Neurology Asia 2021; 26(2) : 361 – 373

Clinical factors associated with cancer-related cognitive impairment in breast cancer patients in Malaysia

[1]Kae Lih Hii *MPM*, [2]Ahmad Hatim Sulaiman PhD, [2]Song Ling Tang *MBBS*, [2]Chong Guan Ng *PhD*

[1]Department of Psychiatry, Hospital Sibu, Sarawak, Malaysia; [2]Department of Psychological Medicine, Faculty of Medicine, University Malaya, Kuala Lumpur, Malaysia

Abstract

Background & Objective: Cancer-related cognitive impairment (CRCI) is an increasingly acknowledged after-effect of breast cancer and its treatment. However, its associated risk factors remain vaguely understood. This study aimed to examine the factors that are associated with cognitive functions in the Malaysia breast cancer population, along with the correlation between perceived and objective cognitive functioning among subjects. *Methods:* This is a cross-sectional study among breast cancer patients from University Malaya Medical Centre, a teaching hospital in Kuala Lumpur, Malaysia. Subjects were assessed using socio-demographic and clinical questionnaires, Digit Symbol Substitution Test (DSST), Perceived Deficit Questionnaire 5-Malay version (PDQ5-M), Positive Emotion Rating Scale-Malay version (PERS-M), and Hospital anxiety and depression scale Malay version (HADS-M). *Results:* Lower education level ($p<0.001$, partial eta^2 0.066) and presence of chronic illness ($p=0.027$, partial eta^2 0.027) were associated with poorer DSST performance. Subjects with higher anxiety levels were observed to have more subjective cognitive concerns, which manifested as higher PDQ5-M score ($p<0.001$, partial eta^2 0.085). There was a reported disparity between subjective and objective measure. *Conclusion:* There is a significant discrepancy between subjective and objective cognitive function assessments. Subjective cognitive concerns were found to be related to psychological distress, whereas those with lower education level and chronic illness had a significant poorer objective cognitive performance. Clinicians should consider above factors in assessing and treating cancer patients presented with CRCI.

Keywords: Cognition, breast neoplasms, cognitive dysfunction, psycho-oncology, drug therapy

INTRODUCTION

Advanced treatment options and early detection through screening programs have greatly increased the survival rate of breast cancer patients. However, many patients experienced side effects that unceasingly impact their daily lives, with cancer related cognitive impairment (CRCI) being identified as one of the most common psychiatric complications[1,2] of breast cancer and its treatment. Based on recommendations by the International Cognition and Cancer Task Force (ICCTF), CRCI is defined as changes in one or more of the four main cognitive domains, i.e., attention, memory, response speed and processing speed.[3]but many fundamental questions require further elucidation, and large samples from several institutions are needed. Two working groups brought together by the International Cognition and Cancer Task Force (ICCTF) Given its significant impact on patients' functional status, the risk of family members and carers experiencing psychological distress, i.e. depressive symptoms and burnout has been established in previous studies as well.[4,5]

As breast cancer has become the most commonly diagnosed cancer worldwide in 2020[6], it is crucial to recognise factors associated with these cognition changes and its impact on increasing number of patients. A recent review found that cancer treatments interact with numerous risk factors, regardless of its direct effect on cognitive function.[7] Early detection of these risk factors would allow targeted interventions to take place, possibly reducing the impact of CRCI among breast cancer population. A recent cross-sectional study in France has shown that cognitive complaints in breast cancer survivors

Address correspondence to: Ng Chong Guan, Department of Psychological Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia. Email: chong_guan@um.edu.my

Date of Submission: 23 February 2021; Date of Acceptance: 2 April 2021

are associated with chemotherapy, age, sleeping difficulties, post-traumatic stress symptoms and employment status.[8] Ahles *et al*. found that older age, with lower cognitive reserve and chemotherapy exposure contributes to the decline in post-treatment processing speed.[9] With these varied results, there is a need for further studies in this field to assess the association between CRCI and multiple aspects – such as socio-demographic characteristics, clinical profiles and psychological factors, particularly positive emotions.

On the other hand, assessment of cognitive impairment can be categorised into two approaches: objective cognitive function, assessed by clinicians using neuropsychological batteries; and subjective cognitive function, usually self-reported by patients using questionnaires. Although the discrepancy between objective and subjective measures of cognitive function in cancer patients have been well-established[10], there is no recognised better validity of either approach to assess cognitive impairment among cancer patients. Understanding the correlation between said measures in the local setting would provide vital baseline data, as well as directions for future research in improving validity of CRCI assessments.

To our knowledge, majority of studies in this field are done in Western countries, with limited published data exploring the factors associated with CRCI in Asia population, specifically in Malaysia. The primary objective of this study was to explore factors associated with CRCI among breast cancer patients in Malaysia. Our secondary objective was to examine the correlation between perceived and objective cognitive functioning among study subjects.

METHODS

This is a hospital-based cross-sectional study conducted from January 2018 to April 2018, involving 188 subjects with breast cancer. The target sample size was 162, determined by identifying the smallest acceptable sample size with ±5% margin of error with 95% confidence interval.[11] Patients were selected through non-probabilistic convenience sampling method, and those who agreed to join the study were screened according to the following inclusion and exclusion criteria. They were then given questionnaires to fill in.

The inclusion criteria were: Aged 18 and above; diagnosis of breast cancer; literate and able to understand the Malay language; and able to give informed consent. The exclusion criteria were: known Neurological disorder (stroke or seizure); intellectual disability; recent head injury; and comorbid severe psychiatric disorder/ psychosis. The comorbid psychiatric condition is excluded using the Mini International Neuropsychiatric Interview (MINI).

The Medical Research Ethical Committee of University Malaya Medical Centre approved the study. Permission to collect data at study sites was granted by Department of Clinical Oncology and Department of Surgery. All participants provided written consent.

Our study involved breast cancer subjects who attended the study site, in both in- and outpatient settings. All potential subjects were approached by the investigator. Patients with clinically significant cognitive decline were referred back to the primary oncology team and neurology/ psychiatry team for further assessment and management. Those who were eligible were given a standardised general description about the study, including the objective, procedure and nature of study, along with a patient information sheet. The confidentiality of data obtained was ensured.

Study instruments

Four sets of instrument were used in this study, along with a socio-demographic questionaire.

Positive Emotion Rating scale Malay version (PERS-M): The original Positive Emotion Rating Scale (PERS) is a self-reported scale used to assess positive emotion.[12] The six domains of positive emotion assessed are interest, gratification, love, contentment, pride and active. Consisting of eight items, it is rated on a one (never) to five (always) Likert scale, yielding maximum score of 40. The cut-off score at 30 demonstrated significant discriminant validity between depressed and non-depressed.12

The PERS-M displayed good internal consistency (Cronbach alpha 0.89) and parallel reliability. Its concurrent validity with Dispositional Positive Emotion Scale was 0.32 ($p < 0.05$) and with Snaith-Hamilton Pleasure Scale was $r=0.77$ ($p<0.01$)[13].

Hospital Anxiety and Depression Scale Malay version (HADS-M): The Hospital Anxiety and Depression Scale (HADS) is a self-reported questionnaire to assess depression and anxiety levels[14]. It has been widely used among the general population including cancer patients.[15] HADS encompasses two subscales, namely

HADS (anxiety) and HADS (depression), each comprising seven items. Items are scored from 0 to 3 with a total maximum score of 21.

It has been validated in the local setting as the HADS-M.[16] HADS-M has an excellent internal consistency, with Cronbach alpha 0.88 for HADS (anxiety) and 0.79 for HADS (depression).[17] For the Malaysian population, the cut-off score was deemed to be appropriate at 8 with sensitivity of 93.2% and specificity of 90.8%.[16]

Perceived Deficit Questionnaire-5 Malay Version (PDQ-5M): Perceived Deficit Questionnaire-5 (PDQ-5) is extracted from the full-length PDQ, which is a part of the Multiple Sclerosis Quality of Life Inventory. It is a 5-item self-reported screening questionnaire to assess subjective cognitive impairment. Each items are scored using a five-point Likert scale, giving a maximum score of 20. Preliminary data suggested to use 10 points as the cut-off for at-risk range.[18]

To cater for local population use in this study, PDQ-5 was translated into Malay version through backward translation and sentence-by-sentence revision. The PDQ-5M has a Cronbach's alpha coefficient of 0.88 and intra-class correlation coefficient of 0.92 with PDQ-5.

Digit Symbol Substitution Test (DSST): The DSST is extracted from the Wechsler Adult Intelligence Scale. It was first developed to measure human associative learning (Jaeger and Domingo, 2016). Its efficacy as a neuropsychological tool to assess objective cognitive function only became evident later. It comprises an array of nine numbers paired with its own symbols. Subjects are asked to enter the matching symbol into the blank boxes as fast as they could within 120 seconds. The scores are based on the number of boxes filled in correctly[19] for its completion, including response speed, set shifting, sustained attention and visual-spatial skills.[20,21] Furthermore, its non-language dependent nature is an eminent advantage over other neuropsychological tools.

Statistical analysis

The data obtained were analysed with Statistical Package for Social Science (SPSS) version 20.0. Socio-demographic and clinical background of subjects were examined using descriptive statistics. Measures of mean and standard deviations were used for continuous variables. The normality of data were examined using Kolmogorov Smirnov test. As the data were normally distributed, parametric test was employed in the study.

General Linear Model (GLM) was used to analyse the association between DSST with the sociodemographic and clinical profiles, PERS, HADS and PDQ5-M. In the univariate-multivariate analyses, the 'time since chemotherapy' variable was further dummy coded in four additional variables, namely 'Chemotherapy received - No', 'Ongoing chemotherapy', 'Completed chemotherapy <5 years' and 'Completed chemotherapy ≥5 years'. Factor analysis was carried out to combine interrelated factors such as hypertension, diabetes mellitus and dyslipidaemia. The regression score created for these combined factors was named as "chronic illness".

Factors with p value <0.05 were subjected to multivariate analysis. However, several statistically significant factors have not been included, as they did not meet Levene's Test for Equality of Variances.

Correlation between subjective cognitive measure (PDQ5-M) and objective cognitive measure (DSST) was assessed using Spearman rank correlation. Effect size calculation for mean performance of subjects in various instruments was carried out using coefficient of determination.

RESULTS

One hundred and eighty eight breast cancer patients were recruited in this study. The average age of subjects was 55 years old (SD =11.42). The exercising frequency was given at cut-off point of 5 times a week, based on recommendations by a systematic review with respect to exercise for patients living with cancer.[22] Other socio-demographic details are described in Table 1. The clinical characteristics of the study patients are listed in Table 2.

Table 3 lists the mean performances of study subjects on PDQ5-M, DSST, PERS=M, and HADS-M.

Correlation between subjective cognitive measure and objective cognitive measure

No significant correlation was demonstrated between objective cognitive measure (DSST) and overall subjective cognitive measure (PDQ5-M). However, the Spearman correlation test conducted for individual items in PDQ5-M revealed a significant negative correlation between two items and DSST. The two items are Item 3 'forget the date unless you looked it up' and item 4 'forget what you talked about after a telephone conversation?'. (Table 4)

Univariate and multivariate analysis between DSST and sociodemographic, clinical data, PERS, HADS, PDQ-5 (Among cancer participants)

Table 5 illustrated the result of General Linear Model (GLM) to analyse the correlates of DSST performance. The 'drug history' variable was removed from the analysis as none of the subjects previously consumed illicit drugs.

Univariate GLM shown that lower education level, being unemployed, chronic illness, positive emotion and depressive symptoms were significantly associated with poor performance in DSST. After adjusting for multivariate through GLM, only lower educational level (partial eta^2 0.066, p<0.001) and chronic illness (partial eta^2=0.027, p=0.027) remain significant.

Of interest, the relationship between subjective cognitive concerns (PDQ5-M) and objective cognitive performance (DSST) was analysed as well. No significant association was shown between PDQ5-M and DSST performance.

Univariate and multivariate analysis of PDQ5-M among breast cancer subject

GLM was conducted for clinical covariates as well to show the association between PDQ5-M and sociodemographic, clinical data, PERS, HADS and DSST, as illustrated in Table 6. The 'drug history' variable was removed from the analysis as none of the subjects previously consumed illicit drugs. The univariate GLM shown that only emotional variables had a significant association with PDQ5-M score; Subjects who reported higher levels of positive emotions (partial eta^2 0.159, p<0.001) were found to have less perceived cognitive complaints. In contrast, those with a higher anxiety (partial eta^2 0.237, p<0.001) and depression level (partial eta^2 0.192, p<0.001) were reported to have more perceived cognitive dysfunction.

After the multivariate adjustment, only positive emotions (partial eta^2 0.040, p=0.006) and anxiety (partial eta^2 0.085, p<0.001) remained significantly associated with the PDQ5-M score.

On the contrary, there was no any significant relationship between the subjective cognitive measure with treatment modalities, such as chemotherapy, types of chemotherapy, time since completion of chemotherapy, endocrine and radiotherapy. (Table 6)

DISCUSSION

To best of our knowledge, this study is among the first to explore factors associated with cancer related cognitive impairment (CRCI) in the Malaysia breast cancer population. Considering the high prevalence of breast cancer and majority were detected through self-examination, encouraging breast self-examination among general population would be vital in primary prevention.[23] The significant impact of cognitive changes on patients' quality of life, along with increased morbidity and heightened distress among patients and caregivers have made it essential to recognise and manage the long-term sequelae of cancer treatments. It is therefore crucial that these are identified by the healthcare practitioners to provide the patients and caregivers efficient support through a global approach.

The common socio-demographic predictors of CRCI from earlier studies include age, education level and premorbid intelligent quotient.[9,24,25] However, only lower education level and presence of chronic illness are significantly associated with poorer objective cognitive function (represented by DSST score) in this study. Consistent with previous literatures, higher education level is linked to better cognitive functioning throughout adulthood[26,27] particularly in measures of attention, verbal measures and complex tasks requiring directed attention.[19]

The association between chronic illness (hypertension, diabetes mellitus and/ or dyslipidaemia) and poorer objective cognitive function is similar to previous findings, where cancer patients with concurrent comorbidities reported poorer response speed and attention.[28] Although its mechanisms remain unclear, some postulated that vascular remodelling and pathological changes to macro- and microvasculature caused cerebral hypoperfusion.[29] Others suggested that chronic medical illness was associated with hyperuricemia[30], which develops oxidative and nitrosative stress[31,32] within the brain vasculature.

Unexpectedly, age was not significantly associated with objective cognitive performance in our study (p=0.07). This could be explained by the comparatively younger age (mean =55.0 ±11.42) of recruited subjects, with only 21.3% (n=40) aged 65 years and above. Besides, the subjects were generally well-educated, which might have suppressed the effect of age – in view of its highest partial eta^2 in this study.

History of receiving chemotherapy, approach and time since completion of chemotherapy are also reported to have no association with DSST performance in this study. Due to the simplicity of study design, subjects who received/ are receiving

Table 1: Socio-demographic characteristics of subjects

Variables	Cancer patient (n=188)	
	Mean (SD)	n (%)
Age	55.0 (11.42)	
Race		
Malay		59 (31.4)
Chinese		100 (53.2)
Indian		24 (12.8)
Others		5 (2.6)
Religion		
Muslim		63 (33.5)
Christian		27 (14.4)
Buddhist		63 (33.5)
Hindu		20 (10.6)
Non-religious		5 (2.7)
Others		10 (5.3)
Marital status		
Single		27 (14.4)
Married		139 (73.9)
Divorced		9 (4.8)
Widowed		13 (6.9)
Education level		
Nil		3 (1.6)
Primary		34 (18.1)
Secondary		87 (46.3)
Tertiary		64 (34.0)
Employment status		
Unemployed		116 (61.7)
Employed		72 (38.3)
Body weight (kg)	60.64 (13.38)	
Height (m)	156.06 (13.79)	
BMI	24.91 (5.43)	
Exercise		
No		57 (30.3)
Yes		131 (69.7)
Exercising frequency per week		
0		56 (29.8)
<5		67 (35.6)
≥5		65 (34.6)
Menstrual status		
Pre-menopause		40 (21.3)
Menopause		148 (78.7)
History of receiving HRT		
No		181 (96.3)
Yes		7 (3.7)
Smoking		
No		186 (98.9)
Yes		2 (1.1)
Alcohol intake		
No		182 (96.8)
Yes		6 (3.2)
History of substance abuse		
No		188 (100.0)
Yes		0

Note: SD, standard deviation; BMI, body mass index; HRT, hormonal replacement therapy

Table 2: Clinical characteristics of study subjects

Variables	Cancer patient (n=188)
	n (%)
Cancer stage	
0	2 (1.1)
1	34 (18.1)
2	69 (36.7)
3	35 (18.6)
4	47 (25.0)
Unsure	1 (0.5)
Approach of chemotherapy	
Nil	42 (22.3)
Neoadjuvant	49 (26.1)
Adjuvant	67 (35.6)
Palliative	30 (16.0)
Number of years since chemotherapy completion	
Nil	41 (21.8)
Ongoing	74 (39.3)
<5	46 (24.5)
≥5	27 (14.4)
Endocrine therapy	
No	118 (62.8)
Yes	70 (37.2)
Radiotherapy	
No	96 (51.1)
Yes	92 (48.9)
Cancer Related Surgery	
No	45 (23.9)
Yes	143 (76.1)
Hypertension	
No	136 (72.3)
Yes	52 (27.7)
Diabetes Mellitus	
No	159 (84.6)
Yes	29 (15.4)
Dyslipidaemia	
No	134 (71.3)
Yes	54 (28.7)

Note: SD, standard deviation; N/A, not applicable

Chemo completion variable was further dummy coded in four additional variables comprising of "No chemo", "Ongoing chemo", "Chemo completion < 5 years" and "Chemo completion ≥ 5 years" in the univariate-multivariate analysis.

Table 3: Mean (SD) performances of subjects on PERS, HADS, PDQ5-M, DSST

Variables	Cancer patient (n=188) Mean (SD)
PERS-M	30.38 (6.65)
HADS-M (ANXIETY)	6.40 (3.89)
HADS-M (DEPRESSION)	4.87 (3.50)
PDQ5-M	6.07 (3.75)
DSST	8.41 (3.37)

Note: SD, Standard deviation; PERS, Positive Emotion Rating Scale; HADS-M (ANXIETY), HADS-M (anxiety) subscale; HADS-M (DEPRESSION), HADS-M (depression) subscale; PDQ5-M, Perceived Deficit Questionnaire-5 Malay version; DSST, Digit Symbol Substitution Test; z score, standardized score

Table 4: Spearman's correlation analyses between PDQ5-M (total), each item in PDQ5-M and DSST

	DSST	Total PDQ	PDQ5(1)	PDQ5(2)	PDQ5(3)	PDQ5(4)
DSST	1.000					
Total PDQ	-0.052	1.000				
PDQ5(1)	0.032	0.614**	1.000			
PDQ5(2)	-0.016	0.777**	0.459**	1.000		
PDQ5(3)	-0.102*	0.707**	0.221**	0.444**	1.000	
PDQ5(4)	-0.102*	0.701**	0.264**	0.393**	0.436**	1.000
PDQ5(5)	0.046	0.681**	0.293**	0.372**	0.361**	0.467**

* Significant at level 0.05 (two-tailed).

** Significant at level 0.01 (two-tailed).

chemotherapy were all grouped together without being stratified according to the chemotherapeutic agents or dosage, which might have contributed to the negative finding. Moreover, since cognitive changes might develop at different time point from the beginning of treatment[25,33,34], it is possible that they were not detected at the time of recruitment. With numerous accumulated incidence of CRCI being attributed to neurotoxic effects of chemotherapy[1,35-37], this outcome requires more evidence before being considered as a valid finding in the present context.

In this study, anxiety symptoms are significantly associated with subjective cognitive concerns, measured by the PDQ5-M score. In the multivariate analyses, subjective cognitive function was associated with higher anxiety but not depression levels, concurring with previous study by Cheung *et al*.[38]. Nonetheless, the processing efficiency theory stated that while anxiety reduces the available capacity to process co-existing tasks in working memory system, it simultaneously enhance the on-task effort by increasing use of processing resources. The crucial difference between performance effectiveness (quality of task performance) and performance efficacy (effectiveness divided by effort) in this theory is highlighted, where anxiety characteristically impairs the latter more. Increased use of processing resources leads to mental fatigue, which might explain the subjective cognitive concerns in this study.

As researchers mainly focused on the negative emotional variables (i.e. anxiety and depression), studies that explored the relationship between positive emotion and cognitive function in cancer patients are relatively scarce. However, it has been well-established that both positive and negative emotions affect cognitive task performance.[39] In this study, those who expressed greater positive emotions reported lesser subjective cognitive complaints (partial eta^2 0.040, p=0.006); while higher anxiety levels (partial eta^2 0.085, p<0.001) are associated with poorer subjective cognitive function. This is in keeping previous study, which demonstrated personality traits of negative affectivity induced negative cognitive self-appraisals.[40] The association between positive emotions and subjective cognitive function could also be explained by the theory of cognitive adaptation, where patients are often able to redefine the experience and regain sense of mastery along with self-enhancement.[41] Being the first in our local setting that attempted to examine the relationship between positive emotion and cognitive function in breast cancer patients, this study could act as a baseline reference for future studies.

Consistent with majority of previous studies[10,27,42], our study did not reported any correlation between subjective complaints and objective cognitive deficit in the breast cancer population. One of the widely accepted explanations by O' Farrell *et al*. stated that objective cognitive performance is caused by underlying neurological changes, whereas subjective cognitive concerns are mainly affected by mental fatigue or psychological distress during assessment.[43] It is also noteworthy that several imaging studies had shown chemotherapeutic agents causing both structural and functional brain changes[44,45], suggesting that subjective cognitive impairment might be the cause, rather than effect of fatigue and psychological distress. Another functional magnetic resonance imaging (fMRI) study by Kesler *et al*. reported that breast cancer

Table 5: Univariate and multivariate analysis between DSST and socio-demographic characteristics, clinical profile, PERS-M, HADS-M, PDQ-5M among subjects

Variables	Univariate-GLM DSST			Multivariate-GLM DSST		
	Mean/b[1] (95% CI)	p value	Partial eta[2]	Adjusted mean/b[2] (95% CI)	p value	Partial eta[2]
Race						
Malay	8.66 (7.80-9.53)	0.499	0.002			
Non-Malay	8.30 (7.72-8.89)					
Race						
Chinese	8.75 (8.09-9.41)	0.146	0.011			
Non-Chinese	8.03 (7.33-8.74)					
Marital status						
Married	8.51 (7.95-9.08)	0.512	0.002			
Single/ Divorced/ Widowed	8.14 (7.19-9.09)					
Education level						
Primary/ Secondary	7.57 (7.01-8.13)	<0.001	0.122	7.87 (7.29-8.46)	<0.001	0.066
Tertiary	10.05 (9.27-10.83)			9.70 (8.92-10.47)		
Employment status						
Unemployed	7.78 (7.18-8.38)	<0.001	0.058	8.45 (7.83-9.08)	0.181	0.010
Employed	9.44 (8.68-10.21)			9.11 (8.39-9.84)		
Exercise						
No	8.14 (7.26-9.02)	0.462	0.003			
Yes	8.53 (7.95-9.12)					
Exercising Frequency per week						
0	8.107 (7.22-9.00)	0.680	0.004			
<5	8.642 (7.83-9.46)	1.000	0.002			
≥5[#]	8.446 (7.62-9.27)	1.000	0.001			
Menstrual status						
Pre-menopause	9.13 (8.08-10.17)	0.133	0.012			
Menopause	8.22 (7.68-8.77)					
Received HRT						
No	8.37 (7.87-8.86)	0.299	0.006			
Yes	9.71 (7.20-12.22)					
Smoking						
No	8.34 (7.90-8.87)	0.276	0.006			
Yes	11.00 (6.31-15.69)					
Alcohol Intake						
No	8.45 (7.95-8.94)	0.500	0.002			
Yes	7.50 (4.79-10.22)					
Stage 4 Cancer						
No	8.27 (7.71-8.83)	0.306	0.006			
Yes	8.85 (7.88-9.82)					

Approach of Chemotherapy						
Nil	8.14 (7.12-9.17)	0.318	0.019			
Neoadjuvant	8.43 (7.48-9.38)	0.660	0.014			
Adjuvant	8.12 (7.31-8.93)	1.000	0.009			
Palliative#	9.43 (8.22-10.64)	0.461	0.017			
Received Chemotherapy						
Yes	8.22 (7.18-9.26)	0.675	0.001			
No	8.47 (7.92-9.02)					
Ongoing Chemotherapy						
Yes	8.49 (7.71-9.26)	0.815	0.000			
No	8.37 (7.75-8.99)					
Completed Chemotherapy <5 Years						
Yes	8.30 (7.32-9.27)	0.799	0.000			
No	8.45 (7.89-9.01)					
Completed Chemotherapy >5 Years						
Yes	8.70 (7.42-9.99)	0.631	0.001			
No	8.37 (7.84-8.89)					
Endocrine therapy						
No	8.42 (7.80-9.03)	0.998	0.000			
Yes	8.41 (7.62-9.21)					
Radiotherapy						
No	8.65 (7.97-9.32)	0.338	0.005			
Yes	8.17 (7.48-8.87)					
Cancer related surgery						
No	8.69 (7.70-9.68)	0.533	0.002			
Yes	8.33 (7.77-8.89)					
Age	-0.04 (-0.08-0.00)	0.074	0.017			
BMI	-0.07 (-0.16-0.02)	0.102	0.014			
Chronic Illness	-0.65 (-1.05- [-0.26])	<0.001	0.054	-0.44 (-0.82- [-0.05])	0.027	0.027
PERS-M	0.12 (0.05-0.19)	<0.001	0.056	0.07 (-0.02-0.15)	0.110	0.014
HADS-M (ANXIETY)	-0.04 (-0.16-0.09)	0.554	0.002			
HADS-M (DEPRESSION)	-0.21 (-0.34- [-0.07])	0.003	0.045	-0.13 (-0.28-0.03)	0.102	0.015
PDQ5-M1	-0.04 (-0.50-0.42)	0.869	0.000			
PDQ5-M2	-0.27 (-0.69-0.14)	0.200	0.009			
PDQ5-M3	-0.39 (-0.83-0.05)	0.085	0.016			
PDQ5-M4	-0.45 (-0.90-0.01)	0.056	0.020			
PDQ5-M5	-0.29 (-0.80-0.22)	0.264	0.007			

b^1=crude regression coefficient; b^2=adjust regression coefficient.
Multicollinearity issue factors: race and religion factors with "Malay"; bodyweight, height with BMI.
= Reference group.
Partial eta^2= estimated effect size.

Table 6: Univariate and multivariate analysis between PDQ5-M and sociodemographic, clinical data, PERS, HADS, DSST (Among cancer subjects

Factors/ Variables	Univariate-GLM PDQ			Multivariate-GLM PDQ		
	Mean/b[1] (95% CI)	p value	Partial eta[2]	Adjusted mean/b[2] (95% CI)	p value	Partial eta[2]
Race						
Malay	6.05 (5.09-7.02)	0.954	0.000			
Non-Malay	6.09(5.43-6.74)					
Race						
Chinese	6.11 (5.37-6.85)	0.890	0.000			
Non-Chinese	6.03 (5.24-6.83)					
Marital Status						
Married	5.94 (5.31-6.57)	0.418	0.004			
Single/ Divorced/ Widowed	6.45 (5.39-7.51)					
Education Level						
Primary/ Secondary	5.77 (5.11-6.44)	0.127	0.012			
Tertiary	6.66 (5.74-7.58)					
Employment status						
Unemployed	6.19 (5.50-6.88)	0.594	0.002			
Employed	5.89 (5.02-6.76)					
Exercise						
No	6.83 (5.85-7.80)	0.070	0.018			
Yes	5.75 (5.11-6.39)					
Exercising Frequency per Week						
0	6.86 (5.87-7.84)	0.154	0.020			
<5	5.96 (5.06-6.85)	1.000	0.002			
≥5[#]	5.52 (4.61-6.44)					
Menstrual status						
Pre-menopause	6.28 (5.10-7.45)	0.704	0.001			
Menopause	6.02 (5.41-6.63)					
Received HRT						
No	5.99 (5.45-6.54)	0.137	0.012			
Yes	8.14 (5.36-10.93)					
Smoking*						
No	6.02 (5.48-6.55)	0.039	0.023			
Yes	11.50 (6.32-16.69)					
Alcohol Intake						
No	6.07 (5.52-6.62)	0.864	0.000			
Yes	6.33 (3.31-9.36)					
Stage 4 Cancer						
No	5.89 (5.27-6.52)	0.253	0.007			
Yes	6.62 (5.54-7.70)					
Approach of Chemotherapy						
Nil	6.24 (5.09-7.39)	0.973	0.001			
Neoadjuvant	6.18 (5.12-7.25)	1.000	0.001			
Adjuvant	5.96 (5.05-6.87)	1.000	0.000			
Palliative#	5.93 (4.57-7.29)	1.000	0.000			

Received Chemotherapy						
Yes	6.07 (4.92-7.23)	0.998	0.000			
No	6.08 (5.46-6.69)					
Ongoing Chemotherapy						
Yes	5.76 (4.90-6.62)	0.351	0.005			
No	6.28 (5.59-6.97)					
Completed Chemotherapy <5 Years						
Yes	6.04 (4.95-7.14)	0.949	0.000			
No	6.09 (5.46-6.71)					
Completed Chemotherapy >5 Years						
Yes	7.00 (5.58-8.42)	0.166	0.010			
No	5.92 (5.34-6.50)					
Endocrine therapy						
No						
Yes	6.14 (5.45-6.82)	0.773	0.000			
	5.97 (5.09-6.86)					
Radiotherapy						
No	5.79 (5.04-6.55)	0.292	0.006			
Yes	6.37 (5.60-7.14)					
Cancer related surgery						
No	6.36 (5.25-7.46)	0.566	0.002			
Yes	5.99 (5.37-6.61)					
Age	-0.03 (-0.08-0.02)	0.216	0.008			
BMI	-0.05 (-0.15-0.05)	0.329	0.005			
Chronic Illness	-0.12 (-0.57-0.34)	0.610	0.001			
PERS	-0.23 (-0.30- [-0.15])	<0.001	0.159	-0.12 (-0.20- [-0.03])	0.006	0.040
HADS-M (ANXIETY)	0.47 (0.35-0.59)	<0.001	0.237	0.32 (0.17-0.48)	<0.001	0.085
HADS-M (DEPRESSION)	0.47 (0.33-0.61)	<0.001	0.192	0.12 (-0.07-0.30)	0.232	0.008
DSST	-0.14 (-0.30-0.02)	0.076	0.017			

b^1=crude regression coefficient; b^2=adjusted regression coefficient.
Multicollinearity issue factors: race and religion factors with "Malay"; bodyweight, height with BMI.
= Reference group.
Partial eta^2= estimated effect size.

patients who underwent chemotherapy exhibited greater and more global neural effort when attempting to recall task information compared to the control group.[46] This might explain the mental fatigue experienced by said population, which may then be reflected in the disparity between objective and subjective cognitive performances.

While objective measures are carried out in a highly controlled environment within time limits, subjective measures are able to capture cognitive performance over a wider timeframe, allowing variations in environment, along with psychological and physical stress. Therefore, it would be ideal to include more ecologically validated objective neuropsychiatry assessments to better replicate patients' condition in real life

scenarios.

There are some limitations in our study. First, its cross-sectional nature signifies that the causal inferences between CRCI and various variables examined in this study could not be established. The nature of study had also made it difficult to assess changes in cognitive function over time, in addition to the onset of cognitive changes that varies among individuals as mentioned earlier. We recommend longitudinal future studies with pre-treatment cognitive assessment and subsequent cognition assessments at intervals to assess subtle yet important cognitive changes with time. Next, the relatively small sample was recruited from a single site, which might not accurately represent the breast cancer population in Malaysia. Including hospitals sites across Malaysia would have greatly enhance the generalisability of this study. Besides, only a single neuropsychological tool was used to assess the cognitive function of subjects, meaning not all cognitive domains were assessed. However, the use of extensive neuropsychological batteries would be impractical in clinical settings as they are both time and resource intensive. Lengthy assessments might result in mental fatigue, which might affect cognitive performance of subjects.

To summarise, subjective cognitive concerns among breast cancer survivors are related to psychological distress i.e. anxiety levels, while higher positive emotions were found to improve perceived cognitive functioning. Subjects with lower education level and chronic illness reported to have poorer objective cognitive performance. The factors identified in this study could serve as a driving force to lay out targeted future interventions for continuum care of breast cancer survivors. Given the reported disparity between subjective and objective cognitive measures, integration of subjective cognitive assessments in clinical consideration is vital to accurately address and manage its impact in patients' daily living.

DISCLOSURE

Financial support: None

Conflicts of interest: None

REFERENCES

1. Schagen SB, Muller MJ, Boogerd W, Mellenbergh GJ, van Dam FSAM. Change in cognitive function after chemotherapy: a prospective longitudinal study in breast cancer patients. *JNCI J Natl Cancer Inst* 2006; 98: 1742-5.
2. Janelsins MC, Kesler SR, Ahles TA, Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatry* 2014; 26: 102-13.
3. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol* 2011; 12: 703-8.
4. Nik Jaafar NR, Selamat Din SH, Mohamed Saini S, *et al*. Clinical depression while caring for loved ones with breast cancer. *Compr Psychiatry* 2014; 55: S52-9.
5. Manicom C. Psychosocial cancer care; There is more to cancer care than medical management. *C Your SA J CPD* 2010; 28: 58-63.
6. Union for International Cancer Control. GLOBOCAN 2020: New Global Cancer Data | UICC. Geneva, Switzerland, 2020 https://www.uicc.org/news/globocan-2020-new-global-cancer-data (accessed Feb 3, 2021).
7. Hardy SJ, Krull KR, Wefel JS, Janelsins M. Cognitive changes in cancer survivors. *Am Soc Clin Oncol Educ B* 2018; 38: 795-806.
8. Boscher C, Joly F, Clarisse B, *et al*. Perceived cognitive impairment in breast cancer survivors and its relationships with psychological factors. *Cancers (Basel)* 2020; 12: 1-13.
9. Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatment-associated cognitive change: An update on the state of the science. *J Clin Oncol* 2012; 30: 3675-86.
10. Hutchinson AD, Hosking JR, Kichenadasse G, Mattiske JK, Wilson C. Objective and subjective cognitive impairment following chemotherapy for cancer: A systematic review. *Cancer Treat Rev* 2012; 38: 926-34.
11. Glenn D. Israel. Determining Sample Size. 1992 http://pioneer.netserv.chula.ac.th/~ppongsa/2900600/LMRM09.pdf (accessed Jan 2, 2021).
12. Ng CG, Zakaria H, Ghaus Z, *et al*. Development and validation of the Positive Emotion Rating Scale (PERS). *Int J Academic Res* 2016; 8(1).
13. Mohamed FA, Ng C G, Ong L Y. The psychometric properties of the Malay version Positive Emotion Rating Scale (PERS-M). *Malaysian J Psychiatry* 2016; 25. https://www.mjpsychiatry.org/index.php/mjp/article/view/398/283 (accessed Feb 5, 2021).
14. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; 67: 361-70.
15. Vodermaier A, Millman RD. Accuracy of the Hospital Anxiety and Depression Scale as a screening tool in cancer patients: A systematic review and meta-analysis. *Support Care Cancer* 2011; 19: 1899-908.
16. Yong HW, Hashim Z, Jamil @ Osman Z. Reliability and validatidity of Hospital Anxiety and Depression Scale (HADS) on breast cancer survivors: Malaysia case study. *Asia Pacific Environmental Health J* 2016; 2(1): 19-24.
17. Yusoff N, Low WY, Yip CH. Psychometric properties of the Malay version of the Hospital Anxiety and Depression Scale: A study of husbands of breast

cancer patients in Kuala Lumpur, Malaysia. *Asian Pacific J Cancer Prev* 2011; 12: 915-7.
18. Sullivan MJ, Edgley K, Dehoux E. A survey of multiple sclerosis: I. Perceived cognitive problems and compensatory strategy use. *Can J Rehabil* 1990; 4: 99-105.
19. Lezak MD, Howieson DB, Loring DW, Hannay HJ, Fischer JS. Neuropsychological assessment, 4th ed. New York, NY, US: Oxford University Press, 2004.
20. Bettcher BM, Libon DJ, Kaplan E, Swenson R, Penney DL. Digit Symbol Substitution Test. In: Encyclopedia of Clinical Neuropsychology. 2011.
21. Jaeger J. Digit symbol substitution test. *J Clin Psychopharmacol* 2018; 38: 513-9.
22. Segal R, Zwaal C, Green E, Tomasone JR, Loblaw A, Petrella T. Exercise for people with cancer: A clinical practice guideline. *Curr Oncol* 2017; 24: 40-6.
23. Sak Y, Faa A, Yaacob Latif J, Tun Razak B, Lumpur K. Breast self examination: To do or not to do? 2006 www.dep.iarc.fr/globocan/globocan.html (accessed March 26, 2021).
24. Raffa RB. A proposed mechanism for chemotherapy-related cognitive impairment ('chemo-fog'). *J Clin Pharm Ther* 2011; 36: 257-9.
25. Bender CM, Sereika SM, Berga SL, *et al*. Cognitive impairment associated with adjuvant therapy in breast cancer. *Psychooncology* 2006; 15: 422-30.
26. Prakash J, Ryali V, Srivastava K, Bhat P, Shashikumar R. Cognitive reserve: The warehouse within. *Ind Psychiatry J* 2011; 20: 79.
27. Janelsins MC, Kohli S, Mohile SG, Usuki K, Ahles TA, Morrow GR. An update on cancer- and chemotherapy-related cognitive dysfunction: Current status. In: Seminars in Oncology. W.B. Saunders, 2011: 431-8.
28. Cheung YT, Shwe M, Chui WK, *et al*. Effects of chemotherapy and psychosocial distress on perceived cognitive disturbances in Asian breast cancer patients. *Ann Pharmacother* 2012; 46: 1645-55.
29. Honjo K, Black SE, Verhoeff NPLG. Alzheimer's disease, cerebrovascular disease, and the β-amyloid cascade. *Can J Neurol Sci* 2012; 39: 712-28.
30. Lin Y, Lai X, Chen G, *et al*. Association among serum uric acid, cardiovascular risk, and arterial stiffness: A cross-sectional study in She ethnic minority group of Fujian Province in China. *J Endocrinol Invest* 2012; 35: 290-7.
31. Hong Q, Qi K, Feng Z, *et al*. Hyperuricemia induces endothelial dysfunction via mitochondrial Na+/Ca2+ exchanger-mediated mitochondrial calcium overload. *Cell Calcium* 2012; 51: 402-10.
32. Khosla UM, Zharikov S, Finch JL, *et al*. Hyperuricemia induces endothelial dysfunction. *Kidney Int* 2005; 67: 1739-42.
33. Ferguson RJ, Ahles TA, Saykin AJ, *et al*. Cognitive-behavioral management of chemotherapy-related cognitive change. *Psychooncology* 2007; 16: 772-7.
34. Koppelmans V, Breteler MMB, Boogerd W, Seynaeve C, Gundy C, Schagen SB. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *J Clin Oncol* 2012; 30: 1080-6.
35. Wefel JS, Kesler SR, Noll KR, Schagen SB. Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA Cancer J Clin* 2015; 65: 123-38.
36. Ahles T, Saykin A, Mcdonald B, *et al*. Longitudinal Assessment of Cognitive Changes Associated With Adjuvant Treatment for Breast Cancer: Impact of Age and Cognitive Reserve. *J Clin Oncol* 2010; 28: 4434-40.
37. Biglia N, Bounous VE, Malabaila A, *et al*. Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study. *Eur J Cancer Care (Engl)* 2012; 21: 485-92.
38. Cheung YT. Chemotherapy-associated cognitive changes in Asian breast cancer patients. 2014. https://scholarbank.nus.edu.sg/handle/10635/53622. ScholarBank@NUS Repository.
39. Anderson AK, Wais PE, Gabrieli JDE. Emotion enhances remembrance of neutral events past. *Proc Natl Acad Sci U S A* 2006; 103: 1599-604.
40. Hermelink K, Küchenhoff H, Untch M, *et al*. Two different sides of 'chemobrain': determinants and nondeterminants of self-perceived cognitive dysfunction in a prospective, randomized, multicenter study. *Psychooncology* 2010; 19: 1321-8.
41. Taylor SE. Adjustment to threatening events: A theory of cognitive adaptation. *Am Psychol* 1983; 38: 1161-73.
42. Pullens MJJ, De Vries J, Roukema JA. Subjective cognitive dysfunction in breast cancer patients: A systematic review. Psychooncology. 2010; 19: 1127-38.
43. O'Farrell E, Smith A, Collins B. Objective–subjective disparity in cancer-related cognitive impairment: does the use of change measures help reconcile the difference? *Psychooncology* 2017; 26: 1667-74.
44. McDonald BC, Saykin AJ. Alterations in brain structure related to breast cancer and its treatment: Chemotherapy and other considerations. Brain Imaging Behav. 2013; **7**: 374-87.
45. Wigmore P. The effect of systemic chemotherapy on neurogenesis, plasticity and memory. *Curr Top Behav Neurosci* 2012; 15: 211-40.
46. Kesler SR, Bennett FC, Mahaffey ML, Spiegel D. Regional brain activation during verbal declarative memory in metastatic breast cancer. *Clin Cancer Res* 2009; 15: 6665-73.