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Effects of depression and anxiety on mortality in a mixed cancer group: a longitudinal approach using standardised diagnostic interviews

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Abstract

***Background*: Distress and psychiatric morbidity in cancer patients are associated with poorer outcomes including mortality. In this study, we examined the prevalence of psychiatric morbidity and its association with cancer survival over time.**

***Methods*: Participants were 467 consecutive adult cancer patients attending oncology follow-ups at a single academic medical centre. Assessment consisted of the Hospital Anxiety and Depression Scale and Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision. Comparison between co-morbid psychiatric cases and non-cases was made in follow-ups of up to 24 months.**

***Results*: Of the 467 patients, 217 of 220 patients with elevated total Hospital Anxiety and Depression Scale scores (≥16) met the criteria for an Axis I disorder at 6 months follow-up, with 102 of the follow-up sample having a persistent diagnosable psychiatric disorder after 1 year. The most frequent initial diagnoses were minor depression (17.6%), major depressive disorder (15.8%) and adjustment disorder (15.8%). Cancer patients without psychiatric morbidity had a survival benefit of 2.24 months or 67 days. Mean survival at 24 months was 20.87 months (95% CI 20.06–21.69) for cancer patients with psychiatric morbidity versus 23.11 months (95% CI 22.78–23.43) for those without ($p < 0.001$ for log rank). After adjusting for demographics and cancer stage on a Cox proportional hazards model, psychiatric morbidity remained associated with worse survival (hazard ratio 4.13, 95% CI 1.32–12.92, $p = 0.015$).**

***Conclusions*: This study contributes to the growing body of evidence linking psychiatric morbidity to cancer mortality. Treating underlying psychiatric conditions in cancer may therefore improve not just quality of life but also survival.**

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Introduction

Psychological distress as well as clinical depression and anxiety to a lesser extent are frequently observed amongst patients with cancer [1]. Although psychiatric morbidity in the general population is strongly associated with increased morbidity and economic consequences as a result of functional disability [2], depression and anxiety in the cancer setting have been shown to be associated with worse outcomes such as poorer quality of life and performance status [3], decreased treatment adherence and increased use of medical services [4]. More importantly, there is growing evidence linking depression to all-cause mortality [5–14]. Treating underlying psychiatric conditions in cancer may therefore improve not just quality of life but also survival.

Much less represented in past studies is how distress can fluctuate over the course of the cancer trajectory and affect prevalence rates [15]. As the prevalence or severity of psychological distress is fluid and variable over time, symptom severity at the time of the first or baseline interview may lose predictive power over time [7,8].

Little consensus exists on definite rates of depression and anxiety in patients with cancer from current studies, whereas fewer studies have been undertaken to examine the impact of depression and anxiety on cancer survival. The studies that do exist are rife with methodological limitations such as small sample sizes and non-usage of standardised diagnostic interviews [15,16].

To overcome some of these limitations and to control for bias associated with the timing of assessment, we followed up on patients at multiple time intervals using both clinical diagnoses according to standardised diagnostic criteria and depressive/anxiety symptoms using self-rated scales.

In the present study, we aimed to examine the prevalence of psychological distress and psychiatric morbidity in a consecutive series of cancer patients in prospective

follow-ups of up to 2 years from diagnosis and to identify the strength of its association with mortality.

Method

Participants and procedure

Adult cancer patients at the oncology clinic of an academic medical centre were consecutively recruited in the waiting area during routine outpatient visits and followed up to 24 months between November 2011 and October 2013.

Eligible patients had to be aged 18 years and above. Patients who were eligible for the study were also required to score ≥8 for either of two subscales on the Hospital Anxiety and Depression Scale (HADS) to screen for psychological distress or probable cases of anxiety and/or depression at baseline (T1) and 4–6 weeks follow-up (T2). Psychiatric morbidity was confirmed via clinical interview using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (SCID; DSM-IV-TR) at 6 months follow-up (T3) and 12–18 months follow-up (T4). Patients who were not aware of their cancer diagnosis, with prior psychiatric history and a life expectancy of less than 3 months were excluded from participating.

Of the 560 consecutive patients approached, 13 declined to participate at baseline. Seventy-eight patients were excluded because of the following: patients being too ill to participate and ineligible after medical record review as they were palliative status patients with life expectancies of less than 3 months ($n=5$), death before the 4–6 weeks follow-up and hence not interviewed for the second time ($n=21$), transfer to other hospitals or management by a different primary team (e.g. surgical, gynaecology, chest team) ($n=37$) and questionnaires with more than 10% of items incomplete because of patients being called in midway for consultation before completing the interview and not continuing the interview within 2 weeks of the initial interview ($n=14$). Only a single patient could not be accounted for ($n=1$). Of the remaining 469 patients, two patients who agreed to complete the HADS but refused to take part in a SCID interview were excluded from the analysis, resulting in a final sample size of $N=467$ (Figure 1).

A total of 467 eligible patients met the criteria for eligibility and underwent assessment using the HADS at baseline (T1) and 4–6 weeks (T2). Of these, 220 patients who scored ≥8 on the HADS were considered probable cases and subsequently underwent a clinical interview using the SCID at 6 months (T3), with 115 patients repeating the assessment at 12–18 months (T4). At 12–18 months follow-up, only 115 were successfully interviewed again. Of the patients that were lost to follow up, 25 were confirmed to be deceased, whereas another 79 were no longer under oncology follow-up or had transferred to other centres.

Clinical interviews (SCIDs) were conducted 6 months after the patient's first visit to the oncology clinic in order to allow time for transient symptoms to abate. Because of scheduling difficulties, we did not conduct clinical interviews for all patients. Fifty-eight patients with stable or improved HADS scores that were borderline high on a single subscale of the HADS did not undergo the SCID. Two patients with probable anxiety and/or depression were not keen on undergoing a psychiatric interview. Date and status of death were determined by phone calls to the patient's home or next of kin, hospital medical records and institutional breast cancer registry database. All deaths were verified with the National Death Registry. The research protocol was reviewed and approved by the institutional ethics board.

Measures

Demographic information was collected using a standardised patient information form, which assessed background patient characteristics. Two other instruments used include the HADS and SCID; DSM-IV-TR. The HADS was used to determine probable cases at T1 and T2, whereas caseness was confirmed using the SCID at T3 and T4.

Hospital Anxiety and Depression Scale

The HADS [17] consists of 14 brief items divided into two subscales designed to screen for anxiety and depressive symptoms. Preliminary testing with 18 patients (male to female ratio = 1:1) conducted in October 2011 for the HADS yielded an α of 0.91. On each subscale, the maximum score is 21, with a score of 0 to 7 considered normal, 8 to 10 as mild distress and 11 to 21 as severe distress, respectively. A subscale cutoff of ≥8 or total score of ≥16 for both subscales was used to identify probable cases [1,18]. A patient was considered a 'probable case' if he or she had a total score of ≥16 on the HADS or a 'probable non-case' with a HADS score within normal thresholds for distress (score of 15 and below).

Structured Clinical Interview

The Structured Clinical Interview for DSM for Axis-I disorders based on DSM-IV-TR [19] was used to assess current psychiatric morbidity. The interviews focused on mood, anxiety and adjustment disorders known to be common in cancer patients. A trained doctoral-candidate level psychologist conducted all interviews on a one-to-one basis. To establish a diagnosis, criteria as per DSM-IV-TR had to be met according to symptom severity and duration. Time to complete the interview ranged from 30 to 90 min.

We assessed inter-rater reliability via double rating of 50 clinical interviews (SCIDs) by a second trained psychologist. Overall agreement on whether a diagnosis should be assigned was excellent at 98%, with a slightly

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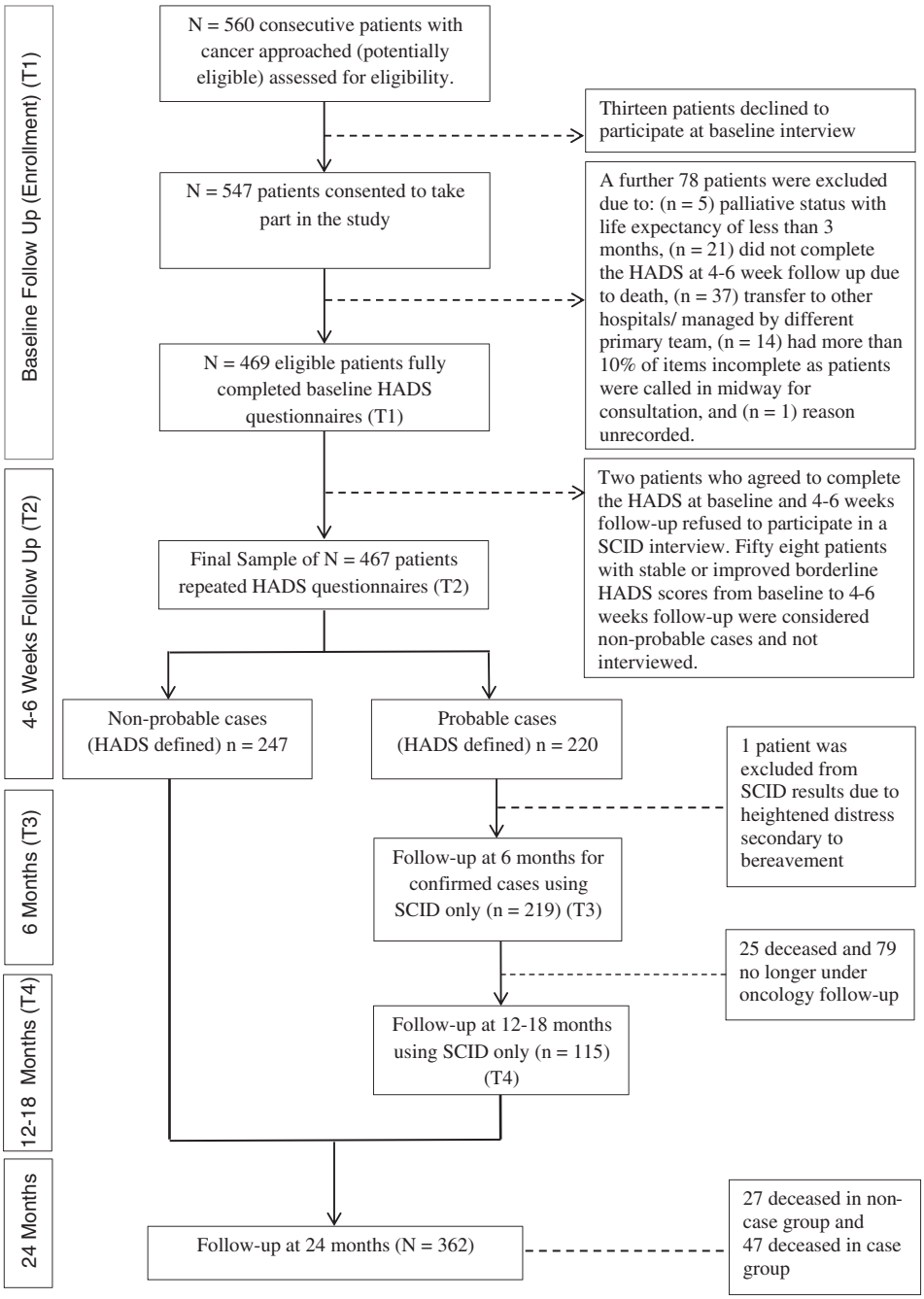

Figure 1. CONSORT diagram detailing recruitment and follow-ups at various time points, one patient was excluded from SCID results due to heightened distress secondary to bereavement

lower agreement of 94–96% on specific diagnostic subtypes. For the purposes of this study, a cancer patient was confirmed as a psychiatric 'case' if they were assigned a diagnosis using the SCID versus 'non-case' if they did not qualify for a diagnosis.

Statistical analyses

On the basis of an estimated response rate of 50% (which produces the largest possible sample size), a margin of error of 5% or a confidence level of 95, at least 218 patients were needed for the study to attain a power of 80%. We calculated the sample size to balance for an estimated attrition rate of 40% at each follow-up. Standard statistics for parametric data were used to calculate prevalence rates for distress and psychiatric morbidity. Overall survival was calculated using the Kaplan–Meier method. Multivariate survival analyses were performed using a Cox proportional hazards model in order to control for potential confounders. Psychiatric status was entered at the

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Table 1. Clinical and demographic characteristics of cancer patients by probable cases and non-cases at initial screening ($N = 467$)

Demographics	Probable non-cases ($n = 247$)	Probable cases ($n = 220$)	No. (%) Patients ($N = 467$)
Mean age ± SD;	54.76 ± 13.52	57.97 ± 12.31	56.21 ± 13.05
Range (years)	18–84	21–93	18–93
Gender			
Male	61	58	119 (25.3)
Female	186	162	348 (74.7)
Age			
18–39	32	18	50 (10.7)
40–54	84	63	147 (31.5)
55–69	98	105	203 (43.5)
>70	33	34	67 (14.3)
Ethnic background			
Malay	67	48	115 (24.6)
Chinese	134	132	266 (57.0)
Indian	38	33	71 (15.2)
Others	8	7	15 (3.2)
Religion			
Islam	69	49	118 (25.3)
Buddhism	95	103	198 (42.4)
Hindu	18	25	43 (9.2)
Christianity	50	30	80 (17.1)
Others	15	13	28 (6.0)
Marital status			
Single	38	18	56 (12.0)
Married	191	173	364 (77.9)
Divorced/separated	8	6	14 (3.0)
Widowed	10	23	33 (7.1)
Highest education level			
Primary	36	58	94 (20.1)
Secondary	94	92	186 (39.8)
University	103	49	152 (32.5)
No formal education	14	21	35 (7.5)
Employment status			
Employed	61	24	85 (18.1)
Retired/unemployed	186	196	382 (81.8)
ECOG performance status[a]			
0	158	130	288 (61.7)
1	72	55	127 (27.2)
2	12	18	30 (6.4)
3	5	17	22 (4.7)
Cancer stage			
I	42	15	57 (12.2)
II	51	31	82 (17.6)
III	43	34	77 (16.5)
IV	95	118	213 (45.6)
Recurrent	4	6	10 (2.1)
Unknown	12	16	28 (6.0)
Cancer type			
Breast	116	75	191 (40.9)
Gastrointestinal	54	48	102 (21.8)
Gynaecological	12	12	24 (5.1)
Head and neck	12	12	24 (5.1)
Lung	4	19	23 (4.9)
Genitourinary	9	13	22 (4.7)
Thyroid	11	7	18 (3.9)
Sarcoma	8	5	13 (2.8)
Haematological	5	5	10 (2.1)
CNS	1	5	6 (1.3)
Others[b]	2	1	3 (0.6)
Unknown primary	9	11	20 (4.3)
Missing	4	7	11 (2.4)

CNS, Central Nervous System.
Numbers should be read horizontally, whereas the percentage read vertically.
[a]ECOG refers to the Eastern Cooperative Oncology Group performance status scoring that consists of a five-point scale: 0, asymptomatic; 1, symptomatic, limited but fully ambulatory; 2, symptomatic, in bed <50% of the day; 3, symptomatic, in bed >50% of the day but bedridden; 4, bedridden, moribund.
[b]Other cancers = skin ($n = 1$), germ cell tumour ($n = 1$) and thymoma ($n = 1$).

first block to independently test the effect of psychiatric morbidity on survival. Age, gender, ethnicity, performance status (Eastern Cooperative Oncology Group (ECOG)), cancer type, cancer stage, marital status and education were entered simultaneously as covariates at the second block. Statistical comparisons were two-sided, using $p < 0.05$ as the level of significance. All analyses were performed using Statistical Package for the Social Sciences (SPSS version 20, IBM Corporation,).

Results

Thirteen patients declined to participate at the baseline interview, giving a response rate of 97.6%. We observed no statistically significant differences in baseline characteristics between non-participants and patients included in the final sample. Clinical and demographic characteristics for all patients are listed in Table 1. The sample was predominantly female, with a mean age of 55 years and of urban domicile. The majority were married with children and educated to secondary school level. None of the patients had a past personal history of cancer or any psychiatric disorder.

Ours is a heterogeneous mixture of different cancer types with breast cancer and gastrointestinal cancers predominant. Overall, almost half of the patients (43.5%) were stage IV, although it should be noted that staging cannot be feasibly compared or accurately aggregated across different cancer types as systems of staging may differ between specific tumour groups. The highest number of cancers by primary site was breast cancer ($n = 191$) and gastrointestinal cancers ($n = 102$) and together comprised approximately two-thirds (62.4%) of all cancer types. The majority of the patients in our sample demonstrated good ECOG performance status (0 to 1) and were mainly attending follow-ups for treatment (Table 1).

Probable caseness was screened using the HADS. Of the 467 patients, probable anxiety and depression based on HADS scores were seen in 159 patients (34%) at

Table 2. Prevalence of psychological distress in cancer patients using the HADS ($N = 467$)

		Probable non-cases ($n = 247$)		Probable cases ($n = 220$)	
		Mean ± SD	95% CI	Mean ± SD	95% CI
Baseline (T1)					
Depression		3.98 ± 8.09	2.97–4.99	8.79 ± 3.86	8.27–9.30
n (%)	Mild	228 (92.3)		90 (40.9)	
	Moderate	13 (5.3)		66 (30.0)	
	Severe	6 (2.4)		64 (29.1)	
Anxiety		5.03 ± 8.05	4.03–6.04	10.08 ± 3.54	9.61–10.55
n (%)	Mild	210 (84.3)		52 (23.6)	
	Moderate	31 (12.4)		73 (33.2)	
	Severe	8 (3.2)		95 (43.2)	
Total		8.98 ± 11.23	7.57–10.38	18.87 ± 6.34	18.03–19.71
Four to six weeks (T2)					
Depression		7.83 ± 19.02	5.45–10.21	11.63 ± 3.61	11.15–12.11
n (%)	Mild	217 (87.1)		28 (12.7)	
	Moderate	17 (6.8)		61 (27.7)	
	Severe	15 (6.0)		131 (59.9)	
Anxiety		8.92 ± 18.79	6.57–11.26	12.83 ± 3.28	12.40–13.27
n (%)	Mild	203 (81.5)		11 (5.0)	
	Moderate	27 (10.8)		41 (18.6)	
	Severe	19 (7.6)		168 (76.4)	
Total		12.15 ± 18.39	9.85–14.44	24.46 ± 6.01	23.67–25.26

HADS, Hospital Anxiety and Depression Scale.
HADS categories by scores: mild = '0–7', moderate = '8–10' and severe = '11–21'.

baseline (T1) and in 236 (51%) at 4–6 weeks follow-up (T2) using a subscale cutoff of ≥8. Using a higher HADS subscale cutoff of ≥11 identified $n = 69$ (T1) and $n = 158$ (T2) of 467 patients as having probable depression or anxiety. Overall, there was an increase in distress across all groups from baseline to follow-up at 4–6 weeks (Table 2).

Caseness was confirmed using the SCID. A total of 217 patients were assigned a psychiatric diagnosis at 6 months follow-up (T3) after the initial HADS screen at T1 and T2. Of these, 76 were assigned two diagnoses. There were 74 cases of major depressive disorder, of which there were 28 cases with a melancholy specifier. At subsequent diagnostic interview at 12–18 months follow-up (T4), 102 diagnoses were assigned to 115 patients. Overall, prevalence of psychiatric comorbidity was approximately 46% in cancer patients attending routine oncology follow-ups. There was a pronounced decrease in rates of anxiety disorders, minor or subsyndromal major depressive disorder as well as adjustment disorder from T3 to T4 (Table 3).

Table 3. Prevalence of psychiatric disorders in cancer patients using the SCID

	6 months follow-up (T3) $n = 219$ (%)[a, b]	12–18 months follow-up (T4) $n = 115$ (%)[b]
Major depressive disorder (MDD)	74 (25.3)	63 (50.8)
With melancholy specifier	28	25
Minor depression/subsyndromal MDD	82 (27.9)	13 (10.5)
Dysthymia	8 (2.7)	19 (15.3)
Generalised anxiety disorder (GAD)	55 (18.8)	22 (17.7)
Adjustment disorder (AD)	74 (25.3)	7 (5.6)
No diagnosable disorder	2 (0.7)	13 (10.5)
Comorbid		
Yes	76	22
No	143	80

SCID, Structured Clinical Interview for DSM-IV-TR.
[a]A single case was excluded from SCID results from T3 onwards due to symptoms being better accounted for by bereavement.
[b]Diagnoses for MDD, MDD-NOS, GAD, dysthymia and AD do not add up to 100% as the figures are inflated by comorbid case (e.g. 293 diagnoses were assigned to 217 patients at T3, whereas 124 diagnoses were assigned to 102 patients at T4).

Survival was calculated from time of enrolment to the time of death between cases versus non-cases as based on whether a patient had ever qualified for a psychiatric disorder. Seventy-four deaths occurred during the 24 months study period (27 in the non-case group, 47 in the case group). The main cause of death was due to cancer progression. The 60-day mortality rate for the overall population was 8.2%. The Kaplan–Meier curves for the overall survival are shown in Figure 2.

Survival analyses differed in the two arms between non-cases and cases as seen in the wide separation of the curves as early as at 9 months. The 24 months survival was 78.64% and 89.07% for cases and non-cases, respectively, with a survival benefit of 2.24 months seen in non-cases. Mean survival was 23.11 months (95% CI 22.78–23.43) for the non-case arm versus 20.87 months (95% CI 20.06–21.69) for the case arm ($p < 0.001$ for log rank).

The Cox model showed that before adjustment, the hazard ratio (HR) for the overall psychiatric morbidity (T3 and T4 SCID) on survival was HR = 2.21 (95% CI 1.31–3.71, $p = 0.003$). Psychological distress as measured using the HADS at baseline (T1) did not appear to predict

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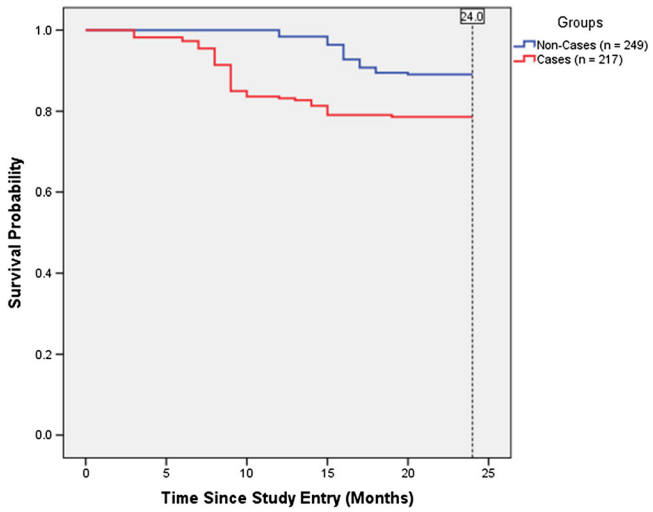

Figure 2. Kaplan–Meier survival curve for psychiatric cases (blue line) versus non-psychiatric cases (red line) using the Structured Clinical Interview for DSM-IV-TR (SCID) ($p<0.001$ for log rank). Median survival was not reached for both groups

mortality (HR = 1.01, 95% CI 0.95–1.08, $p = 0.820$). After controlling for age, gender, ethnicity, performance status (ECOG), cancer type, cancer stage, marital status and education, psychiatric morbidity remained associated with worse survival, with an HR of 4.13 (95% CI 1.32–12.92, $p = 0.015$). None of the covariates were significantly associated with mortality (Table 4).

Discussion

This is one of the few studies to prospectively evaluate depression and anxiety in cancer patients over time using Structured Clinical Interviews (SCID) based on standardised diagnostic criteria. Few previous studies have used gold standard clinical interviews to assess psychiatric morbidity in as many cancer patients, relying instead on questionnaires administered by non-trained personnel or self-report. The majority of published studies in this area are cross-sectional surveys using screening instruments alone [15].

Table 4. Hazard ratio of survival based on psychological distress and psychiatric status

Predictors	Hazard ratio	*p*	95% CI
Overall SCID/psychiatric morbidity (not adjusted)	2.21	0.003*	1.31–3.71
Overall SCID/psychiatric morbidity (adjusted)	4.13	0.015*	1.32–12.92
Baseline HADS (T1)	1.01	0.820	0.95–1.08
4–6 weeks HADS (T2)	1.07	0.034*	1.01–1.14
6 months SCID (T3)	3.96	0.009*	1.42–11.04
12–18 months SCID (T4)	4.60	0.001*	2.05–10.31

All hazard ratios are adjusted for age, gender, ethnicity, performance status (ECOG), cancer type, cancer stage, marital status and education, unless indicated otherwise. Overall SCID is based on the SCID at T3 and T4.
SCID, Structured Clinical Interview for DSM-IV-TR; HADS, Hospital Anxiety and Depression Scale.
*$p < 0.01$.

Our HR of 2.21 before adjustment is similar to other studies [4–6,10,13,20], which examine depression on mortality. After adjusting for age, performance status and cancer stage, our HR of 4.13 was more than twice as high, but this was comparable with another local study [11] which found that cancer patients with depressive symptomology were 4.31 times more likely (than those without) to experience mortality. We believe that our adjusted HR was much higher because of the measurement of psychological distress over time (stable and improved scores were not included) and rigorous criteria used for diagnosing and confirming cases. This is supported by past findings, which show that single measurements of depression (particularly at diagnosis) tend to be less strongly associated with cancer survival compared with chronic or major depression [7].

The survival benefit of 2.24 months in this study is modest when compared with the survival time of 12.57 and 28.5 months in two other studies [9,20] albeit with much smaller sample sizes ($n < 150$). This is important to note as past studies which fail to find a significant effect generally have sample sizes that are twice as large [7]. The median survival was not reached in our study even after 24 months. Our case and non-case groups were however fairly well-balanced from the start, which meant that mortality here was unlikely to be the influence of other clinical factors (compared with studies which did not adjust for this) as supported by the additional step of statistically controlling for covariates which appeared to enhance results.

The level of psychological distress and psychiatric morbidity in this sample of cancer patients—34.1% at T1, 50.5% at T2, 46.7% at T3 and 46.6% at T4, respectively, is generally consistent with findings from the majority of the studies described in this area [9–11,21–27]. Distress at baseline was relatively low, peaking at 4–6 weeks but stabilising from 6 months onwards. As many as 20% of patients without psychological problems at diagnosis develop major affective disorders within the following year [28], whereas up to two-thirds of patients assessed by questionnaire as having a psychiatric disorder may not meet criteria for a subsequent diagnostic interview [29,30].

The significant drop in minor depression, adjustment and anxiety disorders even without treatment after 1 year is highly encouraging and may be explained by natural trajectories of distress over time [31]. An interesting point to note was that psychological distress at baseline (T1) did not appear to predict mortality. Again, this is consistent with the finding that depression present at a single time point which resolves in a timely manner does not pose a risk factor for increased mortality in cancer [9].

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Subsequent psychological distress at 4–6 weeks follow-up (T2) and psychiatric morbidity at 6 months (T3) and 12–8 months (T4) follow-up appeared to increase the risk of mortality by more than fourfold. As the majority of patients, who were probable cases on the HADS, were later confirmed as cases using the SCID, this finding suggests that chronically depressed or anxious cancer patients are at greater risk of mortality. We recommend that efforts to screen for psychological distress be focused around 4–6 weeks onwards. The high rate of psychiatric morbidity makes it essential for clinicians to identify patients most at risk and offer appropriate intervention, as there is good evidence to support the efficacy of monitoring and active treatment.

The high attrition rate due to the substantial number of patients who defaulted from treatment presents a limitation of this study. Psychiatric morbidity at 6 months and 12–18 months follow-up was analysed separately so that results would not be overly impacted by the significant dropout. Caution should be applied in generalising results as another limitation of this study was that it was conducted in a single centre, although this was a tertiary setting which receives nationwide referrals.

Findings from this study should help alert oncologists to the importance and necessity of screening cancer patients exhibiting signs of distress and to refer patients who were screened as probable cases for diagnostic workup. Further research in this area should investigate the use of mental health services in the oncology setting, particularly to determine reasons why patients may not be receptive to offers of treatment and support. This will enable us to identify changes in needs associated with distress tied to different time points in the cancer trajectory.

Conclusion

Our findings support that the role of psychiatric morbidity with regard to mortality in cancer is clinically relevant. Depression and anxiety represent clinically significant issues in their own right, as does treating the cancer itself. Fortunately, depression and anxiety are highly treatable disorders, and with proper intervention, patients with cancer can benefit from both improved quality of life and better survival.

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Conflict of interest

The authors have declared no conflicts of interest.

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