

# Symptom burden in advanced breast cancer patients and its association between death anxiety and psychological distress

Zhongge Su\*, Yuhe Zhou\*, Xinkun Han, Ying Pang, Shuangzhi He, Lili Tang

Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Psycho-Oncology, Peking University Cancer Hospital & Institute, Beijing 100142, China

\*These authors contributed equally to this work.

Correspondence to: Lili Tang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Psycho-Oncology, Peking University Cancer Hospital & Institute, Beijing 100142, China. Email: tanglili\_cpos@126.com.

## Abstract

**Objective:** Recent research has documented psychological distress in advanced breast cancer (ABC) patients, but few studies have examined how death anxiety is affected by the symptom burden. Therefore, this study aims to explore the association among symptom burden, death anxiety and psychological distress (depression and anxiety) in ABC patients.

**Methods:** This cross-sectional study used the Death and Dying Anxiety Scale (DADDS), 9-item Patient Health Questionnaire (PHQ-9), General Anxiety Disorder-7 (GAD-7) and MD Anderson Symptom Inventory (MDASI) to assess death anxiety, depression, anxiety, and symptom burden, respectively. Bias-corrected bootstrapping methods were used to estimate indirect effects and 95% confidence intervals.

**Results:** Two hundred ABC patients completed the questionnaires. All of the respondents were females, with a mean age of  $50 \pm 10$  years. Initial correlation analyses revealed significant associations of death anxiety with depression ( $r=0.57$ ,  $P<0.001$ ), anxiety ( $r=0.60$ ,  $P<0.001$ ) and symptom burden ( $r=0.43$ ,  $P<0.001$ ). Moreover, depression ( $r=0.53$ ,  $P<0.001$ ) and anxiety ( $r=0.45$ ,  $P<0.001$ ) were significantly correlated with symptom burden. An analysis using Hayes' PROCESS macro revealed the partial effecting role of death anxiety in the relationship between depression and symptom burden, and between anxiety and symptom burden (contributions to the total effect of 0.247 and 0.469, respectively).

**Conclusions:** This study provides insight into the relationship between death anxiety and symptom burden. The results suggest that interventions addressing death anxiety may be more effective for alleviating the depression and anxiety experienced by ABC patients with a symptom burden.

**Keywords:** Advanced breast cancer; death anxiety; psychological distress; symptom burden; depression; anxiety

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## Introduction

In China, breast cancer is the most common cancer and the third leading cause of cancer-related deaths in women (1). The incidence and associated mortality of breast cancer have been continuously increasing over the past several years. The median age at diagnosis of breast cancer in Chinese women is approximately 50 years, which is around

10 years younger than that of European and American patients (2). Nearly one-third of patients with early-stage breast cancer will develop advanced breast cancer (ABC) (3), as such, China has a large ABC patient population.

Some side effects inevitably increase in prevalence in parallel with longer survival of ABC patients (4). The burden of disease and side effects are both more severe in ABC than early-stage breast cancer patients. Although

many ABC survivors are psychologically well-adjusted, residual physical and psychological symptoms are nonetheless common. Physical symptoms include pain, fatigue and insomnia, among others (5). Regarding psychological symptoms, approximately 84% of ABCs were found to have clinical anxiety, and 25% had clinical depression (6,7). Psychological conditions, such as depression and anxiety, increase the physical symptom burden (8) of breast cancer patients, and vice versa (9). However, few studies have examined the underlying mechanism in detail.

The most fundamental type of anxiety is death anxiety (10). ABC is a major trauma for many females, and typically causes psychological and social issues, including anxiety and, in particular, death anxiety (i.e., the perceived threat of death in everyday life). The North American Nursing Diagnosis Association International (NANDA-I) defines death anxiety as a “vague uneasy feeling of discomfort or dread generated by perceptions of a real or imagined threat to one’s existence” (11). According to previous studies (12,13), the presence of depression and anxiety predicts death anxiety; moreover, death anxiety is associated with physical suffering. However, few studies have assessed the impact of death anxiety on the relationship between symptom burden and psychological distress. Considering the high prevalence of death anxiety, and its correlations with physical and psychological symptoms, we studied psychological conditions, such as depression and anxiety, in ABC patients, and examined how death anxiety is affected by symptom burden. We hypothesized that death anxiety affects the relationship between symptom burden and psychological distress.

## Materials and methods

### Participants and procedures

A convenience sample was recruited from April 2019 to December 2019 at Peking University Cancer Hospital. The eligibility criteria were as follows: 1) Adult (aged  $\geq 18$  years) female patients; 2) diagnosed with ABC; 3) able to read and speak Chinese fluently; and 4) no cognitive impairment according to medical records and attending oncologist. A brief interview was held to assess patients according to the following exclusion criteria: 1) Major communication difficulties; 2) inability to commit to the investigation (i.e., too ill to participate); or 3) refusal to participate.

All participants in this cross-sectional study were also

enrolled in the single-center Managing Cancer and Living Meaningfully (CALM) clinical trial, which examined the efficacy of a brief psychotherapy intervention for Chinese ABC patients (14). The study was approved by the Institutional Review Board of Peking University Cancer Hospital on April 15, 2019 (2019YJZ23).

The participants were fully informed about the purpose and process of the study before signing the consent form. The questionnaires were anonymized based on the assignment of numbers. A researcher collected the questionnaires once they had been completed, and conducted an audit to ensure that there were no missing data.

### Measures

#### Demographic and clinical characteristics

The participants completed a demographic survey concerned with age, marital status, educational level, employment status, religion, whether they had children, residential area (urban or rural), economic status and experiences associated with death that could induce death anxiety (e.g. death-related events) (15,16). Clinical data, including the date of breast cancer diagnosis, metastasis site and type(s) of treatment, were collected via medical record review.

#### Symptom burden

Symptom burden was assessed with the Chinese version of the MD Anderson Symptom Inventory (MDASI-C) (17). The MDASI (18) was introduced in 2000 to assess symptom burden and interference with daily life in cancer patients. It comprises 19 items, including 13 pertaining to core symptom severity (pain, fatigue, nausea, sleep disturbance, distress, shortness of breath, difficulty remembering things, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness) and 6 assessing symptom interference (general activity, mood, work, relationships with other people, walking, and enjoyment of life). The MDASI-C uses an 11-point response scale (range: 0–10), where higher scores indicate a more severe symptom burden or interference. The internal consistency (reliability) of the MDASI-C is high (range: 0.83–0.90). A score of 5–6 is taken to indicate moderate symptoms, while scores of  $\geq 7$  indicate severe symptoms (17).

#### Death anxiety

The Death and Dying Anxiety Scale (DADDS) (19) was

used to measure death anxiety. The DADDS is suitable for assessing patients with advanced or metastatic cancer, and is specifically used to evaluate the death anxiety of cancer patients. The DADDS quantifies regret regarding lost time and opportunities, fear of the death process, and worry about the impact of death on relatives. It comprises 15 items, each rated on a scale ranging from 0 to 5; thus, total scores range from 0 to 75. Higher scores indicate more severe death anxiety. In our study, the Cronbach's  $\alpha$  was 0.927.

### Depression

Depression was assessed with the 9-item Patient Health Questionnaire (PHQ-9) (20). The PHQ-9 is a self-report depression screening scale used worldwide to assess advanced cancer patients (21). Depression is rated based on nine Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria; the answer options range from 0 (not at all) to 3 (nearly every day), and total scores range between 0 and 27. The Chinese version of the PHQ-9 (22) has good reliability and validity, with a score of 10 being the optimal cutoff for diagnosing depression. In our study, the Cronbach's  $\alpha$  was 0.812.

### Anxiety

Anxiety was assessed with the General Anxiety Disorder-7 (GAD-7) (23). The GAD-7 is a 7-item patient self-report scale based on the diagnostic criteria of the DSM-IV. Each item is scored from 0 (not at all) to 3 (nearly every day), and total scores thus range between 0 and 21. The Chinese version of the GAD-7 (24) has good reliability and validity, with a score of 20 being the optimal cutoff for diagnosing anxiety. In our study, the Cronbach's  $\alpha$  was 0.904.

### Statistical analysis

Because of the exploratory nature of the study, no formal sample size calculation was performed. To characterize the sample, descriptive statistics were generated (median and interquartile range for continuous variables and absolute numbers and percentages for categorical variables). Furthermore, the Mann-Whitney U test was used to analyze depression, anxiety, death anxiety, and symptom burden according to patient characteristics. And the multivariable analysis on the anxiety and depression was examined by logistic regression analysis. The Pearson correlation coefficient and Spearman's rho were utilized to examine the relationships of demographic, clinical and

psychological characteristics with death anxiety, and depressive and anxiety symptoms. To enhance clinical interpretability, we used cutoff points to distinguish between patients with moderate-to-severe and those with severe symptoms. Next, analyses were performed to determine whether death anxiety affects the relationship between symptom burden and psychological distress. The effecting role of death anxiety between symptom burden and depression/anxiety was evaluated by Hayes' PROCESS. PROCESS (25) estimates the indirect effect and bias-corrected confidence intervals (CIs) using bootstrapping. Death anxiety as the possible effector was used in two analyses, one with depression as the dependent variable (DV), and one with anxiety as DV. The model 4 of PROCESS was used with 5,000 bootstrapping samples for all analyses. Statistical analysis was carried out using IBM SPSS statistical (Version 20.0; IBM Corp., New York, USA) and AMOS software (Version 20.0; IBM Corp., New York, USA).  $P < 0.05$  were taken to indicate statistical significance.

## Results

### Patient characteristics

A total of 1,653 patients were screened between April 2019 and December 2019. Of the 347 eligible patients approached, 253 provided informed consent; 42 of those patients refused to complete the study questionnaire because of the nature of the topic (i.e., death), and 11 were unable to complete the questionnaire because of poor physical status. Thus, 200 patients were included in the final analysis (response rate = 79.1%).

There were no differences in sociodemographic or clinical characteristics between respondents and nonrespondents. The mean age of the 200 participants was 50 years. There were 27 (13.5%) participants with moderate-to-severe death anxiety (DADDS score  $\geq 45$ ), 48 (24.0%) with depression (PHQ-9 score  $\geq 10$ ), and 31 (15.5%) with anxiety (GAD-7 score  $\geq 10$ ). The other characteristics are shown in *Table 1*.

### Tested variables according to patient characteristics

The results of the Mann-Whitney U test used to analyze depression, anxiety, death anxiety and symptom burden according to patient characteristics are shown in *Table 2*. Patients with religious beliefs ( $Z = -2.04$ ,  $P = 0.042$ ), and those who had a financial burden ( $Z = -2.16$ ,  $P = 0.031$ ) or

**Table 1** Patients' characteristics (N=200)

Characteristics	n (%)
Age (year)	
$\bar{x}\pm s$	50±10
IQR	43–57
Marital status	
Married	182 (91.0)
Not married	18 (9.0)
Education	
High school and below	124 (62.0)
College school and above	76 (38.0)
Working state	
Employed	119 (59.5)
Unemployed or retired	81 (40.5)
Religion	
Yes	41 (20.5)
No	159 (79.5)
Having children	
Yes	188 (94.0)
No	12 (6.0)
Residential location	
Urban area	159 (79.5)
Rural area	41 (20.5)
Income per month (CNY)	
<7,000	159 (79.5)
≥7,000	41 (20.5)
Financial strain	
Yes	144 (72.0)
No	56 (28.0)
Separation and death in 5 years	
Yes	80 (40.0)
No	120 (60.0)
Life-threatening event in 5 years	
Yes	17 (8.5)
No	183 (91.5)
Metastasis	
Organs	167 (83.5)
Lymph nodes or nearby tissues	33 (16.5)
Surgery	
Yes	164 (82.0)
No	36 (18.0)
Radiotherapy	
Yes	108 (54.0)
No	92 (46.0)

**Table 1** (continued)

**Table 1** (continued)

Characteristics	n (%)
Chemotherapy	
Yes	192 (96.0)
No	8 (4.0)
Endocrinotherapy	
Yes	133 (66.5)
No	67 (33.5)
Comorbidity	
Yes	40 (20.0)
No	160 (80.0)
Illness duration in months	
$\bar{x}\pm s$	75.7±56.8
IQR	35–104
Death anxiety (DADDS)	
$\bar{x}\pm s$	20.6±17.5
IQR	7.0–30.5
None to little (<15)	94 (47.0)
Little to mild (15–29)	54 (27.0)
Mild to moderate (30–44)	25 (12.5)
Moderate to great (45–59)	21 (10.5)
Great to extreme (60–75)	6 (3.0)
Symptom burden (MDASI)	
$\bar{x}\pm s$	1.3±1.8
IQR	0–2
Depression (PHQ-9)	
$\bar{x}\pm s$	4.6±4.9
IQR	1–6
Anxiety (GAD-7)	
$\bar{x}\pm s$	6.7±5.1
IQR	3–9

IQR, interquartile range; CNY, Chinese Yuan; DADDS, Death and Dying Anxiety Scale; MDASI, MD Anderson Symptom Inventory; PHQ-9, 9-item Patient Health Questionnaire; GAD-7, General Anxiety Disorder-7.

had undergone radiotherapy ( $Z=-3.37$ ,  $P<0.001$ ), had higher depression scores.

Anxiety scores were higher in patients with a college education or above ( $Z=-2.43$ ,  $P=0.015$ ), as well as in those who were still working ( $Z=-1.96$ ,  $P=0.050$ ), had a relatively high income ( $Z=-1.99$ ,  $P=0.047$ ), experienced life-threatening events within the last 5 years ( $Z=-2.09$ ,  $P=0.037$ ), had undergone surgery ( $Z=-2.25$ ,  $P=0.025$ ) or radiotherapy ( $Z=-1.98$ ,  $P=0.048$ ), or had comorbidities ( $Z=-2.04$ ,  $P=0.041$ ).

Scores on the death anxiety scale were higher in patients

**Table 2** Difference in depression, anxiety, death anxiety and symptom burden between patient characteristics (N=200)

Characteristics	Depression		Anxiety		Death anxiety		Symptom burden	
	Median (IQR)	Z	Median (IQR)	Z	Median (IQR)	Z	Median (IQR)	Z
Marital status		1.11		-0.68		-0.86		-0.18
Married	6.0 (3.0–9.0)		3.0 (1.0–6.8)		16.0 (7.0–31.8)		1.0 (0–2.0)	
Not married	4.5 (3.0–8.8)		2.0 (1.0–5.8)		13.0 (7.5–22.0)		1.0 (0–1.0)	
Education		1.33		-2.43*		1.14		-0.71
High school and below	6.0 (3.0–9.0)		2.0 (1.0–6.0)		14.5 (7.0–29.3)		1.0 (0–2.0)	
College school and above	6.0 (3.8–9.3)		4.0 (2.0–7.0)		16.5 (8.8–32.3)		2.0 (0–2.0)	
Working state		-0.95		-1.96*		-2.33*		-0.33
Employed	6.0 (3.0–10.0)		3.0 (1.0–8.0)		18.0 (8.5–35.0)		1.0 (0–2.0)	
Unemployed or retired	6.0 (3.0–8.0)		2.0 (1.0–6.0)		12.0 (6.0–21.0)		2.0 (0–2.0)	
Religion		-2.04*		1.26		1.43		-0.80
Yes	8.0 (4.0–11.0)		4.0 (2.0–7.0)		17.0 (9.0–38.0)		2.0 (0–2.0)	
No	6.0 (3.0–9.0)		3.0 (1.0–6.0)		15.0 (7.0–29.0)		1.0 (0–2.0)	
Having children		-0.75		-1.25		1.91		1.04
Yes	6.0 (3.0–9.0)		3.0 (1.0–6.0)		15.0 (7.0–30.0)		1.0 (0–2.0)	
No	7.5 (1.5–16.0)		4.5 (1.3–12.3)		20.0 (10.5–51.8)		1.5 (0–4.0)	
Residential location		-0.21		-0.21		-0.32		-0.47
Urban area	6.0 (3.0–9.0)		3.0 (1.0–6.0)		16.0 (7.0–31.0)		1.0 (0–2.0)	
Rural area	6.0 (3.0–10.0)		2.0 (1.0–6.5)		14.0 (7.0–26.5)		1.0 (0–2.0)	
Income per month (CNY)		-0.65		-1.99*		1.59		-0.05
<7,000	6.0 (3.0–9.0)		2.0 (1.0–6.0)		15.0 (7.0–27.0)		1.0 (0–2.0)	
≥7,000	6.0 (3.5–10.0)		5.0 (2.0–9.5)		23.0 (8.0–37.0)		2.0 (0–2.8)	
Financial strain		-2.16*		-1.87		1.07		-2.28*
Yes	6.0 (3.0–10.0)		3.0 (1.0–7.0)		16.0 (8.0–32.0)		2.0 (0–2.0)	
No	5.0 (2.0–7.8)		2.0 (1.0–5.0)		14.5 (3.3–29.0)		1.0 (0–1.0)	
Separation and death in 5 years		-0.23		-0.92		-0.50		-1.34
Yes	6.0 (3.0–10.0)		3.0 (1.0–7.0)		16.0 (7.0–31.5)		1.0 (0–2.0)	
No	6.0 (3.0–9.0)		3.0 (1.0–6.0)		15.0 (7.0–30.8)		0 (0–2.0)	
Life-threatening events in 5 years		1.18		-2.09*		-3.15**		-2.02*
Yes	6.0 (5.0–13.5)		6.0 (2.0–11.0)		39.0 (16.5–54.5)		1.0 (0–5.0)	
No	6.0 (3.0–9.0)		3.0 (1.0–6.0)		15.0 (7.0–29.0)		0.5 (0–2.0)	
Metastasis		-0.03		-1.26		1.56		-0.13
Organs	6.0 (3.0–9.0)		3.0 (1.0–6.0)		15.0 (7.0–29.0)		1.0 (0–2.0)	
Lymph nodes or nearby tissues	6.0 (3.0–9.5)		3.0 (1.0–10.0)		21.0 (7.5–42.5)		0 (0–2.0)	
Surgery		1.24		-2.25*		-0.33		-0.61
Yes	6.0 (3.0–10.0)		3.0 (1.0–7.0)		15.5 (7.0–30.0)		1.0 (0–2.0)	
No	5.5 (1.3–8.0)		2.0 (0–5.0)		16.0 (5.5–41.8)		0 (0–2.0)	
Radiotherapy		-3.37***		-1.98*		1.22		-3.05**
Yes	6.5 (4.0–11.0)		3.0 (1.0–7.0)		17.0 (8.0–30.8)		1.0 (0–2.0)	
No	4.5 (2.0–8.0)		2.0 (1.0–6.0)		14.5 (6.3–32.8)		0 (0–1.0)	

Table 2 (continued)

Table 2 (continued)

Characteristics	Depression		Anxiety		Death anxiety		Symptom burden	
	Median (IQR)	Z	Median (IQR)	Z	Median (IQR)	Z	Median (IQR)	Z
Chemotherapy		-0.94		-0.91		-0.40		-0.31
Yes	6.0 (3.0–9.0)		3.0 (1.0–6.8)		15.0 (7.0–31.0)		1.0 (0–2.0)	
No	5.5 (1.3–7.8)		2.0 (0.3–5.0)		19.0 (2.5–27.5)		1.0 (0–1.0)	
Endocrinotherapy		-0.49		-0.14		-0.51		-0.13
Yes	6.0 (3.0–9.0)		3.0 (1.0–6.0)		16.0 (7.0–29.5)		0.5 (0–2.0)	
No	6.0 (3.0–10.0)		3.0 (1.0–7.0)		15.0 (8.0–36.0)		1.0 (0–2.0)	
Comorbidity		-0.80		-2.04*		-2.39*		-0.60
Yes	6.0 (2.0–9.0)		2.0 (0.3–4.0)		10.5 (5.3–22.5)		2.0 (0–1.8)	
No	6.0 (3.0–9.0)		3.0 (1.0–7.0)		17.0 (8.0–33.5)		1.0 (0–2.0)	

CNY, Chinese Yuan; IQR, interquartile range; \*, P<0.05; \*\*, P<0.01; \*\*\*, P<0.001.

who were still working ( $Z=-2.33$ ,  $P=0.020$ ), had experienced life-threatening events within the last 5 years ( $Z=-3.15$ ,  $P=0.002$ ), or had comorbidities ( $Z=-2.39$ ,  $P=0.017$ ). Patients with a financial burden ( $Z=-2.28$ ,  $P=0.023$ ), as well as those who experienced life-threatening events within the last 5 years ( $Z=-2.02$ ,  $P=0.044$ ) or had undergone radiotherapy ( $Z=-3.05$ ,  $P=0.002$ ), experienced a greater symptom burden. The multivariable analysis shows that depression and anxiety are affected by patients' employment, religion and financial strain (Supplementary Table S1).

**Symptom burden and interference**

Table 3 (Figure 1) presents the median and interquartile range for symptom data, in decreasing order of severity. All symptoms except nausea and vomiting were reported to be moderate to severe by at least 10.0% of the patients. The seven most severe MDASI symptoms, in decreasing order of magnitude, were fatigue, difficulty remembering, disturbed sleep, pain, distress, dry mouth and sadness. More than 26.0% of the patients reported moderate-to-severe fatigue, difficulty remembering or disturbed sleep (score of  $\geq 5$  on the 0–10-point scale). Severe fatigue, difficulty remembering and disturbed sleep (score of  $\geq 7$ ) were reported by more than 10.5% of patients. Pain, distress and lack of appetite were reported to be severe by at least 7.0% of the patients.

**Effecting role of death anxiety in relationship between psychological distress and symptom burden**

Covariates were identified based on the results of the

Mann-Whitney U test of patient characteristics. As Table 4 indicates, after controlling for employment status, religion, financial strain, life-threatening events, radiotherapy and comorbidities, the results of partial correlation analyses showed significant associations of psychological distress and death anxiety with symptom burden. Moreover, death anxiety was significantly correlated with depression ( $r=0.57$ ,  $P<0.001$ ), anxiety ( $r=0.60$ ,  $P<0.001$ ) and symptom burden ( $r=0.43$ ,  $P<0.001$ ).

Depression ( $r=0.53$ ,  $P<0.001$ ) and anxiety ( $r=0.45$ ,  $P<0.001$ ) were both correlated with symptom burden. An indirect effect of depression on symptom burden (via death anxiety) was demonstrated by analysis using Hayes' PROCESS macro, thus supporting the hypothesis that death anxiety affects the relationship between symptom burden and psychological distress.

The results for specific parameters are shown in Table 5 and Figure 2. The bootstrapping method was used; the results of indirect effect show that death anxiety significantly affected the relationship between symptom burden and anxiety (95% CI=0.08–0.23,  $P<0.001$ ), and depression (95% CI=0.15–0.35,  $P<0.001$ ), respectively; all the results do not include zero. Therefore, death anxiety can be considered to a moderator between anxiety/depression and symptom burden; and the contribution of the effect to the total effect in these two cases was  $0.144/0.582=0.2474$  (24.74%) and  $0.230/0.490=0.4694$  (46.94%), respectively.

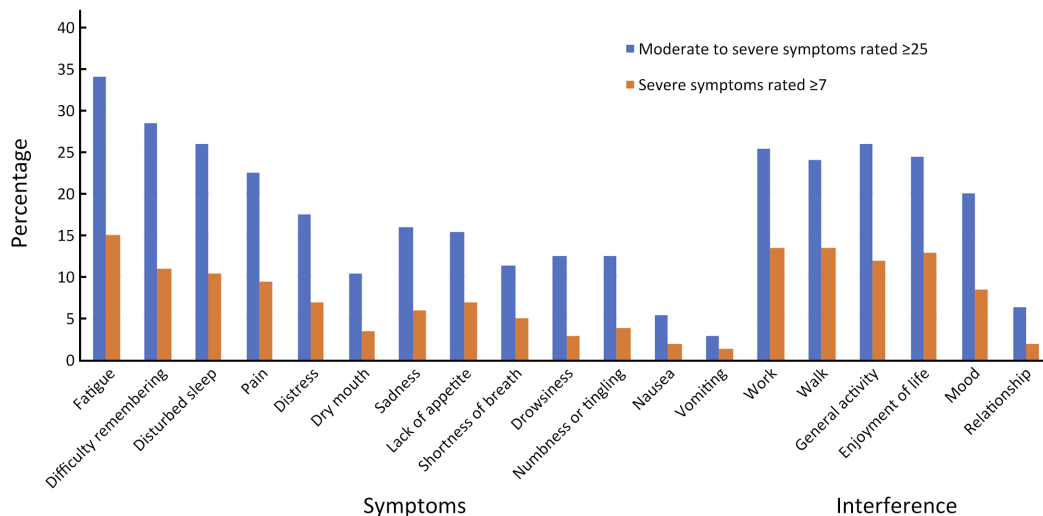
**Discussion**

To our knowledge, the current study is the first to examine

**Table 3** Descriptive statistics for symptoms and interference (N=200)

Variables	Scores [median (IQR)]	n (%)	
		Moderate to severe symptoms (rated $\geq 5$ )	Severe symptoms (rated $\geq 7$ )
<b>Symptom*</b>			
Fatigue	3 (1–5)	68 (34.0)	30 (15.0)
Difficulty remembering	2 (0–5)	57 (28.5)	22 (11.0)
Disturbed sleep	2 (0–5)	52 (26.0)	21 (10.5)
Pain	1 (0–4)	45 (22.5)	19 (9.5)
Distress	1 (0–3)	35 (17.5)	14 (7.0)
Dry mouth	1 (0–3)	21 (10.5)	7 (3.5)
Sadness	0 (0–3)	32 (16.0)	12 (6.0)
Lack of appetite	0 (0–3)	31 (15.5)	14 (7.0)
Shortness of breath	0 (0–2)	23 (11.5)	10 (5.0)
Drowsiness	0 (0–3)	25 (12.5)	6 (3.0)
Numbness or tingling	0 (0–2)	25 (12.5)	8 (4.0)
Nausea	0 (0–1)	11 (5.5)	4 (2.0)
Vomiting	0 (0–0)	6 (3.0)	3 (1.5)
<b>Interference#</b>			
Work	1 (0–5)	51 (25.5)	27 (13.5)
Walk	1 (0–4)	48 (24.0)	27 (13.5)
General activity	1 (0–5)	52 (26.0)	24 (12.0)
Enjoyment of life	1 (0–4)	49 (24.5)	26 (13.0)
Mood	1 (0–3)	40 (20.0)	17 (8.5)
Relationship	0 (0–0)	13 (6.5)	4 (2.0)

IQR, interquartile range; \*, higher scores indicate greater symptom severity (0, symptom not present; 10, symptom as bad as you can imagine); #, higher scores indicate greater symptom interference (0, does not interfere; 10, completely interferes).



**Figure 1** Descriptive statistics for symptoms and interference.

the associations of physical symptom burden with death anxiety and psychological distress among a sample of Mainland Chinese ABC patients. This study supported the

relationships of physical symptoms with depression and anxiety reported in many previous studies. According to our results, a high symptom burden is associated with



**Table 4** Partial correlations among study variables (N=200)

Variables	r	
	Depression	Anxiety
Depression	–	–
Anxiety	0.70***	–
Death anxiety	0.57***	0.60***
Symptom burden	0.53***	0.45***

\*\*\*, P<0.001.

various physical and psychosocial problems in Chinese breast cancer patients (26). Western studies also showed that most of the physical problems experienced by breast cancer patients were associated with anxiety and, in particular, depression (8). In addition, Grotmol *et al.* found that breast cancer patients with a relatively poor prognosis and depression reported a significantly higher symptom burden (27).

More than half of the ABC patients in our study experienced at least moderate fatigue, as well as difficulty remembering and disturbed sleep. These results are largely consistent with those of a previous study reporting the most common severe symptoms in advanced cancer patients in China (17); these symptoms are treatment targets in early-stage breast cancer patients (28). Symptom management is an essential component of treatment and palliative care for advanced cancer patients. A previous study showed that systematic symptom monitoring can significantly prolong the survival of cancer patients (by 5.2 months) (29). Assessment of fatigue (30), cognitive functions (31) and sleep problems (32) seems to be adequate. These studies show the importance of a scientific approach to symptom management, which can achieve excellent results.

In the current study, the ABC patients' physical symptoms were related to psychological problems such as depression and anxiety. Patients with a larger symptom burden also tended to have a higher risk of depression and/or anxiety. This confirms that breast and general cancer patients with symptoms such as pain (33,34), fatigue

(35-37) and/or insomnia (38) are more likely to experience depression and/or anxiety.

There are also studies reporting that breast and general cancer patients experiencing more severe psychological distress in turn suffer more with physical symptoms (39-42). Moreover, depression and anxiety are associated with cancer-specific mortality (43). Taken together, the data show that cancer patients' physical symptoms are highly related to their mental status. Thus, clinical interventions targeting not just physical symptoms, but also psychological ones, would be more effective for breast cancer patients; addressing depression and/or anxiety is essential to aid the diagnosis and treatment of breast cancer patients.

We also found that symptom burden had a significant and positive relationship with death anxiety. The effect of symptom burden on death anxiety has been documented in the literature; for example, pain is a well-recognized risk factor for death anxiety (13,44,45). We speculate that death anxiety and symptom burden may both worsen without effective treatment. However, interventions aiming to alleviate death anxiety have not been widely used in the treatment of cancer patients in China, because of a lack of awareness and inequalities in medical resource allocation (46). It is important to recognize the need for both symptom and death anxiety management. Interventions targeting both physical and psychological symptoms to alleviate death anxiety may lead to better outcomes. One study showed that the Dying Well Education Program decreased the fear of death in Korean women with breast cancer (47). A well-designed death education program can help individuals prepare for their death, enjoy the present moment, and live a meaningful life.

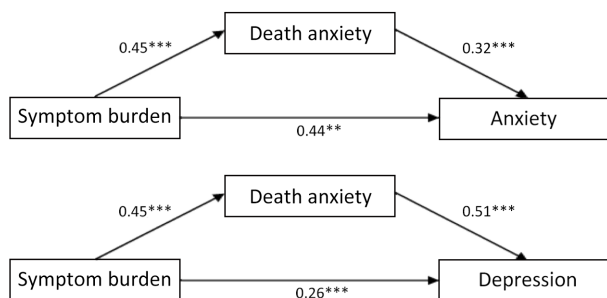
The findings of this study need to be considered in the context of certain limitations. First, this cross-sectional study had a relatively small sample size and thus is not representative of the entire ABC patient population. Second, the lack of a control group and long-term follow-up data limit our ability to draw conclusions regarding the impact of death anxiety. Ideally, early-stage patients should have been used as a control group. A previous study (48)

**Table 5** Effecting results of symptom burden on death anxiety and psychological distress

Path	a	b	c'	ab	95% CI	P
SB → Depression	0.45	0.51	0.26	0.23	0.15–0.35	<0.001
SB → Anxiety	0.45	0.32	0.44	0.14	0.08–0.23	<0.001

SB, symptom burden; 95% CI, 95% confidence interval; a, pathway between symptom burden and death anxiety; b, pathway between death anxiety and psychological distress; c', direct effect pathway between symptom burden and psychological distress; ab, indirect effect pathway between symptom burden and psychological distress.





**Figure 2** Models depicting the effect of symptom burden on psychological distress through death anxiety. \*\*,  $P < 0.01$ ; \*\*\*,  $P < 0.001$ .

showed that the death anxiety of ABC patients is significantly higher than that of early-stage patients, suggesting that death anxiety could impact the relationship between psychological distress and physical burden in different disease stages. Furthermore, patients who are economically advantaged may have been overrepresented in this study, so the findings need to be replicated in less affluent, i.e., rural, areas. Finally, patient-reported outcomes (PROs) are considered a potential source of bias; although PROs highlight the emotional experience of individual patients, the application of psychiatric diagnostic criteria by a practicing psychiatrist is also important.

This study revealed a moderating role of death anxiety in the association between the somatization of psychological symptoms and symptom burden among ABC patients, which could inform future prevention and treatment measures aiming to alleviate physical symptoms. Death anxiety is a sensitive topic; such that most patients, relatives and clinical workers prefer to avoid discussing it, and even related topics. However, addressing death anxiety may be important for reducing general anxiety and depression in patients with a symptom burden. ABC patients, oncologists and psycho-oncologists in China should thus devote more attention to death anxiety. Death anxiety should be considered in the treatment plan, alongside depression, anxiety and physical symptoms.

## Conclusions

This study showed that death anxiety affected the relationships of depression and anxiety with physical symptoms in ABC patients. Thus, special attention should be paid to the measurement and treatment of death anxiety. Although the current study exposes a partial relationship between death anxiety, symptom burden and psychological distress among cancer patients, the real-world clinical

situation could be much more complicated among cancer patients' psychological distress and symptom burden. For example death anxiety among cancer patients could be caused by more than one single variable (symptom burden); symptom burden and death anxiety could impact on each other rather than one-way influences. Therefore, more qualitative and quantity clinical data are needed in the future to help us understand more detailed mechanisms among these variables, and how they impacted each other. A case-control study is needed to further explore the impact of death anxiety on the relationship between psychological distress and physical symptom burden in various cancer stages.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Table S1** Multivariable analysis on anxiety and depression

Variables	Depression		Anxiety	
	OR	95% CI	OR	95% CI
College school and above	0.834	0.37, 1.88	1.196	0.47, 3.05
Employed	1.444	0.69, 3.02	2.795*	1.06, 7.40
Religion	2.331*	1.04, 5.23	1.088	0.40, 3.00
Income $\geq$ 7,000 CNY	2.268	0.84, 6.14	2.421	0.83, 7.06
Financial strain	3.125*	1.19, 8.19	2.856	0.94, 8.66
Life-threatening events in 5 years	0.897	0.26, 3.07	1.161	0.31, 4.37
Surgery	1.695	0.56, 5.15	1.100	0.35, 3.49
Radiotherapy	2.118	0.99, 4.52	1.466	0.61, 3.53
Comorbidity	0.941	0.38, 2.33	0.678	0.21, 2.24

CNY, Chinese Yuan; OR, odds ratio; 95% CI, 95% confidence interval; \*,  $P < 0.05$ .