General Psychiatry

Depressive symptoms and immune depletion in Chinese patients with advanced hepatocellular carcinoma: a multicentre study on their correlation

Yan Zhang,[1] Wei Zhou,[2] Zhiping Ma,[1] Zutao Chen,[1] Naiping Li,[3] Xiaomin Zhu,[4] Yunhai Yao [1]

To cite: Zhang Y, Zhou W, Ma Z, *et al*. Depressive symptoms and immune depletion in Chinese patients with advanced hepatocellular carcinoma: a multicentre study on their correlation. *General Psychiatry* 2025;**38**:e101822. doi:10.1136/gpsych-2024-101822

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/gpsych-2024-101822).

YZ and WZ contributed equally.

Received 09 August 2024
Accepted 17 February 2025

[1]Department of Infectious Disease, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China
[2]Department of Infectious Disease, Huai'an Hospital of Huai'an City, Huai'an, Jiangsu, China
[3]The Second Xiangya Hospital of Central South University, Changsha, Hunan, China
[4]Suzhou Psychiatric Hospital, Soochow University Affiliated Guangji Hospital, Suzhou, Jiangsu, China

Correspondence to
Yunhai Yao;
498525605@qq.com

To the editor:

The liver's immune-privileged status allows for a unique microenvironment that supports tumour growth and metastasis.[1] In hepatocellular carcinoma (HCC), the balance between cytotoxic T lymphocytes and regulatory T cells plays a crucial role in determining patient outcomes.[2] The expression of programmed cell death ligand 1 (PD-1) and other immune checkpoint molecules contributes to a pro-tumourigenic microenvironment and is associated with poor prognosis. Additionally, the heterogeneity of the immune microenvironment adds complexity to disease progression and treatment response.

The relationship between depression in patients with cancer and the immune system is complex. Depression has been linked to changes in T cell subsets, such as reduced levels of CD3+CD8+ and CD3+ T cells in patients with major depressive disorder.[3] In patients with HCC and depression, upregulation of PD-1 expression on natural killer (NK) cells contributes to immune dysfunction and disease progression.[4] Furthermore, decreased expression of co-stimulatory receptor CD28 on T lymphocytes in patients with depression may lead to adverse prognosis.[5] The relationship between the neuroendocrine and immune systems in the context of HCC is a vital area of research, with implications for understanding pathogenesis and developing therapeutic strategies.

This study aimed to examine the current understanding of depressive symptoms in patients with HCC, focusing on the modulation of immune responses.

This multi-centre study enrolled 160 patients with advanced HCC from three hospitals, diagnosed and treated between 1 January 2018 and 31 December 2019. All patients met the criteria outlined in the latest Chinese Guidelines for Diagnosis and Treatment of Primary Liver Cancer (2024 edition) and had a performance status of 3–4/Child-Pugh C. Eligible patients completed a questionnaire, and their clinical data were collected for analysis. Exclusion criteria included refusal to complete the questionnaire, presence of other malignant tumours, severe organ dysfunction, mental disorders, common severe complications and participation in other tumour-related research projects. This study was approved by the ethics committee of our hospital (Approval No. 2023-334). Informed consent was obtained from all participants.

DEPRESSION DIAGNOSIS

The diagnosis of depression was based on clinical observation and evaluation of patients' symptoms, self-rating scales, imaging and laboratory examinations. Two questionnaires were used: (1) questionnaire of basic information, including gender, age, address, education, medical history, previous treatment, family history of mental illness, and first occurrence or recurrence; and (2) 9-item Patient Health Questionnaire (PHQ-9). All patients completed the PHQ-9 (Chinese version) screening scale, which was used to classify the severity of depression. The total score of PHQ-9 ranged between 0 and 27 points, with scores of ≥5, ≥10 and ≥15 points indicating mild, moderately severe and severe depression symptoms, respectively.

FLOW CYTOMETRY

Fresh blood samples (5 mL) were collected from each patient in heparinised tubes after completing the questionnaire. The blood samples were fully hemolysed with red blood cell lysate, vortexed and incubated at room temperature for 10 min. Then, the samples

were centrifuged at 2100 rpm for 10 min. The supernatant was discarded, and 2 mL Phosphate Buffered Saline (PBS) was added before another centrifugation. Various antibodies, including PerCP-labelled CD3, APC-labelled CD4 and APCCy7-labelled CD8, were used to identify the samples. PD1-PE and CD28-FITC antibodies were added to identify the expression of CD3CD28, CD4CD28, CD8CD28, CD3PD1, CD4PD1 and CD8PD1. The data were analysed using FACS Express V.3.0 software. All antibodies were purchased from RaiseCyte, China.

Clinical data of the included patients were recorded using Excel, and statistical analyses were performed using SPSS V.21.0. Measurement data were presented either as mean (SD) for normally distributed variables or median (quartile range) for non-normally distributed variables. Influential factors of depression in patients with HCC were identified by using an ordinal logistic regression analysis. One-way analysis of variance and independent sample t-test were adopted for multigroup and two-group comparisons, respectively. A p value <0.05 was considered statistically significant.

DEMOGRAPHIC AND CLINICAL DATA

This study included 160 Chinese Han patients with HCC, with a mean age of 60.82 (11.62) years old. The cohort included 124 (77.50%) males, and the primary cause of HCC was virus (hepatitis B virus (HBV)+hepatitis C virus), accounting for 75.63% of the cases. Most patients (88.13%) were from rural regions with an education level of bachelor's degree or below. Meanwhile, 70 cases (43.75%) experienced recurrence after surgery, 49 cases (30.63%) progressed after interventional therapy and 41 cases (25.63%) had no surgical indication. A tumour size of <2 cm was found in 30.63% of the cases, most of which were isolated space-occupying lesions (65.00%). According to PHQ-9, 52 patients exhibited varying degrees of depression: 9 had minimal (5.63%) symptoms, 28 had mild depression (17.50%), 13 had moderately severe depression (8.13%) and 2 had severe depression (1.25%).

INFLUENCING FACTORS OF DEPRESSION

As presented in table 1, the ordinal regression analysis identified gender (female), education level (bachelor's degree or above) and medical history (recurrence after radical surgery and progression after interventional therapy) as factors correlated with depression in patients with HCC (all p<0.05).

Table 1 Ordinal regression analysis of factors correlated with depression status in patients with HCC (n=160)

Variables	Result			
	β value	S	Z value	P value
Female	−1.02	0.42	5.96	0.022
Age	0.01	0.01	0.26	0.607
Aetiologies	−0.17	0.45	0.59	0.702
Place of residence	0.35	0.45	0.59	0.441
Complications	−0.25	0.48	0.27	0.566
Education (bachelor's degree or above)	1.18	0.58	4.18	0.038
WBC	0.02	0.07	0.14	0.726
PLT	−0.00	0.00	0.29	0.585
HGB	−0.01	0.01	1.59	0.297
TBil	0.00	0.00	0.60	0.443
GGT	0.00	0.00	3.35	0.073
ALT	0.00	0.00	0.01	0.978
AST	0.00	0.00	0.24	0.625
AFP	0.00	0.00	0.03	0.946
Tumour size	−0.42	0.43	0.97	0.322
Total number of tumours	0.46	0.41	1.28	0.261
Medical history				
Radical surgery	1.64	0.51	10.48	0.014
Interventional therapy	1.13	0.46	5.93	0.017

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HCC, hepatocellular carcinoma; HGB, haemoglobin; PLT, platelet; S, standard error; TBil, total bilirubin; WBC, white blood cell.

FLOW CYTOMETRY

Based on the PHQ-9 classification of depression severity, two patients with severe depression were categorised into the moderately severe depression group (Severe group). Nine patients with minimal depression were included in the minor depression, dysthymia and mild depression group (Minimal/Minor group). Patients without depression were classified into the no depression (NE) group. We compared CD28/PD1 results among the three groups. Compared with the NE group, the Severe group exhibited significantly lower levels of CD3CD28, CD4CD28 and CD8CD28, and significantly higher levels of CD3PD1, CD4PD1 and CD8PD1 (all p<0.05) (figure 1). However, inter-group comparison revealed no significant differences between the Minimal/Minor group and the NE group (all p>0.05).

Cancer-associated depression is a significant yet often overlooked comorbid mental health disorder that impacts the entire disease trajectory of patients.[6] It affects not only patients' quality of life but also their immune function and overall prognosis, despite advanced cancer treatments.[7] A study of 64 247 patients with HCC (n=64 247) revealed a 25% depression rate, with higher education levels linked to increased risk and female gender associated with a reduced risk. In contrast, a population-wide cohort retrospective study from A retrospective study from Japan showed HCC patients had increased risks of insomnia and depression after diagnosis.[8] The study also noted a higher overall survival rate in patients with depression compared with those without. In this present study among Chinese Han patients with HCC, we report a depression rate of 32.50%, with female gender, higher education and prior treatments (radical surgery and

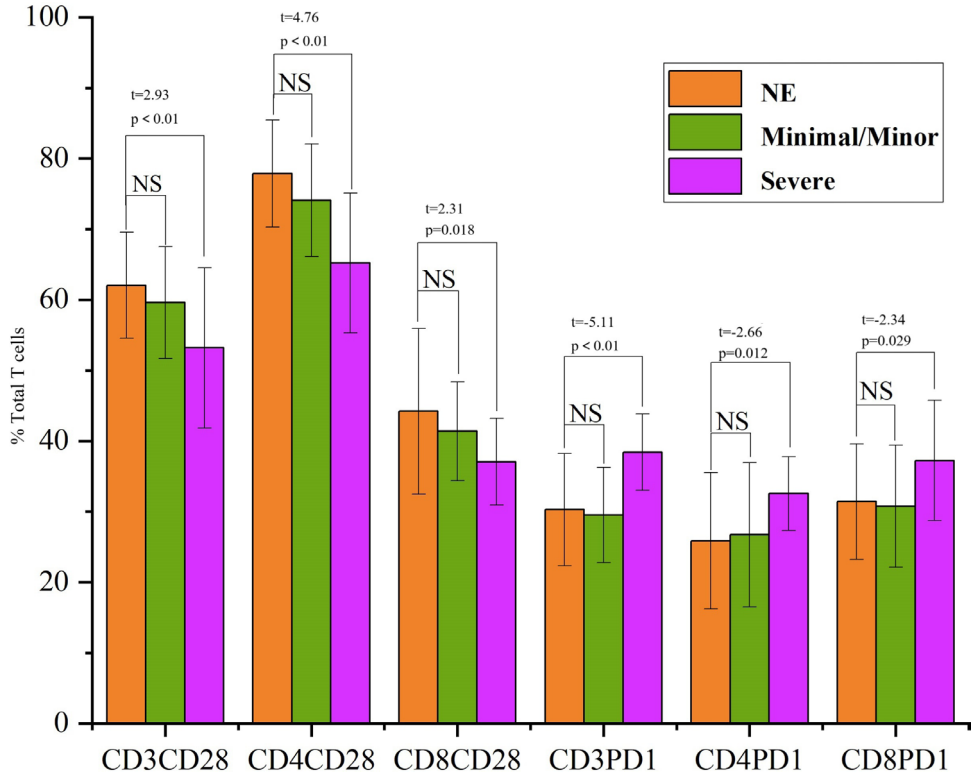

Figure 1 Detection of CD3CD28, CD4CD28, CD8CD28, CD3PD1, CD4PD1 and CD8PD1 in the peripheral blood of patients with hepatocellular carcinoma. Minimal/Minor, minor depression, dysthymia and mild depression; NE, no depression; NS, not significant; Severe, severe and moderately severe depression.

interventional therapy) as risk factors. The potential psychological impacts and mental trauma for these patients require further exploration through large-scale multicentre cohort studies.

The immune system plays a crucial role in HCC prognosis, with disruptions affecting disease progression. Immune cells, cytokines and immune checkpoints are key elements. T cells, particularly CD28 and PD-1, are central to the immune system's ability to regulate tumour growth.[9] A previous study highlighted the significance of NK cell receptors in antitumour immune responses in HCC, especially in HBV-related HCC, suggesting that targeting the NK cell receptor-ligand system may enhance the efficacy of immunotherapy.[10] CD28 expressed on T cells can transduce co-stimulatory signals necessary for T cell activation and proliferation.[11] As a prevalent mental health disorder, depression has been increasingly recognised for its intricate relationship with the immune system. Besides psychological ailment, depression also has profound implications for individuals' immune function.[12] Patients with major depressive disorder have lower levels of CD3+CD8+ and CD3+ T cells.[13] Depression can also exacerbate disease progression due to immune dysregulation, leading to serious adverse events.[14] CD28 is involved in cytokine production and T cell proliferation, and it is implicated in the compensatory immune-regulatory system, suggesting its potential role in modulating the immune response in depression.[15] Recent research has suggested a link between PD-1-mediated inhibition of CD28 signalling and depressive symptoms. Our study found that peripheral blood CD3CD28, CD4CD28 and CD8CD28 decreased, while CD3PD1, CD4PD1 and CD8PD1 increased in patients with severe depression compared with those without depression. No significant change was found in patients with mild depression. These findings suggest that severe depression in patients with HCC may impact their immune system, potentially influencing prognosis.

LIMITATIONS

This study included exclusively Chinese Han patients and had a small sample size, particularly for severe depression. The small sample size and the number of variables included in the regression analysis may have introduced bias, highlighting the need for a larger cohort in future studies. Additionally, the limited experimental data and lack of post-intervention research call for further experiments to validate the findings and guide future research.

CONCLUSIONS

Depressive symptoms in patients with HCC are associated with immune functions and patients' demographic characteristics. Further research is needed to explore the mechanisms underlying this association and to develop more effective therapeutic strategies.

Acknowledgements Sincere thanks to each subject who participated in this clinical trial. We express our sincere appreciation to our colleagues for their support and assistance in this research.

Contributors Study concept and design: YY. Analysis and interpretation of data: YZ, WZ. Drafting of the manuscript: ZM, ZC, NL. Critical revision of the manuscript for important intellectual content: XZ, YY. Statistical analysis: YZ, WZ. YZ and WZ contributed equally to this work.

Funding This work was supported by Jiangsu Commission of Health (No. x202308); The Suzhou Gusu Health Talents Scientific Research Project (No. GSWS2021052).

Competing interests None declared.

Patient consent for publication Consent obtained from next of kin.

Ethics approval This study involves human participants and was approved by Ethics Committee of The First Affiliated Hospital of Soochow University No. 2023-334. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Yunhai Yao http://orcid.org/0000-0003-2645-2913

REFERENCES

1 Bai X, Zhou Y, Yokota Y, *et al*. Adaptive antitumor immune response stimulated by bio-nanoparticle based vaccine and checkpoint blockade. *J Exp Clin Cancer Res* 2022;41:132.
2 Cheruku S, Rao V, Pandey R, *et al*. Tumor-associated macrophages employ immunoediting mechanisms in colorectal tumor progression: current research in Macrophage repolarization immunotherapy. *Int Immunopharmacol* 2023;116:109569.
3 Zhao Y, Jia Y, Shi T, *et al*. Depression promotes hepatocellular carcinoma progression through a glucocorticoid-mediated upregulation of PD-1 expression in tumor-infiltrating NK cells. *Carcinogenesis* 2019;40:1132–41.
4 do Sacramento PM, Sales M, Kasahara T de M, *et al*. Major depression favors the expansion of Th17-like cells and decrease the proportion of CD39+Treg cell subsets in response to myelin antigen in multiple sclerosis patients. *Cell Mol Life Sci* 2022;79:298.
5 Sun HZ, Song YL, Wang XY. Effects of different anesthetic methods on cellular immune and neuroendocrine functions in patients with hepatocellular carcinoma before and after surgery. *J Clin Lab Anal* 2016;30:1175–82.
6 Polityńska B, Pokorska O, Wojtukiewicz AM, *et al*. Is depression the missing link between inflammatory mediators and cancer? *Pharmacol Ther* 2022;240:108293.
7 Tan DJH, Quek SXZ, Yong JN, *et al*. Global prevalence of depression and anxiety in patients with hepatocellular carcinoma: systematic review and meta-analysis. *Clin Mol Hepatol* 2022;28:864–75.
8 Akada K, Koyama N, Miura Y. Nationwide database analysis of insomnia, depression, and sleeping pill prescriptions in hepatocellular carcinoma patients. *Curr Med Res Opin* 2022;38:1333–1339.
9 Sun C, Sun H, Zhang C, *et al*. NK cell receptor imbalance and NK cell dysfunction in HBV infection and hepatocellular carcinoma. *Cell Mol Immunol* 2015;12:292–302.
10 Esensten JH, Helou YA, Chopra G, *et al*. CD28 costimulation: from mechanism to therapy. *Immunity* 2016;44:973–88.
11 Cai L, Wei L, Yao J, *et al*. Impact of depression on the quality of sleep and immune functions in patients with coronary artery disease. *Gen Psychiatr* 2022;35:e100918.
12 Zhang H, Ding L, Shen T, *et al*. HMGB1 involved in stress-induced depression and its neuroinflammatory priming role: a systematic review. *Gen Psych* 2019;32:e100084.
13 Maes M, Rachayon M, Jirakran K, *et al*. Role of T and B lymphocyte cannabinoid type 1 and 2 receptors in major depression and suicidal behaviours. *Acta Neuropsychiatr* 2024;36:287–98.
14 Ye S, Chen W, Zheng Y, *et al*. Peripheral lymphocyte populations in ovarian cancer patients and correlations with clinicopathological features. *J Ovarian Res* 2022;15:43.
15 Rachayon M, Jirakran K, Sodsai P, *et al*. T cell activation and deficits in T regulatory cells are associated with major depressive disorder and severity of depression. *Sci Rep* 2024;14:11177.

Yunhai Yao, Deputy Chief Physician, graduated from Xiangya School of Medicine in China with a master's degree in Internal Medicine in 2013. After graduation, he has been working in the Department of Infectious Diseases and Hepatology at the First Affiliated Hospital of Soochow University in China and has long been engaged in the treatment of complications of end-stage liver diseases, including liver cancer. In 2018, he was awarded the Gold Medal for Speeches by the Chinese Society of Hepatology, Chinese Medical Association, and serves as a committee member of the Infectious Diseases and Liver Cancer Society. His main research interests focus on the complications of hepatocellular carcinoma, including depression and anxiety.