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Association of anxiety and depression with chronic liver diseases in patients with noncardiac chest pain

A cross-sectional study

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Abstract

Causes of chest pain can vary from benign to life-threatening conditions, and in many cases not necessary of cardiac origin. A possible reason for noncardiac chest pain could be anxiety or depression caused by chronic liver diseases. The aim of this study was to investigate the association of anxiety and depression with chronic liver disease in patients with noncardiac pain.

Patients with chest tightness or pain referred for treadmill exercise testing were recruited from a regional hospital in southern Taiwan. Medical records of the patients were used to define the presence and type of chronic liver disease. Multiple logistic regression analyses were conducted to assess the association of anxiety and depression with chronic liver disease.

A total of 2537 patients with liver function test results and abdominal sonography data were analyzed, and 1965 patients showed a negative treadmill exercise testing. The mean age of these 1965 patients was 51.9 years and 54.2% were male. The prevalence of alcoholic liver disease, hepatitis B, hepatitis C, and fatty liver disease was 10.6%, 10.9%, 3.7%, and 27.0%, respectively. Results from multiple logistic regression analyses showed that the risk of anxiety (adjusted odds ratio [aOR] = 1.83, $P < .001$) and depression (aOR = 1.85, $P < .001$) was significantly higher in patients with alcoholic liver disease. Anxiety was significantly higher in patients with fatty liver disease (aOR = 1.30, $P = .031$), and the risk of depression was significantly higher in patients with chronic hepatitis C (aOR = 2.18, $P = .005$).

In conclusion, in patients with noncardiac chest pain, alcoholic liver disease was significantly associated with anxiety and depression, while those with fatty liver and chronic hepatitis C were associated with anxiety and depression, respectively. Clinicians should be vigilant to these correlations in their practice.

Abbreviations: ALT = alanine aminotransferase, aOR = adjusted odds ratio, AST = aspartate aminotransferase, C-CBI = Chinese version of the Copenhagen Burnout Inventory, DAA = direct-acting antivirals, ECG = electrocardiography, g = gram, HADS = Hospital Anxiety and Depression Scale, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HDL-C = high-density lipoprotein cholesterol, HRmax = maximum age-predicted heart rate, LDL-C = low-density lipoprotein cholesterol, MET = metabolic equivalent of task, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio, PSQI = Pittsburgh Sleep Quality Index, RNA = ribonucleic acid, SD = standard deviation, TNF-α = tumor necrosis factor-alpha.

Keywords: anxiety, chronic liver diseases, depression, nonischemic chest pain

1. Introduction

Anxiety and depression are common complaints among outpatient settings,[1] including patients who present with chest pain. A cross-sectional study of 250 patients referred for evaluation of chest pain found that the prevalence of anxiety and depressive symptoms were 42% and 31%, respectively.[2] A prospective cohort study of 500 low- to moderate-cardiac risk emergency department patients showed that depression was a significant independent predictor of 30-day chest pain recurrence, regardless of significant cardiac ischemia on stress testing.[3] Causes of chest pain can vary from benign to life-threatening conditions, and in many cases are not necessarily of cardiac origin. The prevalence of noncardiac chest pain was estimated to be more than 50% of all chest pain cases presenting at the emergency department.[4] In patients without cardiac disease, chest pain can be caused by psychological and psychiatric factors.[5]

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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In the basic theory of traditional Chinese medicine, the Qi of the body flows in a continuous and circular way through a system consisting of 12 meridians. Of these, the liver meridian is considered to be associated with psychological and blood-related problems. The main functions of the liver meridian include smoothing the flow of blood and energy to the whole body; regulating bile secretion and store blood; connecting with the tendons, nails, and eyes.[6] Imbalance in the liver meridian is associated with not only diseases of the liver as defined by the organ anatomy, but emotional changes, such as anger and bitterness, as well as a number of psychosomatic disorders, such as depression, anxiety, and insomnia. However, few studies have specifically explored whether anxiety and depression were associated with different types of chronic liver disease. It is plausible that one of the reasons for noncardiac chest pain is anxiety or depression, which is in turn caused by chronic liver diseases. Hence, the aim of this study was to investigate the association of anxiety and depression with various chronic liver disease in patients referred for treadmill exercise testing due to chest tightness or pain.

2. Methods

2.1. Study design and study population

A cross-sectional study design was used to recruit patients with chest tightness or pain referred for treadmill exercise testing at a regional hospital in southern Taiwan between January 2015 and February 2018. Patients who had an implanted pacemaker or atrial fibrillations were excluded. In addition, those with contraindications for the stress test were excluded.

The study protocols were approved by the Institutional Review Board of Chia-Yi Christian Hospital, Taiwan (CYCH-IRB No. 2019058). All patients provided written informed consent.

2.2. Treadmill exercise testing

After supine and standing electrocardiography (ECG), heart rate, and blood pressure were obtained, symptom-limited treadmill exercise testing using the standard Bruce protocol was conducted (GE T-2000 treadmill, CardioSoft diagnostic software version 5.20, Marquette ECG analysis program, GE Medical Systems IT, Inc., Milwaukee, USA). Blood pressure was measured using a Suntech 4240 monitor (Suntech Medical Instruments, Raleigh, NC) from the left brachial artery. Patients were encouraged to achieve a goal of 85% of the maximum age-predicted heart rate (HRmax) (beats/min). Functional capacity was estimated based on a range of speeds and grades of the treadmill and was expressed in metabolic equivalent of task. ECG, heart rate, and blood pressure were recorded at each stage of exercise, peak exercise, and every minute in the recovery phase up to 6 minutes. A positive ischemic ST-segment response was defined as the horizontal or downsloping ST-segment depression of >1 mm below baseline taken 80 ms after the J-point.

2.3. Clinical measurement

An electronic medical chart review was conducted to obtain measurements of liver function and reports of abdominal sonography of the patients who had completed the treadmill exercise test. Only patients with liver function measurement and abdominal sonography within 2 years prior to or after the date of the treadmill exercise test were included in this study.

Elevated serum aminotransferases were defined as alanine aminotransferase (ALT) > 44 U/L or aspartate aminotransferase (AST) > 37 U/L in men and ALT or AST > 31 U/L in women. The possible causes of chronic liver disease were classified as the following 4 types: (1) alcoholic liver disease was defined as alcohol consumption of 10 g/day or more in women and 20 g/day or more in men during 1 year and the presence of elevated aminotransferases or fatty liver change or cirrhotic changes by abdominal sonography; (2) chronic hepatitis B was defined by the presence of hepatitis B surface antigen (HBsAg); (3) chronic hepatitis C was defined by the presence of antihepatitis C virus (HCV) antibody and/or HCV-RNA; and (4) fatty liver disease, including nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD), was defined as fatty liver change by abdominal sonography with or without elevated aminotransferases and in the absence of any of the causes of chronic liver diseases listed earlier.

Body weight and body height of the patients were measured before the treadmill exercise test. Data on HbA1c, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin, hematocrit, and medication use were also obtained from the electronic medical records.

2.4. Questionnaires

The patients were asked to complete a questionnaire on the history of diseases (including hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, chronic obstructive pulmonary disease, renal disease, and liver disease), smoking, drinking, exercise, self-perceived health status, sleep quality, job stress, anxiety, and depression.

Smoking and alcohol use were defined as daily use in the past month. Exercise was defined as engaging in physical activity at least 3 days a week for more than 30 minutes each time. Sleep quality over the previous 1-month period was assessed using the Pittsburgh Sleep Quality Index. A Pittsburgh Sleep Quality Index global score of >5 was defined as poor sleep quality.[7]

Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression status. The HADS is a well-validated screening tool initially designed to assess the psychological distress of medically ill patients,[8] and it has been extensively used in clinical settings and research.[9] The scale is composed of 2 7-item subscales for measuring anxiety and depression. Item responses are recorded on a 4-point Likert-type scale (0–3) with a total score ranging from 0 to 21 points for each subscale. A cutoff score of >8 in each subscale is indicative of anxiety and depression, respectively.

In addition, job stress was assessed using the work-related burnout subscale of the Chinese version of the Copenhagen Burnout Inventory (C-CBI). The subscale consists of 7 questions based on a 5-point Likert response scale of 100 (always), 75 (often), 50 (sometimes), 25 (seldom), and 0 (never/almost never). The mean score for the subscale was further categorized into quartiles for subsequent data analysis. Scores of <45, 45 to 60, >60 were defined as mild, moderate, and severe levels, respectively. For patients who were not working, they were assigned to a "not working" category.[10] In the present study, the Cronbach alpha coefficient for the work-related burnout subscale was 0.871.

2.5. Statistical analysis

Continuous and categorical variables were expressed as mean with standard deviation and number with percentage. Analysis of variance and Chi-square test were used to compare the demographic and clinical characteristics of the study patients with the results of treadmill exercise testing and with different chronic liver diseases. Multiple logistic regression analyses with a backward elimination procedure based on the likelihood ratio test were conducted to assess the association of anxiety and depression with chronic liver disease. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 27.0.1.0 (IBM Corp., Armonk, NY). A 2-tailed P value of <.05 was considered statistically significant.

3. Results

A total of 2825 patients completed the treadmill exercise test and 2537 patients with liver function test results and abdominal sonography data were analyzed. Table 1 shows the demographic and clinical factors according to myocardial ischemia by the results of treadmill exercise testing. A total of 1965 patients (77.4%) showed a negative result, 428 patients (16.9%) showed positive myocardial ischemia, and 144 patients (5.7%) were unable to gain 85% of the maximal aged-predicted heart rate. There were significant differences among the 3 groups in age, hypertension, type 2 diabetes mellitus, coronary artery disease, smoking, exercise, depression, self-perceived health status, and work stress.

Table 2 shows the demographic and clinical data of patients with different liver diseases and without liver disease. Age, sex, body mass index, hypertension, type 2 diabetes mellitus, hyperlipidemia, smoking, alcohol use, depression measured by HADS, work-related burnout, ALT, AST, total cholesterol, triglycerides, HDL-C, LDL-C, gamma-glutamyltransferase, hemoglobin, hematocrit, direct-acting antivirals (DAA)-HBV, interferon-α, and benzodiazepine use were significantly different among the 5 groups of patients.

Table 3 shows the results of multiple logistic regression analyses for anxiety and depression. First, the risk of anxiety (adjusted odds ratio [OR] = 1.83, $P < .001$) and depression (adjusted OR = 1.85, $P < .001$) was significantly higher in patients with alcoholic liver disease. Second, the risk of anxiety was significantly higher in patients with fatty liver disease (adjusted OR = 1.30, $P = .031$). The risk of depression was only marginally associated with fatty liver disease (adjusted OR = 1.26, $P = .091$). Third, the risk of depression was significantly higher in patients with chronic hepatitis C (adjusted OR = 2.18, $P = .005$). The risk of anxiety and depression was not significantly associated with hepatitis B.

4. Discussion

Anxiety and depression are common in patients with chronic diseases.[11] However, their risk of these mental conditions has not been fully explored in different types of chronic liver diseases. In

Table 1

Demographic and clinical factors between patients according to the results of treadmill exercise testing for myocardial ischemia (N = 2537).

	Treadmill exercise testing for myocardial ischemia			
	Mean (standard deviation) or number (%)			
Variable	Negative 1965 (77.4)	Positive 428 (16.9)	Inconclusive 144 (5.7)	*P*
Age	51.9 (11.9)*	56.1 (10.9)†	54.7 (11.7)†	<.001
Sex, male	1065 (54.2)	245 (57.2)	77 (53.5)	.496
Body mass index				.129
Normal or underweight	742 (37.8)	148 (34.6)	41 (28.5)	
Overweight	602 (30.6)	144 (33.6)	47 (32.6)	
Obese	621 (31.6)	136 (31.8)	56 (38.9)	
Hypertension	625 (31.8)*	185 (43.2)†	68 (47.2)†	<.001
Type 2 diabetes mellitus	224 (11.4)*	79 (18.5)†	43 (29.9)‡	<.001
Coronary artery disease	239 (12.2)*	81 (18.9)†	39 (27.1)†	<.001
Hyperlipidemia	333 (16.9)	93 (21.7)	26 (18.1)	.064
Smoking	340 (17.3)*	65 (15.2)*	42 (29.2)†	.001
Alcohol use	351 (17.9)	61 (14.3)	27 (18.8)	.180
Exercise	620 (31.6)*	167 (39.0)†	41 (28.5)*†	.006
Anxiety	1101 (56.0)	218 (50.9)	80 (55.6)	.157
Depression	493 (25.1)*	79 (18.5)†	47 (32.6)*	.001
Sleep quality, PSQI > 5	216 (11.0)	38 (8.9)	21 (14.6)	.147
Self-perceived health status				<.001
Very good or good	220 (11.2)*	50 (11.7)*	8 (5.6)*	
Fair	1202 (61.2)*	247 (57.7)*	64 (44.4)†	
Poor or very poor	543 (27.6)*	131 (30.6)*	72 (50.0)†	
Work stress				.012
Mild	964 (78.4)*	198 (82.5)*,†	55 (75.3)†	
Moderate	176 (14.3)*	31 (12.9)*	11 (15.1)*	
Severe	90 (7.3)*	11 (4.6)*	7 (9.6)*	
Not working	735 (37.4)*	188 (43.9)†	71 (49.3)†	
Treadmill exercise test				
Resting heart rate, beats/min	71.0 (11.4)*	70.3 (10.9)*	66.1 (11.1)†	<.001
Peak heart rate, beats/min	154.3 (14.1)*	148.5 (17.3)†	125.0 (16.7)‡	<.001
Resting SBP, mm Hg	123.2 (18.3)*	128.7 (18.8)†	123.9 (20.0)*	<.001
Resting DBP, mm Hg	74.0 (12.4)	74.2 (12.7)	73.9 (11.9)	.933
Maximum SBP, mm Hg	165.2 (26.4)*	168.3 (26.9)*	155.7 (29.4)†	<.001
Maximum DBP, mm Hg	80.5 (14.4)*	79.1 (15.7)*	75.5 (14.0)†	<.001
MET	9.7 (1.9)*	9.0 (1.9)†	9.3 (8.6)*,†	<.001
Electrocardiogram findings				
APC	93 (4.7)*	20 (4.7)*,†	14 (9.7)†	.028
VPC	249 (12.7)*	35 (8.2)†	17 (11.8)*,†	.034
Af	2 (0.1)	1 (0.2)	0 (0.0)	.705
SVT	8 (0.4)	1 (0.2)	0 (0.0)	.656
VT	3 (0.2)	2 (0.5)	0 (0.0)	.355

Af = atrial fibrillation, APC = atrial premature complex, DBP = diastolic blood pressure, MET = metabolic equivalent of task, PSQI = Pittsburgh Sleep Quality Index, SBP = systolic blood pressure, SVT = supraventricular tachycardia, VPC = ventricular premature complex, VT = ventricular tachycardia.

Table 2

Demographic and clinical data of patients with and without different chronic liver diseases (N = 1965).

	Number (%) or mean (SD)						
		Patients classified by chronic liver disease					
Variable	All patients, 1965 (100)	Alcoholic liver disease 209 (10.6)	Chronic hepatitis B 215 (10.9)	Chronic hepatitis C 72 (3.7)	Fatty liver disease 531 (27.0)	Normal 938 (47.74)	*P*
Age, yr	51.9 (11.9)	49.2 (9.8)	51.4 (9.4)	56.7 (9.2)	54.4 (11.2)	50.9 (13.1)	<.001
Sex, male	1065 (54.2)	188 (90.0)	142 (66.0)	25 (34.7)	272 (51.2)	438 (46.7)	<.001
Body mass index							<.001
Normal or underweight	742 (37.8)	61 (29.2)	83 (38.6)	28 (38.9)	141 (26.6)	429 (45.7)	
Overweight	602 (30.6)	65 (31.1)	65 (30.2)	26 (36.1)	181 (34.1)	265 (28.3)	
Obese	621 (31.6)	83 (39.7)	67 (31.2)	18 (25.0)	209 (39.4)	244 (26.0)	
Hypertension	625 (31.8)	64 (30.6)	73 (34.0)	28 (38.9)	202 (38.0)	258 (27.5)	<.001
Type 2 diabetes mellitus	224 (11.4)	16 (7.7)	29 (13.5)	11 (15.3)	87 (16.4)	81 (8.6)	<.001
Coronary artery disease	239 (12.2)	19 (9.1)	33 (15.3)	6 (8.3)	74 (13.9)	107 (11.4)	.139
Hyperlipidemia	333 (16.9)	42 (20.1)	34 (15.8)	14 (19.4)	113 (21.3)	130 (13.9)	.004
Smoking	340 (17.3)	90 (43.1)	38 (17.7)	13 (18.1)	55 (10.4)	144 (15.4)	<.001
Alcohol use	351 (17.9)	206 (98.6)	34 (15.8)	5 (6.9)	0 (0.0)	106 (11.3)	<.001
Exercise	620 (31.6)	60 (28.7)	69 (32.1)	25 (34.7)	179 (33.7)	287 (30.6)	.611
Sleep quality, PSQI > 5	216 (11.0)	18 (8.6)	20 (9.3)	13 (18.1)	68 (12.8)	97 (10.3)	.103
HADS, anxiety	1101 (56.0)	129 (61.7)	124 (57.7)	40 (55.6)	299 (56.3)	509 (54.3)	.380
HADS, depression	493 (25.1)	67 (32.1)	55 (25.6)	26 (36.1)	130 (24.5)	215 (22.9)	.014
Self-perceived health status							.149
Very good or good	543 (27.6)	49 (23.4)	57 (26.5)	29 (40.3)	146 (27.5)	262 (27.9)	
Fair	1202 (61.2)	136 (65.1)	140 (65.1)	39 (54.2)	318 (59.9)	569 (60.7)	
Poor or very poor	220 (11.2)	24 (11.5)	18 (8.4)	4 (5.6)	67 (12.6)	107 (11.4)	
Work-related burnout							<.001
Mild	964 (49.1)	134 (64.1)	106 (49.3)	26 (36.1)	248 (46.7)	450 (48.0)	
Moderate	176 (9.0)	22 (10.5)	23 (10.7)	6 (8.3)	37 (7.0)	88 (9.4)	
Severe	90 (4.6)	7 (3.3)	11 (5.1)	2 (2.8)	28 (5.3)	42 (4.5)	
Not working	735 (37.4)	46 (22.0)	75 (34.9)	38 (52.8)	218 (41.1)	358 (38.2)	
eGFR, mL/min/1.73m^2	108.3 (29.8)	106.6 (26.5)	105.6 (29.5)	111.3 (26.8)	107.5 (31.1)	109.6 (30.0)	.375
ALT	43.7 (116.8)	58.3 (104.1)	76.3 (316.3)	65.2 (101.0)	44.7 (51.7)	29.5 (27.9)	<.001
AST	41.4 (139.5)	61.7 (161.7)	74.3 (349.1)	54.4 (82.3)	34.1 (34.6)	28.5 (31.2)	.006
HbA1c	6.6 (1.6)	6.5 (2.2)	6.6 (1.4)	6.3 (1.1)	6.8 (1.6)	6.5 (1.5)	.269
Total cholesterol	206.2 (42.1)	207.2 (45.6)	193.1 (45.7)	207.5 (38.7)	208.9 (41.1)	207.2 (40.7)	.006
Triglycerides	177.0 (169.4)	239.6 (285.5)	162.9 (157.9)	160.2 (149.8)	184.9 (146.5)	159.5 (142.7)	<.001
HDL-C	54.5 (15.5)	50.4 (14.4)	52.1 (15.9)	55.7 (14.6)	53.3 (14.3)	57.0 (16.4)	<.001
LDL-C	128.2 (33.7)	130.0 (36.1)	121.8 (32.5)	130.8 (31.9)	132.5 (32.4)	126.0 (34.2)	.021
Glucose	110.9 (36.0)	111.2 (34.6)	111.5 (31.5)	112.7 (27.6)	114.2 (39.9)	108.0 (35.0)	.176
Gamma-glutamyltransferase	114.4 (359.8)	308.3 (765.5)	70.2 (103.8)	77.8 (107.8)	95.7 (222.1)	30.9 (42.4)	.015
Hemoglobin	14.3 (1.7)	15.2 (1.5)	14.7 (1.4)	14.0 (1.7)	14.4 (1.6)	13.9 (1.7)	<.001
Hematocrit	42.2 (4.2)	44.2 (4.3)	43.4 (3.5)	41.6 (4.2)	42.6 (4.1)	41.3 (4.1)	<.001
Medications							
β-Blockers	485 (24.7)	46 (22.0)	56 (26.0)	16 (22.2)	139 (26.2)	–	.231
Corticosteroids	81 (4.1)	12 (5.7)	5 (2.3)	5 (6.9)	22 (4.1)	–	.615
DAA-HCV	2 (0.1)	0 (0)	1 (0.5)	1 (1.4)	0 (0)	–	.054
DAA-HBV	4 (0.2)	0 (0)	4 (1.9)	0 (0)	0 (0)	–	.004
Interferon-α	1 (0.1)	0 (0)	0 (0)	1 (1.4)	0 (0)	–	.047
Levodopa	2 (0.1)	1 (0.5)	0 (0)	0 (0)	0 (0)	–	.591
Methyldopa	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	–	>.999
Benzodiazepines	140 (7.1)	12 (5.7)	13 (6.0)	12 (16.7)	49 (9.2)	–	.009
H2-blocker	19 (1.0)	3 (1.4)	2 (0.9)	0 (0)	8 (1.5)	–	.085
Tamoxifen	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0.2)	–	.687
Verapamil	17 (0.9)	3 (1.4)	4 (1.9)	1 (1.4)	3 (0.6)	–	.522

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DAA-HBV = direct-acting antiviral therapy for hepatitis B virus, DAA-HCV = direct-acting antiviral therapy for hepatitis C virus, eGRF = estimated Glomerular filtration rate, HADS = Hospital Anxiety and Depression Scale, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PSQI = Pittsburgh Sleep Quality Index, SD = standard deviation.

this cross-sectional study of 2537 patients with chest tightness or pain referred for treadmill exercise testing, 1965 (77.4%) of them were tested to be negative for myocardial ischemia. Of these 1965 patients, 47.7% had no chronic liver disease. Multiple logistic regression analysis showed that alcoholic liver disease was significantly and independently associated with both anxiety and depression. In addition, fatty liver disease was significantly and independently associated with anxiety, whereas chronic hepatitis C was significantly and independently associated with depression.

Chronic alcohol consumption and dependence are associated with an increased risk of developing many healthy problems, including liver disease, psychiatric disease, cardiovascular diseases, neurologic disease, and malignant neoplasms. Moreover, the effect of alcohol consumption on coronary artery disease, hypertension, and stroke is presented as a J-shape dose-response relationship.[12] A meta-analysis of 156 studies showed that the risk of coronary artery disease decreased by 20% with the consumption of 0 to 20 g/day of alcohol, and the protective

Table 3

Multiple logistic regression analysis of anxiety and depression in patients with different chronic liver diseases.

Variable	Anxiety		Depression	
	Adjusted odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
Chronic liver disease				
Normal	1.00		1.00	
Alcoholic liver disease	1.83 (1.31–2.57)	<.001	1.85 (1.29–2.64)	<.001
Chronic hepatitis B	1.27 (0.92–1.76)	.146	1.22 (0.84–1.76)	.292
Chronic hepatitis C	1.00 (0.60–1.68)	.993	2.18 (1.26–3.78)	.005
Fatty liver disease	1.30 (1.02–1.64)	.031	1.26 (0.96–1.66)	.091
Age, yr	0.97 (0.96–0.98)	<.001	0.97 (0.96–0.98)	<.001
Sex				
Male	1.00			
Female	1.43 (1.16–1.76)	<.001		
Body mass index				
Normal or underweight	1.00			
Overweight	0.77 (0.61–0.98)	.032		
Obese	0.77 (0.60–0.97)	.029		
Exercise			0.66 (0.51–0.86)	.002
Sleep quality, PSQI > 5	1.46 (1.05–2.02)	.024	2.43 (1.76–3.35)	<.001
Self-perceived health status				
Very good or good	1.00		1.00	
Fair	1.87 (1.37–2.56)	<.001	1.84 (1.15–2.94)	.011
Poor or very poor	4.29 (3.01–6.11)	<.001	3.09 (1.90–5.04)	<.001
Work-related burnout				
Mild	1.00		1.00	
Moderate	2.63 (1.80–3.85)	<.001	2.99 (2.10–4.25)	<.001
Severe	8.73 (3.94–19.38)	<.001	5.50 (3.39–8.91)	<.001
Not working	1.43 (1.14–1.80)	.002	1.61 (1.24–2.10)	<.001

Other variables included in the model evaluation: alcohol use, ALT, AST, coronary artery disease, eGFR, HbA1c, HDL-C, hematocrit, hemoglobin, hyperlipidemia, hypertension, LDL-C, smoking, total cholesterol, treadmill exercise test results, triglycerides, and type 2 diabetes mellitus.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, eGFR = estimated glomerular filtration rate, HbA1c = glycosylated hemoglobin, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PSQI = Pittsburgh Sleep Quality Index.

effect of alcohol was up to 72 g/day, although, the level of alcohol consumption was related to an increased risk of liver disease.[13] However, the risk of development of coronary artery disease was found to increase when alcohol consumption was more than 89 g/day.[14] The reduction in coronary artery disease from moderate alcohol intake may be mediated by increased fibrinolysis because alcohol polyphenols can modulate endothelial cell fibrinolytic protein (t-PA, u-PA, PAI-1, u-PAR, and Annexin-II) expression at the cellular, molecular, and gene levels to increase fibrinolytic activity.[15] This can, in turn, decrease the acute atherothrombotic consequences (e.g., plaque rupture) of myocardial infarction. Conversely, activation of the sympathetic nervous system with heavy alcohol consumption might explain the associated increase in coronary artery disease.[16]

Chronic alcohol dependence is related to mood disorders because of the psychoactive properties of alcohol. Depression and anxiety are the most frequent symptoms that precede and succeed alcohol abuse. Based on the data from the National Inpatient Sample 2011 in the United States, the prevalence of anxiety disorder (8.84% vs 7.54% vs 7.91%), depression (3.96% vs 2.12% vs 3.21%) were significantly higher among hospitalized patients with alcohol liver disease compared with chronic liver diseases not caused by alcohol, and patients without liver diseases.[17] Moreover, in a study of 143 alcohol dependents of either East Indian ancestry or African ancestry, and 109 controls matched by age, sex, and ethnicity, 39% of the participants of East Indian ancestry and 37% of participants of the African ancestry had alcohol dependence combined with major depression caused by alcohol or drug use. The severity of depression was significantly associated with the severity of alcohol dependence.[18] In addition, a study on 1767 patients from various specialized treatment settings in 8 European countries showed that high levels of alcohol consumption (mean level of daily ethanol intake of 141.1 g) existed with comorbidities of alcohol consumption, including liver problems of 19.6%, depression of 43.2%, and anxiety of 50.3%.[19]

In this study, fatty liver disease was found to be significantly and independently associated with anxiety (adjusted OR = 1.30). A study on 878 patients with chronic liver disease recruited at an outpatient liver center from a tertiary care medical center showed that those with NAFLD had a significantly higher prevalence of depression (27.2%) than patients with hepatitis B (3.7%) or that reported for the general population (2–5%).[20] In addition, a study of 36 patients with histologic evidence of NASH on liver biopsy and 36 matched controls found that patients with NASH had a significantly increased risk of both lifetime major depressive disorder (OR = 3.8, P = .018) and lifetime generalized anxiety disorder (OR = 5.0, P = .005).[21] Moreover, the risk of depression increased in proportion to the severity of ultrasonographically detected NAFLD (mild fatty liver: adjusted OR = 1.14 and moderate to severe fatty liver: adjusted OR = 1.32) in 112,797 Korean adults participating in the Kangbuk Samsung Health Study cohort.[22] A recent retrospective cohort study of 39,742 adult patients also revealed an increased risk of anxiety disorder (adjusted hazard ratio = 1.23, P < .001) and depression (adjusted hazard ratio = 1.21, P < .001) in patients with NAFLD.[23] Although the exact mechanism between NAFLD and anxiety disorder is still unknown, there are a few possible explanations. First, the correlation of NAFLD with obesity and diabetes mellitus,[24] both of which have been strongly associated with depression symptoms, could be another explanation. Nevertheless, the significant association between fatty liver disease and anxiety observed in the present study was independent of body mass index and diabetes mellitus, suggesting that there are other underlying mechanisms. Second, the association might be explained by their shared pathogenesis mediated by the immune-inflammatory, oxidative and nitrosative stress pathways.[25]

HCV infection is a worldwide problem and is one of the major causes of chronic liver diseases. The global prevalence is about 2% to 3%, and more than 0.35 million people die of HCV-related conditions each year.[26] HCV infection is associated with chronic hepatitis, cirrhosis, hepatic failure, and hepatocellular carcinoma. HCV infection is also associated with psychiatric disorders, including alcohol abuse, drug abuse, and depression.[27] Findings from the National Health and Nutrition Examination Survey (NHANES 2005–2010) showed that only chronic hepatitis C, but not chronic hepatitis B, alcohol-related liver disease, or nonalcoholic fatty liver disease, was strongly associated with depression.[28] The prevalence of depressive symptoms among patients with HCV infection was found to be between 21% and 58.6%.[29] The prevalence of depression in patients with HCV was about 1.5 to 4.0 times higher than the general population.[30]

The mechanism of high prevalence of depression among patients with HCV infection may be multifactorial. First, direct HCV neuroinvasion of HCV is possible. HCV-RNA has been detected in the brain of chronically infected patients with neuropsychiatric disorders.[31] Second, chronic HCV infection is associated with systemic and brain inflammation.[32] Higher TNF-α plasma levels in HCV infection patients could lead to depressive symptoms.[33] Third, immune activation of serotoninergic activity could be associated with depression in patients with HCV infection.[34]

The standard therapy for HCV infection is antiviral therapy with long-acting peginterferon alpha, oral ribavirin, and DAA-HCV therapy. Depression is one of the most common side effects of antiviral therapy. A meta-analysis revealed that a quarter of patients with HCV infection who started to receive interferon and ribavirin therapy would develop a major depressive episode.[35] In addition, in a cohort of 91 patients with hepatitis C, the incidence of major depression and any depressive disorder during DAA-HCV therapy was found to be 13% and 46.3%, respectively.[36] Nevertheless, in the present study, one of the 102 patients with HCV infection had received DAA-HCV therapy and 1 patient with HCV infection received both DAA-HCV and interferon therapy. Both of them did not have depression. Therefore, DAA-HCV and interferon did not appear to be the cause of depression in our study.

This study has some limitations. The cross-sectional design precluded the determination of causal relationships between chronic liver disease, anxiety, and depression. Second, the severity of chronic liver disease is not available. Third, the precise level of alcohol consumption was not available, which precluded the analysis of whether a dose-response relationship exists.

5. Conclusions

Findings from this study showed that in patients with noncardiac chest pain, alcoholic liver disease was significantly associated with anxiety and depression, while those with fatty liver and chronic hepatitis C were associated with anxiety and depression, respectively. Clinicians should be vigilant to these correlations in practice.

Author contributions

Conceptualization: R.-Y.C., H.-L.T., and S.H.-H.H.; methodology: R.-Y.C.; formal analysis: R.-Y.C. and M.K.; investigation: R.-Y.C.; writing – original draft: R.-Y.C.; writing – review & editing: M.K., R.-Y.C., H.-L.T., and S.H.-H.H. All authors have read and agreed to the published version of the manuscript.

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