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Emotional Distress in Newly Diagnosed Cancer Outpatients: Do Depression and Anxiety Predict Mortality and Psychosocial Outcomes After 1 Year?

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Abstract

Background and Objective: Metastatic progression predicts cancer mortality but there are conflicting findings on the effects of emotional distress (depression and anxiety) on mortality. Although survival time continues to be an important outcome in cancer care, psychosocial wellbeing is recognized to be a clinically significant and meaningful subjective outcome. This prospective study examined the effects of depression and anxiety on cancer mortality and psychosocial wellbeing across the first year of diagnosis.

Methods: Participants were 221 newly diagnosed adult cancer patients who were assessed on depression, anxiety, and life satisfaction. Mortality was formulated as cancer deaths occurring between baseline and December 2014 (timescale in months). Cox proportional-hazards models were conducted to examine if baseline depression and anxiety predict cancer mortality with adjustments for cancer stage at diagnosis (early/advanced), metastatic cancer, cancer site, medical comorbidities, and demographic variables age, gender, and ethnicity. Logistic regressions were conducted to examine if the baseline depression and anxiety predict depression, anxiety, and poor life satisfaction at 12-month follow-up.

Results: There were 31 incident cancer deaths within the study period (14% mortality). Cancer mortality was predicted by metastatic cancer, female gender, and Hepatitis B diagnosis. Depression at 12-month follow-up was predicted only by baseline depression. Anxiety was predicted by baseline depression and anxiety. Additionally, poor life satisfaction was predicted by baseline depression.

Conclusion: The present study adds to existing research by examining the role of depression and anxiety on cancer mortality and psychosocial outcomes early in the course of cancer, with considerations for potential confounding medical variables. Potential implications from the study include the importance of screening and supportive inventions for depression and anxiety post cancer diagnosis so as to prevent or reduce the risk of persistent emotional distress and improve patients' quality of life.

Keywords: Depression; Anxiety; Emotional distress; Survivorship; Metastasis; Cancer

Introduction

Cancer refers to a cluster of diseases in which cells divide uncontrollably, spread abnormally, and invade nearby tissues [1]. Despite medical advancements in early detection and treatment, cancer continues to be the leading cause of death worldwide and may account for about 11 million deaths in the next 15 years [2]. Rates of cancer mortality differ according to cancer site and stage at diagnosis, and a poorer prognosis has been associated with advanced stage and/or metastatic cancers [1,3]. Importantly, the diagnosis, course, and treatment of cancer can be an incredibly stressful experience. A significant proportion of patients may experience emotional distress and poor psychosocial wellbeing over the course of treatment and survivorship [4,5].

Emotional distress such as depression and anxiety are prevalent in patients with cancer, with prevalence rates of depression ranging from 12.9-16.5%, and anxiety from 19.0-22.6% in newly diagnosed cancer patients [6]. Previous studies have largely focused on and examined the deleterious effects of depression in cancer patients. Among these, persistent depression has been found to be associated with chronic pathophysiological effects (e.g. immunosuppression) [7], low health help-seeking behaviors [8], poor adherence to cancer treatment [9], and severe cognitive and functional impairments [10] –all of which could contribute to an increased risk of cancer mortality [11-13].

In a recent prospective study examining the effect of depression on cancer mortality among newly diagnosed (within 3 month of diagnosis) patients with lung cancer, Sullivan and colleagues observed that depression (measured on the Center for Epidemiologic Studies Depression scale) at baseline (5 months after diagnosis; adjusted HR=1.17, 95% CI 1.03 to 1.32, p=0.01) predicted cancer mortality, and persistent depression at follow-up (12 months after diagnosis; adjusted HR=1.42, 95% CI 1.15 to 1.75, p=0.001) predicted cancer mortality [14]. Complementing the findings by Sullivan and colleagues [14], results from a large prospective population study comprising mixed cancer patients (range 1 to 10 years after receiving a diagnosis of either endometrial cancer, colorectal cancer, lymphoma, or multiple myeloma) show that clinical depression (measured on the Hospital Anxiety and Depression Scale) was an independent predictor for all-cause mortality (Adjusted HR = 2.07. 95% CI 1.56 to 2.74, p<0.0001) [13].

While there is extensive research on depression and its influence on mortality in cancer patients, anxiety has often been conceptualized together with comorbid depression as emotional distress, and assessed

with self-report measures such as the General Health Questionnaire (GHQ-12) which includes symptoms of depression, anxiety, and post-traumatic stress [15,16]. In a recent study that pooled data from 16 prospective cohort studies, emotional distress (measured on the GHQ-12) was significantly associated with cancer mortality across multiple cancer sites (Adjusted HR=1.32, 95% CI 1.18 to 1.48) [15]. However, there are some inconsistencies in the literature on the effects of emotional distress (comorbid depression and anxiety) on cancer mortality. For example, a previous study's findings show that emotional distress (measured on the GHQ-12) predicted cancer mortality only in individuals with recurrent cancer at baseline assessment (Adjusted HR=1.97, 95% CI 1.05 to 3.71, p=0.035), but not in individuals newly diagnosed with cancer [16].

Although survival time continues to be an important outcome in cancer care, it is not sufficient. Psychosocial wellbeing has been recognized to be a clinically significant and meaningful subjective outcome [17,18]. Psychosocial wellbeing encompasses positive attributes of empowerment, self-awareness, faith and purpose, achieving meaningful interpersonal relationships, and having adaptive adjustment to a cancer diagnosis [18]. A recent study with newly diagnosed cancer patients identified that depression and anxiety at baseline predicted later depression, anxiety, and poor quality of life at 3-month and 6-month follow-ups [19]. The study's findings suggest that depression and anxiety may have pervasive effects on psychosocial wellbeing over time although some limitations include not accounting for medical variables, and the lack of assessment beyond the 6-month follow-up [19].

In line with the international call [12] for more research to investigate the effect of depression and anxiety on cancer mortality and psychosocial wellbeing with adjustment for confounding medical variables (e.g. comorbidities, metastasis, cancer treatment etc.), the present study aimed to investigate the relative predictive value of depression and anxiety on cancer mortality and psychosocial outcomes at the first year of follow-up in newly diagnosed cancer patients.

Methods

Participants and procedure

The study was part of a prospective cohort study among patients newly diagnosed with cancer; the study period was from July 2013 to December 2014 [20]. Participants were adult patients recruited from a university cancer center in Singapore. Patients were included if they received a cancer diagnosis within 3 months at the time of study participation, and had no previous history of cancer (diagnosis not attributed to metastatic or recurrent causes). Patients provided written informed consent and completed a set of questionnaires at baseline and 12-month follow-up and relevant medical information was obtained from medical records. The study protocol was approved by the National Healthcare Group Domain-specific Review Board (Reference: 2013/00294).

Measurements

Demographic information obtained through self-report included patients' age, gender, and ethnicity. Medical information obtained through medical records included cancer mortality (death due to cancer within 12-month follow-up), cancer site (breast, colorectal, gynecological, haematological, head and neck, lung, pancreatic, colorectal, and renal cancers), cancer stage (early=stage I/II, advanced=stage III/IV), presence of metastatic progression within 12 months (yes/no), received chemotherapy (yes/no), time since diagnosis

(months), and medical comorbidities such as diabetes mellitus, hypertension, hyperlipidemia, and Hepatitis B.

Depression and anxiety was assessed using the 14-item Hospital Anxiety and Depression Scale [21]. Previous research has validated the use of the HADS in the local cancer population [22]. Participants were asked how they felt in the past week on a 4-point Likert scale (e.g. 0=*not at all* to 3=*most of the time*); higher scores indicate higher anxiety/ depression. Anxiety and depression subscale scores of above 7 indicate possible clinical caseness [21]. Cronbach's alpha were 0.84 (baseline) and 0.91 (follow-up) for anxiety, and 0.79 (baseline) and 0.89 (follow-up) for depression.

Life satisfaction was assessed using the Satisfaction with Life Scale, a 5-item scale designed to measure global cognitive judgments of satisfaction with one's life (e.g. "In most ways my life is close to my ideal") [23]. Participants were asked to rate their agreeableness for each item on a 7 point Likert-type scale (ranging from 1= *strongly disagree* to 7=*strongly agree*); higher scores indicate greater life satisfaction. Scores below 20 indicate dissatisfaction with life [23]. Cronbach's alpha was 0.87 at 12-month follow-up.

Statistical analyses

Cox proportional-hazards models were conducted to examine if baseline clinical depression and anxiety predict cancer mortality with adjustments for cancer stage at diagnosis (early/advanced), metastatic cancer, cancer site, medical comorbidities, and demographic variables age, gender, and ethnicity. Mortality was formulated as cancer deaths occurring between baseline and December 2014 (timescale in months). Logistic regressions were conducted to examine if the baseline clinical depression and anxiety predict clinical depression, clinical anxiety, and poor life satisfaction at 12-month follow-up. All analyses were conducted using SPSS 20.0.

Results

A total of 221 patients completed baseline assessment (67.4% female, mean age=49.21 years, SD=9.36, range 22 to 64 years), and 124 patients completed 12-month follow-up (response rate=56.1%). Of the 221 patients (mean time since diagnosis=2.12 months, SD=1.05), 35% had breast cancer, 18% gastrointestinal, 11% gynecological, 10% head and neck, 13% hematological, 8% had lung cancer, 4% had pancreatic cancer, and 1% had other cancers. More than half of the patients were diagnosed with early-stage cancer (68%). Most of the participants survived past the first year of follow-up. There were 31 incident cancer deaths within the study period (14% mortality). Colorectal cancer contributed to the highest proportion of deaths (29%), followed by lung (23%) and head and neck cancers (16%).

In terms of emotional distress, 41% of the patients had clinically significant anxiety and 26% had depression at baseline; 50% had clinically significant anxiety and 38% had clinically significant depression at 12-month follow-up.

Cancer mortality within the first year was predicted only by metastatic cancer (HR=6.14, 95% CI 2.51-15.0, p<0.001), female gender (HR=0.28, 95% CI 0.11-0.70, p<0.01), Hepatitis B diagnosis (HR=7.31, 95% CI 1.21-44.2, p<0.05), but not clinical depression and anxiety. Tables 1-3 present the results on psychosocial outcomes with adjustment for socio-demographic and medical variables. Clinical depression at 12-month follow-up was predicted only by baseline clinical depression (OR=5.46, 95% CI 1.66-18.0, p<0.01). Clinical anxiety was predicted by baseline clinical depression (OR=12.4, 95% CI 2.26-22.5, p<0.001) and anxiety (OR=3.10, 95% CI 1.11-8.70, p<0.05).

Additionally, poor life satisfaction was predicted by baseline clinical depression (OR= 6.24, 95% CI 1.88-20.7, $p<0.01$).

Discussion

Few researches have examined the role of depression and anxiety on cancer-related outcomes early in the course of cancer. The present study examined the predictive value of clinical depression and anxiety on cancer mortality and psychosocial outcomes at the first year of follow-up in newly diagnosed cancer patients.

Variable (N = 221)	N (%)
Age (M ± SD)	49.21 ± 9.36
Gender	
Male	72 (33)
Female	149 (67)
Ethnicity	
Chinese	134 (61)
Malay	36 (16)
Indian	24 (11)
Eurasians	27 (12)
Cancer Type	
Breast	78 (35)
Nasopharyngeal	22 (10)
Gynecologic	29 (11)
Haematological	18 (13)
Lung	11 (8)
Colorectal	39 (18)
Pancreas	8 (4)
Renal	2 (1)
Cancer Stage	
Early (stage I/II)	151 (68)
Late (stage III/IV)	70 (32)
Metastatic Cancer	61 (27)
Received chemotherapy	206 (93)
Cancer Mortality[a]	
Breast	2 (7)
Nasopharyngeal	5 (16)
Gynecologic	2 (7)
Haematological	2 (7)
Lung	7 (23)
Colorectal	9 (29)
Pancreas	3 (10)
Renal	1 (3)
Chemotherapy	206 (93)
Time from diagnosis (M ± SD)	2.12 ± 1.05
Chronic Conditions[b]	
Diabetes mellitus	24 (11)
Hypertension	21 (10)
Hyperlipidemia	34 (15)
Respiratory disease	10 (5)
Hepatitis B	3 (1)
Psycho-social factors	
Clinical depression (baseline)	57 (26)
Clinical depression (12-month)	45 (38)
Clinical anxiety (baseline)	89 (41)
Clinical anxiety (12-month)	60 (50)
Poor life satisfaction (12-month)	27 (22)

Note: Percentage values are used as valid percentages (of participants) and not exact percentages of total sample.
[a]Percentage values are based on the total number of cancer deaths in the present sample (31/221; 14.0% mortality).
[b]Figures reflect binary-coded (yes/no) variables.

Table 1: Socio-demographic and clinical characteristics.

Variable	Multivariate-Adjusted model	
	HR	**95% CI**
Age	0.97	0.93 – 1.02
Gender (male)	reference	--
Gender (female)	0.28**	0.11 - .70
Ethnicity (Chinese)	reference	--
Ethnicity (Malay)	0.46	0.11 – 1.88
Ethnicity (Indian)	0.52	0.14 – 1.88
Ethnicity (Others)	0.37	0.05 – 2.88
Cancer stage (early)	reference	--
Cancer stage (advanced)	1.07	0.46 – 2.88
Metastasis (no)	reference	--
Metastasis	6.14***	2.51 – 15.0
Chemotherapy (no)	reference	--
Chemotherapy	1.32	0.164 – 10.5
Diabetes mellitus (no)	reference	--
Diabetes mellitus	1.06	0.31 – 3.62
Hypertension (no)	reference	--
Hypertension	2.16	0.57 – 7.77
Hyperlipidemia (no)	reference	--
Hyperlipidemia	1.07	0.32 – 3.63
Respiratory disease (no)	reference	--
Respiratory disease	0.61	0.06 – 6.34
Hepatitis B (no)	reference	--
Hepatitis B	7.31*	1.21 – 44.2
Clinical depression (no)	reference	--
Clinical depression	1.08	0.52 – 3.51
Clinical anxiety (no)	reference	--
Clinical anxiety	1.35	0.40 – 2.90

*$p < 0.05$, **$p <0.01$, ***$p <0.001$

Table 2: Results from Cox regression models for demographic and medical variables, emotional distress and cancer mortality.

	Clinical Depression (12-month)		Clinical Anxiety (12-month)		Poor life satisfaction (12-month)	
Baseline predictors	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Emotional distress						
Clinical depression (no)	reference	--	reference	--	reference	--
Clinical depression	5.46**	1.66 – 18.0	12.4***	2.26 – 22.5	6.24**	1.88 – 20.7
Clinical anxiety (no)	reference	--	reference	--	reference	--
Clinical anxiety	2.12	0.78 – 5.74	3.10*	1.11 – 8.70	0.77	0.26 – 2.26

Multivariate-adjusted logistic models include age, gender, ethnicity, metastasis, cancer stage, chemotherapy, diabetes, hypertension, hyperlipidemia, respiratory disease.
*$p < 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$.

Table 3: Results from logistic regression analyses on depression, anxiety, and life satisfaction at 12-month follow-up.

Firstly, our findings showed that metastatic cancer predicted a six-fold increased risk of cancer mortality. This was consistent with previous research establishing the role of metastasis as a robust predictor of mortality [3,24]. Clinical depression and anxiety were not found to predict mortality. Our finding on depression and anxiety differed from studies which found support for the association between depression and mortality [8,14] as well as emotional distress (depression and anxiety) and mortality [15]. One possibility could be the presence of psychological resources such as hope, mindfulness, and spirituality

which could have buffered some of the deleterious effects of clinical depression and anxiety [25-27]. While psychological resources may not prevent the onset of depression and anxiety, they may encourage health help-seeking behaviors which could have influenced cancer mortality [8]. Alternatively, some patients may have experienced transient symptoms of depression and anxiety during the initial reaction to their diagnosis, and may have adjusted positively over time [14].

In terms of psychosocial outcomes, clinical depression at baseline was found to predict a five-fold increased risk of clinical depression, and clinical anxiety at baseline predicted a three-fold increased risk of clinical anxiety at 12-month follow-up. This was consistent with previous research which showed that baseline depression predicted 3-month and 6-month depression in a sample of newly diagnosed cancer patients; similarly, baseline anxiety predicted later anxiety [14]. However, compared to the specificity observed by Hulbert-Williams and colleagues [14], the current study found that baseline clinical depression also predicted a six-fold increased risk of poor life satisfaction and a twelve-fold increased risk of clinical anxiety at 12-month follow-up. One potential reason may be that the adverse impact of depression (characterized by new-onset and persistent depression) is more extensive by the first year after cancer diagnosis, and more research is needed to examine the effect of depression on psychosocial wellbeing beyond the first year of diagnosis [9].

Conclusion and Limitations

Limitations to the study should be considered. First, the sample comprised a mixed-cancer population which may limit the generalizability of the findings to a specific cancer type. Second, the sample only included ambulatory outpatients, thus results may not generalize to inpatients that may have more severe medical complications. Third, cancer mortality and psychosocial wellbeing were limited to the first year of follow-up with newly diagnosed patients; it is uncertain how depression and anxiety might influence mortality and psychosocial wellbeing over five or ten-year follow-up. Finally, the present study did not include other potential variables that may have an influence on cancer mortality such as health behaviors, personality traits, or perceived/actual social support. Future prospective studies should build on the present study's findings to generate more compelling hypotheses by considering the roles of intra/interpersonal resources and health behaviors on cancer mortality.

Notwithstanding the limitations, the current study adds to existing research by examining the role of depression and anxiety on cancer mortality and psychosocial outcomes early in the course of cancer, with considerations for established cancer-related variables as well as potential confounding socio demographic and medical variables. Potential implications from the study include the importance of screening and supportive inventions for depression and anxiety post cancer diagnosis so as to prevent or reduce the risk of persistent emotional distress and improve patients' quality of life.

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