

Anxiety and depression in recurrent gastric cancer

Their prevalence and independent risk factors analyses

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Abstract

Various anxiety and depression-related risk factors have been reported in cancer patients. However, little is known about the anxiety and depression-related risk factors in recurrent gastric cancer patients. Therefore, our aim was to investigate the prevalence and risk factors for anxiety and depression in recurrent gastric cancer patients.

Totally 82 recurrent gastric cancer patients were consecutively recruited, and their clinical features were collected from hospital's electronic medical records. Besides, 80 newly diagnosed gastric cancer patients and 80 healthy controls were enrolled. Their anxiety and depression status was assessed using Hospital Anxiety and Depression Scale (HADS).

The HADS-anxiety score (9.1 ± 3.4 , 7.2 ± 3.0 , 4.8 ± 2.7 , respectively) and the percentage of anxiety patients (52.4%, 33.8%, 11.3%, respectively) were increased in recurrent gastric cancer patients compared to newly diagnosed gastric cancer patients and healthy controls; Also, the HADS-depression score (7.9 ± 3.1 , 6.7 ± 2.6 , 4.1 ± 2.8 , respectively) and the percentage of depression patients (41.5%, 25.0%, 8.8%, respectively) had similar trends. Forward stepwise multivariate logistic regression revealed that age ≥ 60 years, diabetes, tumor-node-metastasis (TNM) stage at diagnosis, shorter time to recurrence and distant metastasis at recurrence were independent risk factors for anxiety occurrence, whereas age ≥ 60 years, diabetes, tumor location at diagnosis (cardia vs gastric antrum) and shorter time to recurrence were independent risk factors for depression occurrence.

The prevalence of anxiety and depression is such high, and their relevant risk factors include age ≥ 60 years, diabetes and shorter time to recurrence in recurrent gastric cancer patients.

Abbreviations: HADS = Hospital Anxiety and Depression Scale, HADS-A = HADS anxiety, HADS-D = HADS depression, HCs = healthy controls.

Keywords: anxiety, depression, prevalence, recurrent gastric cancer, risk factors

1. Introduction

Over 1,000,000 new cases of gastric cancer are estimated to have occurred during 2018, making it the fifth most frequently diagnosed malignancy globally.^[1] Since the early symptoms are relatively hidden, most gastric cancer patients are diagnosed at

advanced stage. Despite of the improvement of gastric cancer management, the recurrence rate is still high in China.^[2] Due to the despair from recurrence and body discomfort caused by continuous treatment, parts of gastric cancer patients in face of recurrence are likely to have psychiatric disorders, particular in anxiety and depression.^[3,4] Of note, anxiety and depression also accelerate the development and progression of gastric cancer via multiple mechanisms (such as affecting reactive oxygen species-activated ABL1^[5] and regulating the hypothalamic-pituitary-adrenal axis (such as FK506 binding protein 5 gene polymorphisms),^[4] thereby causing disease deterioration and increasing recurrence in gastric cancer patients. Taken together, there is such a high prevalence and perniciousness of anxiety and depression in patients with various cancers. However, the prevalence and risk factors for anxiety and depression are still unclear in recurrent gastric cancer patients. Thus, attention should be turned to recurrent gastric cancer patients, which may be helpful to improve their prognosis.

Existing data clarify various anxiety and depression-related risk factors in cancer patients (such as lack of surgery as well as young age in lung cancer patients,^[6] metastasis as well as previous episodes of anxiety and depression in breast cancer patients,^[7] and age ≥ 65 years, education duration < 9 years, marry status of single/divorced/widowed, unemployment before surgery, diabetes, hyperlipidemia as well as worse tumor features in prostate cancer patients).^[8] However, little is known about the anxiety and depression-related risk factors in recurrent gastric cancer patients.

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Therefore, our aim was to investigate the prevalence and potential risk factors for anxiety and depression in recurrent gastric cancer patients.

2. Methods

2.1. Subjects

A total of 82 recurrent gastric cancer patients admitted to our hospital from May 2018 to July 2020 were consecutively recruited in this study. The screening criteria were: previous surgery for gastric cancer; had gastric cancer recurrence after surgery; age ≥ 18 years; without uncontrolled basic diseases (eg, hypertension, diabetes or arrhythmia); and without cognitive impairment and could finish study questionnaires independently. In addition, 80 age- and gender-matched newly diagnosed gastric cancer patients and 80 age- and gender-matched healthy subjects were enrolled as disease controls and healthy controls (HCs), respectively. This study was approved by the Ethics Committee of our hospital. Written informed consents were obtained from the subjects before they participated in the study.

2.2. Data collection and assessment

The clinical features of recurrent gastric cancer patients were collected from hospital's electronic medical records, which included: demographics, complications, tumor features at diagnosis, time to recurrence, recurrent tumor location and distant metastases status at recurrence. The anxiety and depression status of recurrent gastric cancer patients before initiation of treatment were assessed using Hospital Anxiety and Depression Scale (HADS); meanwhile for determination of anxiety, the sensitivity and specificity were 0.84 and 0.64 with a cutoff value of HADS anxiety (HADS-A) score of 7 or higher^[9]; for determination of depression, the sensitivity and specificity were 0.82 and 0.78 with a cutoff value of HADS depression (HADS-D) score of 7 or higher.^[10] The anxiety and depression status of newly diagnosed gastric cancer patients were evaluated before initiation of treatment, and the anxiety as well as depression status of HCs were evaluated at the enrollment. There were 2 independent parts in HADS, 1 was related to HADS-A, another was associated with HADS-D. In HADS-A, a total of 7 items about anxiety were listed, and each item was scored from 0 to 3. In HADS-D, there were 7 items about depression, each item was scored from 0 to 3 as well. The total score of HADS-A and HADS-D ranging from 0 to 21, respectively. Patients with HADS-A or HADS-D score ≥ 8 were divided into anxiety group or depression group, respectively; others with HADS-A or HADS-D score < 8 were divided into nonanxiety group or nondepression group, correspondingly.^[11]

2.3. Statistical analysis

Student *t* test, Chi-square test and Wilcoxon rank sum test were used for analyzing the statistical difference between 2 groups. Univariate logistic regression model was used to analyze the factors related to anxiety or depression. Forward stepwise multivariate logistic regression model was used to screen the factors independently associated with anxiety or depression. SPSS 22.0 (IBM, Chicago, IL) was used to perform the statistical analyses. GraphPad Prism 7.01 (GraphPad Software, San Diego, CA) was used for figures making. *P* value $< .05$ was considered significant.

3. Results

3.1. Recurrent gastric cancer patients' characteristics

The mean age was 58.1 ± 11.4 years, and there were 46 (56.1%) males as well as 36 (43.9%) females in recurrent gastric cancer patients. Besides, the detailed information of recurrent gastric cancer patients about current smoke, current drink, education duration, marry status, employed status, complications, tumor features at diagnosis, tumor location, pathological grade, tumor size, tumor-node-metastasis (TNM) stage, time to recurrence, recurrent tumor location, and distant metastases at recurrence was presented in Table 1.

3.2. Anxiety and depression

Regarding anxiety, the HADS-A score in recurrent gastric cancer patients, newly diagnosed gastric cancer patients and HCs was

Table 1
Characteristics of recurrent gastric cancer patients.

Items	Recurrent gastric cancer patients (N=82)
Demographics	
Age (yr), mean \pm SD	58.1 \pm 11.4
Gender, no. (%)	
Male	46 (56.1)
Female	36 (43.9)
Current smoke, no. (%)	22 (26.8)
Current drink, no. (%)	31 (37.8)
Education duration (yr), mean \pm SD	10.1 \pm 3.8
Marry status, no. (%)	
Married	49 (59.8)
Single/divorced/widowed	33 (40.2)
Employment status, no. (%)	
Employed	21 (25.6)
Unemployed	61 (74.4)
Complications	
Hypertension, no. (%)	38 (46.3)
Hyperlipidemia, no. (%)	19 (23.2)
Diabetes, no. (%)	14 (17.1)
<i>H. pylori</i> infection, no. (%)	34 (41.5)
Tumor features at diagnosis	
Tumor location, no. (%)	
Cardia	31 (37.8)
Gastric body	32 (39.0)
Gastric antrum	19 (23.2)
Pathological grade, no. (%)	
G1	11 (13.4)
G2	47 (57.3)
G3	24 (29.3)
Tumor size (cm), mean \pm SD	3.6 \pm 1.2
TNM stage, no. (%)	
I	5 (6.1)
II	39 (47.6)
III	38 (46.3)
Time to recurrence, no. (%)	
< 3 yr	22 (26.8)
3–5 yr	29 (35.4)
≥ 5 yr	31 (37.8)
Recurrent tumor location, no. (%)	
Cardia	32 (39.0)
Gastric body	39 (47.6)
Gastric antrum,	11 (13.4)
Distant metastases at recurrence, no. (%)	
No	59 (72.0)
Yes	23 (28.0)

SD = standard deviation.

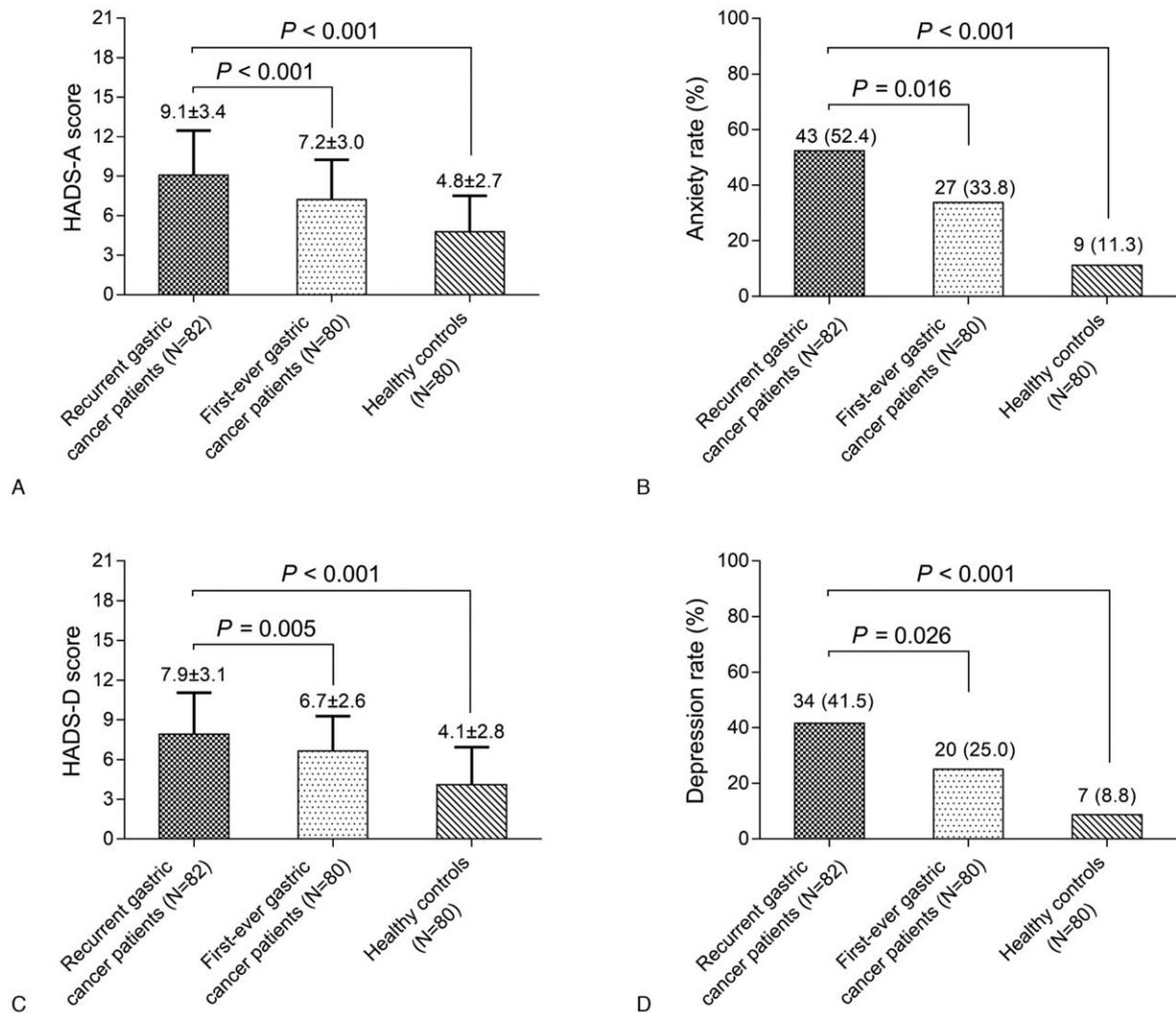


Figure 1. Comparison of anxiety and depression among recurrent gastric cancer patients, newly diagnosed gastric cancer patients and HCs. Comparison of HADS-A score (A) and anxiety rate (B) among recurrent gastric cancer patients, newly diagnosed gastric cancer patients and HCs; Comparison of HADS-D score (C) and depression rate (D) among recurrent gastric cancer patients, newly diagnosed gastric cancer patients and HCs. HADS-A = Hospital Anxiety and Depression Scale for anxiety, HADS-D = Hospital Anxiety and Depression Scale for depression, HCs = health controls.

9.1 ± 3.4, 7.2 ± 3.0 and 4.8 ± 2.7, respectively. Compared to newly diagnosed gastric cancer patients ($P < .001$) and HCs ($P < .001$), the HADS-A score was obviously increased in recurrent gastric cancer patients (Fig. 1A). Besides, there were 43 (52.4%) recurrent gastric cancer patients, 27 (33.8%) newly diagnosed gastric cancer patients and 9 (11.3%) HCs with anxiety, and the percentage of anxiety patients in recurrent gastric cancer patients was increased compared to newly diagnosed gastric cancer patients ($P = .016$) and HCs ($P < .001$) (Fig. 1B).

Regarding depression, The HADS-D score in recurrent gastric cancer patients, newly diagnosed gastric cancer patients and HCs was 7.9 ± 3.1, 6.7 ± 2.6 and 4.1 ± 2.8, respectively. Compared to newly diagnosed gastric cancer patients ($P = .005$) and HCs ($P < .001$), the HADS-D score was obviously increased in recurrent gastric cancer patients (Fig. 1C). Besides, there were 34 (41.5%) recurrent gastric cancer patients, 20 (25.0%) newly diagnosed gastric cancer patients and 7 (8.8%) HCs with depression, and the percentage of depression patients in recurrent gastric cancer patients was increased compared to newly

diagnosed gastric cancer patients ($P = .026$) and HCs ($P < .001$) (Fig. 1D).

3.3. Correlation of clinical characteristics with anxiety

Compared to recurrent gastric cancer patients without anxiety, recurrent gastric cancer patients with anxiety presented with increased single/divorced/widowed status ($P = .034$), diabetes ($P = .006$), TNM stage ($P = .016$), and distant metastasis at recurrence ($P = .015$), but decreased time to recurrence ($P = .005$) (Table 2).

3.4. Risk factors affecting anxiety in recurrent gastric cancer patients

Univariate logistic regression showed that age ≥ 60 years ($P = .029$), single/divorced/widowed status ($P = .036$), diabetes ($P = .014$), TNM stage at diagnosis ($P = .017$), shorter time to recurrence ($P = .002$) and distant metastasis at recurrence

Table 2**Comparison of clinical characteristics between recurrent gastric cancer patients with or without anxiety.**

Items	Recurrent gastric cancer patients		P value
	Nonanxiety (n = 39)	Anxiety (n = 43)	
Demographics			
Age (yr), mean ± SD	57.7 ± 10.3	58.5 ± 12.4	.741
Gender, no. (%)			.066
Male	26 (66.7)	20 (46.5)	
Female	13 (33.3)	23 (53.5)	
Current smoke, no. (%)	11 (28.2)	11 (25.6)	.789
Current drink, no. (%)	13 (33.3)	18 (41.9)	.426
Education duration (yr), mean ± SD	10.1 ± 4.1	10.0 ± 3.5	.923
Marry status, no. (%)			.034
Married	28 (71.8)	21 (48.8)	
Single/divorced/widowed	11 (28.2)	22 (51.2)	
Employment status, no. (%)			.127
Employed	13 (33.3)	8 (18.6)	
Unemployed	26 (66.7)	35 (81.4)	
Complications			
Hypertension, no. (%)	15 (38.5)	23 (53.5)	.173
Hyperlipidemia, no. (%)	7 (17.9)	12 (27.9)	.286
Diabetes, no. (%)	2 (5.1)	12 (27.9)	.006
<i>H. pylori</i> infection, no. (%)	14 (35.9)	20 (46.5)	.330
Tumor features at diagnosis			
Tumor location, no. (%)			.487
Cardia	15 (38.5)	16 (37.2)	
Gastric body	13 (33.3)	19 (44.2)	
Gastric antrum	11 (28.2)	8 (18.6)	
Pathological grade, no. (%)			.171
G1	8 (20.5)	3 (7.0)	
G2	21 (53.9)	26 (60.5)	
G3	10 (25.6)	14 (32.5)	
Tumor size (cm), mean ± SD	3.5 ± 1.2	3.7 ± 1.2	.610
TNM stage, no. (%)			.016
I	4 (10.3)	1 (2.3)	
II	22 (56.4)	17 (39.5)	
III	13 (33.3)	25 (58.2)	
Time to recurrence, no. (%)			.005
<3 yr	5 (12.8)	17 (39.5)	
3–5 yr	13 (33.3)	16 (37.2)	
≥5 yr	21 (53.9)	10 (23.3)	
Recurrent tumor location, no. (%)			.882
Cardia	15 (38.5)	17 (39.5)	
Gastric body	18 (46.2)	21 (48.9)	
Gastric antrum	6 (15.3)	5 (11.6)	
Distant metastases at recurrence, no. (%)			.015
No	33 (84.6)	26 (60.5)	
Yes	6 (15.4)	17 (39.5)	

SD = standard deviation.

Bold values indicate that these comparisons are statistically significant.

($P=.018$) were related to anxiety occurrence. Further forward stepwise multivariate logistic regression revealed that age ≥ 60 years ($P=.002$), diabetes ($P=.025$), TNM stage at diagnosis ($P=.019$), shorter time to recurrence ($P=.008$) and distant metastasis at recurrence ($P=.014$) were independent risk factors for anxiety (Fig. 2).

3.5. Correlation of clinical characteristics with depression

Compared to recurrent gastric cancer patients without depression, more recurrent gastric cancer patients with depression were

females ($P=.022$), with diabetes ($P=.012$) and increased time to recurrence ($P=.004$) (Table 3).

3.6. Risk factors affecting depression in recurrent gastric cancer patients

Univariate logistic regression showed that female ($P=.024$), diabetes ($P=.018$) and shorter time to recurrence ($P=.002$) were related to depression occurrence. Further forward stepwise multivariate logistic regression revealed that age ≥ 60 years ($P=.032$), diabetes ($P=.013$), tumor location at diagnosis (cardia vs gastric antrum) ($P=.012$) and shorter time to recurrence ($P<.001$) were independent risk factors for depression (Fig. 3).

4. Discussion

Anxiety and depression in cancer patients have been a hot topic in clinical research. Existing evidence shows that the prevalence of anxiety and depression are 6.49% and 66.72%, respectively in Chinese cancer patients.^[12] Whereas it is still obscure for the prevalence of anxiety and depression in recurrent gastric cancer patients. In the present study, we discovered that the proportions of anxiety and depression were 52.4% and 41.5% in recurrent gastric cancer patients, which were increased compared to newly diagnosed gastric cancer patients and HCs, which might be caused by that gastric patients in face of recurrence trended to have huge mental stress again to loss self-confidence and even produce despair form cancer and death, subsequently resulted in increased anxiety and depression occurrence.

Exploring the risk factors of anxiety and depression in cancer patients is essential to reduce the occurrence of anxiety and depression, or even avoid these psychological disorders, eventually improve the prognosis in cancer patients. Recently, several studies clarify various risk factors-related to anxiety and depression in cancer patients. For instance, postoperative pain and combined liver disease have been reported to be independent risk factors for postoperative anxiety, while low literacy, postoperative pain, high clinical stage, and combined liver disease are considered as independent risk factors for postoperative depression in endometrial cancer patients.^[5] Besides, shorter time since diagnosis and higher number of comorbid diseases relate to higher anxiety occurrence, whereas female sex and higher number of comorbid diseases correlate with higher depressive occurrence in colorectal cancer patients.^[13] Another current study displays that functional impairment, pretreatment physical symptom burden, fatigue, and clinician-rated performance status are risk factors for depression in lung cancer patients.^[14] Although a number of researchers have discovered a variety of factors influencing the prevalence of anxiety and depression in patients with several cancers, limited relevant information in recurrent gastric cancer patients is found.

In the present study, we excluded the patients with uncontrolled basic diseases (eg, hypertension, diabetes or arrhythmia) due to that the inclusion of these patients might influence the result of this study and lead to a low compliance of patients in this study.^[15–17] Besides, we discovered that age ≥ 60 years, diabetes, TNM stage at diagnosis, shorter time to recurrence and distant metastasis at recurrence could independently related to anxiety occurrence in recurrent gastric cancer patients. There were

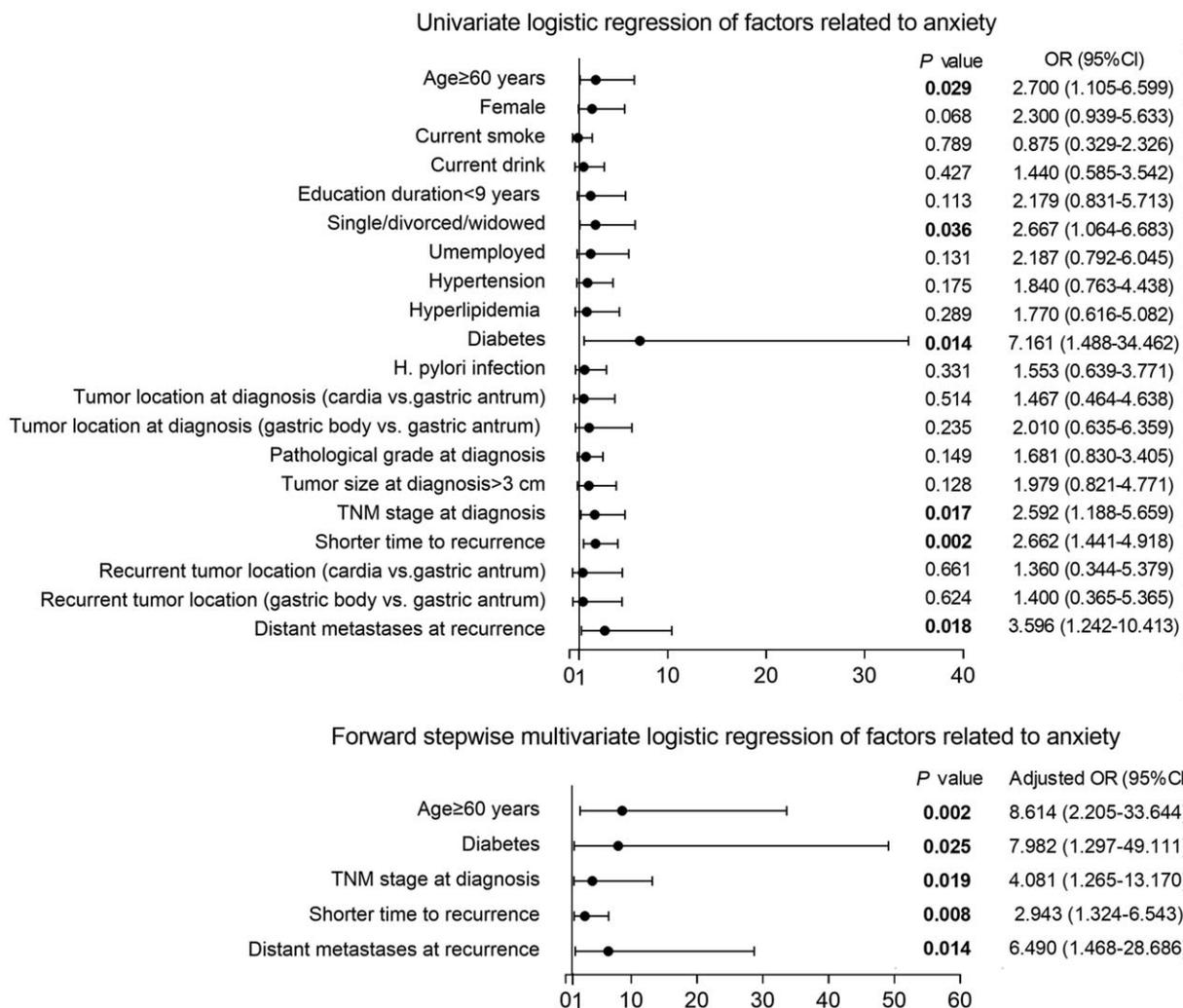


Figure 2. Univariate logistic regression and forward stepwise multivariate logistic regression of factors related to anxiety. CI = confidence interval, OR = odds ratio, TNM = tumor lymph nodes metastasis.

several possible explanations: regarding age ≥60 years, older patients had poor Immune ability and physical basis. Hence, when occurring with recurrence, they presented with huge psychological stress from recurrent symptoms and fear of death, thereby increasing anxiety occurrence.^[18] Regarding diabetes, long history of diabetes was related to poor Immune function and microvascular erosion, recurrent gastric cancer patients with diabetes appeared to be more difficult to fight cancer cells.^[18] Regarding TNM stage at diagnosis, high TNM stage meant difficult to be treated, thus, recurrent gastric cancer patients with high TNM stage were related to poor treatment efficacy and high risk of complications, which might increase patients' anxiety. Regarding shorter time to recurrence and distant metastasis at recurrence, patients might be difficult to accept, and it was easy to loss self-confidence for treatment, thereby caused anxiety.

In terms of depression, we also found that age ≥60 years, diabetes, tumor location at diagnosis (cardia vs gastric antrum) and shorter time to recurrence were independent risk factors for depression in recurrent gastric cancer patients. Probable reasons

might exist as follows: regarding age ≥60 years, according to above-mentioned evidence, older patients exerted high risk of anxiety, meanwhile, they might present with increased depression occurrence due to poor immune ability and worse body conditions.^[19] Regarding diabetes, diabetes was related to chronic hypercortisolemia and the sympathetic nervous system, thereby correlated with the hypothalamus–pituitary–adrenal axis, eventually increased depression occurrence in recurrent gastric cancer patients.^[20,21] Regarding tumor location at diagnosis (cardia vs gastric antrum), recurrent gastric cancer at cardia usually presented with high grade of malignancy, hence, they might have more despair in face of recurrence at cardia compared to gastric antrum, subsequently increased depression occurrence in recurrent gastric cancer patients. Regarding shorter time to recurrence, it was difficult to accept the recurrence news for gastric cancer patients during the short time, hence, high risk of depression might occur in gastric cancer patients with short time to recurrence.

These finding indicated that we might carry out the risk stratification of gastric cancer patients with the finding from this

Table 3
Comparison of clinical characteristics between recurrent gastric cancer patients with or without depression.

Items	Recurrent gastric cancer patients		P value
	Nondepression (n = 48)	Depression (n = 34)	
Demographics			
Age (yr), mean \pm SD	59.1 \pm 11.0	56.8 \pm 12.0	.374
Gender, no. (%)			.022
Male	32 (66.7)	14 (41.2)	
Female	16 (33.3)	20 (58.8)	
Current smoke, no. (%)	15 (31.3)	7 (20.6)	.283
Current drink, no. (%)	17 (35.4)	14 (41.2)	.596
Education duration (yr), mean \pm SD	10.2 \pm 3.6	9.9 \pm 4.1	.730
Marry status, no. (%)			.547
Married	30 (62.5)	19 (55.9)	
Single/divorced/widowed	18 (37.5)	15 (44.1)	
Employment status, no. (%)			.164
Employed	15 (31.3)	6 (17.6)	
Unemployed	33 (68.8)	28 (82.4)	
Complications			
Hypertension, no. (%)	21 (43.8)	17 (50.0)	.576
Hyperlipidemia, no. (%)	9 (18.8)	10 (29.4)	.260
Diabetes, no. (%)	4 (8.3)	10 (29.4)	.012
<i>H. pylori</i> infection, no. (%)	19 (39.6)	15 (44.1)	.681
Tumor features at diagnosis			
Tumor location, No. (%)			.319
Cardia	15 (31.3)	16 (47.1)	
Gastric body	20 (41.7)	12 (35.3)	
Gastric antrum	13 (27.0)	6 (17.6)	
Pathological grade, no. (%)			.089
G1	7 (14.6)	4 (11.8)	
G2	31 (64.6)	16 (47.0)	
G3	10 (20.8)	14 (41.2)	
Tumor size (cm), mean \pm SD	3.5 \pm 1.2	3.7 \pm 1.2	.480
TNM stage, no. (%)			.116
I	4 (8.3)	1 (2.9)	
II	25 (52.1)	14 (41.2)	
III	19 (39.6)	19 (55.9)	
Time to recurrence, no. (%)			.004
<3 yr	7 (14.6)	15 (44.1)	
3–5 yr	17 (35.4)	12 (35.3)	
\geq 5 yr	24 (50.0)	7 (20.6)	
Recurrent tumor location, no. (%)			.157
Cardia	15 (31.3)	17 (50.0)	
Gastric body	27 (56.3)	12 (35.3)	
Gastric antrum	6 (12.4)	5 (14.7)	
Distant metastases at recurrence, no. (%)			.219
No	37 (77.1)	22 (64.7)	
Yes	11 (22.9)	12 (35.3)	

SD = standard deviation.

Bold values indicate that these comparisons are statistically significant.

study and realizing the individualized therapy based on this risk stratification to further improved the psychological outcomes of gastric cancer patients. For instance, if the gastric cancer patients were accompanied with the following disease features such as: age \geq 60 years, diabetes, TNM stage at diagnosis, shorter time to recurrence, distant metastasis at recurrence, tumor location at diagnosis (cardia vs gastric antrum), and shorter time to recurrence, then more actively psychological invention should be given to these patients, such as antidepressants (selective serotonin reuptake inhibitors) etc, while this viewpoint needed to be verified in the further study.^[22]

Several limitations should be considered in this study. The main limitation was that the anxiety and depression assessments

were completed by HADS that was based on patients' self-report, thus probably causing evaluation bias from patients. Besides, only one tool of HADS for anxiety and depression assessment in these recurrent gastric cancer patients might cause bias in our findings. Hence, further study with other tools for anxiety and depression assessment in recurrent gastric cancer patients was needed. Furthermore, a further study was needed to evaluate that how to realize the individualized therapy based on this risk stratification from with the finding from this study.

In a word, the prevalence of anxiety and depression is such high, and their relevant risk factors include age \geq 60 years, diabetes and shorter time to recurrence in recurrent gastric cancer patients.

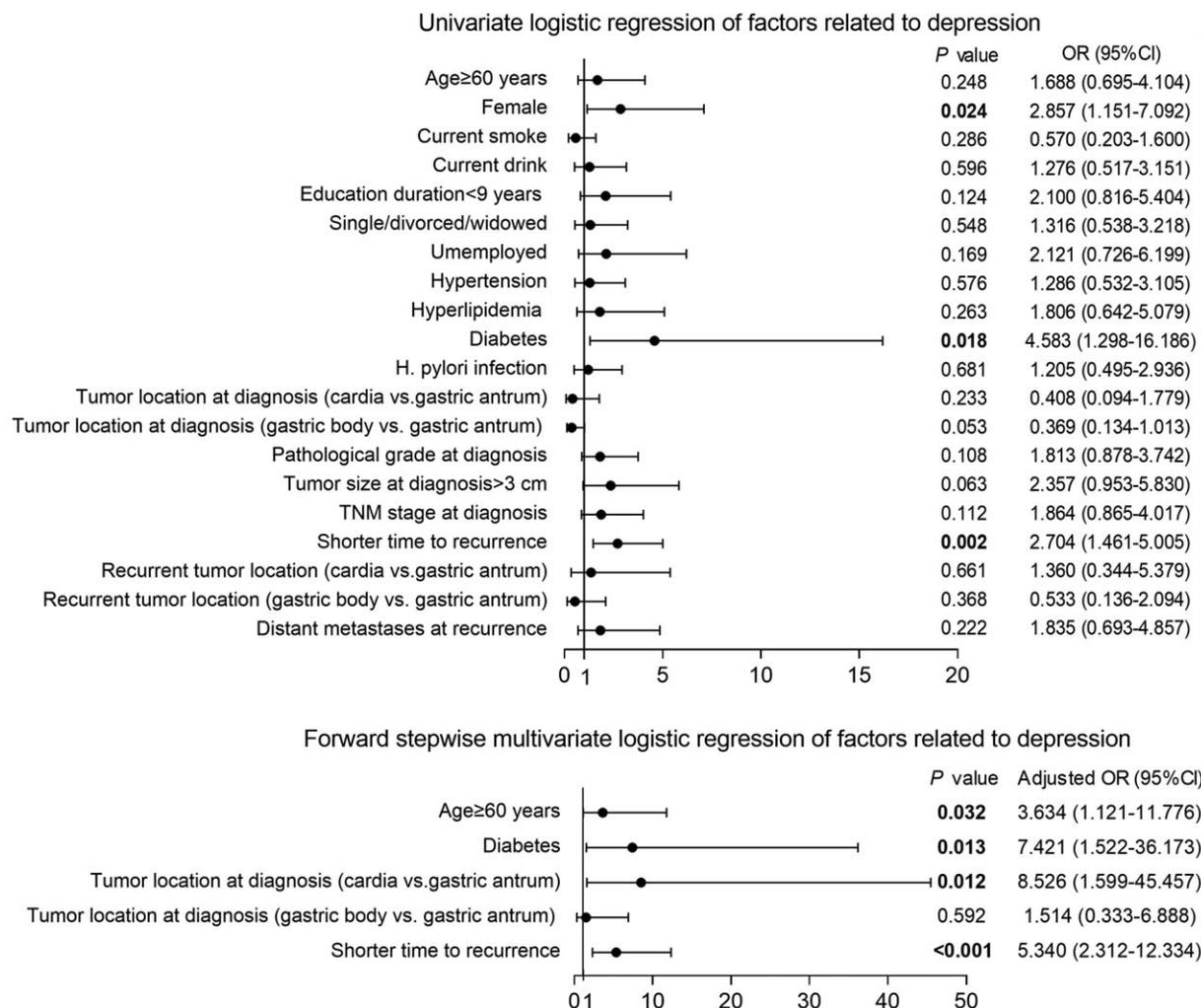


Figure 3. Univariate logistic regression and forward stepwise multivariate logistic regression of factors related to depression. CI = confidence interval, OR = odds ratio, TNM = tumor lymph nodes metastasis.

Author contributions

Conceptualization: Lisha Zhang.

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Formal analysis: Lisha Zhang.

Writing – original draft: Lisha Zhang.

Writing – review & editing: Lisha Zhang.

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