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ORIGINAL ARTICLE

Anxiety and depression during 3-year follow-up period in postoperative gastrointestinal cancer patients: prevalence, vertical change, risk factors, and prognostic value

Jiaying Li[1] · **Chongyi Ma**[2]

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Abstract

Background Anxiety and depression are common issues in gastrointestinal cancer, bringing negative impacts on patients' quality of life and long-term prognosis. This study aimed to identify the prevalence, longitudinal variation, risk factors, and prognostic value of anxiety and depression in postoperative gastrointestinal cancer patients.

Methods A total of 320 gastrointestinal cancer patients after surgical resection (210 colorectal cancer (CRC) patients and 110 gastric cancer (GC) patients) were enrolled in this study. During the 3-year follow-up period, Hospital Anxiety and Depression Scale (HADS)-anxiety (HADS-A) and HADS-depression (HADS-D) scores were determined at baseline, 12th month (M12), 24th month (M24), and 36th month (M36).

Results The prevalence of anxiety and depression at baseline was 39.7% and 33.4% in postoperative gastrointestinal cancer patients, respectively. Female (vs. male), single/divorced/widowed (vs. married), CRC (vs. GC), hypertension, higher TNM stage, neoadjuvant chemotherapy, and postoperative complications were independent risk factors of anxiety or depression in patients with gastrointestinal cancer (all $P < 0.050$). Furthermore, anxiety ($P = 0.014$) and depression ($P < 0.001$) were associated with shortened overall survival (OS); after further adjustment, depression was independently linked with shortened OS ($P < 0.001$), while anxiety was not. During the follow-up period, HADS-A score (from 7.78 ± 3.180 to 8.57 ± 2.854, $P < 0.001$), HADS-D score (from 7.23 ± 2.711 to 8.01 ± 2.786, $P < 0.001$), anxiety rate (from 39.7 to 49.2%, $P = 0.019$), and depression rate (from 33.4 to 42.6%, $P = 0.023$) were all gradually increased from baseline to M36.

Conclusion Anxiety and depression gradually exacerbate and relate to poor survival in postoperative gastrointestinal cancer patients.

Keywords Anxiety and depression · Gastrointestinal cancer · Risk factor · Survival · Vertical change

Introduction

Gastrointestinal cancer, responsible for nearly 26% of cancer cases and 35% of related deaths worldwide in 2018, brings huge burdens to global public health [1–3]. Surgery (including mucosal resection, radical resection, etc.) is the primary treatment strategy for resectable gastrointestinal cancer [4–6]. However, the overall prognosis of gastrointestinal cancer is poor; many patients still undergo disease recurrence or progression after surgical resection, which greatly impacts patients' confidence towards treatment [3, 7]. Besides, operative complications and side effects of the adjuvant treatments bring sustained physical burdens to gastrointestinal cancer patients, which further leads to mental disorders (such as anxiety and depression) and ultimately impacts their clinical outcomes [8–10].

Anxiety and depression are two prevalent issues occurring in gastrointestinal cancer patients, which have been reported in several studies [11–15]. For instance, one study shows that the prevalence of anxiety and depression in colorectal cancer (CRC) patients is nearly 20.9% and 19.0%, correspondingly [15]. Another study discloses that the respective anxiety and depression rates are 33.8% and

✉ Chongyi Ma
yi89038475@163.com

[1] Department of Colorectal Cancer Surgery, The Second Affiliated Hospital of Harbin Medical University, Harbin 150086, China

[2] Department of Cardiovascular Surgery, The Second Affiliated Hospital of Harbin Medical University, No. 246 Xuefu Road, Nangang District, Harbin, Heilongjiang 150086, China

25.0% in gastric cancer (GC) patients [11]. Additionally, several studies also notice the negative correlation of anxiety and depression with survival in gastrointestinal cancer [16–18]. For example, one study identifies that depression is an independent risk factor for survival in CRC patients [18]. Nevertheless, the aforementioned studies only focus on a single cancer type or only detect anxiety and depression at patient's enrollment; meanwhile, the evidence for their risk factors and prognostic value is still inadequate.

Consequently, this study determined anxiety and depression at multiple timepoints during a 3-year follow-up period, aiming to identify their prevalence, vertical change, risk factors, and impact on survival in postoperative gastrointestinal cancer patients.

Methods

Subjects

This study consecutively enrolled 320 patients with gastrointestinal cancer (210 CRC patients and 110 GC patients) who received surgical resection from February 2017 to June 2019. Inclusion criteria were as follows: (i) newly diagnosed as CRC or GC by pathological examination; (ii) aged ≥ 18 years; (iii) received surgical resection; (iv) abled to complete questionnaire evaluation. Exclusion criteria were as follows: (i) distant metastasis; (ii) had moderate or above cognitive impairment that affected the assessment of the questionnaire; (iii) concomitant with other malignancies. The study was permitted by Ethics Committee. The informed consent was signed by each subject or his/her guardian.

Data collection

For all subjects, the clinical characteristics were obtained after enrollment, including demographics (age, gender, nationality, education duration, marital status, employment status before surgery, smoker, drinker), chronic disease (hypertension, hyperlipidemia, diabetes), cancer-related features (*Helicobacter pylori* (*H. pylori* infection), diagnosis, tumor size, pathological grade, T stage, N stage, M stage, tumor-nodes-metastasis (TNM) stage), and treatment-related information (neoadjuvant chemotherapy, surgery, postoperative complications, adjuvant chemotherapy).

Assessment and follow-up

After discharge, all subjects were followed up until death or lost to follow-up or at the endpoint of 36 months. Hospital Anxiety and Depression Scale (HADS) questionnaires, including HADS-anxiety (HADS-A) and HADS-depression (HADS-D), were completed to assess the anxiety and depression of all subjects at baseline, 12 months after baseline (M12, window period ± 1 month), 24 months after baseline (M24, window period ± 1 month), and 36 months after baseline (M36, window period ± 1 month) [19]. The total score of each HADS score was 21 points (HADS-A > 7 was defined as anxiety; HADS-D > 7 was defined as depression). Besides, the overall survival (OS) was evaluated based on the survival status of patients.

The median follow-up was 36 months with a range of 3.3 to 36 months. During it, forty-six patients were lost to follow-up, and seventy-seven patients died. For survival assessment, patients who were thought to be alive at the time of final analysis or lost to follow-up were censored at their last date of disease assessment. For HADS score evaluation, data of patients lost to followed were excluded from the analysis.

Statistics

SPSS v25.0 (IBM Corp., USA) was used for data analyses. GraphPad Prism v7.01 (GraphPad Software Inc., USA) was used for figure construction. Univariable or multivariate logistic regression analyses were applied for evaluating the risk factors of anxiety or depression. Univariable or multivariate Cox's regression analyses were applied for assessing the risk factors associated with OS. Both two above multivariate regression analyses were via the step-forward method. The relationship between survival data and anxiety or depression at baseline was displayed via Kaplan–Meier curves, in which log-rank test was used. Analysis of variance (ANOVA) for repeated measurement was utilized to show the change in HADS-A score or HADS-D score over time. Chi-square test for trend was used to analyze the variation of anxiety and depression rates over time. χ^2 test was utilized for comparing the difference of anxiety or depression rates between CRC and GC patients. $P < 0.05$ was considered significant.

Results

Clinical characteristics

Among 320 patients with gastrointestinal cancer (comprising 210 CRC patients and 110 GC patients), there were 120 (37.5%) females and 200 (62.5%) males, whose mean age was 62.0 ± 11.2 years (Table 1). With respect to the pathological grade, 57 (17.8%), 209 (65.3%), and 54 (16.9%) patients were assessed as grade 1, grade 2, and grade 3, correspondingly. Besides, 44 (13.8%), 163 (50.9%), and 113 (35.3%) patients were assessed as TNM stage I, II, and III, accordingly. A total of 127 (39.7%) and 107 (33.4%) patients suffered from anxiety and depression at baseline,

Table 1 The demographics and disease histories of patients with gastrointestinal cancer

Items	Patients ($N=320$)
Age (years), mean ± SD	62.0 ± 11.2
Gender, no. (%)	
Female	120 (37.5)
Male	200 (62.5)
Nationality, no. (%)	
Han	313 (97.8)
Others	7 (2.2)
Education duration (years), median (IQR)	9.0 (7.0–12.0)
Marital status, no. (%)	
Single/divorced/widowed	95 (29.7)
Married	225 (70.3)
Employment status before surgery, no. (%)	
Unemployed	228 (71.3)
Employed	92 (28.7)
Smoker, no. (%)	102 (31.9)
Drinker, no. (%)	80 (25.0)
Hypertension, no. (%)	127 (39.7)
Hyperlipidemia, no. (%)	63 (19.7)
Diabetes, no. (%)	44 (13.8)
H. pylori infection positive, no. (%)	138 (43.1)

SD standard deviation, *IQR* interquartile range, *H. pylori Helicobacter pylori*

Table 2 The disease status and treatment of patients with gastrointestinal cancer

Items	Patients ($N=320$)
Diagnosis, no. (%)	
CRC	210 (65.6)
GC	110 (34.4)
Pathological grade, no. (%)	
Grade 1	57 (17.8)
Grade 2	209 (65.3)
Grade 3	54 (16.9)
Tumor size (cm), median (IQR)	4.0 (3.0–5.0)
T stage, no. (%)	
T_1	11 (3.4)
T_2	35 (10.9)
T_3	270 (84.4)
T_4	4 (1.3)
N stage, no. (%)	
N_0	170 (53.1)
N_1	89 (27.8)
N_2	55 (17.2)
N_3	6 (1.9)
M stage (M_0), no. (%)	320 (100.0)
TNM stage, no. (%)	
I	44 (13.8)
II	163 (50.9)
III	113 (35.3)
Neoadjuvant chemotherapy, no. (%)	40 (12.5)
Surgery	320 (100.0)
Postoperative complications, no. (%)	111 (34.7)
Adjuvant chemotherapy, no. (%)	225 (70.3)
Anxiety at baseline, no. (%)	127 (39.7)
Depression at baseline, no. (%)	107 (33.4)

IQR interquartile range, *CRC* colorectal cancer, *GC* gastric cancer, *TNM* tumor-nodes-metastasis

respectively (Table 2). Concerning the treatment about the anxiety and depression, 120 (37.5%) patients received soporifics; 89 (27.8%) patients administrated anxiolytics (benzodiazepines); 71 (22.2%) patients received antidepressants (selective serotonin reuptake-inhibitors).

Risk factors for anxiety

Female (vs. male) (odds ratio (OR) = 1.878, $P=0.008$), single/divorced/widowed (vs. married) marital status (OR = 1.887, $P=0.010$), higher pathological grade (OR = 1.474, $P=0.049$), higher N stage (OR = 1.586, $P=0.001$), high TNM stage (OR = 1.707, $P=0.003$), neoadjuvant chemotherapy (vs. no) (OR = 3.738, $P<0.001$), and postoperative complications (vs. no) (OR = 2.096, $P=0.002$) were linked with increased anxiety risk in patients with gastrointestinal cancer. After adjusted by multivariate Cox's regression analysis, it was observed that female (vs. male) (OR = 2.183, $P=0.005$), single/divorced/widowed (vs. married) marital status (OR = 1.991, $P=0.011$), CRC (vs. GC) (OR = 1.907, $P=0.035$), higher TNM stage (OR = 1.685, $P=0.012$), neoadjuvant chemotherapy (vs. no) (OR = 5.421, $P<0.001$), and postoperative complications (vs. no) (OR = 2.324, $P=0.001$) were independently related to elevated anxiety risk (Table 3).

Risk factors for depression

Regarding depression, female (vs. male) (OR = 1.901, $P=0.008$), single/divorced/widowed (vs. married) marital status (OR = 2.366, $P=0.001$), hypertension (OR = 1.844, $P=0.011$), higher pathological grade (OR = 1.788, $P=0.005$), higher N stage (OR = 1.612, $P=0.001$), high TNM stage (OR = 1.685, $P=0.005$), neoadjuvant chemotherapy (vs. no) (OR = 2.804, $P=0.003$), postoperative complications (vs. no) (OR = 1.937, $P=0.007$), and adjuvant chemotherapy (vs. no) (OR = 2.015, $P=0.012$) were linked with elevated depression risk. While female (vs. male) (OR = 2.361, $P=0.002$), single/divorced/widowed (vs. married) marital status (OR = 2.330, $P=0.002$), hypertension (vs. no) (OR = 1.713, $P=0.039$), higher TNM stage (OR = 1.883, $P=0.003$), neoadjuvant chemotherapy (vs. no)

Table 3 The risk factors for anxiety at baseline in patients with gastrointestinal cancer via univariate and multivariate logistic regression analyses

Factors	*P* value	OR (95% CI)
Univariate logistic regression		
Age, ≥ 60 years vs. < 60 years	0.085	1.505 (0.946–2.396)
Gender, female vs. male	0.008	1.878 (1.183–2.981)
Nationality, Han vs. other	0.863	0.875 (0.192–3.976)
Education duration, < 9 years vs. ≥ 9 years	0.056	1.559 (0.988–2.461)
Marital status, single/divorced/widowed vs. married	0.010	1.887 (1.160–3.070)
Employment status before surgery, unemployed vs. employed	0.165	1.431 (0.863–2.374)
Smoker, yes vs. no	0.394	0.810 (0.498–1.315)
Drinker, yes vs. no	0.211	0.713 (0.420–1.211)
Hypertension, yes vs. no	0.192	1.355 (0.859–2.139)
Hyperlipidemia, yes vs. no	0.153	1.500 (0.861–2.612)
Diabetes, yes vs. no	0.242	1.464 (0.773–2.775)
H. pylori infection, positive vs. negative	0.096	1.468 (0.934–2.308)
Diagnosis, CRC vs. GC	0.263	1.313 (0.815–2.116)
Higher pathological grade	0.049	1.474 (1.001–2.171)
Tumor size, ≥ 4 cm vs. < 4 cm	0.168	1.379 (0.873–2.179)
Higher T stage	0.100	1.532 (0.922–2.544)
Higher N stage	0.001	1.586 (1.203–2.090)
Higher TNM stage	0.003	1.707 (1.202–2.424)
Neoadjuvant chemotherapy, yes vs. no	< 0.001	3.738 (1.847–7.569)
Postoperative complications, yes vs. no	0.002	2.096 (1.310–3.354)
Adjuvant chemotherapy, yes vs. no	0.240	1.348 (0.819–2.219)
Multivariate logistic regression		
Gender, female vs. male	0.005	2.183 (1.273–3.747)
Marital status, single/divorced/widowed vs. married	0.011	1.991 (1.173–3.377)
Diagnosis, CRC vs. GC	0.035	1.907 (1.047–3.473)
Higher TNM stage	0.012	1.685 (1.123–2.528)
Neoadjuvant chemotherapy, yes vs. no	< 0.001	5.421 (2.268–12.958)
Postoperative complications, yes vs. no	0.001	2.324 (1.385–3.899)

OR odds ratio, *CI* confidence interval, *H. pylori Helicobacter pylori, CRC* colorectal cancer, *GC* gastric cancer, *TNM* tumor-nodes-metastasis

(OR = 2.610, $P = 0.013$), and postoperative complications (vs. no) (OR = 1.962, $P = 0.012$) were independently linked with increased depression risk (Table 4).

Correlation of anxiety and depression with OS1

11Anxiety at baseline ($P = 0.014$, Fig. 1A) and depression at baseline ($P < 0.001$, Fig. 1B) were associated with shortened OS in patients with gastrointestinal cancer. To further identify the influence of anxiety and depression on OS, univariate Cox's regression analyses were conducted, which showed that anxiety at baseline (vs. no) (hazard ratio (HR) = 1.742, $P = 0.015$) and depression at baseline (vs. no) (HR = 2.806, $P < 0.001$) were both related to shortened OS in patients with gastrointestinal cancer. While after adjusted by the multivariate Cox's regression analysis, only depression at baseline was the independent factor of shorter OS (HR = 2.301, $P < 0.001$) (Table 5).

Vertical variation of anxiety and depression during the 3-year follow-up period

HADS-A score ($P < 0.001$, Fig. 2A), HADS-D score ($P < 0.001$, Fig. 2B), anxiety rate ($P = 0.019$, Fig. 2C), and depression rate ($P = 0.023$, Fig. 2D) were all gradually increased from baseline to M36 in patients with gastrointestinal cancer. Specifically, HADS-A score at baseline, M12, M24, and M36 was 7.78 ± 3.18, 7.92 ± 2.85, 8.33 ± 2.85, and 8.57 ± 2.85, correspondingly (Fig. 2A). HADS-D score at the aforementioned timepoints was 7.23 ± 2.71, 7.37 ± 2.52, 7.70 ± 2.68, and 8.01 ± 2.79, accordingly (Fig. 2B). Furthermore, the anxiety rate at baseline, M12, M24, and M36 was 39.7%, 42.8%, 46.7%, and 49.2% (Fig. 2C), correspondingly, while the respective depression rate was 33.4%, 34.9%, 38.9%, and 42.6% (Fig. 2D). Additionally, anxiety rate at M0, M12, M24, and M36 was not different between GC patients and CRC patients (all $P > 0.050$); meanwhile,

Table 4 The risk factors for depression at baseline in patients with gastrointestinal cancer via univariate and multivariate logistic regression analyses

Factors	*P* value	OR (95% CI)
Univariate logistic regression		
Age, ≥ 60 years vs. < 60 years	0.071	1.564 (0.962–2.544)
Gender, female vs. male	0.008	1.901 (1.181–3.058)
Nationality, Han vs. other	0.596	0.663 (0.146–3.019)
Education duration, < 9 years vs. ≥ 9 years	0.134	1.433 (0.895–2.295)
Marital status, single/divorced/widowed vs. married	0.001	2.366 (1.438–3.892)
Employment status before surgery, unemployed vs. employed	0.078	1.622 (0.947–2.777)
Smoker, yes vs. no	0.592	0.872 (0.527–1.441)
Drinker, yes vs. no	0.117	0.637 (0.363–1.120)
Hypertension, yes vs. no	0.011	1.844 (1.149–2.957)
Hyperlipidemia, yes vs. no	0.143	1.527 (0.867–2.690)
Diabetes, yes vs. no	0.432	1.301 (0.675–2.510)
H. pylori infection, positive vs. negative	0.657	1.112 (0.696–1.775)
Diagnosis, CRC vs. GC	0.488	1.191 (0.727–1.952)
Higher pathological grade	0.005	1.788 (1.787–2.692)
Tumor size, ≥ 4 cm vs. < 4 cm	0.405	1.222 (0.762–1.962)
Higher T stage	0.249	1.358 (1.808–2.282)
Higher N stage	0.001	1.612 (1.217–2.135)
Higher TNM stage	0.005	1.685 (1.170–2.428)
Neoadjuvant chemotherapy, yes vs. no	0.003	2.804 (1.431–5.496)
Postoperative complications, yes vs. no	0.007	1.937 (1.197–3.135)
Adjuvant chemotherapy, yes vs. no	0.012	2.015 (1.165–3.483)
Multivariate logistic regression		
Gender, female vs. male	0.002	2.361 (1.361–4.096)
Marital status, single/divorced/widowed vs. married	0.002	2.330 (1.359–3.993)
Hypertension, yes vs. no	0.039	1.713 (1.027–2.858)
Higher TNM stage	0.003	1.883 (1.242–2.856)
Neoadjuvant chemotherapy, yes vs. no	0.013	2.610 (1.219–5.587)
Postoperative complications, yes vs. no	0.012	1.962 (1.158–3.325)

OR odds ratio, *CI* confidence interval, *H. pylori Helicobacter pylori, CRC* colorectal cancer, *GC* gastric cancer, *TNM* tumor-nodes-metastasis

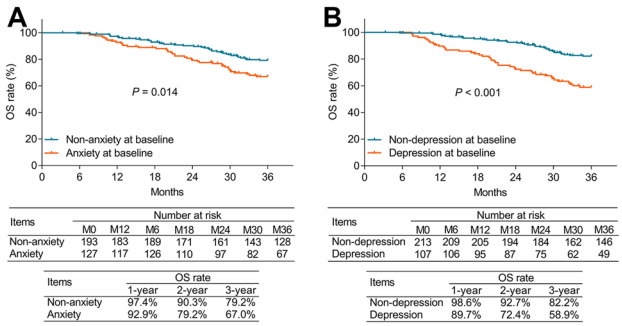

Fig. 1 Anxiety and depression at baseline linked with shorter OS in patients with gastrointestinal cancer. Association of anxiety at baseline (**A**) and depression at baseline (**B**) with OS in patients with gastrointestinal cancer

depression rate M0, M12, M24, and M36 was not varied between GC patients and CRC patients (all $P > 0.050$) (Supplementary Table 1).

Subgroup analysis

In CRC patients, female (vs. male), single/divorced/widowed (vs. married) marital status, higher pathological grade, higher TNM stage, postoperative complications (vs. no), and adjuvant chemotherapy (vs. no) were independently related to increased anxiety or depression risk (all OR > 1.00, $P < 0.050$). While in GC patients, female (vs. male), neoadjuvant chemotherapy (vs. no), and postoperative complications (vs. no) were independent factors for elevated anxiety or depression risk (all OR > 1.00, $P < 0.050$) (Table 6).

Table 5 The risk factors for OS in patients with gastrointestinal cancer via univariate and multivariate Cox's regression analyses

Factors	*P* value	HR (95% CI)
Univariate Cox's regression		
Anxiety at baseline, yes vs. no	0.015	1.742 (1.114–2.725)
Depression at baseline, yes vs. no	< 0.001	2.806 (1.791–4.397)
Age, ≥ 60 years vs. < 60 years	0.978	1.006 (0.638–1.587)
Gender, female vs. male	0.429	0.826 (0.515–1.325)
Nationality, Han vs. other	0.555	1.811 (0.252–13.026)
Education duration, < 9 years vs. ≥ 9 years	0.857	1.043 (0.663–1.640)
Marital status, single/divorced/widowed vs. married	0.719	0.912 (0.552–1.506)
Employment status before surgery, unemployed vs. employed	0.130	1.503 (0.886–2.548)
Smoker, yes vs. no	0.107	0.653 (0.389–1.097)
Drinker, yes vs. no	0.806	0.937 (0.558–1.573)
Hypertension, yes vs. no	0.195	1.345 (0.859–2.104)
Hyperlipidemia, yes vs. no	0.352	1.285 (0.758–2.178)
Diabetes, yes vs. no	0.289	0.673 (0.324–1.399)
H. pylori infection, positive vs. negative	0.751	1.075 (0.687–1.684)
Diagnosis, CRC vs. GC	0.017	1.878 (1.118–3.154)
Higher pathological grade	< 0.001	2.870 (1.956–4.213)
Tumor size, ≥ 4 cm vs. < 4 cm	0.163	1.392 (0.875–2.214)
Higher T stage	0.001	3.149 (1.623–6.109)
Higher N stage	< 0.001	1.914 (1.510–2.425)
Higher TNM stage	< 0.001	3.558 (2.338–5.415)
Neoadjuvant chemotherapy, yes vs. no	0.270	1.399 (0.770–2.539)
Postoperative complications, yes vs. no	0.753	1.077 (0.677–1.714)
Adjuvant chemotherapy, yes vs. no	0.003	2.585 (1.396–4.786)
Multivariate Cox's regression		
Depression at baseline, yes vs. no	< 0.001	2.301 (1.462–3.620)
Higher pathological grade	< 0.001	2.229 (1.506–3.299)
Higher TNM stage	< 0.001	2.888 (1.908–4.369)

OS overall survival, *HR* hazard ratio, *CI* confidence interval, *H. pylori Helicobacter pylori, CRC* colorectal cancer, *GC* gastric cancer, *TNM* tumor-nodes-metastasis

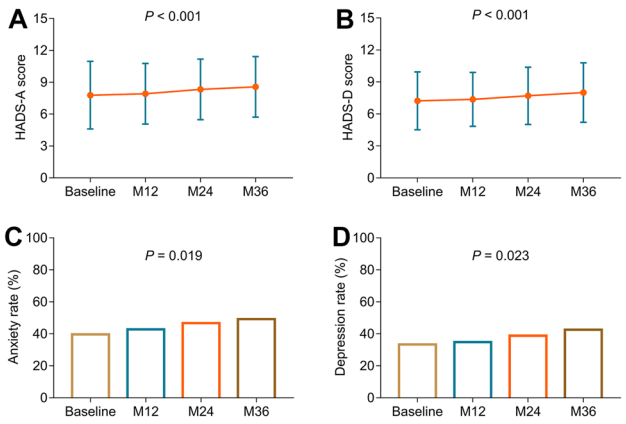

Fig. 2 HADS-A score, HADS-D score, anxiety rate, and depression rate gradually increased during 3-year follow-up in patients with gastrointestinal cancer. Variations of HADS-A score (**A**), HADS-D score (**B**), anxiety rate (**C**), and depression rate (**D**) at baseline, M12, M24, and M36 in patients with gastrointestinal cancer

In CRC patients, anxiety ($P = 0.022$, Fig. 3A) and depression ($P < 0.001$, Fig. 3B) were associated with shorter OS. During the 3-year follow-up, HADS-A score ($P < 0.001$, Fig. 3C) and HADS-D score ($P < 0.001$, Fig. 3D) gradually elevated from baseline to M36, but anxiety rate ($P = 0.077$, Fig. 3E) and depression rate ($P = 0.077$, Fig. 3F) only exhibited increasing trends (without statistical significance) during the follow-up period. Regarding GC patients, anxiety ($P = 0.535$, Fig. 3G) and depression ($P = 0.115$, Fig. 3H) were not correlated with OS. HADS-A score ($P < 0.001$, Fig. 3I) and HADS-D score ($P < 0.001$, Fig. 3J) both gradually increased from baseline to M36; nonetheless, anxiety rate ($P = 0.086$, Fig. 3K) and depression rate ($P = 0.129$, Fig. 3L) displayed a climbing trend (lacked statistical significance) from baseline to M36.

Table 6 The independent risk factors for anxiety and depression at baseline in respective CRC and GC patients

Factors	*P* value	OR (95% CI)
CRC patients		
Anxiety at baseline		
Gender, female vs. male	0.048	1.879 (1.005–3.513)
Marital status, single/divorced/widowed vs. married	0.020	2.114 (1.127–3.968)
Higher TNM stage	0.008	1.809 (1.165–2.811)
Postoperative complications, yes vs. no	0.020	2.074 (1.124–3.828)
Depression at baseline		
Marital status, single/divorced/widowed vs. married	0.001	2.931 (1.524–5.638)
Higher pathological grade	0.004	2.296 (1.301–4.053)
Postoperative complications, yes vs. no	0.036	1.990 (1.045–3.790)
Adjuvant chemotherapy, yes vs. no	0.006	2.724 (1.328–5.589)
GC patients		
Anxiety at baseline		
Gender, female vs. male	0.029	3.157 (1.123–8.875)
Neoadjuvant chemotherapy, yes vs. no	< 0.001	14.907 (4.854–45.781)
Postoperative complications, yes vs. no	0.020	3.439 (1.218–9.713)
Depression at baseline		
Gender, female vs. male	0.020	3.166 (1.198–8.368)
Neoadjuvant chemotherapy, yes vs. no	< 0.001	6.149 (2.254–16.776)
Postoperative complications, yes vs. no	0.051	2.611 (0.995–6.854)

CRC colorectal cancer, *GC* gastric cancer, *OR* odds ratio, *CI* confidence interval, *TNM* tumor-nodes-metastasis

Discussion

Anxiety and depression, two common mental disorders in gastrointestinal cancer patients, arise more and more attention in recent years, whose prognostic value has been noticed in a minority of studies [9, 16, 17]. For instance, one previous study shows that anxiety and depression are related to lower OS in CRC patients [16]. Another study finds that disease-free survival (DFS) and OS are both worse in anxiety (vs. non-anxiety) GC patients and depression (vs. non-depression) GC patients [17]. However, the relevant evidence is still not adequate. In the present study, anxiety and depression at baseline were both associated with shortened OS in patients with gastrointestinal cancer, while only depression at baseline was the independent risk factor for worse OS. Probable reasons were as follows: (1) Anxiety and depression intensified social isolation and suicidal tendency; subsequently, the desire for survival and compliance towards treatment of gastrointestinal cancer patients were reduced [20, 21]. As a result, anxiety and depression were linked with shortened OS in gastrointestinal cancer patients. (2) Since depression lasted for a longer duration and elicited more profound changes in behavior (including anhedonia, psychomotor retardation, and fatigue) compared with anxiety, the negative impact of depression was beyond anxiety [22, 23]. Hence, only depression was the independent risk factor for poor OS in patients with gastrointestinal cancer.

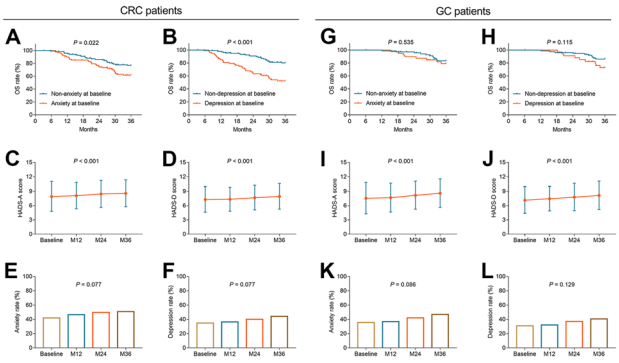

Fig. 3 Subgroup analysis of anxiety and depression in CRC and GC patients. Correlation of anxiety at baseline (**A**) and depression at baseline (**B**) with OS in CRC patients. Longitudinal change of HADS-A score (**C**), HADS-D score (**D**), anxiety rate (**E**), and depression rate (**F**) from baseline to M36 in CRC patients. Correlation of anxiety at baseline (**G**) and depression at baseline (**H**) with OS in GC patients. Longitudinal change of HADS-A score (**I**), HADS-D score (**J**), anxiety rate (**K**), and depression rate (**L**) from baseline to M36 in GC patients

Aside from the prognostic value, this study also determined the vertical variation of anxiety and depression within 3-year follow-up period, which showed that the severity and incidence of anxiety and depression were all gradually increased from baseline to M36 in patients

with gastrointestinal cancer. The possible explanations were those: (1) Postoperative complications would cause long-term function impairments in gastrointestinal cancer patients, whose anxiety and depression degrees were then exacerbated [24–26]. (2) After surgery treatment, some patients underwent adjuvant therapies, while the adverse events brought uncomfortable and painful feelings to patients [27, 28]. (3) Many gastrointestinal cancer patients experienced disease recurrence, which made them lose confidence towards the subsequent treatment [29, 30]. Consequently, anxiety and depression of gastrointestinal cancer patients became more severe during the 3-year follow up. Additionally, it was worth mentioning that although the accuracy of HADS was not as good as some other scales (such as Zung SAS/SDS and Hamilton scales), while due to its evaluating convenience, HADS was relatively more suitable for long-term follow-up duration and would be helpful for increasing patient compliance. Therefore, this study utilized HADS for anxiety and depression assessment.

For the purpose of providing more effective and specific interventions against anxiety and depression, some previous studies explore the risk factors of anxiety and depression in gastrointestinal cancer [11, 16]. For instance, one study discloses that the risk factors of anxiety and depression occurrence include age ≥ 60 years, higher TNM stage at diagnosis, diabetes, distant metastasis, tumor location at diagnosis (cardia vs. gastric antrum), and recurrence in GC patients [11]. Partially in line with the previous studies, this study recognized that the independent risk factors of anxiety or depression in patients with gastrointestinal cancer included female (vs. male), single/divorced/widowed (vs. married), higher TNM stage, neoadjuvant chemotherapy, and postoperative complications. The probable explanations were listed as follows: (1) Female patients were more likely to experience anxiety and depression feelings following hormonal flux, while the sensitivity of males towards emotional change was relatively weak [31, 32]. (2) Single/divorced/widowed patients lacked enough care and support compared with married patients, which made them harder to overcome negative emotions. (3) Patients with higher TNM stage obtained limited treatment efficacy and unsatisfying clinical outcomes, then their anxiety and depression degrees were aggravated [33]. (4) Neoadjuvant chemotherapy and postoperative complications added uncomfortable experiences and reduced patients' quality of life, which led to elevated anxiety and depression risk [34].

Some limitations were noticed in this study. Firstly, although HADS questionnaires were common scales for anxiety and depression determination with delightful convenience, some other questionnaires (such as Zung self-rating anxiety scale/self-rating depression scale or Hamilton scales) should also be considered for comprehensively exploring anxiety and depression in gastrointestinal cancer. Secondly, this was a single-center study; thus, further multiple-center studies were warranted for eliminating selective bias and verifying the findings. Thirdly, the anxiety and depression status in recurrent gastrointestinal cancer patients was unclear in this study. Fourthly, anxiety and depression might affect the treatment compliance; however, this study did not record the cancer drug retention rate, which should be investigated in further studies. Fifthly, because of the limited number of investigators and that many patients came from other provinces, the DFS data was hard to precisely collect. Meanwhile, this study aimed to evaluate the correlation of anxiety and depression with survival, and the OS data was easier to obtain. Consequently, this study only analyzed the OS data. The association of anxiety and depression with DFS in gastrointestinal cancer patients should be evaluated in further studies.

In summary, our study not only discloses exacerbated anxiety and depression with prognostic value in postoperative gastrointestinal cancer patients, but also identifies several risk factors which may help their prevention, which is helpful for clinical management of gastrointestinal cancer patients' mental disorder. However, the findings warrant further verification in multi-center studies with a larger sample size and more assessment scales.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval The study was permitted by Ethics Committee. The informed consent was signed by each subject or his/her guardian.

Competing interests The authors declare no competing interests.

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