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COGNITIVE IMPAIRMENT AMONG CANCER PATIENTS EXPERIENCING CHEMOTHERAPY

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Key words: Cancer, Chemotherapy, Radiotherapy, Cognitive impairment

Abstract

The aim of the present study was to investigate whether chemotherapy had any particular role on cognitive impairment i.e. difficulties in executive functioning, working memory, naming ability, attention, language, abstraction, orientation, and visuo-spatial constructional and recall ability, among cancer patients in Bangladesh. Sixty cancer patients and thirty healthy individuals were recruited for this study by purposive sampling. Among these cancer patients 30 had experienced chemotherapy and remain 30 had experienced radiotherapy/ surgery/no treatment at all. We used Rey-Osterrieth Complex Figure test and Montreal Cognitive Assessment to investigate cognitive impairment and Bangla version of Depression, Anxiety and Stress Scale to assess emotional distress. Findings revealed that cancer patients in general experience significantly more cognitive difficulties than healthy individuals. Regarding the attention, visual and auditory memory and executive ability the problems are more dominant. Chemotherapy group performed in all aspects of cognitive testing significantly lower than other treatment group. Statistical tests indicated no role of emotional distress on neuropsychological performance. Males with cancer are more vulnerable to cognitive impairment. In a nutshell, this study indicates that cancer patients in Bangladesh experience cognitive impairment and especially patients treated with chemotherapy are more likely to experience cognitive impairment.

Introduction

Cancer is the uncontrolled growth of cells, which can invade and spread to distant parts of the body(1). In Bangladesh it is one of the leading causes of morbidity and mortality. It ranks sixth among principal causes of death in our country(2). The number of new cases and number of cancer deaths per year are 141.1 thousand 103.3 thousand, respectively. New and old cases constitute 124.8 thousand. Therefore, the number of cancer patients in Bangladesh is not negligible and each day an increasing number of people are affected by this fatal disease.

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Tremendous advancement in technology has been made to treat these growing numbers of individuals with cancer. There are a number of treatment options for cancer such as surgery, chemotherapy, radiotherapy, immunotherapy etc. Cancer treatments especially chemotherapy and radiotherapy have many side effects. Side-effects can be physical and emotional or psychological. Physical side effects include vomiting, nausea, fatigue, and diarrhoea etc. Non-physical treatment side effects, such as anger, anxiety, depression, and post-traumatic stress symptoms etc. are also common[3-5]. Although some side effects are well recognized and effectively managed, other side effects are more subtle, such as cognitive impairment[6].

Cognitive impairment means problems with memory, executive functioning, processing speed, attention, multitasking, word finding etc. Nearly 20-30% of cancer patients who undergo chemotherapy experience some degree of post-chemotherapy cognitive impairment[7]. Up to 75% of cancer patients experience cognitive impairment during or after treatment of their cancer. For many (up to 35%), this persists for months or years following treatment[8]. Cognitive deficits or impairment that occurs from cancer or its treatment may be subtle or dramatic, temporary or permanent, and stable or progressive[9]. Kohli and colleagues[10] studied self-reported cognitive deficits in cancer patients and found that some cognitive problems are more severe in those who receive chemotherapy than in those who receive only radiation and surgery. In a prospective study Wefel and colleagues[11] found that 33% of breast cancer patients demonstrated cognitive impairments prior to starting treatments, 61% demonstrated a decline in their cognitive function relative to their baseline performance 3 weeks post chemotherapy, and 50% of patients who declined demonstrated improvement 1st year post chemotherapy. In another study, this group of researchers found that a subgroup of breast cancer survivor continued to experience cognitive decline over time after treatment[12]. This cognitive deficit is associated with stress, depression and anxiety[13], which may influence the negative prognosis as well.

Bangladesh is a cancer prone country but we don't have any studies on cognitive impairment of cancer patients due to chemotherapy. Therefore, the general objective of the present study was to see whether cancer and its treatment especially chemotherapy had any impact on cognitive functioning. The study also investigated whether cancer patients experience more cognitive impairment compared to healthy individuals; whether patients treated with chemotherapy experience more cognitive impairment compared to patients treated with other therapies; weather cognitive deficits among cancer patients with chemotherapy varies with emotional distress and demographic properties.

Materials and Methods

Participants: A total of 95 participants, age between 20 to 50 years, took part in this study. Data are presented on 60 cancer patients and 30 normal control sample. Rest 5 patients withdrawn from the middle of the study. Among 60 cancer patients 30 had undergone chemotherapy. Rest 30 patients were non-chemotherapy or other treatment patients. All of them were literate. There were 30 healthy individuals who did not have current medical conditions, significant past medical and psychiatric diagnosis. For selecting participants purposive sampling was used. The demographic data are shown in Table 1.

Table 1. Demographic data of the participants (N=90).

	Cancer patients: chemotherapy group (n=30)	Cancer patients: other treatment group (n=30)	Healthy individual group (n=30)
Mean age (Sd.)	32.70 (10.24)	31.40 (8.752)	27.83 (10.03)
Gender (n)	20 (M), 10 (F)	14 (M), 16 (F)	5 (M), 25 (F)
Educational qualification (n)			
Primary-higher secondary	19	22	8
Honors- PhD.	11	8	22
Occupation (n)			
Employed	20	16	28
Unemployed	10	14	02
Habitat (n)			
Urban	16	19	30
Rural	14	11	00
Mean Dose (Sd.)	10.3 (5.468)	13.50 (11.834)	
Diagnosis (n)			
Carcinoma	24	25	N/A
Lymphoma	3	4	
Leukemia	3	1	
Stage (n)			
I	18	22	N/A
II	12	8	

Sd= standard deviation; n= number of patients in each group; N= total number of participants; M= male; F= female.

Measures: We used Rey 15 item effort test (FIT), Rey–Osterrieth Complex Figure test (RCFT), Montreal Cognitive Assessment (MOCA), and Bangla version of Depression, Anxiety and Stress Scale (DASS- 21 BV) in this study. Structured Interview method was also used.

FIT was developed by Andre Rey[14] to assess symptom validity or malingering or exaggeration of memory complaints. It is also known as a measure of effort. It has high inter-rater reliability, very good specificity but poor sensitivity. A recognition trial was added to increase both sensitivity and specificity of FIT[15]. Cut-off score for both recall and recognition trial is 9. We used the Bangla version of this effort test adapted by Hossain and Quinn[16].

RCFT was devised by the Swiss psychologist Andre Rey[17]. Standardized procedures for this test were published by Osterreith[18]. The test permits the evaluation of different functions, such as visuo-spatial abilities, attention, planning and working memory. There are four phases of this test; copy, immediate recall, delayed recall and recognition. In our present study, only the copy and delayed recall conditions were used.

MOCA was developed by neurologist Nasreddine *et al.*[19] as a rapid, reliable and sensitive screening test of mild cognitive impairment. It assesses different cognitive domains; attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. The total possible score is 30 points; a score of 26 or above is considered normal. We used Bangla version of this test in our study.

DASS- 21 BV is a twenty-one items self-report questionnaire which measures the severity of core symptoms of depression, anxiety and stress. The original DASS-21 was developed by Lovibond and Lovibond[20]. The Bangla version of this scale was translated and validated by Alim and colleagues[21]. The scale of DASS has been shown to have high internal consistency reliability.

Our structured interview includes demographic information, such as age, sex, religion, educational qualification, occupation, habitat, marital status, family pattern and support, rating of quality of family relationship, diagnosis and first date of diagnosis, stage of cancer, method of treatment, dosage and subjective rating of cognitive impairment after diagnosis and treatment.

Procedure: After getting ethical approval from Clinical Psychology Department of Dhaka University and official permission from different tertiary level hospitals we approached the prospective participants from both indoor and outdoor. Next the informed consents and signatures from the participants were taken. Then each participant's demographic data was collected by using structured interview method. After interviewing we administered both the recall and recognition trial FIT consecutively. After administering FIT, we provided the participants with ROCF test. Next, we administered Bangla version of MOCA. In the last task participants were asked to rate each of the items or statements DASS-21 BV on a four-point Likert scale (0, 1, 2, or 3). In case of healthy participants, we approached through social media. When they agreed, he/she then invited to the lab of Clinical Psychology department, Dhaka

University. We followed similar steps that were followed while collecting data from the cancer patients in collecting data when they came to the lab.

Analysis: Participants' demographic properties or characteristics were summarized by using descriptive statistics, such as frequency, mean, and standard deviation. We also used inferential statistics, such as independent sample t-test, Pearson-r, and analysis of covariance (ANCOVA). The IBM SPSS version 20 was used for all statistical analyses.

Results and Discussion

To see whether participants of this study were engaged with their full effort we used Rey 15 item memory test. Both cancer patients and healthy control group passed the test which indicates all the participants were involved with good effort in their cognitive testing. This also indicates the validity of their performance on neuropsychological testing applied for.

To achieve our first objective, we aimed to determine whether cancer patients experience more cognitive impairment compared to healthy individuals. In terms of overall cognitive ability cancer patients experienced significantly more cognitive impairment than healthy individuals [$t_{(88)} = -7.06$, $p < 0.05$] which is shown in the Table 2. In addition to that we have analyzed and found different specific cognitive abilities, such as orientation, attention, visuospatial and executive ability, auditory delayed memory, abstraction, visual planning and organization capacity and visual memory, based on which cancer and healthy individual groups were significantly different. The results are presented in Figs 1 and 2. The above results indicate that cancer plays a significant negative role in overall and specific cognitive performance. These results are consistent with the findings of previous studies[8,22], where they reported cognitive impairment among cancer patients who had undergone treatment.

Table 2. Mean cognitive abilities for cancer and healthy control sample assessed by MOCA and their test of significance.

	N	Mean	Sd.	df	t	Sig (2-tailed)
Cancer	60	21.32	4.24	88	-7.06	0.001*
Healthy Control	30	27.03	1.77			

*Statistically significant p values ($p < 0.05$).

Then we investigated the difference of cognitive performance between chemotherapy and other treatment group. Results revealed that (Table 3) neuropsychological performance was impaired for both groups of patients since their mean scores were less than cut-off point 26. However, cancer patients with chemotherapy treatment performed significantly lower than other treatment patients in overall cognitive ability as assessed

by MOCA [$t_{(43.11)}$ = -11.580, $p < 0.01$] (Table 3). Then we analyzed each of the separate seven domains of the MOCA. Results of separate cognitive domain indicated noteworthy difference between chemotherapy and other treatment group for visuo-spatial and executive functioning, memorizing ability, language, attention, and orientation, but not for naming ability (Fig. 3). This means that patients who experienced chemotherapy performed significantly less well than other treatment group patients in above-mentioned six cognitive domains. We further investigated the difference in cognitive performance on the basis of visuospatial planning and organization ability and visual

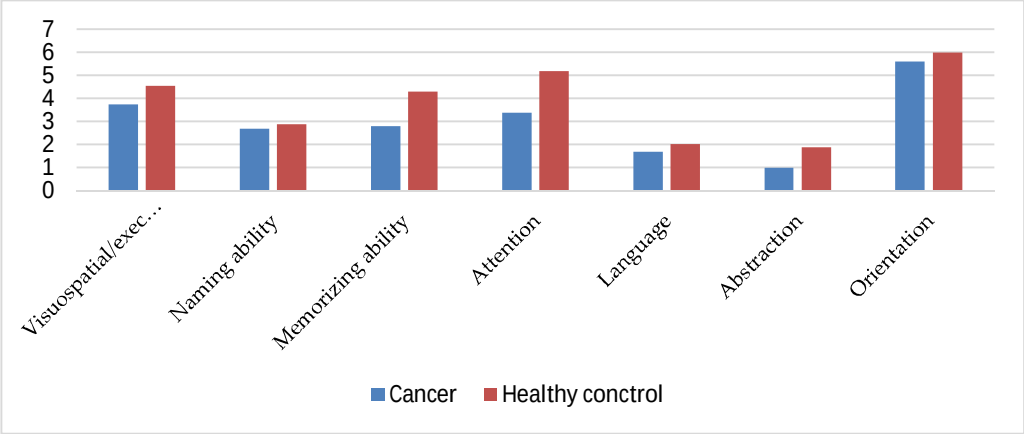

Fig. 1. Cognitive performance in specific domains assessed by MOCA for cancer and healthy control groups.

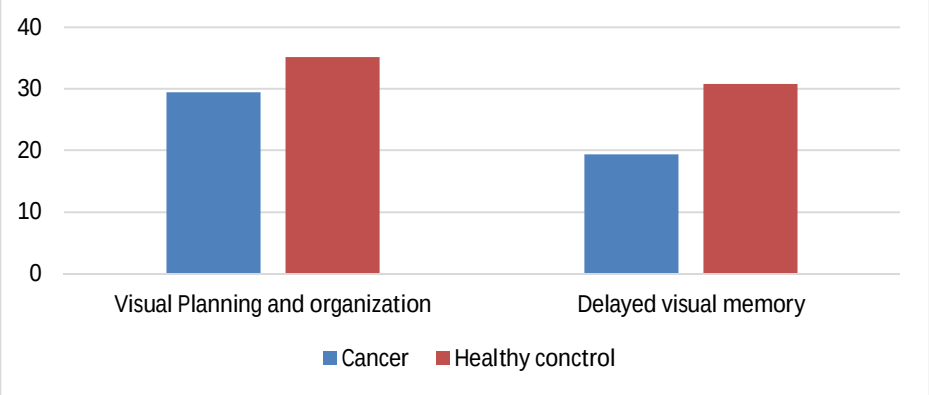

Fig. 2. Cognitive performance in specific domains assessed by RCFT for cancer and healthy control groups.

memory ability for both chemotherapy and other treatment group. Results indicate that visuospatial planning and organizational skills significantly differs between these groups i.e. other treatment group performed better than the chemotherapy group (Table 4).

Results also revealed that both groups have different visuospatial recall abilities i.e. patients who experienced chemotherapy had lower visuospatial memory than other treatment group patients (Table 4). Our findings are consistent with those of the studies[8,10,23] where researchers found that cognitive problems in patients with chemotherapy were more severe than those who only receive loco-regional therapy, such as radiation, surgery, and/or healthy controls. Some researchers[24,25,26] found cognitive impairment in the domain of executive function, memory, and attention among patients treated with chemotherapy. Our findings were also consistent with those studies.

Table 3. Mean differences of overall cognitive abilities between chemotherapy and other treatment groups.

	N	Mean	Sd.	t	df	Sig (2-tailed)	Partial eta squared
Chemotherapy	30	17.80	2.964	-11.580	43.11	.001*	0.69
Other treatment group	30	24.84	1.510				

*Statistically significant p values ($p < 0.05$).

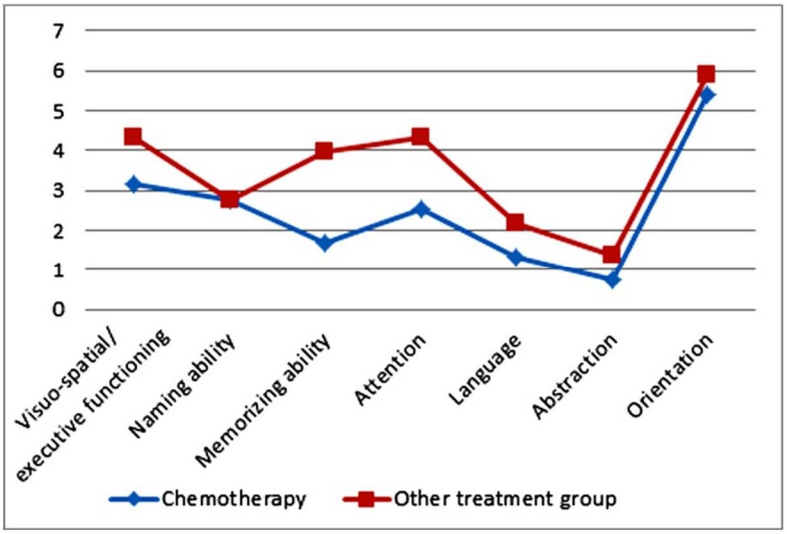

Fig. 3. Cognitive performance in separate domains of MOCA for chemotherapy and other treatment group.

In order to investigate the impact of other factors such as emotional distress on cognitive functioning of cancer patients, we ran a correlation analysis and it revealed that a significant negative correlation exists between cognitive ability (measured by MOCA and RCFT) and affective impairment (measured by DASS) ($r= -0.49$, $r= -0.37$; $p < 0.05$). When this confounded factor was included in the ANCOVA as covariates, the differences

between groups on neuropsychological performance was significant i.e. emotional disturbances affect the correlation between treatment differences and neuropsychological performances[27] but its impact is not significant (Tables 5 and 6). Findings from studies[13,28] revealed effect of mood disturbances in cognitive abilities. Our results support these findings. Though mood disturbances were correlated with cognitive ability, the effect was not significant ($p = 0.12$ and $p = 0.42$) (Tables 5 and 6).

Table 4. Mean visuospatial planning and organization skill and visuospatial memory ability for chemotherapy and other treatment group and test of significance.

	Sample group	N	Mean	Sd.	t	df	Sig (2-tailed)
Visuospatial planning and organizational skill	Chemotherapy	30	27.85	7.60	-2.10	58	0.04*
	Other treatment	30	31.08	3.57			
Visuospatial memory ability	Chemotherapy	30	15.18	5.83	-6.07	58	0.001*
	Other treatment	30	23.66	4.94			

*Statistically significant p values ($p < 0.05$).

Table 5. Separate effects of treatment and emotional distress on overall cognitive performance.

Source	Sum of squares	df	F	Sig (2-tailed)	Partial eta squared
Treatment	503.439	1	93.379	0.001*	0.621
Emotional distress	13.659	1	2.533	0.12	0.043

*Statistically significant p values ($p < 0.05$).

Table 6. Separate effects of treatment and emotional distress on visuospatial recall ability.

Source	Sum of squares	df	F	Sig (2-tailed)	Partial eta squared
Treatment	2912.74	1	26.96	0.001*	0.32
Emotional distress	72.44	1	0.67	0.42	0.012

*Statistically significant p values ($p < 0.05$).

Lastly, we explored the differences in age, gender, educational qualification, occupation, habitat, stage and types of cancer on cognitive performance. Results indicated that except gender differences no other variables have significant impact on

cognitive decline. When we analysed the gender differences on overall cognitive ability, we found significant difference (Tables 7 and 8), but when we analysed visuospatial recall ability, we did not find any significant difference between gender and cognitive impairment. These results partially support the findings of other studies[27,29] where researcher reported that both men and women were equally experienced cognitive decline.

One limitation of the present study was the lack of pre-treatment assessment and randomization. There is no perfect design for a study addressing the issue of cognitive impairment in cancer patients treated with chemotherapy because randomization to receive and not receive chemotherapy is unethical. Furthermore, many other factors may affect cognition: genetic predisposition, medical problems, supportive care medication such as antiemetic and opioids. We did not account for these factors in our present study. This was another limitation of our study. Small sample size (N = 90) might be a limitation of our research. Generalizability might thus be limited for our present study. Future studies may investigate the cognitive decline in cancer patients using pre-treatment assessment with large sample size.

Table 7. Mean overall cognitive abilities of male and female patients and test of significance.

	N	Mean	Sd.	t	df	Sig (2-tailed)
Male	34	20.24	4.56	-2.34	58	0.02*
Female	26	22.73	3.36			

*Statistically significant p values ($p < 0.05$).

Table 8. Mean value of male and female patients of chemotherapy group on overall cognitive abilities and test of significance.

	N	Mean	Sd.	t	df	Sig (2-tailed)
Male	20	17.05	3.01	-2.06	28	0.04*
Female	10	19.30	2.31			

*Statistically significant *p* values ($p < 0.05$).

Implications: The consistency of the present findings with those of earlier studies that evaluated cognitive function in patients treated with chemotherapy supports strongly the existence of an effect. The documentation of cognitive impairment has substantial implications for assessing cancer patients (especially those are treated with chemotherapy) before and after medical therapy and proper counseling and psychosocial support as per need of the individual patient. On the basis of our findings, we have

proposed a model or algorithm which depicts the vicious cycle of cognitive impairment and possible psychological intervention and its outcome. The model is shown in the Fig. 4.

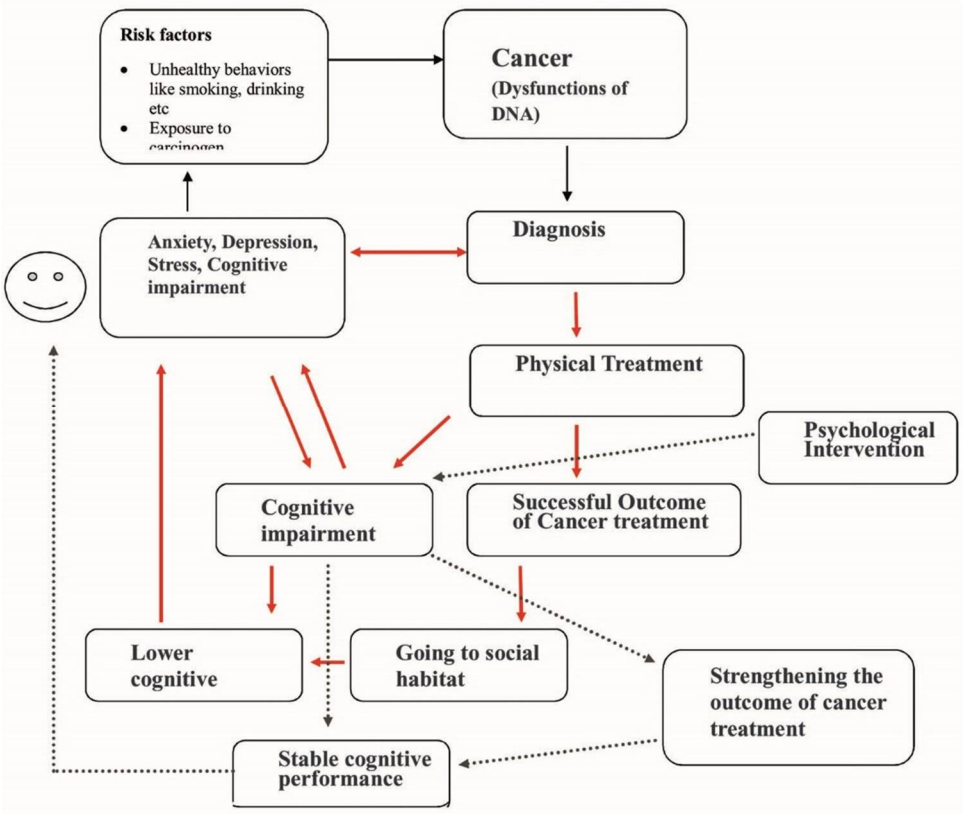

Fig. 4. Vicious cycle of cognitive impairment, cancer suffering and possible psychological intervention.

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