antineoplastic treatment side effects (e.g., chemotherapy, radiotherapy, surgery, and medications) [5,6]

The assessment of Maximal Respiratory Pressure (MRP) is performed to evaluate quantitatively the strength of the respiratory muscles. The measurement of the respiratory muscle strength may be helpful for the assessment of the impact of chronic diseases or their treatment on the respiratory muscles, as in the case of breast cancer treated with radiotherapy. [7]

The examination of the Maximal Respiratory Pressures with the respiratory pressure meter is easy to perform, low cost, and non-invasive in clinical practice. The maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) reflect the respiratory muscle’s ability to generate force during a short quasi-static contraction.

The study of Santos et al. showed a reduction in maximum respiratory pressure measurements after radiotherapy. Dunlap et al. reported that radiation doses between 5000 cGy and 6000 cGy in the chest wall are strongly correlated with the development of toxicity that includes muscle, connective tissue, the neurovascular bundle, and bone, consequently causing fibrosis of intercostal muscles, a fact that may explain the reduction of maximum inspiratory pressure.

Even when the respiratory muscle is located outside the radiation field, it can often receive an off-target dose in chest radiotherapy, causing contractile dysfunction due to deoxyribonucleic acid (DNA) damage, and oxidative stress to myofibrils, affecting muscle morphology, reactive oxygen species production, and angiogenesis.

There are two types of radiotherapy: EBRT and IBRT (brachytherapy). In EBRT there are 2D Conformal, 3D conformal, IMRT (intensity modulated radiotherapy), IGRT (image-guided radiotherapy), SRT (stereotactic radiotherapy), and PROTON beam therapy.

In 2D radiotherapy, a single beam of radiation delivered to the patient from several directions is often front or back and both sides.

The simulation aims to accurately target or localize the volume that is to be treated. This technique is well-established quick and reliable.

With the adjuvant of novel Cancer-related fatigue models, respiratory muscle strength could be the objective measure that partially explains tiredness and exhaustion experienced by cancer patients.

How does a radiation beam affect the Lungs and respiratory muscles?

Radiation is energy in the form of waves or high-speed particles. Ionizing radiation refers to three types of emissions—alpha, beta, and gamma—with therapeutic radiation being predominantly gamma.

↓

Radiation injury results from two primary mechanisms: direct DNA damage and the generation of reactive oxygen species.

↓

The generation of Reactive oxygen species is more prominent in respiratory-induced fibrosis.

↓

There is the interaction of ionizing radiation with water molecules to form free radicals, including superoxide, hydrogen peroxide, and hydroxyl radical.

↓

Free radicals damage all components of cells, including proteins, nucleic acids, and lipids. Injured cells release chemoattractant molecules that trigger nonspecific inflammation.

↓

Neutrophils are the first inflammatory cells to arrive at the site of injury.

↓

When these cells come into contact with collagen fragments and fibronectin, they release proinflammatory cytokines like tumor necrosis factor-alpha (TNF-α), IL-1, and IL-6 that perpetuate the development of ROS and lead to even greater local inflammation.

↓

Then monocyte and Lymphocyte arrived at the site of the lesion.

↓

Monocyte differentiates into Two sets of macrophages M1(classically activated pro-inflammatory) and M2 (alternatively activated anti-inflammatory) M2 secrete platelet-derived growth factor which promotes the migration of fibroblast into injured tissue and also secretes TGFβ which differentiate fibroblast into myofibroblast.

↓

In response to TGF-β, myofibroblasts secrete excess collagen, fibronectin, and proteoglycans which are responsible for the increased stiffness and thickening of the tissue.

↓

Excess collagen reduces vascularity over time.

↓

This makes fibrotic areas susceptible to physical trauma and gradual ischemia, which may lead to loss of function, tissue atrophy, reduction in the number of fibroblasts, or necrosis.

What is Cancer-Related Fatigue?

National Comprehensive Cancer Network (NCCN) defined Cancer cancer-related fatigue 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.

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) is a unidimensional, 13-item scale that asks respondents to rate statements regarding their fatigue experience and its impact on their daily life. Sample items include: "I feel fatigued;" "I feel weak all over;" and "I feel listless (washed out)". All items are rated using a 5-point intensity rating scale. By scoring convention, after appropriate reverse scoring of 11 items, lower scores on the FACIT Fatigue subscale indicate greater levels of fatigue.

MATERIALS & METHODS

STUDY DESIGN:

- Research design: an observational, prospective study
- Place of study: Radiotherapy and Breast OPD, Tertiary Health Care Hospital.

Standard protocol of radiation at tertiary health care hospital:

- Type of radiation is 2 D radiation.
- Each Patient received 25 cycles or 15 cycles of radiation as per the area involved.
- 25 cycles divided into 5 weeks (5 days- from Monday to Friday/ per week)
- 15 cycles divided into 3 weeks (5 days- from Monday to Friday/ per week).

SAMPLE POPULATION: Breast cancer patients undergoing radiotherapy.

DURATION OF STUDY: After approval from MUHS, 6 months for data collection and 4 months for data analysis

SAMPLE SIZE:

The sample size was determined by medical records of radiotherapy OPD. The total number of patients who came in for Radiation OPD per month was five Therefore, 5×6(months) = 30 patients for 6 months Thus, the minimum sample size was 30.

10% of patients who were not willing to participate or fell into exclusion criteria were added to the above number of patients. 10/100×30=3 Therefore, 30+3= 33

TOTAL SAMPLE SIZE = 33

ELIGIBILITY CRITERIA

INCLUSION CRITERIA:

1. Female patients (above 18 years)
2. Breast cancer patients undergoing radiotherapy.

EXCLUSION CRITERIA:

1. Chronic conditions (stroke, Chronic Obstructive
2. Pulmonary Disease, Lung pathology) Any Metastatic breast cancer patient
3. Not willing to participate
4. Illiterate patients

STUDY MATERIAL:

1. Respiratory Pressure Meter (Intra class coefficient=0.8)
2. Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale (Intra class coefficient = 0.95).
3. Pen and Paper.
4. Chair for the patient to be seated

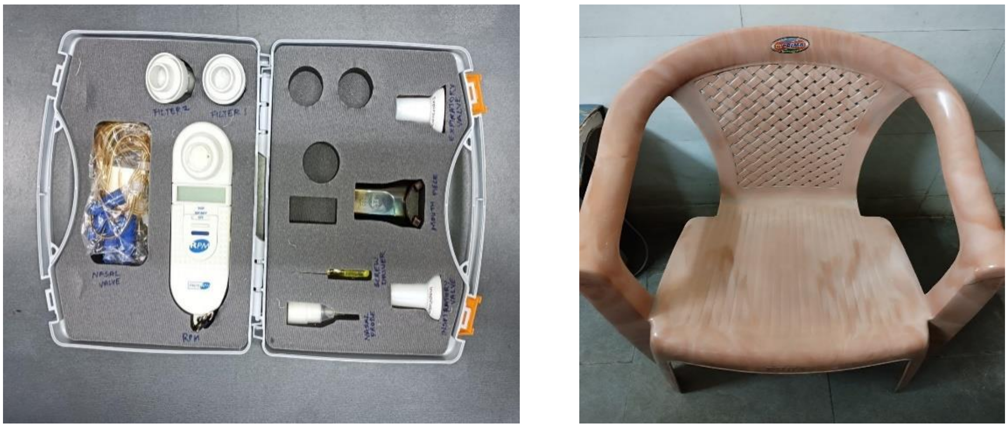


Figure A. Materials used 1. Respiratory pressure meter 2. chair

STUDY PROCEDURE

1. Procedure for Measurement of Maximum Respiratory pressure

The MicroRPM (Micro Medical/ CareFusion, Kent, United Kingdom) is a modern manometer that was recently used in studies that recorded Maximum inspiratory pressure and Maximum expiratory pressure.

It is a small, portable, lightweight, non-invasive, mouth-pressure manometer with a rubber-flanged mouthpiece and a small monitor that digitally displays the test results in cm H2O.

Before the measurements, each participant performed 5 maximum inspiratory and 5 maximum expiratory warm-up efforts to familiarize themselves with the procedure.

The participant was asked to hold the gauge with both hands and to close his or her lips firmly around the flanged mouthpiece. We applied a nose clip to avoid nasal air leaks.

For the MEP maneuver, the participant was asked to inhale as much as possible and then to exhale maximally for more than one second against the resistance of the gauge.

For the MIP maneuver the participant was asked to exhale as much as possible (to residual volume) and then to inhale maximally for more than one second against the resistance of the gauge.

All measurements were recorded on data record form for analysis.

Fig. Respiratory Pressure meter (MicroRPM) [16] (Intra class coefficient=0.87)

2. Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F)

The FACIT Fatigue Scale is a short, 13-item, easy-to-administer tool that measures an individual's level of fatigue during their usual daily activities over the past week.

Scoring and Interpretation: The level of fatigue is measured on a five-point Likert scale (4 = not at all fatigued to 0 = very much fatigued). The score ranges between 0-52. A score of less than 30 indicates severe fatigue, the higher the score, the better the quality of life Psychometric properties: High internal validity (Cronbach’s alpha = 0.96) and high test-retest reliability (Intra class coefficient = 0.95).

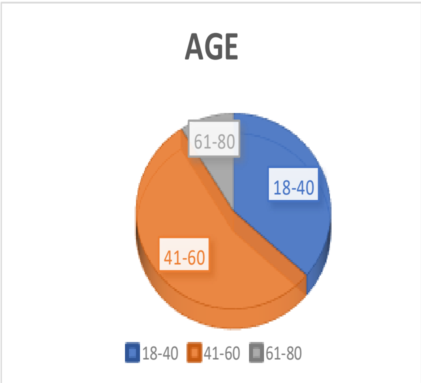
Figure B. MIP and MEP measurement by using respiratory pressure meter (MicroRPM)

STATISTICAL ANALYSIS

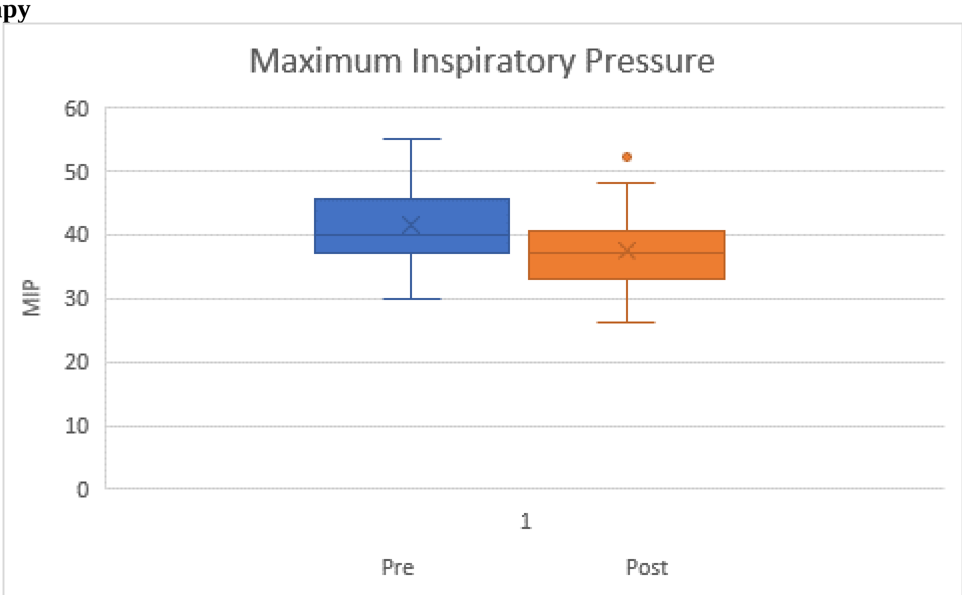
- Statistical Package for Social Sciences (SPSS version 22.0, IBM Corporation, USA) was used to analyse the data.
- The data was checked for normality using the Shapiro-Wilk test.
- The paired statistical comparisons of the distribution of categorical variables were tested using Wilcoxon's signed rank test.
- The paired statistical comparisons of means of continuous variables were done using paired t-test.
- For ease of analysis, the data was segregated into: i. Demographic data. ii. Descriptive statistics- Mean, Standard Deviation, Score of FACIT-F scale, Maximum Inspiratory Pressure, and Maximum Expiratory Pressure.
- The Pearson correlation analysis was conducted between Cancer-related fatigue and Respiratory muscle strength.
- The confidence interval was set at 95% and the significance level at 0.05. The data will be considered significant if $p < 0.05$.

Tables and Graphs

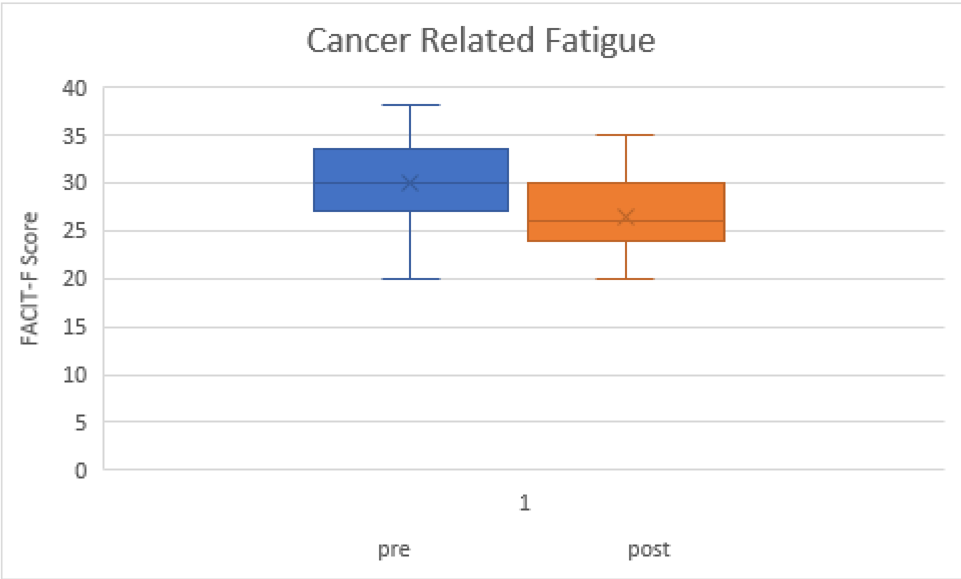
Graph 1: Age distribution of the participants



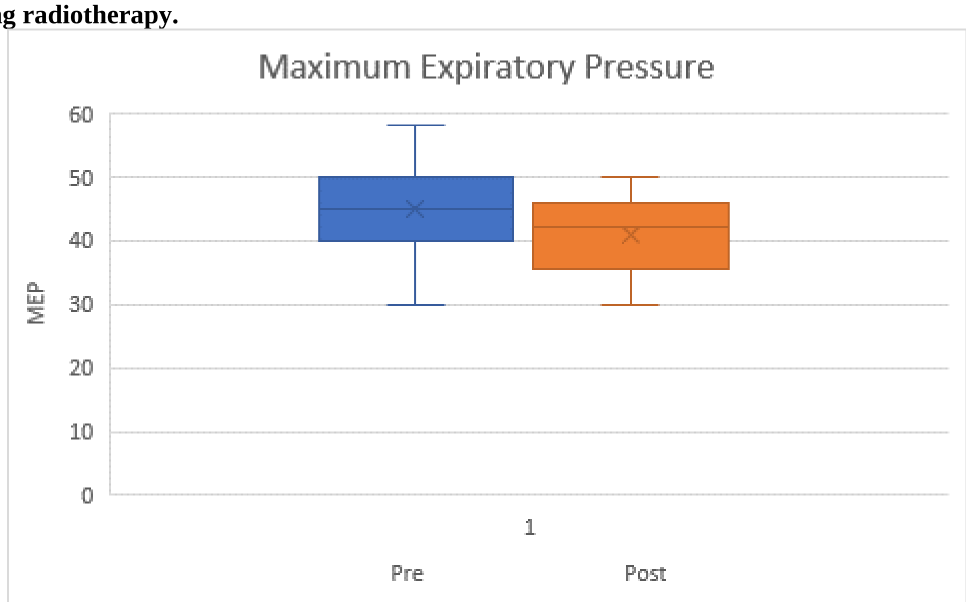
Graph 2: Box and plot distribution of Cancer Related Fatigue in breast cancer patients undergoing radiotherapy



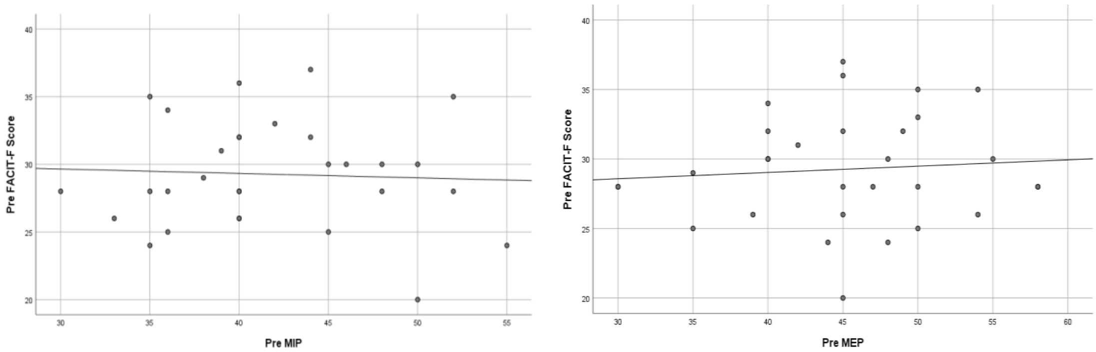
Graph 3: Box and plot distribution of Maximum Inspiratory Pressure in breast cancer patients undergoing radiotherapy.



Graph 4: Box and plot distribution of Maximum Expiratory Pressure in breast cancer patients undergoing radiotherapy.

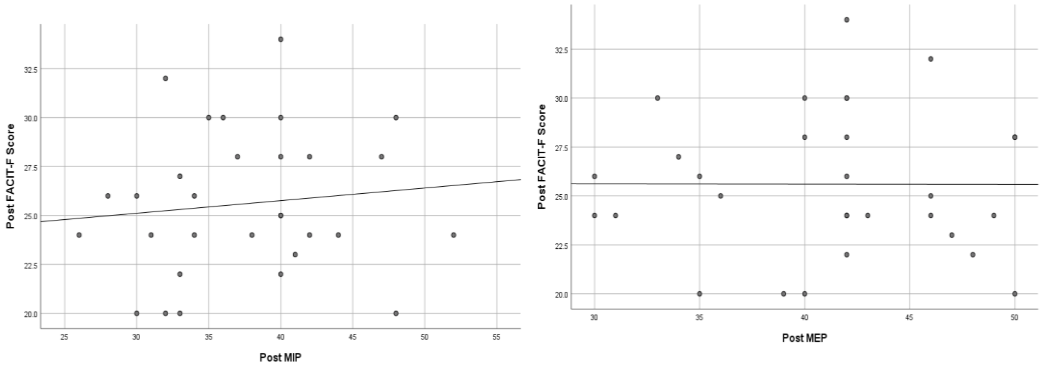


Graph 5.a&b Scatter Diagram between FACIT-F score and MIP (pre-Radiotherapy)



Inference: The above scatter diagram plot between FACIT-F score and MIP & MEP (pre-Radiotherapy) shows no correlation between CRF and Respiratory muscle strength

Graph 6.a&b Scatter Diagram between FACIT-F score and MIP (post-Radiotherapy)



Inference: The above scatter diagram plot between FACIT-F score and MIP & MEP (post Radiotherapy) shows no correlation between CRF and Respiratory muscle strength.

RESULT

The mean age of participants was 46.53 years. Pre-radiotherapy, the mean FACIT-F score was 29.27, indicating moderate fatigue, which decreased significantly to 25.60 post-radiotherapy ($p < 0.001$). Similarly, pre-radiotherapy, the mean Maximum Inspiratory Pressure (MIP) was 41.80 cm H2O, and the mean Maximum Expiratory Pressure (MEP) was 45.20 cm H2O, both of which decreased significantly post-radiotherapy ($p < 0.001$). However, Pearson correlation analysis did not reveal a significant correlation between CRF and RMS pre- or post-radiotherapy.

DISCUSSION

Breast cancer is the most common malignancy affecting women and its incidence is increasing by 1% per year. Nowadays it is often detected at an early stage and it is often managed with surgery, radiotherapy, and systemic chemotherapy. Radiotherapy has an important role in treating breast cancer by optimizing locoregional control and survival.[9]

Radiotherapy reduces the mortality rate in breast cancer patients. It improves survival in several categories of women with early breast cancer when irradiating the breast or chest wall with or without the regional lymph nodes exposing the lungs is unavoidable and this incidental exposure may increase the risk of subsequent primary lung cancer, pneumonitis, and lung fibrosis [10]

This study aimed to find out the correlation between cancer-related fatigue and respiratory muscle strength in breast cancer patients undergoing radiotherapy.

In this study, 33 participants in the age group of 18-65 years who meet the inclusion criteria and were willing to participate were recruited from the Physiotherapy and Radiation Oncology OPD of a tertiary health care hospital.

In our study, the age distribution of the participants ranges from 18-80 with a mean of 46.53±6.277. The age group between 18 to 40 years is 36%, 41 to 60 years are 54.54%, and 61 to 80 years are only 9 %.

In our study, cancer-related fatigue was assessed pre and post-radiotherapy by using the FACIT-F scale.

In our study, Table No. 2 shows descriptive statistics in which, the mean and standard deviation of FACIT-F score (pre-radiotherapy) was 29.27±4.332 & (post radiotherapy) was 25.60±4.664. Graph 2 shows descriptive statistics of FACIT-F score which was seen higher pre than post radiotherapy.

The difference in FACIT-F score is due to the indirect effect of radiation beam particles in aggravating the inflammation process in lung tissue which reduces the patient's performance and causes fatigue.

Cancer patients may experience fatigue due to several demographic, medical, psychological, behavioural, and biological variables. Marriage status and economic level are two demographic characteristics that have been connected to cancer-related fatigue.

Over the past two decades, a number of molecular pathways relating to cancer-related fatigue have been researched. These include changes in ATP and muscle metabolism, anemia, cytokine dysregulation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and 5-hydroxytryptophan neurotransmitter dysregulation. Dysregulation of cytokines, with a focus on proinflammatory cytokines, has attracted the greatest empirical research and supporting evidence to date. [12]

In our study its shows descriptive statistics in which, the mean and standard deviation of Maximum inspiratory pressure (pre-radiotherapy) was 41.80 ± 6.277 & (post-radiotherapy) was 37.53 ± 6.394, and Table 4 shows descriptive statistics in which, the mean and standard deviation of Maximum Expiratory pressure was (pre radiotherapy) was 45.20 ± 7.270 & (post radiotherapy) was 41.13 ± 5.981.

The reduced MIP and MEP in our study supports the findings of Thays Mello de Avila et al.in which a study of maximal respiratory pressure before and after exposure to breast radiotherapy showed a significant decrease in maximal inspiratory pressure in women. The negative impact on the respiratory system was characterized by diaphragm muscle weakness.[13]

Radiation-induced lung toxicity included three phases: acute, subacute, and late phase.

The acute phase can start right away or take days to develop. In this stage, the DNA damage caused by radiation to the lung tissue is repaired. Base alterations, complicated single- and double-strand breaks, DNA crosslinks, and bulky lesions resulting from direct ionizing processes or indirectly mediated by free reactive oxygen species (ROS).[10]

DNA damage induced senescence and death of alveolar type I and II cells result in loss of barrier function and reduced surfactant production, and decreased surface tension leads to interstitial oedema and further reduction of the alveolar septa.

The microvascular system of the lung tissue and particularly endothelial cells are also affected by radiation.[10]

Suesada MM, Carvalho HD et. al. concluded that, after radiotherapy, significant decreases in respiratory muscle strength, chest wall mobility, exercise capacity, and pulmonary function test results ($p < 0.05$). DLCO was unchanged. HRCT showed changes related to radiotherapy in 87% of the patients, which was more evident in the patients submitted to SCLN irradiation. V25% significantly correlated with radiation pneumonitis. [15]

Radiation-induced fibrosis (RIF), which can affect the skin and subcutaneous tissue, lungs, gastrointestinal and genitourinary tracts, as well as any other organs in the treatment field, is a significant contribution to patient morbidity. According to Jeffrey M. Straub et al., radiation exposure causes inflammation and ultimately encourages fibroblasts to transdifferentiate into myofibroblasts.[17]

This explains that decreases in respiratory muscle strength, chest wall mobility, exercise capacity, and pulmonary function test contribute to the reduction of MIP and MEP post-radiotherapy.

Cancer-related fatigue and Respiratory muscle strength

In our study, we found there is no correlation between cancer-related fatigue and respiratory muscle strength.

There was no correlation between the FACIT-F score and the value of MIP and MEP.

Pearson correlation analysis was conducted to examine the relationship between Cancer Related Fatigue and Respiratory Muscle Strength. The analysis revealed that the correlation between these two variables was not statistically significant.

The estimated prevalence of fatigue during treatment ranges from 25% to 99%, depending on the patient population, type of treatment received, and method of assessment.

In most studies, 30–60% of patients report moderate to severe fatigue during therapy, which in some cases might lead to treatment discontinuation.[12]

Although the Pearson correlation analysis did not establish a significant relationship between cancer-related fatigue and respiratory muscle strength, it is important to interpret this finding cautiously. Other factors not accounted for in this study, such as psychological and emotional variables, could contribute to cancer-related fatigue independently of respiratory muscle strength.

Julienne E. Bower et al. described the etiology of CRF as probably involving the dysregulation of several physiological and biochemical systems. Mechanisms proposed as underlying CRF include 5-HT neurotransmitter dysregulation, vagal afferent activation, alterations in muscle and ATP metabolism, hypothalamic–pituitary–adrenal axis dysfunction, circadian rhythm disruption, and cytokine dysregulation.[12]

Future research could delve deeper into the potential mechanisms linking cancer-related fatigue and respiratory muscle strength. Additionally, exploring the impact of other variables, such as emotional well-being, inflammation markers, and treatment-related factors, on cancer-related fatigue would provide a more comprehensive understanding of the correlation between CRF and respiratory muscle strength.

Despite the lack of a significant correlation, the increase in cancer-related fatigue and decrease in respiratory muscle strength after radiotherapy highlights the potential need of incorporating interventions aimed at enhancing patients' overall well-being during and after radiotherapy. In this study, 33 participants in the age group of 18-65 years who meet the inclusion criteria and were willing to participate were recruited from the Physiotherapy and Radiation Oncology OPD of a tertiary health care hospital.

In our study, the age distribution of the participants ranges from 18-80 with a mean of 46.53±6.277. The age group between 18 to 40 years is 36%, 41 to 60 years are 54.54 %, and 61 to 80 years are only 9 %.

In our study, cancer-related fatigue was assessed pre and post-radiotherapy by using the FACIT-F scale.

Radiation-induced fibrosis (RIF), which can affect the skin and subcutaneous tissue, lungs, gastrointestinal and genitourinary tracts, as well as any other organs in the treatment field, is a significant contribution to patient morbidity. According to Jeffrey M. Straub et al., radiation exposure causes inflammation and ultimately encourages fibroblasts to transdifferentiate into myofibroblasts.[17]

This explains that decreases in respiratory muscle strength, chest wall mobility, exercise capacity, and pulmonary function test contribute to the reduction of MIP and MEP post-radiotherapy.

In our study, we found there is no correlation between cancer-related fatigue and respiratory muscle strength.

There was no correlation between the FACIT-F score and the value of MIP and MEP.

CONCLUSION

The result of this study supports the null hypothesis. There is no correlation between Cancer-related fatigue and Respiratory muscle strength in breast cancer patients undergoing radiotherapy at a tertiary health care hospital.

Declaration by Authors

Ethical Approval: Approved

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