

Fear of Cancer Recurrence Is Highly Prevalent and Linearly Associates With Anxiety and Depression in Chinese Breast Cancer Patients

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Abstract

Objective: To characterize the fear of cancer recurrence (FCR) and its relationship with anxiety and depression and quality of life (QoL) among Chinese breast cancer (BC) patients in China.

Methods: Patients completed the questionnaires of QLQ-C30, QLQ-BR32 and HAD to assess FCR, QoL, anxiety and depression before radiotherapy. A cross-sectional analysis was performed. Chi-square and non-parametric tests and multivariate ordinal logistic regressions (mOLR) were utilized for reference analysis. Final covariates included age, BMI, TNM, surgery, chemotherapy, pain, and sleep disturbance.

Results: From July 2015 to December 2016, 463 patients were prospectively enrolled. Their age mean (range) were 47 (19 - 89) years old. In total, 327 patients (70.6%) reported having FCR 'a little bit' (51.2%), 'some' (12.1%) and 'very much' (7.3%) in the past week. FCR severity ordered above (incl. 'no') was associated with anxiety score (median 1.5, 5.0, 7.0, 8.5 and level ('abnormal' rate 0%, 3.4%, 12.5%, 26.5%), depression score (median 2.0, 4.0, 6.0, 6.5) and level ('abnormal' rate 2.2%, 3.4%, 5.4%, 17.7%) (all $p < 0.001$). mOLR showed that compared to 'no', three higher levels of FCR were associated with one level increase of anxiety with OR (p) as 1.983 (0.076), 4.291 (0.001), 8.282 (<0.001) and depression with OR (p) as 1.903 (0.062), 2.262 (0.065), 4.205 (0.004), respectively. FCR severity also was inversely associated with most QoL function scores ($p < 0.001$).

Conclusions: FCR was prevalent in Chinese BC patients and linearly associated with anxiety, depression and low QoL. It seems that a single-item question for FCR is a valid surrogate tool for distress screening in this population.

Introduction

Fear of cancer recurrence (FCR) is a common experience for patients [1]. FCR is usually defined as "fear, worry, or concern relating the possibility that cancer will come back or progress" [2]. It ranges from normal psychological fear to persistent and excessive worry which can compromise physical and mental functioning, increase healthcare utilization, and negatively impact the quality of life (QoL) [2 - 5]. FCR is a significant contributor to distress which is now regarded as the sixth vital sign in cancer patients [6]. For reasons possibly related to the prolonged (neo)adjuvant chemotherapy and radiotherapy (RT) after surgery, FCR is more prevalent among breast cancer (BC) patients than other cancer populations [7,8]. After controlling for common risk factors, there still have been no consistent conclusions that Asian women especially Chinese are associated with higher prevalence and severity of FCR and diagnosis distress than others [9 - 11]. However, compared to many developed countries, Chinese BC patients in mainland China usually are characterized with younger onset age, larger tumor size, more metastatic lymph nodes, and preference to mastectomy over breast conserving surgery (BCS) [12,13]. In order to clarify the situation, we had designed a prospective and longitudinal cohort study to investigate how the FCR uniquely presents, progresses, and associates with QoL over time in this population.

In this study, we reported the prevalence of FCR and characterize its relationships with anxiety, depression and QoL before RT in this cohort. We hypothesized that the FCR severity would provide clinical values in predicting distress and assisting patient management in Chinese BC patients.

Methods

Study design and data collection

All Chinese women who had unilateral BC and admitted for postoperative RT from July 2015 to December 2016 at our institution were consecutively enrolled. Inclusion criteria included (1) ≥ 18 years old (2) within 180 days after surgery (3) RT on chest wall/breast, axillary, supraclavicular and subclavian with/out internal mammary lymphatic regions (4) lack of other malignant diseases or poorly-controlled chronic diseases such as diabetes, CVD, liver or kidney or immune disease (5) capability to fill out questionnaires. Exclusion criteria included history or diagnosis of psychological or mental illness, personal major events within 6 months such as divorce, serious illness or death of immediate family members.

Data were collected at baseline (admission date ± 2 days) from the medical charts and fulfilled questionnaires of the Chinese versions of EORTC QLQ-C30 (C30) and QLQ-BR23 (BR23) and Hospital Anxiety and Depression Scale (HADS). This study was approved by the Research Ethics Committee of the Fourth Hospital of Hebei Medical University (FHHBU #2015-166). All participants have been provided with the written informed consent.

Questionnaires in brief and FCR measure

C30 consists of 30 item questions (Q). Its 6th Q (C30-Q6) to 28th Q (C30-Q28) asks about how often the patient had a specific symptom 'in the past week' with four choices of 'no', 'a little', 'some', 'very much' provided. Under the study protocol, the C30-Q9 (i.e. "have you ever had pain?"), C30-Q11 (i.e. "have you ever felt poor sleep?"), and C30-Q22 (i.e. "have you ever felt worried about anything") were the data source of pain, sleep disturbance, and general worry, respectively.

BR23 consists of 23 item Qs related to BC. Except that its three items (BR23-Q14, BR23-Q15 and BR23-Q16) are about sexual life quality 'in the past four weeks', others ask about the frequency of one specific event occurred 'in the past week' with the same four choices provided as C30. Under the study protocol, the BR23-Q13 (i.e. "have you been worried about your future health (about tumor recurrence or progression)?") was defined as the data source of FCR severity. Of note, we deliberately inserted a few Chinese words in the parentheses of BR23-Q13 to point out its different content from the C30-Q22.

HADS has 7-item Qs for each subscale of anxiety and depression. Each item has a 4-point Likert scale (scored from 0 to 3 indicating the distress increases). Except that total score was calculated by adding up the item scores, three levels of "normal", "borderline", and "abnormal" of anxiety and depression severities were also classified for each subscale by using the standard cutoff values of 0 - 7, 8 - 10, and 11 - 21, respectively. Of note, the Chinese version of HADS in this study had demonstrated the excellent internal consistency with Cronbach α value of 0.87 for the anxiety subscale and 0.80 for the depression subscale.

QoL functioning scores were calculated by using the scoring rule and standard formula on C30 and BR23 published by EORTC.

Statistical methods

Continuous and categorical variables were analyzed by using descriptive statistics. Chi-square and Kruskal-Wallis analysis of variance were used for comparison. Independent relationships between FCR severity and dependent variables were estimated by multivariate ordinal logistic regression models. Odds Ratio (OR) and its 95% confidence interval (CI) and p value were reported. Two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed with SAS 9.4.

Results

Baseline characteristics

A total of 463 women were enrolled and analyzed (Table 1). There was a fair agreement between the general worry (C30-Q22) and FCR with the weighted kappa coefficient as 0.40 (95%CI 0.33- 0.46, $p < 0.0001$).

1.1. Relations of FCR with anxiety and depression

Table 2 shows that there were significant relationships between anxiety and depression scores with FCR, pain, and sleep disturbance (all $p < 0.001$). As the FCR severity went up, the four medians of anxiety and scores seemed to be one-dimensional (Figure 1A, 1B; both $p < 0.001$ at linear regression).

Table 3 shows that there were also significant relationships between anxiety and depression levels with FCR, pain and sleep disturbance ($p < 0.001$ or $p = 0.014$). As the FCR severity went up, the 'abnormal' patient proportions on anxiety were 0%, 3.4%, 12.5%, 26.5%, and on depression were 2.2%, 3.4%, 5.4%, and 17.7%, respectively.

1.2. Ordinal logistic regression analysis

Three-levels of anxiety and depression - 'normal', 'borderline' and 'abnormal' - as the dependent variables had been validated to fit the ordinal logistic regression models by holding the assumption of proportional odds for the FCR and final covariates. Table 4 shows that compared with "no", other three higher FCR severities were associated independently with one level increase of anxiety with OR (p) as 1.983 (0.076), 4.291 (0.001), 8.282 (<0.001), and with one level increase of depression with OR (p) as 1.903 (0.062), 2.262 (0.065), and 4.205 (0.004), respectively. Figure 1C, 1D indicated that both relationships appeared to be linear (both $p < 0.001$ at linear regression).

Of note, age, TNM stage, and education were not independently associated with anxiety and depression levels (all $p > 0.05$, data not shown). Differently from pain, sleep disturbances at levels of "some" (OR 2.476, $p = 0.021$) and "very much" (OR 2.947, $p = 0.043$) had independent relationships with one level increase of anxiety, and at level of "very much" (OR 2.861, $p = 0.049$) had relationship with one level increase of depression.

1.3. FCR associated with most QoL measures

There were also strong statistical correlations between FCR and most QoL functioning scores (data not shown). Chi-square and p values for each QoL functioning (F) analyzed were as follows: physical F. 29.5 and $p < 0.001$, role F. 46.9 and $p < 0.001$, emotional F. 133.9 and $p < 0.001$,

cognitive F. 70.4 and $p < 0.001$, social F. 88.1 and $p < 0.001$, global health F. 66.8 and $p < 0.001$, body image F. 185.6 and $p < 0.001$, sexual F. 4.6 and $p = 0.205$, sexual enjoyment F. 0.8 and $p = 0.858$.

Discussion

This study showed that more than 70% of Chinese BC patients admitted for RT had reported having some FCR and over 7% reported FCR at level of “*very much*” in the last week. FCR severity was found to be linearly associated with score and level of anxiety and depression. FCR was also found to be negatively linked to most of their QoL scores. These results have suggested that among Chinese BC patients, FCR is prevalent and a single-item question for FCR assessment could be a valid surrogate tool in screening their distress.

FCR is a bio-psychosocial presentation with numerous factors involved dynamically [3,9]. Most studies have concluded that FCR is independently associated with younger age, recent diagnosis, feeling sad, severe side effects, poorly-controlled pain, chemotherapy, and RT [3, 6 - 8, 14, 15]. There have been few studies on FCR which mainly targeted on Chinese BC patients [11, 16]. Through analyzing 174 Chinese BC patients at 8-week postsurgery, Ng et al. found that the patient proportions under the nonclinical, subclinical, and clinical FCR category were 54.3%, 31.2% and 14.5%, respectively [16]. In that study, the Chinese version of Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF) had been used and demonstrated a strong internal consistency with Cronbach $\alpha = 0.87$ [16]. The FCRI-SF, which has 9 items and each item is on a 5-point Likert scale (0=“*not at all*”; 4 = “*a great deal or all the time*”), is often used to screen for clinical levels of FCR. However, the cut-off values of FCRI-SF have been controversial because of inadequate sensitivity and specificity statistics [17, 18]. In this study, we did not use the FCRI-SF as the research focused on how the FCR changes over time.

It was one unexpected finding from this study - there were linear relationships between the FCR and anxiety and depression in Chinese BC patients. FCR is clearly regarded as one of leading factors to cause distress in BC or other cancer survivors [6, 19 - 20]. As there are still some challenges of using the NCCN Distress Thermometer (DT, a single digit of 0 (*none*) to 10 (*the highest*) score in the last week) in BC patients [21 - 22], we hereby hypothesized that FCR could be one single-item surrogate tool for screening distress in Chinese population. In fact, we are constantly confronted with difficulties in using DT at our institution as follows – the current different translations of “*distress*” in Chinese often get the patient confused about its contents; many low-educated Chinese patients have difficulty in filling out the DT questionnaire independently in writing; patients often have one arbitrary choice of one digit in the middle range of DT score like 5 to 7; many clinical departments could not provide one quite or private setting for effective communication in a short time. In this study, we took advantage of using a single-item question of QLQ-BR23 on assessing FCR and found that the patient’s response to FCR held linear relationships with distress. Given the effectiveness of interventions on FCR established in RCTs, it is of great interest for further study to determine the validity of using such a single-item question for screening and treatment in this population [23 - 25].

FCR was also found to be linked to many domains of QoL in Chinese BC patients just as in other populations [19, 26]. However, there are conflicting results of FCR relationships with QoL domains from one systematical review of 11 studies on different cancer survivors.³ It seemed that lower FCR predicted higher emotional or mental functioning but not physical functioning and social functioning [3]. However, Ashing et al. prospectively studied 137 Asian American BC survivors over one year (208 participants at the baseline) and found that greater FCR at baseline predicted poorer outcomes one-year later including lower physical, emotional and functional well-beings, and QoL specific to BC (all $p < 0.01$) [27]. Interestingly, the multiple regression analyses showed that Chinese women ($n = 70$) reported lower FCR both at baseline ($p = 0.004$) and after 1-year ($p = 0.012$), compared to other Asian women [27]. In that study, FCR was examined with one item, “*I worry about my cancer coming back or spreading*” from 0 (*not at all*) to 4 (*very much*), which was included in the Functional Assessment of Cancer Treatment for BC (FACT-B, version 4) as one additional item. Therefore, it become more intriguing to validate a single-item question on screening FCR, examine how FCR emerges, develops and associates differently with QoL in Chinese BC patients.

2.1. Study limitations

The strengths of this study included (1) FCR before RT as baseline data given the stabilized impacts from surgery and chemotherapy (2) adjustment of confounding variables including age, disease stage, surgery type, pain, and sleep disturbance in analysis (3) simple and clear assessment of FCR by using a single question. The study limitations included (1) FCRI-SF was not used for comparison (2) the cross-sectional data could not reflect the FCR change and determine the causal relationships of FCR with dependent variables (3) we could not generalize this study finding to Chinese BC patients in other regions for certain.

2.2. Clinical implications

To our best knowledge, this is one of the largest prospective studies to investigate FCR and its associations with psychological distress and QoL in Chinese BC patients in recent years. The study finding have indicated that the clinical importance of FCR in this population, and future studies should attend to its major factors and effective interventions.

Conclusions

In summary, as high as 71% of Chinese breast cancer patients reported FCR in the past week before RT. FCR severity was independently and almost linearly associated with anxiety, depression and lower QoL. Given the limitations of DT use, it appears that FCR could be used as a single surrogate tool for distress screening in this population.

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

Not applicable

Authors' contributions

Z Li supervised this study. Z Li, Y Li and Y Liu were principally responsible for study design, analysis and manuscript writing. J Zhang, X Ji, Z Zhao, X Duan, W Geng and J Yin were responsible for data collection, quality control and partially contributed to the analysis. Y Li contributed significantly to discussion and manuscript revision.

Ethics approval

This study was approved by the Research Ethics Committee of the Fourth Hospital of Hebei Medical University (FHHBU #2015-166) in China.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

All authors read and approved the final manuscript for publication.

Conflicts of interest

The funding source was not involved in any stage of the research process. The authors declared that they have no competing interests.

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Tables

Table 1. Baseline characteristics (N = 463)

Variable	Class	n	Mean ±std	Percent	Median (Q1 – Q3)	Minimum – Maximum
Age, years		463	47.2±9.56	100	48(42.0 – 54.0)	19 - 89
BMI, kg/m ²		463	25.9±3.33	100	25.9(23.7 – 28.0)	14.8 - 39.1
Breast with tumor	left	234		50.5		
	right	229		49.5		
TNM stage	I	51		11.0		
	II	177		38.2		
	III	221		47.7		
	IV	14		3.0		
Surgery	BCS	77		16.6		
mastectomy		386		83.4		
ALND	no	62		13.4		
	yes	401		86.6		
Education	illiteracy	15		3.2		
	elementary	73		15.8		
	junior high school	203		43.8		
	high school	101		21.8		
	college & above	71		15.3		
FCR severity	'no'	136		29.4		
	'a little bit'	237		51.2		
	'some'	56		12.1		
	'very much'	34		7.3		
HAD score	anxiety	451	4.9±3.35		5.0(2.0 – 7.0)	0.0 – 20.0
	depression	454	4.5±3.23		4.0(2.0 – 6.0)	0.0 – 18.0
Anxiety level	'normal'	373		80.6		
	'borderline'	54		11.7		
	'abnormal'	24		5.2		
	missing	12		2.6		
Depression level	'none/mild'	373		80.6		
	'moderate'	61		13.2		
	'severe'	20		4.3		
	missing	9		1.9		
Pain ^a	'no'	173		37.4		
	'a little bit'	239		51.6		
	'some'	49		10.6		
	'very much'	2		0.0		
Sleep disturbance ^a	'no'	192		41.5		
	'a little bit'	182		39.3		
	'some'	65		14.0		

Note: All values reported as N (%) unless otherwise noted.

Abbreviations: std, standard deviation; Q1, first quartile; Q3, third quartile; BMI, body mass index; ALND, axillary lymph node dissection; BCS, breast-conserving surgery; HADS, Hospital Anxiety and Depression Scale.

^a From the EORTC QLQ-C30 questionnaire item #9 and #11.

Table 2. Relationships of anxiety and depression scores with pain, sleep disturbance and FCR ($N = 463$)

Variable	class	Anxiety score ($N_1=451$)					Depression score ($N_2=454$)				
		n	mean± std	median	<i>F</i>	<i>p</i>	n	mean± std	median	<i>F</i>	<i>p</i>
Pain ^a	'no'	166	3.69±2.99	3.5	43.5	<0.001	170	3.53±3.02	3.0	35.9	<0.001
	'a little bit'	234	5.35±3.17	6.0			233	4.80±3.15	5.0		
	'some & very much'	51	6.86±3.85	6.0			51	6.25±3.34	6.0		
Sleep ^a disturbance	'no'	186	3.98±2.92	4.0	35.3	<0.001	189	3.72±2.83	3.0	29.9	<0.001
	'a little bit'	177	4.95±2.93	5.0			179	4.50±3.11	4.0		
	'some'	64	6.33±3.71	6.5			62	5.56±2.93	5.5		
	'very much'	24	8.00±5.03	7.5			24	7.67±4.89	6.5		
FCR	'no'	130	2.26±2.47	1.5	146.8	<0.001	135	3.03±2.88	2.0	70.1	<0.001
	'a little bit'	231	5.34±2.59	5.0			229	4.54±2.92	4.0		
	'some'	56	7.16±3.17	7.0			56	5.96±3.09	6.0		
	'very much'	34	8.44±3.96	8.5			34	7.5±3.63	6.5		

Note: all *F* and *p* values were from the Kruskal-Wallis analysis of variance as anxiety and depression scores were not normally distributed.

Abbreviation: FCR, fear of cancer recurrence; N_1 or N_2 , number of patients with non-missing values; std, standard deviation.

^a From the EORTC QLQ-C30 questionnaire item #9 and #11.

Table 3. Relationship of anxiety and depression levels with FCR, pain, and sleep disturbance

Variable	class	Anxiety level (n, %)				<i>p</i>	Depression level (n, %)				<i>p</i>
		normal	borderline	abnormal	missing		normal	borderline	abnormal	missing	
Pain ^a	'no'	152 87.9%	11 6.4%	3 1.7%	7 4.1%	<.001	151 87.3%	13 7.5%	6 3.5%	3 1.7%	0.014
	'a little bit'	189 79.1%	33 13.8%	12 5.0%	5 2.1%		188 78.7%	35 14.6%	10 4.2%	6 2.5%	
	'some & very much'	32 62.8%	10 19.6%	9 17.7%	0 0.0%		34 66.7%	13 25.5%	4 7.8%	0 0.0%	
Sleep ^a disturbance	'no'	169 88.0%	12 6.3%	5 2.6%	6 3.1%	<.001	168 87.5%	16 8.3%	5 2.6%	3 1.6%	<.001
	'a little bit'	148 81.3%	26 14.3%	3 1.7%	5 2.8%		144 79.1%	29 15.9%	6 3.3%	3 1.7%	
	'some'	44 67.7%	11 16.9%	9 13.9%	1 1.5%		47 72.3%	13 20.0%	2 3.1%	3 4.6%	
	'very much'	12 50.0%	5 20.8%	7 29.2%	0 0.0%		14 58.3%	3 12.5%	7 29.2%	0 0.0%	
FCR	'no'	126 92.7%	4 2.9%	0 0.0%	6 4.4%	<.001	122 89.7%	10 7.4%	3 2.2%	1 0.7%	<.001
	'a little bit'	197 83.1%	26 11.0%	8 3.4%	6 2.5%		191 80.6%	30 12.7%	8 3.4%	8 3.4%	
	'some'	36 64.3%	13 23.2%	7 12.5%	0 0.0%		41 73.2%	12 21.4%	3 5.4%	0 0.0%	
	'very much'	14 41.2%	11 32.4%	9 26.5%	0 0.0%		19 55.9%	9 26.5%	6 17.7%	0 0.0%	

Note: *p* values reported as the Chi-square test was conducted without the 'missing' category.

Abbreviations: FCR, fear of cancer recurrence.

^a From the EORTC QLQ-C30 questionnaire item #9 and #11.

Table 4. Ordinal logistic regression analysis

Outcome	Variable	class	Univariate			Multivariate		
			OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Anxiety	Pain ^a	'no'	1.000		<i>ref.</i>	1.000		<i>ref.</i>
		'a little bit'	1.841	(1.064 - 3.185)	0.029	1.434	(0.780 - 2.638)	0.246
		'some & very much'	4.081	(1.994 - 8.351)	0.000	1.894	(0.828 - 4.332)	0.131
	Sleep ^a	'no'	1.000			1.000		<i>ref.</i>
		disturbance 'a little bit'	1.610	(0.910 - 2.849)	0.102	1.270	(0.677 - 2.382)	0.457
		'some'	3.447	(1.767 - 6.725)	0.000	2.476	(1.147 - 5.346)	0.021
		'very much'	7.092	(2.971 - 16.931)	<.001	2.947	(1.035 - 8.390)	0.043
	FCR	'no'	1.000		<i>ref.</i>	1.000		<i>ref.</i>
		'a little bit'	2.482	(1.209 - 5.095)	0.013	1.983	(0.931 - 4.222)	0.076
'some'		6.406	(2.783 - 14.747)	<.001	4.291	(1.770 - 10.400)	0.001	
'very much'		14.693	(6.004 - 35.956)	<.001	8.282	(3.053 - 22.469)	<.001	
Depression	Pain ^a	'no'	1.000			1.000		<i>ref.</i>
		'a little bit'	1.831	(1.067 - 3.141)	0.028	1.555	(0.868 - 2.784)	0.138
		'some & very much'	3.148	(1.517 - 6.535)	0.002	1.757	(0.763 - 4.045)	0.185
	Sleep ^a	'no'	1.000		<i>ref.</i>	1.000		<i>ref.</i>
		disturbance 'a little bit'	1.800	(1.032 - 3.138)	0.038	1.475	(0.812 - 2.680)	0.202
		'some'	2.634	(1.326 - 5.235)	0.006	1.989	(0.920 - 4.298)	0.080
		'very much'	5.835	(2.420 - 14.069)	<.001	2.861	(1.005 - 8.140)	0.049
	FCR	'no'	1.000		<i>ref.</i>	1.000		<i>ref.</i>
		'a little bit'	2.131	(1.126 - 4.033)	0.020	1.903	(0.969 - 3.737)	0.062
'some'		3.028	(1.346 - 6.812)	0.007	2.262	(0.950 - 5.388)	0.065	
'very much'		6.677	(2.834 - 15.732)	<.001	4.205	(1.578 - 11.208)	0.004	

Note: Age, BMI, education, tumor breast, TNM stage, surgery, ALND, pain, and sleep disturbance were included as the final covariate in multivariate analysis on the basis of univariate analysis results and literature review.

Abbreviation: FCR, fear of cancer recurrence; OR, Odd Ratio; CI, confidence interval; ref., reference.

^a From the EORTC QLQ-C30 questionnaire item #9 and #11.

Figures

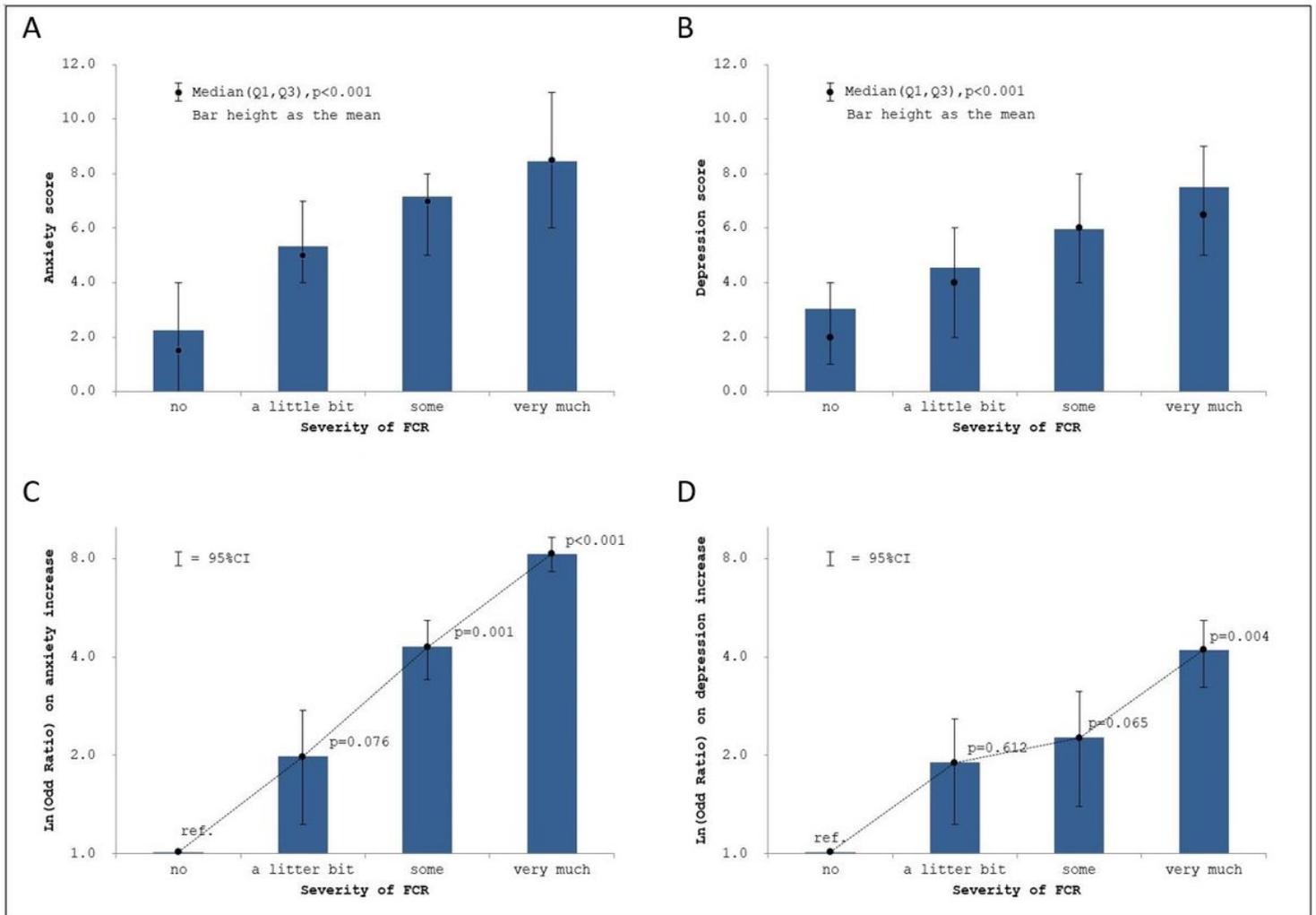


Figure 1

Relationships of severity of FCR with anxiety and depression