Effects of Chemotherapy and Psychosocial Distress on Perceived Cognitive Disturbances in Asian Breast Cancer Patients

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BACKGROUND: There is conflicting evidence on the effect of chemotherapy and psychosocial distress on perceived cognitive changes in cancer patients.

OBJECTIVE: To compare the severity of perceived cognitive disturbance in Asian breast cancer patients receiving chemotherapy and those not receiving chemotherapy, and identify clinical characteristics associated with perceived cognitive disturbances.

METHODS: A cross-sectional, observational study was conducted at the largest cancer center in Singapore. Breast cancer patients receiving chemotherapy and not receiving chemotherapy completed the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30), and Beck Anxiety Inventory to assess their perceived cognitive functioning, health-related quality of life, and anxiety, respectively. Multiple regression was conducted to delineate the factors associated with perceived cognitive disturbances.

RESULTS: A total of 85 breast cancer patients receiving chemotherapy and 81 not receiving chemotherapy were recruited. Chemotherapy patients experienced more fatigue (QLQ-C30 fatigue scores: 33.3 vs 22.2 points; $p = 0.005$) and moderate-to-severe anxiety (21.9% vs 8.6%; $p = 0.002$) compared to non-chemotherapy patients. Non-chemotherapy patients reported better perceived cognitive functioning than those who received chemotherapy (FACT-Cog scores: 124 vs 110 points, respectively; $p < 0.001$). Chemotherapy and endocrine therapy were strongly associated with perceived cognitive disturbances ($p < 0.001$ and 0.021, respectively). The interacting effect between anxiety and fatigue was moderately associated with perceived cognitive disturbances ($\beta = -0.29$; $p = 0.037$).

CONCLUSIONS: Chemotherapy and endocrine treatment were associated with significant cognitive disturbances among Asian breast cancer patients. Psychosocial factors could be used to identify cancer patients who are more susceptible to cognitive disturbances in the clinical setting.

KEY WORDS: anxiety, cancer, chemobrain, cognitive function, psycho-oncology, psychosocial distress, quality of life.

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Besides physical adverse effects, cancer patients receiving chemotherapy are often affected by treatment-related psychosocial distress such as anxiety, depression, and cognitive changes.[1-3] These psychosocial disturbances can cause a significant negative impact on patients' quality of life and daily functioning.[4,5]

Among breast cancer patients, perceived cognitive impairment and mood disorders are implicated as components of a common symptom cluster experienced by patients treated with chemotherapy.[6] We recently published a qualitative focus group study on multiethnic breast cancer patients and observed the significant impact of psychosocial distress on cognitive disturbances.[7] Participants described chemotherapy as "potent" and "toxic," and they alleged that "their brain cells were affected by chemotherapy," leading to perceived cognitive disturbances. More importantly, participants perceived that cancer-related fatigue and anxiety heavily contributed to their cognitive decline. Treatment-related mood changes, such as anxiety and depression, have affected many participants mentally, emotionally, and psychologically.[7] Hence, recent efforts have been focused on investigating the re-

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lationships between psychosocial distress and cognitive impairment.

Notably, an increasing number of studies have been conducted to investigate cognitive changes in breast cancer patients after chemotherapy.[8-12] In the literature, this phenomenon is termed as *chemobrain* or *chemofog*.[9,11,12] It is observed that cancer patients often experience a subtle, yet notable, change in cognitive function after receiving chemotherapy. These cognitive deficits can include difficulties in concentration, memory, speech and language, decision making, and learning new concepts or tasks.[7,10,12] A number of studies acknowledge that these cognitive impairments may be further exacerbated by patients' underlying psychosocial symptoms such as anxiety, depression, and fatigue.[12-15] One systematic review[13] found evidence for the association of subjective or perceived cognitive changes with anxiety, depression, psychological distress, fatigue, and poorer health status. However, current evidence is insufficient to conclude the causal relationship between psychological distress and persistence of cognitive problems.[13]

Moreover, whether these symptoms are largely driven by systemic treatment is still debatable in the literature.[1,13] Cognitive problems experienced by cancer patients might have been caused by distress associated with their cancer diagnosis. Some studies also suggested that cognitive disturbances and psychosocial disturbances may exist prior to the cancer treatment administration.[16-18] Furthermore, it has been proposed that interacting effects might exist among psychological, psychosocial, and demographic factors,[19] but to what extent these interacting effects may affect cognition have not been well expounded within existing psycho-oncological studies.

In view of the poor understanding of the psychosocial impacts of cancer treatment and their effects on perceived cognitive disturbances, this study was designed to compare the severity of perceived cognitive disturbance in Asian breast cancer patients receiving chemotherapy and those not receiving chemotherapy. In addition, this study was designed to identify potential interacting clinical and psychosocial factors associated with perceived cognitive disturbances in Asian breast cancer patients.

Methods

A single-center, cross-sectional, observational study was conducted at the ambulatory clinics of National Cancer Centre Singapore, the largest ambulatory cancer center where 65% of the cancer population in Singapore is treated annually. This study was approved by the SingHealth Institutional Review Board prior to its inception.

PATIENTS

Two groups of breast cancer patients were recruited in this study: one consisted of patients who had received chemotherapy and the other consisted of patients who did not receive chemotherapy. Specifically, the chemotherapy arm consisted of patients who were receiving anthracycline-based chemotherapy at the point of recruitment or within the past year. The non-chemotherapy arm consisted of eligible patients who did not have prior exposure to chemotherapy. All eligible patients were required to be: diagnosed with breast cancer by a medical oncologist, older than 21 years, and able to read and understand either English or Mandarin. Patients were excluded if they had brain metastasis or were mentally incompetent to give informed consent.

STUDY PROCEDURE

Patients' demographics and clinical information, such as cancer stage, Eastern Cooperative Oncology Group (ECOG) performance status, hemoglobin level at the point of recruitment, and medication history, were collected through existing clinical databases. A 25-minute interview was conducted privately by trained investigators with the patient upon recruitment. During the interview, patients completed 3 sets of self-reporting tools on their perceived impact of chemotherapy on cognitive functioning, health-related quality of life, and anxiety.

Perceived Cognitive Disturbances

The Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog) version 3 was utilized to assess perceived cognitive disturbances.[20] Thirty-three items are used to evaluate cognitive disturbances in the domains of mental acuity, attention and concentration, memory, and verbal fluency. There are 4 subscales within FACT-Cog: (1) perceived cognitive problems (eg, "My thinking has been slow"; "I have had trouble remembering where I put my things, like my keys and wallet"), (2) perceived cognitive abilities (eg, "I have been able to concentrate"; "I have been able to pay attention and keep track of what I am doing without extra effort"), (3) comments from others (eg, "Other people have told me that I seemed to have trouble remembering information"; "Other people have told me that I seemed confused"), and (4) impact of cognitive impairments on quality of life (eg, "These problems have interfered with the quality of my life"). Patients rate on a 5-point Likert scale the frequency with which each statement has occurred in the past week from the day of administration (0 = never; 4 = several times a day). Both English and Chinese versions of FACT-Cog were utilized in this study. The Chinese version was translated based on standard guidelines by the Functional Assessment of Chronic Illness Therapy (FACIT)[21,22] and the International Society for Pharmacoeconomics and Outcomes Research.[23] This recommended process consisted of 2 independent forward

translations, a backward translation, and a final reconciled version that was approved by FACIT.

Health-Related Quality of Life

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, referred to as QLQ-C30 hereafter) was used to assess health-related quality of life in cancer patients.[24] It consists of 5 functional scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, nausea and vomiting, and pain), 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), and a global health status scale. Of interest to this study is the cognitive functioning scale, which contains 2 items that investigate memory ("Have you had difficulty remembering things?") and attention deficits ("Have you had difficulty in concentrating on things, like reading a newspaper or watching television?") in the past week. All QLQ-C30 items have 4 response options (not at all, a little, quite a bit, and very much), except for the 2 items assessing global quality of life, which used a 7-point scale. The English and Chinese versions of QLQ-C30 were utilized in this study.[25] Both versions display good psychometric properties within the local cancer population and the Chinese QLQ-C30 is shown to be equivalent to the English version.[25,26]

Anxiety

Anxiety was measured using the Beck Anxiety Inventory (BAI), which is a validated questionnaire that consists of 21 anxiety-associated items for which patients rate the severity level on a scale of 0-3.[27] Each item is descriptive of subjective, neuropsychological, somatic, or panic-related symptoms of anxiety. A total score can be tabulated and patients' anxiety is classified as severe (score of 26-63), moderate (score of 16-25), mild (score of 8-15), and absence of anxiety (score of 0-7). The BAI is demonstrated to have a high internal consistency, with Cronbach α ranging from 0.92 to 0.94 for adults and test-retest reliability (1-week interval) of 0.75.

STATISTICAL ANALYSIS

Sample size calculation was conducted prior to initiation of this study. In a study that was conducted to validate the English version of the QLQ-C30 in the Singaporean cancer population, the median score of cognitive functioning was 92 points.[25] In another study that evaluated the clinical significance of QLQ-C30 score changes, for patients who indicated "a little" change either for better or for worse, the mean change in scores was between 5 and 10 points.[28] Considering a 2-sided significance level of $\alpha = 0.05$ and a power of 80% ($\beta = 0.20$), a calculated sample size of 80 chemotherapy and 80 non-chemotherapy patients was needed to observe a 10-point difference in the QLQ-C30 cognitive functioning score between the 2 groups.

All statistical analyses were performed using SPSS version 19. Descriptive statistics were used to describe demographic and clinical characteristics of the sample. Comparison of baseline characteristics between chemotherapy and non-chemotherapy arms was conducted using independent *t*-test or Mann-Whitney *U* test for continuous measures. χ^2 or Fisher exact tests were used for testing differences in categorical measures. Standard protocols provided by FACIT and EORTC were used to tabulate the total scores for the FACT-Cog and QLQ-C30, respectively. The Mann-Whitney *U* test was conducted to evaluate difference in QLQ-C30 cognitive functioning and FACT-Cog scores between the chemotherapy and non-chemotherapy arms. All 2-tailed significance tests were conducted using a significance level of $p < 0.05$.

The effect of associated factors on perceived cognitive functioning, which was depicted by the total FACT-Cog score, was evaluated using linear regression analysis. Documented clinically relevant factors, such as age,[29] menopausal status,[3,30] baseline intelligence (education level as the surrogate marker),[29] fatigue,[30,31] anxiety,[13] and receipt of antihormonal or endocrine therapy,[32,33] were included in the linear regression analysis. For other exploratory variables to be included in the linear regression model, it must be statistically significant at a cutoff p value of 0.1 in the univariate analysis and considered clinically relevant, based on consensus among the clinicians in the research team. This approach was adopted to prevent detraction from the statistical power by including clinically irrelevant variables in the model.

Exploratory univariate analysis of variance was also applied to identify potential statistically significant and clinically relevant interacting variables that might be associated with perceived cognitive functioning. The pairs of variables involved in the exploratory analysis were: (1) fatigue and anxiety,[2,5] (2) fatigue and chemotherapy status (defined as currently receiving chemotherapy at the time of recruitment),[3,5] (3) anxiety and chemotherapy status,[2] (4) postmenopausal status and fatigue,[3,30] and (5) fatigue and hemoglobin level at the point of recruitment.[34] Statistically significant interacting terms were entered into the regression model using mean deviations. Residual analysis and collinearity diagnostics were performed to ensure the validity of the linear regression model.

Since the subjective neuropsychological tool, FACT-Cog, had not yet been extensively validated in the local population, an exploratory analysis on the internal consistency of FACT-Cog was conducted by evaluating the Cronbach α of the FACT-Cog subscales. Concurrent validity of FACT-Cog was assessed by its strength of correlation with the validated QLQ-C30 cognitive functioning scale. As such, the research team had established a priori that the QLQ-C30 cognitive functioning subscale should not be included as an independent variable in the regression model (regardless of the univariate analysis results), as it might measure the same con-

structs as the total FACT-Cog scores, hence reducing the validity of the regression model.

Results

BASELINE CHARACTERISTICS OF PARTICIPANTS

A total of 166 patients participated in the study (85 chemotherapy patients and 81 non-chemotherapy patients). Baseline characteristics are presented in Table 1. The majority (78.9%) of patients were Chinese early-stage breast cancer patients. Patients in the non-chemotherapy group were older relative to the chemotherapy patients (mean [SD] 54.1 [10.2] vs 51.0 [9.2] years; p = 0.042). Statistically significant differences were not observed among race, education level, menopausal status, and ECOG status. However, non-chemotherapy patients had a higher mean hemoglobin level than chemotherapy patients (12.7 [1.5] vs 11.5 [1.3] g/dL; p < 0.001). There were more patients with stages 1 and 2 breast cancer among those who did not receive chemotherapy (84.0% vs 48.2%; p = 0.043). The majority of the chemotherapy patients had completed chemotherapy within a mean duration of 6.3 (4.3) months at the point of recruitment.

HEALTH-RELATED QUALITY OF LIFE

Statistically significant differences in the QLQ-C30 scores were not detected between the groups, with the exception of the cognitive functioning scale, fatigue scale, and dyspnea (Table 2). Non-chemotherapy patients reported better perceived cognitive functioning than chemotherapy patients (100 vs 83.3 points; p < 0.001). The median cognitive functioning score of 100 for the non-chemotherapy patients indicated that a significant proportion of those patients perceived that they had an intact cognitive function (Table 2). Chemotherapy patients experienced considerably more fatigue than non-chemotherapy patients, as observed by the moderately large difference of 11.1 points in the median QLQ-C30 fatigue scale (33.3 vs 22.2 points; p = 0.005).

ANXIETY

Patients in this study manifested varying degree of anxiety states (Figure 1). Overall, chemotherapy patients experienced more anxiety-related symptoms than the non-chemotherapy patients. Patients in the chemotherapy group achieved a higher median BAI score (9.5 vs 5 points; p < 0.001) than did patients in the non-chemotherapy group. More chemotherapy patients experienced moderate-to-severe anxiety, as compared to the non-chemotherapy group (21.9% versus 8.6%; p = 0.002). With regards to the BAI subscales, chemotherapy patients reported marginally more anxiety-related panic and neuropsychological and subjective symptoms than non-chemotherapy patients (Table 2).

Table 1. Baseline Characteristics of Patients

Characteristic	Chemotherapy		p Value[a]
	Receiving (n = 85)	Not Receiving (n = 81)	
Age (years), mean (SD)	51 (9.2)	54.1 (10.2)	**0.042**
Education (years), mean (SD)	9.7 (4.3)	9.7 (3.6)	0.76
Education, n (%)			
none	4 (4.7)	3 (3.7)	
primary (elementary)	22 (25.9)	17 (21)	
secondary (junior high)	35 (41.2)	42 (51.9)	0.64
pre-university (senior high)	8 (9.4)	8 (9.9)	
graduate/postgraduate	16 (18.8)	11 (13.6)	
Race, n (%)			
Chinese	65 (76.5)	66 (81.5)	
Indian	1 (1.2)	2 (2.5)	0.63
Malay	14 (16.5)	7 (8.6)	
other[b]	5 (5.9)	6 (7.4)	
Marital status, n (%)			
single	19 (22.4)	8 (9.9)	
married	57 (67.1)	66 (81.5)	**0.047**
divorced	8 (9.4)	3 (3.7)	
widowed	1 (1.2)	4 (4.9)	
Cancer stage, n (%)			
0	0 (0)	2 (2.5)	
1	11 (12.9)	26 (32.1)	**0.043**
2	30 (35.3)	42 (51.9)	
3	34 (40)	8 (9.9)	
4	10 (11.8)	3 (3.7)	
ECOG performance status, n (%)			
0	59 (69.4)	64 (79)	
1	25 (29.4)	15 (18.5)	0.28
2	1 (1.2)	1 (1.2)	
3	0 (0)	1 (1.2)	
Endocrine treatment, n (%)[c]	59 (69.4)	2 (2.5)	**0.012**
Postmenopausal, n (%)	46 (54.1)	43 (53.1)	0.85
Chemotherapy status, n (%)			
completed	59 (69.4)		
still receiving	26 (31.7)		
Chemotherapy regimens, n (%)			
AC-based[d]	64 (75.4)		
FEC-based[e]	15 (17.7)		
other	6 (7.1)		
Hemoglobin level (g/dL), mean (SD)[f]	11.5 (1.3)	12.7 (1.5)	**<0.001**

ECOG = Eastern Cooperative Oncology Group.
[a]Bolded p values are statistically significant.
[b]Patients of other races included 2 Filipinos, 2 Burmese, and 1 Arab.
[c]Receipt of anastrozole, exemestane, letrozole, or tamoxifen.
[d]AC-based = doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 3 times weekly for 4 cycles.
[e]FEC-based = epirubicin 75-100 mg/m^2, cyclophosphamide 500 mg/m^2, and fluorouracil 500 mg/m^2 3 times weekly for 4 cycles.
[f]Missing data on 3 patients.

PERCEIVED COGNITIVE DISTURBANCES

Generally, chemotherapy patients reported more perceived cognitive disturbances than non-chemotherapy patients (Figure 2). The median FACT-Cog scores for the chemotherapy patients were 14 points lower than the non-chemotherapy group (110 vs 124 points; $p < 0.001$). Analysis of the FACT-Cog subscales revealed that "perceived cognitive impairment," "reduced cognitive abilities," and poorer cognitive impairment–associated quality of life were more prevalent in chemotherapy patients (Table 2).

FACTORS ASSOCIATED WITH PERCEIVED COGNITIVE DISTURBANCES

Perceived cognitive disturbances were significantly correlated with anxiety ($r = -0.58$; $p < 0.001$), fatigue ($r = -0.36$; $p < 0.001$), QLQ-C30 global health status ($r = 0.47$;

Table 2. Comparison of Quality of Life and Anxiety Between Breast Cancer Patients Receiving Chemotherapy and Not Receiving Chemotherapy

Characteristic	Receiving Chemotherapy (n = 85) Median	1st Quartile	3rd Quartile	Not Receiving Chemotherapy (n = 81) Median	1st Quartile	3rd Quartile	p Value[a]
EORTC QLQ-C30[b]							
Functional[c]							
cognitive	83.3	66.7	100	100	83.3	100	**<0.001**
emotional	83.3	66.7	91.7	83.3	66.7	95.8	0.197
physical	86.7	76.7	93.3	86.7	80	93.3	0.281
role	100	83.3	100	100	83.3	100	0.501
social	100	66.7	100	83.3	66.7	100	0.905
Global health status[c]	66.7	50	83.3	66.7	58.3	83.3	0.262
Symptom scales[d]							
fatigue	33.3	11.1	44.4	22.2	11.1	33.3	**0.005**
nausea and vomiting	0	0	0	0	0	0	0.669
pain	16.7	0	33.3	16.7	0	16.7	0.096
Single items[d]							
appetite	0	0	0	0	0	0	0.415
constipation	0	0	33.3	0	0	0	0.138
diarrhea	0	0	0	0	0	0	0.819
dyspnea	0	0	33.3	0	0	0	**0.005**
financial	33.3	0	66.7	33.3	0	66.7	0.638
insomnia	33.3	0	66.7	0	0	33.3	0.183
Beck Anxiety Inventory score							
Total[d]	9.5	4	14.3	5	2	8	**<0.001**
autonomic[d,e]	1	0	3	0	0	1	
neuropsychological[d,e]	2	1	5	1	0	2	
panic[d,e]	1	0	6	0	0	2	
subjective[d,e]	3	0	6	2	0	5	
FACT-Cog score							
Total[e,f]	110	94.5	121.5	124	113.5	129	**<0.001**
perceived cognitive impairment[e,f]	63	51.5	68	68	63	71	
comments from others[e,f]	16	14	16	16	15.6	16	
perceived cognitive abilities[e,f]	21	16	23.5	25	21	28	
impact on quality of life[e,f]	13.5	10.5	16	14	13.5	16	

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-Cog = Functional Assessment of Cancer Therapy–Cognitive Function.
[a]Bolded p values are statistically significant.
[b]Maximum score for all EORTC QLQ-C30 subscales is 100.
[c]A higher score is indicative of better functioning/health status.
[d]A higher score is indicative of more symptoms/difficulties.
[e]Inferential statistics tests were not conducted on the subdomain scales to avoid problems with multiple comparisons within the same tool.
[f]A higher score is indicative of better cognitive functioning. Maximum total score is 132.

$p < 0.001$), QLQ-C30 emotional functioning ($r = 0.52$; $p < 0.001$), and QLQ-C30 cognitive functioning scale ($r = 0.77$; $p < 0.001$). Higher levels of anxiety and fatigue were associated with more perceived cognitive disturbances. Although patient-specific parameters such as age, menopausal status, and educational status were documented in the literature as clinically relevant predictors, they did not correlate with perceived cognitive functioning in our analysis. On univariate analysis, patients who were receiving endocrine therapy reported more cognitive disturbances than those who did not receive endocrine therapy ($p = 0.011$). There were no statistically significant associations between perceived cognitive disturbances and staging of the cancer, ECOG status, type of chemotherapy regimen (AC-based [doxorubicin and cyclophosphamide] vs FEC-based [fluorouracil, epirubicin, and cyclophosphamide]), type of endocrine therapy (tamoxifen vs aromatase inhibitors), and patients' chemotherapy treatment status (completed chemotherapy vs currently receiving chemotherapy).

Univariate analysis of variance identified 2 pairs of interacting variables. Results showed that a significant interacting effect was observed between anxiety and fatigue ($F = 13.47$; $p < 0.001$), and a weaker interacting effect between fatigue and hemoglobin level ($F = 9.32$; $p = 0.048$). No statistically significant interactions were identified among other characteristics.

Associated factors of perceived cognitive functioning were explored using multivariate linear regression modeling (Table 3). The total variance explained by the linear regression model was 65.3%. Results suggested that there was an 8.74-point (95% CI –9.40 to –4.21) decrease in FACT-Cog total score in a patient who was exposed to chemotherapy, compared to a patient who was not ($p < 0.001$). The receipt of endocrine therapy was also a significant pharmacologic factor associated with perceived cognitive disturbances ($B = –5.23$, CI –7.11 to –0.21; $p = 0.021$).

Psychosocial factors with a statistically significant association with perceived cognitive functioning included anxiety, emotional functioning, and global health status. Although the association between perceived cognitive functioning and fatigue alone was not statistically significant, the interaction effect between anxiety and fatigue was moderately associated with perceived cognitive disturbances, relative to fatigue alone ($\beta = –0.293$; $p = 0.037$ vs $\beta = –0.071$; $p = 0.59$, respectively).

EXPLORATORY ANALYSIS OF THE PSYCHOMETRIC PROPERTIES OF FACT-Cog

FACT-Cog subscales displayed high internal consistency, with Cronbach α ranging from 0.76 to 0.94. There is also a strong correlation between the QLQ-C30 cognitive functioning scale and total FACT-Cog score ($r = 0.77$; $p < 0.001$).

Discussion

This study sought to delineate the effects of chemotherapy on the severity of perceived cognitive disturbances and

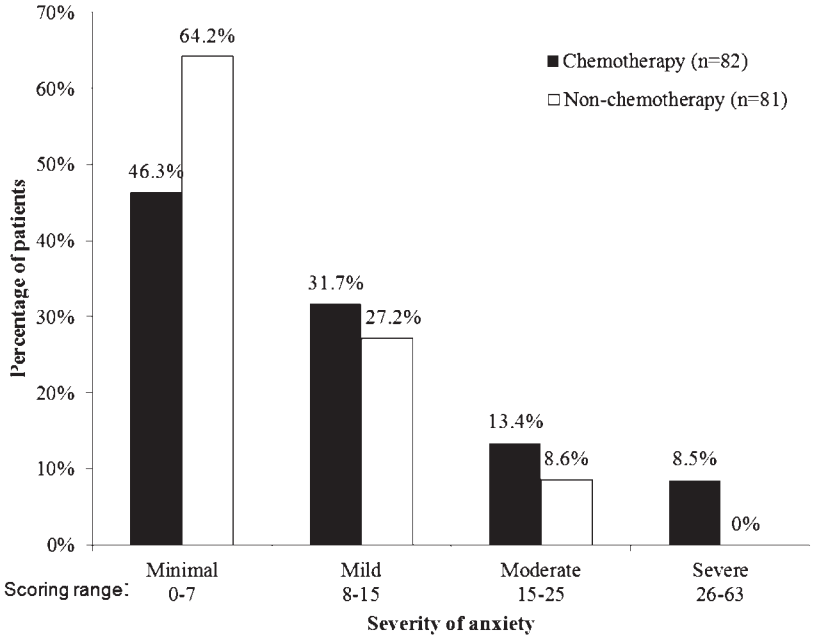

Figure 1. Comparison of severity of anxiety between patients receiving chemotherapy and those not receiving chemotherapy (n = 163). Data are missing from 3 patients receiving chemotherapy, as those patients declined to answer some questions in the Beck Anxiety Inventory.

psychological distress in a sample of Asian breast cancer patients. Chemotherapy, endocrine therapy, and various components of quality of life, including global health status and emotional functioning, were associated with cognitive disturbances among the patients in this study. More importantly, our results are novel because we have successfully explored the interacting effects of psychosocial factors that are associated with perceived cognitive disturbances. The combination effects of anxiety and fatigue impacted patients' perceived cognitive disturbances more strongly than each individual effect alone. This is in agreement with current evidence that cognitive disturbance in cancer patients is a multifactorial phenomenon and is related to psychological distress.[13,35]

This is also one of the first published studies that evaluated perceived cognitive disturbances among Asian breast cancer patients. Currently, there is a lack of robust studies to evaluate Asians' experience with cognitive changes in cancer patients, except for 2 recent studies that used the Attentional Function Index (AFI) to measure patients' perceived cognitive function.[1,14] The Korean study reported a mean AFI score (SD) of 66.22 (13.4) points (out of a total score of 100 points) in their population of breast cancer patients and identified mood disturbance as a statistically significant predictor of cognitive function in 118 breast cancer patients.[14] However, the validity of this cross-sectional study was limited by the absence of controls who were not receiving chemotherapy. Notably, our findings were in contrast with another Asian study that explored the trajectory of perceived attentional function from before surgery to 24 months after surgery in 200 Chinese breast cancer patients.[1] In that study, the mean baseline AFI score was high, at 8.2 (out of a total score of 10 points), and dropped at 1 month after surgery to 6.5. After adjusting for covariates, perceived attentional function was not associated with adjuvant treatment ($p = 0.721$). However, this study was also limited by a small sample size for each treatment modality. Results from these studies were inconclusive, as attentional function was the only domain of interest tested.

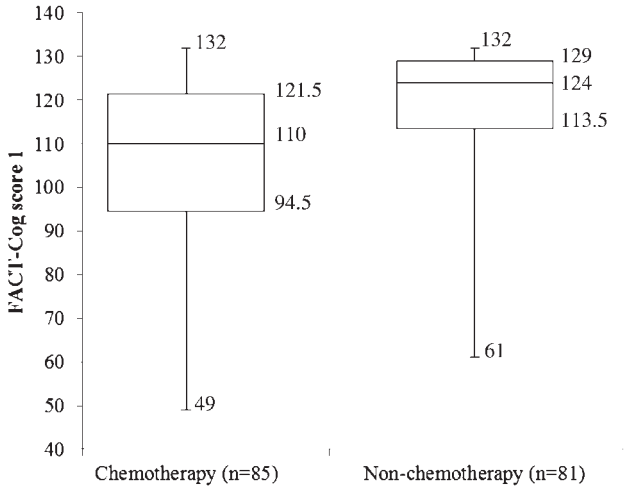

Figure 2. Comparison of Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog) total scores between patients receiving chemotherapy and those not receiving chemotherapy (n = 166). Total FACT-Cog score is 132. A higher score is indicative of a better perceived cognitive functioning.

Other than the above-mentioned reasons, the use of FACT-Cog, an in-depth neuropsychological tool, might have explained the disparity of our findings. Although FACT-Cog had not been validated extensively in our local population, exploratory analysis of the psychometric properties of FACT-Cog had revealed high internal consistencies for all the subscales. FACT-Cog total score also displayed good concurrent validity, as is evident by its strong correlation with the validated QLQ-C30 cognitive functioning scale. As a previous local study had identified the limitations of the QLQ-C30 cognitive functioning scale,[25] we propose that FACT-Cog is more comprehensive and robust to evaluate cancer patients' perceived cognitive disturbances in the clinical setting. However, similar to the AFI, there is currently no cutoff point or published minimal clinically important difference to quantify a clinically significant change in the perceived cognitive impairment using FACT-Cog. It is anticipated that with more validation work, a psychometrically robust tool can be utilized to quantify the effect of chemotherapy on the severity and prevalence of perceived cognitive changes in cancer patients.

Chemotherapy is shown to cause a negative impact on patients' psychological status, as reflected in the higher levels of anxiety experienced by chemotherapy patients. Ours is one of the few studies that utilized the BAI to evaluate cancer patients' anxiety symptoms. Although only marginal differences in total BAI and subdomain scores were detected between the 2 groups, anxiety could have negatively impacted patients' perceived cognitive function and other treatment outcomes. One study had demonstrated elevated anxiety and psychological distress in women with breast cancer even prior to cancer diagnosis; patients' anxiety and psychological distress were strongly associated with quality of life, anxiety, depressive symptoms, and fatigue after cancer treatment.[16] Contrary to what was expected, patients' quality of life aspects did not differ much between the chemotherapy and non-chemotherapy groups. This might be due to response shift, which involved changes in the internal standards, values, and the conceptualization of quality of life observed in cancer survivors.[36] Notably, a majority of our chemotherapy patients who had completed chemotherapy might have been the cancer survivors who were responsible for this adaptive process. Therefore, a baseline measurement is essential to accurate assessment of the effects of chemotherapy on psychological and quality of life changes. Unfortunately, the cross-

sectional design of this study did not allow for comparison of changes in psychological distress and perceived cognitive disturbances within individual patients across different time points of their treatments. It is anticipated that future cohort studies will provide more insights to the clinical course of these psychological distress parameters in cancer patients.

Our results suggested that psychosocial factors can play a significant role in self-perceived cognitive disturbances. There is strong evidence in the literature to support determinants such as psychological distress and cancer-related fatigue as predictors for perceived cognitive functioning.[12,13,15] Cancer-related fatigue is defined as a "distressing persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment."[37] As reflected through this definition and current literature, fatigue can affect cancer patients cognitively and emotionally.[2,5] In our study, the severity of fatigue was not associated with perceived cognitive disturbances in the regression model. This deviation from current evidence can be explained by the large proportion of patients who were relatively young, ambulating, had early-stage disease, did not have clinically-significant anemia (mean hemoglobin level 11.5 [1.3] g/dL) and were not expected to experience significant fatigue. However, our results suggested that a breast cancer patient with both cancer-related fatigue and anxiety might have a higher risk of perceived cognitive disturbances. The interacting effects between fatigue and anxiety were strongly associated with perceived cognitive deficits. Qualitative results from our focus group study with 43 local breast cancer patients revealed that patients identified anxiety and fatigue as top contributing factors to their post-chemotherapy cognitive changes.[7] It is hence proposed that psychosocial factors could be used as predictors in the identification of at-risk patients who may be more susceptible to cognitive disturbances in a clinical setting. These patients may benefit from psychosocial interventions during the course of their cancer treatments.

Concurring with current evidence, our results identified the receipt of endocrine therapy to be strongly associated with perceived cognitive disturbances. One study detected more severe perceived cognitive functioning and attentional problems in breast cancer patients who had been exposed to tamoxifen or aromatase inhibitors than in those who had never had any exposures.[38] Conflicting evidence suggests that aromatase inhibitors have fewer neurocognitive effects than tamoxifen on patients.[33,39] This is a topic of significant value, as breast cancer patients who have estrogen receptor–positive cancer cells typically receive endocrine therapy. Future studies can be targeted at evaluating whether aromatase inhibitors are indeed associated with less perceived cognitive impairment in breast cancer patients.

Table 3. Factors Associated with Perceived Cognitive Functioning (n = 166)[a]

Variable[b]	Unstandardized Coefficient (B)	95.0% CI for B		Standard Error	Standardized Coefficient (β)	p Value[c]
		Lower Bound	Upper Bound			
Receipt of chemotherapy	–8.74	–9.40	–4.21	2.45	–0.24	**<0.001**
Demographic factors						
age	–0.09	–0.14	0.20	0.05	–0.06	0.73
years of education	0.03	–0.42	0.25	0.17	0.04	0.23
Clinical and pharmacologic factors						
hemoglobin level	–0.32	–1.30	1.45	2.45	–0.02	0.56
postmenopausal status	–1.17	–2.43	2.37	1.09	–0.12	0.33
received endocrine treatment	–5.23	–7.11	–0.21	2.10	–0.13	**0.021**
Psychosocial factors						
anxiety (Beck Anxiety Inventory total score)	–0.40	–0.76	–0.05	0.18	–0.17	**0.037**
QLQ-C30 emotional functioning	0.21	0.06	0.36	0.07	0.22	**0.002**
QLQ-C30 global health status	0.18	0.016	0.28	0.19	0.11	**0.034**
QLQ-C30 fatigue scale	–0.03	–0.18	0.02	0.23	–0.07	0.59
Interaction between fatigue and anxiety	–0.87	–0.930	–0.00	0.01	–0.29	**0.037**
Interaction between fatigue and hemoglobin level	–0.01	–0.07	0.06	0.03	–0.02	0.82

QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

[a]Adjusted $R^2 = 0.653$; $p < 0.001$.

[b]Only the clinically relevant variables that were statistically significant at a cutoff p value of 0.1 on univariate analysis were included in the regression model. Variables that were statistically insignificant on univariate analysis were cancer staging level, Eastern Cooperative Oncology Group status, type of chemotherapy regimen (AC-based [doxorubicin and cyclophosphamide] vs FEC-based [fluorouracil, epirubicin, and cyclophosphamide]), type of endocrine treatment (tamoxifen vs aromatase inhibitors), and patients' chemotherapy status (completed chemotherapy vs currently receiving chemotherapy).

[c]Bolded p values are statistically significant.

Interestingly, several documented clinically relevant demographic and clinical characteristics were not identified as significant in the regression model. Age, menopausal status, educational status, and patients' most recent hemoglobin level failed to reach statistical significance after adjusting for other variables. One study demonstrated that age and pretreatment cognitive reserve were related to posttreatment decline in processing speed in women exposed to chemotherapy.[29] Anemia, particularly a decrease of the hemoglobin level to less than 12 g/dL, was also associated with cognitive impairment.[12,34,40,41] We postulate that such deviations from current evidence might have occurred because these associations were concluded by studies that utilized objective neuropsychological tools. Perceived cognitive impairment, using subjective reporting tools, has been shown to correlate poorly with objective tools.[13] Instead, perceived cognitive impairment is associated with emotional distress and psychosocial predictors.

Although information is scarce, studies have even attempted to examine the role of biological determinants of perceived cognitive changes.[42-45] One study found that increases in interleukin-6 and interleukin-8 were both associated with increases in reported cognitive difficulties in breast cancer patients who received anthracycline-based chemotherapy.[42] Although results were not statistically significant due to an underpowered sample size, these relationships might be reflective of cognitively associated inflammation that has increased during chemotherapy. Furthermore, it has been widely acknowledged that cytokines and inflammatory markers are associated with cancer-related symptom clusters, such as fatigue, depression, and stress.[46] The advancement of cancer treatment has improved the survival rate tremendously; the challenge lies ahead in improving the quality of life and psychological well-being in cancer survivors. Future studies could be targeted at the identification of clinical and biological predictors for the management of psychological, psychosocial, and cognitive disturbances in cancer patients.

Information bias might pose a potential problem to our study, as patients who had received chemotherapy might be more critical of their cognitive status due to effects of priming and preexisting knowledge of cognitive impairment in cancer patients.[47] However, priming is unlikely, as qualitative results from a local focus group study revealed that Asian patients were generally unfamiliar with the potential neurocognitive toxicity of chemotherapy.[7] We acknowledge that the chemotherapy and non-chemotherapy groups differed in certain baseline demographics and clinical characteristics, such as age, cancer staging, and hemoglobin levels. Hence, the difference in the severity of perceived cognitive disturbances might have been confounded by these factors, as they might potentially influence patients' choice to receive or decline chemotherapy treatment. Therefore, our strategic choice of using a regression model had overcome this limitation by offering a valuable insight on the effect of these factors on perceived cognitive functioning, in the presence of other independent variables.

Other psychosocial factors that may potentially affect cognition were not evaluated in this study due to resource and time constraints within a clinical setting. However, the emotional functioning subscale in the validated QLQ-C30 could briefly examine the mood changes experienced by patients, even though it lacks comprehensiveness. The inclusion of depression and psychological distress in future studies may improve our understanding of the multifactorial nature of cognitive changes in cancer patients. The cross-sectional design of this study provided an exploratory examination of associated factors of perceived cognitive disturbances. Future cohort studies with baseline measurements of psychosocial and clinical variables should be conducted to explore the causal relationships between these variables and perceived cognitive disturbances.

Concurring with current evidence, fatigue and psychological distress such as anxiety and perceived cognitive disturbances are relevant among Asian breast cancer patients. Other than the receipt of chemotherapy, factors associated with perceived cognitive disturbances included concomitant receipt of endocrine therapy, poor emotional functioning, and poor global health status. Breast cancer patients experiencing both fatigue and anxiety are at a greater disposition to experience postchemotherapy cognitive changes. To further validate these results, future studies should include well-designed cohort studies and utilize both subjective and objective neuropsychological assessments to quantify the prevalence, severity, and impact of this problem in Asia. With more rigorous validation studies, the English and Chinese versions of FACT-Cog are potentially comprehensive tools to detect cognitive disturbances in the clinical setting.

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