• *CLINICAL RESEARCH* •

Impact of comorbid anxiety and depression on quality of life and cellular immunity changes in patients with digestive tract cancers

Fu-Ling Zhou, Wang-Gang Zhang, Yong-Chang Wei, Kang-Ling Xu, Ling-Yun Hui, Xu-Sheng Wang, Ming-Zhong Li

Fu-Ling Zhou, Wang-Gang Zhang, Kang-Ling Xu, Department of Hematology and Oncology, Second Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China
Yong-Chang Wei, Xu-Sheng Wang, Department of Medical Oncology, First Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China
Ling-Yun Hui, Research Center of Medical Laboratory, First Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China
Ming-Zhong Li, Department of Radical Oncology, First Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China
Co-first-authors: Fu-Ling Zhou and Wang-Gang Zhang
Correspondence to: Dr. Wang-Gang Zhang, Department of Hematology and Oncology, Second Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China. tcdj1971@eyou.com
Telephone: +86-29-87679457   Fax: +86-29-87678599
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Abstract

AIM: A study was performed to investigate the impact of comorbid anxiety and depression (CAD) on quality of life (QOL) and cellular immunity changes in patients with digestive tract cancers.

METHODS: One hundred and fifty-six cases of both sexes with cancers of the digestive tract admitted between March 2001 and February 2004 in the Department of Medical Oncology, First Affiliated Hospital of Xi'an Jiaotong University were randomly enrolled in the study. Depressive and anxiety disorder diagnoses were assessed by using the Structured Clinical Interview for DSM-IV. All adult patients were evaluated with the Hamilton depressive scale (HAMD, the 24-item version), the Hamilton anxiety scale (HAMA, a modified 14-item version), quality of life questionnaire-core 30 (QLQ-C30), social support rating scale (SSRS), simple coping style questionnaire (SCSQ), and other questionnaires, respectively. In terms of HAMD $\geq$ 20 and HAMA $\geq$ 14, the patients were categorized, including CAD (n = 31) in group A, anxiety disorder (n = 23) in group B, depressive disorder (n = 37) in group C, and non-disorder (n = 65) in group D. Immunological parameters such as T-lymphocyte subsets and natural killer (NK) cell activities in peripheral blood were determined and compared among the four groups.

RESULTS: The incidence of CAD was 21.15% in patients with digestive tract cancers. The average scores of social support was 43.67±7.05 for 156 cases, active coping 20.34±7.33, and passive coping 9.55±5.51. Compared with group D, subjective support was enhanced slightly in group A, but social support, objective support, and utilization of support reduced, especially utilization of support with significance (6.16 *vs* 7.80, *P*<0.05); total scores of active coping decreased, while passive coping reversed; granulocytes proliferated, monocytes declined, and lymphocytes declined significantly (32.87 *vs* 34.00, *P*<0.05); moreover, the percentage of CD3, CD4, CD8 and CD56 in T lymphocyte subsets was in lower level, respectively, and CD56 showed a significant decline in group A (26.02 *vs* 32.20, *P*<0.05), however, CD4/CD8 ratio increased. Physical function, role function, fatigue, sleeplessness and constipation had significant changes among different groups by one-way ANOVA, and group A was in poor QOL. It revealed that global health-related quality of life (QL) were positively correlated with active coping and CD56; CAD was negatively correlated with QL, active coping and CD56. Furthermore, the step-wise regression analysis suggested that utilization of support, CD56, active coping, fatigue, sleeplessness and depression were significant factors contributing to QOL.

CONCLUSION: CAD, which can impair QOL and cellular immunity, occurs with a higher incidence in patients with digestive tract cancers. Hence, it is essential to improve mental health for them with specifically tailored interventions.

INTRODUCTION

Comorbid anxiety and depression (CAD) occurs at a high rate in primary care, and is costly to both the individual and society. CAD is significantly associated with special conditions, such as severe symptom, chronic course, social functional lesion, suicidal ideation, bad prognosis, and so on. When severe enough, it may cause negative effects on the antitumor therapy, immunological function, as well as the quality of life[1-4]. Distress, social support, and coping style are the most important psychosocial factors in this approach. As a psychotic or neurotic condition, doctors and mental-health professionals have increasingly recognized

the effects of CAD, however, to date, few studies have systematically examined the clinical correlates of CAD or its effect on patients with digestive tract cancers. Cancers of the digestive tract pose complicated public health problems worldwide[5-7]. These cancers are associated with high morbidity and mortality[8-11], in which esophageal, gastric, colorectal and liver cancers are among the top 10 malignant tumors in China and account for 63% of total cancer mortality[12-14]. In this study, we therefore tested the data on the changes of QOL aspects and immunological parameters in patients with digestive tract cancer suffering from CAD. The Hamilton rating scales and other questionnaires, as well as the immunological parameters were investigated in an attempt to provide guidelines for the means of psychological therapy in the clinical practice and for the evaluation, diagnosis, and management of CAD in the primary care setting.

MATERIALS AND METHODS

Patients

One hundred and fifty-six patients, 69 women and 87 men, with newly diagnosed cancers of the digestive tract, were registered to the protocol between March 2001 and February 2004 in the Department of Medical Oncology, First Affiliated Hospital of Xi'an Jiaotong University. Eligibility criteria required that the patients be of age over 18 years and speak Chinese. Patients with known confusion or judged too ill to participate were excluded from the investigation. None of the patients had central nervous system disease, uncontrolled infections, or other malignancies. All cases were finally verified by the histopathologic examination, including 39 esophageal, 45 gastric, 9 liver, 5 duodenal, 5 gall bladder, 4 pancreatic, 42 colonic and 7 rectal cancer cases. The medical records for these patients were reviewed by investigators and abstracted for the case's characteristics such as obvious symptoms. The average age was 58±9 years with education background of 21 graduated from primary school, 58 from junior high school and 77 from senior high school or above. Their performance status (PS) was defined by Eastern Cooperative Oncology Group and social information such as marital and employment status were obtained in the interview. Depressive and anxiety disorder diagnoses were assessed by using the Structured Clinical Interview for DSM-IV. All adult patients were categorized into four groups in terms of the Hamilton scales.

Psychological measurements

Hamilton depressive scale (HAMD) The 24-item HAMD[15-17], a commonly used clinician-rated depression symptom rating scale, includes 24 items rated on a scale of 0-2, 0-3, or 0-4 (total score range: 0-75). The HAMD was administered by experienced clinical raters certified to have a high rate of interrate reliability and level of procedural integrity. HAMD index, equal to or above 20, suggested the presence of depression. It was not meant for HAMD index to offer a strict diagnostic guideline but rather to denote levels of depression in symptomatology that may be of clinical significance.

Hamilton anxiety scale (HAMA) A modified 14-item version[18], just like the HAMD system, includes 14 items rated on a scale of 0-2, 0-3, or 0-4 (total score range: 0-56). The cases were categorized into two levels of psychological conditions. Level 1, the HAMA index below 14, was considered as no significant psychopathology; level 2, the HAMA Index equal to or above 14, suggested the presence of anxiety.

Quality of life questionnaire-core 30 (QLQ-C30) The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30, version 3.0), the most frequently used health-related quality of life (HRQOL) instruments, consists of 30 items that list the functioning and symptoms of cancer patients[19,20]. One is global health-related quality of life (QL), and the other six multi-item function scales are scored: physical function (PF), role function (RF), cognitive functioning (CF), emotional function (EF), and social function (SF). Furthermore, nine single-item symptom scales are assessed: fatigue (FA), pain (PA), nausea and vomiting (NV), dyspnea (DY), sleeplessness (SL), loss of appetite (AP), constipation (CO), diarrhea (DI), and financial difficulties (FI). The scales are linearly transformed according to the EORTC guidelines - all scales range from 0 to 100, in which a higher scale score represents a higher level of functioning. With respect to the single-item scales, a higher score indicates more symptoms or problems. EORTC QLQ C-30 is a cancer-specific questionnaire translated into various languages and validated in several European countries. In this rearrangement of the EORTC, the Cronbach's reliability coefficients are high[21].

Social support rating scale (SSRS) Social support was assessed by the patients' perception of support from their family or social members. The SSRS has ten selective items, which was employed to evaluate total social support, the levels of objective and subjective as well as the utility of this support[22].

Simple coping style questionnaire (SCSQ) There are some relationships between coping and psychosocial adjustment of patients[23,24]. The SCSQ contains 20 items on a two-point scale (active versus passive coping). Overall, the SCSQ active coping index was shown to be relatively valid with a high internal consistency that was exhibited by an alpha coefficient of 0.89, while the SCSQ passive coping index was shown to be relatively valid with a high internal consistency that was exhibited by an alpha coefficient of 0.78.

Study protocols

The study protocol was in accordance with the guidelines for clinical research and was approved by the Institutional Review Board and the Ethical Review Committee of the hospital cancer center. Informed consent was provided according to the Declaration of Helsinki after all subjects had been fully informed of its purpose. In order to make the patients understand and complete the questionnaires correctly, each item for the psychological measurements was explained by the specialist doctors in a quiet environment before the investigation.

On the day of the experiment, 3.5 mL of peripheral blood was drawn from each patient and anticoagulated by ethylenediaminetetra-acetic acid (EDTA), in which 50 μL of blood was quantified with Sysmes KX-21 blood counter

(Japan) for the measurement of lymphocytes, granulocytes and monocytes. The other 3.0 mL of blood sample was used to determine natural killer (NK) cells (CD_{56}) and T lymphocyte subsets with EPICS ELITE flow cytometer (USA) by individuals blinded to the clinical data for the patients in our immunology laboratory.

Statistical analysis

An individual patient was regarded as a unit. Data were expressed as mean±SD of the mean. Demographic variables were analyzed by descriptive statistics to evaluate the clinical and sociodemographic characteristics of the studied samples. Comparisons between experimental groups were performed by One-Way ANOVA. Pearson correlations were adopted to note the correlation among CAD and other variables. Moreover, contributing factors of QOL were assessed by linear regression. For all statistical evaluations, *P* values of 0.05 or less were considered to indicate significance. All data analyses were conducted using SPSS 11.5 for Windows statistical software.

RESULTS

Incidence of CAD in cancer patients

One hundred and fifty-six individuals were categorized into four groups in terms of HAMD and HAMA index scores according to DSM-IV criteria. The patients with CAD (*n* = 31) in group A, anxiety disorder (*n* = 23) in group B, depressive disorder (*n* = 37) in group C, and no disorder (*n* = 65) in group D. The incidence of CAD was 21.15% in patients with digestive tract cancers. Furthermore, the differences of index scores listed in Table 1 were significant among four groups.

Table 1 Changes of HAMD and HAMA scores in different group

Group	Case (%)	DSM-IV	
	156	HAMD	HAMA
A	33 (21.15)	31.92±9.06[b]	21.75±7.96[d]
B	23 (14.74)	18.92±9.14	17.75±5.94[d]
C	35 (22.44)	25.92±8.17[b]	11.92±6.10
D	65 (41.67)	16.33±6.25	8.19±3.70
F		39. 78	35.25
P		0.00	0.00

[b]*P*<0.01 *vs* group D; [d]*P*<0.01 *vs* group D.

The comparison of social support, coping style and cellular immunity

The total scores of social support was from 26 to 55 in the 156 cases, active coping from 6 to 35, and passive coping from 1 to 20. Meanwhile, the average of social support was 43.67±7.05 for 156 cases, active coping 20.34±7.33, and passive coping 9.55±5.51. Compared with group D, subjective support was enhanced slightly in group A, but social support, objective support, and utilization of support reduced, especially utilization of support with significance (6.16 *vs* 7.80, *P*<0.05); total scores of active coping decreased, while passive coping reversed. As for the parameter changes of cell-mediated immunology in

peripheral blood, granulocytes proliferated, monocytes declined, and lymphocytes declined significantly (32.87 *vs* 34.00, *P*<0.05); moreover, the percentage of CD3, CD4, CD8 and CD56 in T lymphocyte subsets was in lower level, respectively, and CD56 showed a significant decline in group A (26.02 *vs* 32.20, *P*<0.05). The changes of social support, coping style and cellular immunity findings were summarized in Table 2.

Table 2 Comparison of social support, coping style and cellular immunity in group A, B and C with group D

Item	Standard scores				*P*		
	A	B	C	D	P1	P2	P3
Social support	43.14	42.25	44.00	44.30	0.62	0.82	0.86
Subjective support	25.00	26.00	25.17	23.50	0.50	0.35	0.48
Objective support	11.50	12.25	12.00	12.00	0.54	0.90	1.00
Utilization of support[a,c]	6.16	5.75	6.83	7.80	0.04	0.03	0.37
Active coping	20.71	20.25	19.50	21.60	0.62	0.53	0.37
Passive coping	11.43	9.75	7.17	9.10	0.12	0.72	0.76
Lymphocyte[a](%)	32.87	29.20	37.20	34.00	0.01	0.33	0.39
Granulocyte (%)	62.70	68.30	58.75	56.90	0.11	0.19	0.81
Monocyte (%)	4.07	2.50	4.14	6.08	0.49	0.18	0.33
CD_3[f] (%)	52.00	52.60	42.50	59.57	0.21	0.25	0.00
CD_4[d] (%)	25.10	37.30	22.85	25.55	0.88	0.00	0.24
CD_8[d,e] (%)	31.30	19.30	34.10	38.12	0.24	0.00	0.03
CD_{56}[a] (%)	26.02	23.20	30.65	32.20	0.02	0.11	0.42

[a]*P*<0.05 *vs* group D; [c]*P*<0.05, [d]*P*<0.01 *vs* group D; [e]*P*<0.05, [f]*P*<0.01 *vs* group D.

QOL in patients with digestive tract cancer

The average of global QL were 41.67, 56.67, 35.00, 66.67, respectively, for patients in group A, B, C and D. It indicated that group A was in poor QOL, and the changes of physical function, role function, fatigue, sleeplessness and constipation were significant among different groups by one-way ANOVA (Table 3).

Table 3 Analysis of QOL in patients with digestive tract cancer

	Standard scores				*P*		
	A	B	C	D	P1	P2	P3
Global QL	41.67	56.67	35.00	66.67	0.20	0.71	0.12
Function							
PF[a]	61.43	68.33	69.33	74.67	0.04	0.52	0.12
RF[a]	67.62	70.83	70.00	76.67	0.02	0.44	0.15
EF	75.00	47.92	93.33	90.00	0.11	0.24	0.25
CF	66.67	50.00	73.33	86.67	0.36	0.69	0.16
SF	47.62	54.17	63.33	56.67	0.79	0.50	0.65
Symptom							
FA	50.79	16.67	24.44	25.56	0.10	0.17	0.12
NV	21.43	33.33	10.00	20.00	0.57	0.56	0.93
PA	25.67	29.17	23.03	16.67	0.43	0.26	0.52
Single item							
DY	23.33	16.67	23.00	6.00	0.10	0.12	0.10
SL[b,c]	41.00	36.00	18.33	13.33	0.00	0.04	0.36
AP	61.00	41.67	33.33	23.33	0.40	0.23	0.05
CO[a,d]	55.67	16.67	50.00	10.00	0.04	0.76	0.00
DI	22.33	16.67	15.32	12.15	0.05	0.17	0.14
FI	83.33	66.67	41.67	46.67	0.29	0.55	0.26

[a]*P*<0.05, [b]*P*<0.01 *vs* group D; [c]*P*<0.05 *vs* group D; [d]*P* <0.01 *vs* group D.

Correlation analysis of CAD patients

Pearson correlation analysis was performed among multiple variables in group A (Table 4). It revealed that QL were positively correlated with active coping and CD56 ($P<0.05$); depression was negatively correlated with lymphocyte ($P<0.05$); passive coping was negatively correlated with CD56 ($P<0.05$); CAD was negatively correlated with QL, active coping and CD56.

Table 4 Pearson correlation analysis among multiple variables in group A

Variable	QL	Social support	Depression	Anxiety	Active coping	Passive coping
QL	1.00	0.18	−0.28	−0.07	0.42[a]	0.02
Social support	0.18	1.00	−0.06	−0.13	0.17	0.05
Depression	−0.28	−0.06	1.00	0.31	−0.07	−0.15
Anxiety	−0.07	−0.13	0.31	1.00	−0.29	−0.05
Active coping	0.42[a]	0.17	−0.07	−0.29	1.00	0.28
Passive coping	0.02	0.05	−0.15	−0.05	0.28	1.00
Age (yr)	−0.10	−0.28	0.09	0.02	−0.001	0.12
Lymphocyte	0.08	0.07	−0.66[a]	0.21	0.36	0.37
Granulocyte	−0.22	−0.18	0.08	0.06	−0.44	0.39
Monocyte	0.41	0.35	0.14	−0.28	0.37	0.23
CD3	0.18	0.15	−0.32	−0.17	0.09	0.34
CD4	−0.04	−0.22	−0.07	0.31	−0.24	−0.03
CD8	−0.18	−0.03	0.21	−0.05	0.08	−0.06
CD56	0.67[a]	0.24	−0.36	−0.19	0.43	−0.82[b]

[a]$P<0.05$, [b]$P<0.01$.

Factors contributing to QOL

In clinical trials, there were many issues related to QOL, such as social support, active coping, fatigue, depression, monocyte, CD3, CD56, and so on. However, the step-wise regression analysis suggested that utilization of support, CD56, active coping, fatigue, sleeplessness and depression were the significant factors contributing to QOL (Table 5).

Table 5 Multivariate analysis of contributing factors of QOL with step-wise regression in patients with digestive tract cancer

Model	Unstandardized coefficients (B)	Standardized coefficients (β)	t	P
Utilization of support	1.05	1.32	3 245.61	0.000
CD56	0.16	0.69	2 860.22	0.001
Active coping	0.79	0.77	1 288.73	0.011
FA	−0.16	−0.13	−148.03	0.010
SL	−0.04	−0.02	−144.74	0.014
Depression	−0.001	−0.005	−16.67	0.038

DISCUSSION

Increasing evidence suggests that psychosocial factors such as stress and depression may have a harmful impact on the course of many diseases, such as cardiovascular disease[25,26], functional disorder and cancer[27-30], and may heighten susceptibility to infectious diseases[31,32]. As psychosocial stress has been suspected as a risk factor for cancer, an association between mental disorders and cancer has been reported in many clinical studies within patients. In this research, we

have used data gathered in a 3-year consecutive study to examine the comorbidity in adult patients. The findings both confirm and extend the previous results.

Cancer of the gastrointestinal tract is a major health problem in China, especially for the elderly. Results indicated that Chinese patients newly diagnosed with gastrointestinal tract cancer experienced a range of symptoms associated with cancer and its treatment that resulted in varying degrees of symptom distress, anxiety and depression[33,34]. More than 20% of the cancer patients have elevated scores on the Hospital Anxiety and Depression Scale (HADS) subscales depression and anxiety in Harter's report[35]. In the present cohort, there were clear and consistent trends that the average age was 58 ± 9 years and the rates of CAD are 21.15% in patients with digestive tract cancers.

High level of social support appears to play a protective role in psychological adjustment of cancer patients[36]. Social networks, including marital/partner status; number of children, relatives, and friends; and the frequency of religious and community participation, may have an important relation with HRQOL-particularly, mental health-among female long-term colorectal cancer survivors[37]. Indeed, social support in the form of marriage, frequent daily contact with others, and the presence of a confidante may all have protective values against cancer progression. The current study showed that utilization of support went down significantly in group A, but the total scores of social support were close in four groups. It is considered that the family pay attention to patients in need and highlight their problems.

Coping with cancer is multidimensional scaling. There is a significant association between patients who scored highly on the HADS and dissatisfaction with the information provided. Young patients, women, patients with advanced tumors and those who had been treated with both surgery and radiotherapy reported worse function. The worse the functional domain, the more likely it was to be associated with anxiety, depression and ineffective coping style[38]. Use of a logistic regression model showed that those patients most likely to be suffering from severe psychological distress had a worse coping style, measured by the Mental Adjustment to Cancer Scale (MACS)[39]. In this study, patients' passive coping of their disease remained relatively stable, whereas their use of active coping strategies decreased remarkably.

Psychosocial factors influence disease-resistance capabilities via the neuroimmune connection. Some immunological parameters such as T lymphocyte subsets and NK cells are thought to play a central role in antitumour immunity[40-42]. For instance, the growth of malignancies was observed to be inhibited by the activated tumor-specific T cells and the depressed activity of NK cells was probably related to the tumor enlargement and dissemination[43,44]. Suppressive effects of CAD on immune function were well documented in our study, providing further evidence for the specificity of immune changes in psychiatric disorders. Granulocytes proliferated, monocytes declined, and lymphocytes declined significantly; moreover, the percentage of CD3, CD4, CD8 and CD56 in T lymphocyte subsets was in lower level. Thus, it is reasonable to hypothesize that CAD may contribute to impairing immunity, and thereby delay

the recovery of immune mechanisms that may be important for cancer resistance.

In the last decade of clinical research, there has been increasing interest in the evaluation of quality of life. Accurate assessment of the QOL of patients can provide important clinical information to physicians, especially in the area of oncology[45-47]. Changes in QOL are important indicators of the impact of a new cytotoxic therapy, which can affect a patient's willingness to continue treatment, and may aid in defining response in the absence of quantifiable endpoints such as tumor regression[48-51]. The results obtained from the validated QLQ-C30 were used to evaluate the physical role, emotional, cognitive and social functioning, global health status as well as energy and sleep[52]. Then, it revealed that QL were positively correlated with active coping and CD56; CAD was negatively correlated with QL, active coping and CD56. Furthermore, use of a step-wise regression model suggested that utilization of support, CD56, active coping, fatigue, sleeplessness and depression were significant factors contributing to QOL. Our findings were consistent with the reports that patients who showed high levels of anxiety or depression had more health problems[53-56].

Quality of life, symptom management, and social support are the traditional foci for the practise of psychosocial oncology. The current paradigm for research in this area primarily assesses patient responses to cancer-related CAD and illuminates the necessity of ameliorating the negative aspects of those responses. Findings from this research provides insight into the importance of ongoing QOL assessment, symptom management, and intervention to improve QOL of Chinese cancer patients. In brief, CAD, which can impair QOL and cellular immunity, occurs with a higher incidence in patients with digestive tract cancers. Hence, it is essential to improve mental health for them with specifically tailored interventions.

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