Association of anxiety and depression with chronic liver diseases in patients with noncardiac chest pain
A cross-sectional study

Rei-Yeuh Chang, MD, MSca,b, Sheri Hsueh-Hua Ho, MDc, Han-Lin Tsai, MDa, Malcolm Koo, PhDd,e,*

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 lipo protein cholesterol, HFmax = 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-\( \alpha \) = tumor necrosis factor-alpha.

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

1. Introduction
Anxiety and depression are common complaints among outpatient settings, 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. 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. 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. In patients without cardiac disease, chest pain can be caused by psychological and psychiatric factors.

The authors have no funding and conflicts of interest to disclose.

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

a Division of Cardiology, Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-yi City, Taiwan. b Min-Hwei Junior College of Health Care Management, Tainan City, Taiwan. c Sheri Hsueh-Hua Ho Family Medicine Clinic, Irvine, CA. d Graduate Institute of Long-term Care, Tzu Chi University of Science and Technology, Hualien City, Hualien, Taiwan, and e Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada.

* Correspondence: Malcolm Koo, PhD, Graduate Institute of Long-term Care, Tzu Chi University of Science and Technology, Hualien City, Hualien 970302 Taiwan (e-mail: m.koo@utoronto.ca).

Copyright © 2022 the Author(s). Published by Wolters Kluwer Health, Inc.
This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Chang R-Y, Hsueh-Hua Ho S, Tsai H-L., Koo M. Association of Anxiety and Depression with Chronic Liver Diseases in Patients with Noncardiac Chest Pain: A Cross-Sectional Study. Medicine 2022;101:31(e29620).
Received: 1 January 2022 / Received in final form: 21 April 2022 / Accepted: 4 May 2022
http://dx.doi.org/10.1097/MD.0000000000029620
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. 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 pain in liver disease. 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 (CYCHRIB 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.

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, and it has been extensively used in clinical settings and research. The scale is composed of 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. 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).

| 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)            | 240 (57.2)             | 77 (39.5)                | .306 |
| 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 (66.6)            | 218 (50.9)             | 80 (55.6)                | .157 |
| Depression                                          | 493 (26.1)*            | 79 (18.5)†             | 47 (32.6)*               | .001 |
| Sleep quality, PSQI > 5                            | 216 (11.0)             | 38 (8.9)               | 21 (14.8)                | .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 (14.2)*            | 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                             |                        |                       | <.001 |
| 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)*          | 148.3 (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)              | .003 |
| 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                          |                        |                       | .028 |
| APC                                                | 93 (4.7)*              | 20 (4.7)†              | 14 (8.7)†                |      |
| 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 |

ALT = arterial 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.
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. 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
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 was found to increase when alcohol consumption was related to an increased risk of liver disease.\[16\] However, the risk of development of coronary artery disease was found to increase when alcohol consumption was more than 89 g/day.\[15\] This can, in turn, decrease the acute atherothrombotic consequences (e.g., plaque rupture) of myocardial infarction. Conversely, activation of the sympathetic nervous system with high 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 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.\[24\]
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 0.33 million people die of HCV-related conditions each year.[24] 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.[25] 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.[21] 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 infection was about 1.5 to 4.0 times higher than the general population.[10]

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 neuro-psychiatric disorders.[22] Second, chronic HCV infection is associated with systemic and brain inflammation.[12] Higher TNF-α plasma levels in HCV infection patients could lead to depressive symptoms.[23] Third, immune activation of serotonergic activity could be associated with depression in patients with HCV infection.[13]

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.[26] 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.[30] Nevertheless, in the present study, one of the 102 patients with HCV infection who 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.

References

[1] Wang J, Wu X, Lai W, et al. Prevalence of depression and depressive symptoms among outpatients: a systematic review and meta-analysis. BMJ Open. 2017;7:e017173.

[2] Rohani A, Akbari V, Zarei F. Anxiety and depression symptoms in chest pain patients referred for the exercise stress test. Heart Views. 2011;12:161–4.

[3] Kim Y, Soiffer M, Paradise S, et al. Depression is associated with recurrent chest pain with or without coronary artery disease: a prospective cohort study in the emergency department. Am Heart J. 2017;191:47–54.

[4] Lenfant C. Chest pain of cardiac and noncardiac origin. Metabolism. 2010;59(Suppl 1):541–6.

[5] Jonsbu E, Dammen T, Morken G, et al. Cardiac and psychiatric diagnoses among patients referred for chest pain and palpitations. Scand Cardiovasc J. 2009;43:256–9.

[6] Liu ZW, Shu J, Tu JY, et al. Liver in the Chinese and western medicine. Integr Med Int. 2017;4:39–45.

[7] Buyse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193–213.

[8] Zigmund AS, Smith R. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.

[9] Bjelland I, Dahl AA, Haug TT, et al. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002;52:69–77.

[10] Fong TC, Ho RT, Ng SM. Psychometric properties of the Copenhagen Burnout Inventory–Chinese version. J Psychiatr. 2014;148:235–66.

[11] Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry. 2007;29:147–55.

[12] Emberson JR, Bennett DA. Effect of alcohol on risk of coronary heart disease and stroke: causality, bias, or a bit of both? Vasc Health Risk Manag. 2006;2:239–49.

[13] Adachi M, Brenner DA. Clinical syndromes of alcoholic liver disease. Dig Dis. 2005;23:255–62.

[14] Corrao G, Bagnardi V, Zambon A, et al. A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med. 2004;38:613–9.

[15] Boosy FM, Pan W, Grenett HE, et al. Mechanism by which alcohol and wine polyphenols affect coronary heart disease risk. Ann Epidemiol. 2007;17(5 Suppl):S24–S.

[16] Randin D, Vollenweider F, Tappy L, et al. Suppression of alcoholic steatohepatitis by dexamethasone. N Engl J Med. 1995;332:1733–7.

[17] Jinjuvadia R, Jinjuvadia C, Puangsricharoen P, et al. Concomitant psychiatric and nonalcohol-related substance use disorders among hospitalized patients with alcoholic liver disease in the United States. Alcohol Clin Exp Res. 2018;42:397–402.

[18] Shafe S, Gilder DA, Montante-Jaime LK, et al. Co-morbidity of alcohol dependence and select affective and anxiety disorders among individuals of East Indian and African ancestry in Trinidad and Tobago. West Indian Med J. 2009;58:164–72.

[19] Rehm J, Allamani A, Aubin HJ, et al. People with alcohol use disorders in specialized care in eight different European countries. Alcohol Alcohol. 2013;48:310–8.

[20] Weinstein AA, Kallman Price J, Stepanova M, et al. Depression in patients with nonalcoholic fatty liver disease and chronic viral hepatitis B and C. Psychosomatics. 2011;52:127–32.

[21] Surdea-Blaga T, Dumitrașcu DL. Depression and anxiety in non-alcoholic steatohepatitis: is there any association? Rom J Intern Med. 2011;49:273–80.

[22] Jung JY, Park SK, Oh CM, et al. Non-alcoholic fatty liver disease and its association with depression in Korean general population. J Korean Med Sci. 2019;34:e199.

[23] Labenz C, Huber Y, Michel M, et al. Nonalcoholic fatty liver disease increases the risk of anxiety and depression. Hepatol Commun. 2020;4:1293–301.

[24] Preis K, Brennan L, Clarke D. A systematic review of variables associated with the relationship between obesity and depression. Obes Rev. 2013;14:906–18.

[25] de Melo LGR, Nunes SOV, Anderson G, et al. Shared metabolic and immune-inflammatory, oxidative and nitrosative stress pathways in the metabolic syndrome and mood disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2017;78:34–50.

[26] Averhoff FM, Glass N, Holtzman D. Global burden of hepatitis C: considerations for healthcare providers in the United States. Clin Infect Dis. 2012;55(Suppl 1):S10–5.

[27] Machado Dde A, Silva GF, et al. Depressive symptoms and harmful alcohol use in hepatitis C patients: prevalence and correlates. Rev Soc Bras Med Trop. 2014;47:149–57.
[28] Lee K, Ongonsuren M, Younoszai Z, et al. Association of chronic liver disease with depression: a population-based study. Psychosomatics. 2013;54:52–9.

[29] Yu ML, Yeh ML, Tsai PC, et al. Huge gap between clinical efficacy and community effectiveness in the treatment of chronic hepatitis C: a nationwide survey in Taiwan. Medicine (Baltim). 2015;94:e690.

[30] Nelligan JA, Loftis JM, Matthews AM, et al. Depression comorbidity and antidepressant use in veterans with chronic hepatitis C: results from a retrospective chart review. J Clin Psychiatry. 2008;69:810–6.

[31] Fletcher NF, McKeating JA. Hepatitis C virus and the brain. J Viral Hepat. 2012;19:301–6.

[32] Zampino R, Marrone A, Restivo I, et al. Chronic HCV infection and inflammation: Clinical impact on hepatic and extra-hepatic manifestations. World J Hepatol. 2013;5:528–40.

[33] Loftis JM, Huckans M, Ruimy S, et al. Depressive symptoms in patients with chronic hepatitis C are correlated with elevated plasma levels of interleukin-1beta and tumor necrosis factor-alpha. Neurosci Lett. 2008;430:264–8.

[34] Maes M, Ringel K, Kubera M, et al. Increased autoimmune activity against 5-HT: a key component of depression that is associated with inflammation and activation of cell-mediated immunity, and with severity and staging of depression. J Affect Disord. 2012;136:386–92.

[35] Udina M, Castellví P, Moreno-Españo J, et al. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. J Clin Psychiatry. 2012;73:1128–38.

[36] Egmond E, Mariño Z, Navines R, et al. Incidence of depression in patients with hepatitis C treated with direct-acting antivirals. Braz J Psychiatry. 2020;42:72–6.