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Factors affecting anxiety, depression, and stress among patients with hepatocellular carcinoma during COVID-19 pandemic

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Abstract. – OBJECTIVE: Patients with chronic disease whose treatments are limited may experience depression, anxiety, and stress-related symptoms, as well as an increase in the levels of these conditions. This study aims to determine the factors affecting the depression, stress, and anxiety levels of hepatocellular carcinoma (HCC) patients due to the fear of COVID-19 exposure.

PATIENTS AND METHODS: 118 patients with advanced HCC treated with non-transplant treatment options or on the waiting list due to the lack of a donor were enrolled. To evaluate the stress, depression, and anxiety levels during the COVID-19 process, Depression Anxiety Stress Scales (DASS-21) and the Coronavirus Anxiety Scale (CAS) were administered to 118 patients through a face-to-face interview. Sociodemographic and clinical characteristics were recorded, and the primary endpoint measure was the total score of DASS. In addition, the multilayer perceptron (MLP) model was constructed to predict the scores of the DASS-21 total.

RESULTS: There were significant differences between DASS depression (p=0.010; p=0.030) DASS anxiety (p=0.010; p=0.010) and DASS total (p=0.046; p=0.023) scores in terms of gender and protective effect of the vaccine. Also, a significant difference between gender for the CAS scale was determined (p=0.044). The median score of the DASS total in the COVID-19 group was higher than in the non-COVID-19 group; however, the increase was not significant. MLP model revealed that chronic disease, gender, age, place of residence, smoking, type of vaccine, and COVID-19 exposure were the most important predictors for the DASS total.

CONCLUSIONS: Chronic disease, gender, and age were prominent factors in predicting the DASS-21 total score in HCC patients. Therefore, the crucial factors were clinically considered for managing depression, stress, and anxiety in HCC patients.

Key Words:
Hepatocellular carcinoma, COVID-19 pandemic, Depression, Anxiety, Stress.

Introduction

The most frequent primary cancer of the liver is hepatocellular carcinoma (HCC), the second greatest cause of cancer-related death worldwide. It is the fifth most frequent cancer in males and the seventh most prevalent cancer in women globally, with over half a million new cases identified yearly[1,2]. Treatment of the HCC varies across regions or countries according to the demographic characteristics, stage of the tumor, socioeconomic condition, and availability of treatment options[3,4]. However, effective treatment for HCC patients in the advanced stage is quite difficult because the disease can usually be diagnosed at an advanced stage[3]. If HCC is diagnosed at an early stage, it can be treated curatively by surgical resection or liver transplantation. However, most patients with HCC have a poor prognosis with a survival time of less than one year owing to the advanced disease and underlying liver dysfunction[5]. Cancer patients' mental states and behavioral patterns may change due to heavy treatment exposure, and thence, anxiety, stress, and depression levels might increase[6].

With the COVID-19 pandemic, education, commerce, and social activities have been halted almost everywhere in the world. Transportation restrictions, social isolation, quarantine measures, and curfews have become commonplace, and the

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concept of a "new normal" has emerged. Recent research on COVID-19 reported that this disease might cause fundamental changes in many societies' psychological and social implications. Therefore, mental disorders such as anxiety, depression, and post-traumatic stress have evolved in the communities[7,8]. These developing psychological disorders may be more common in people with chronic diseases and cancer, and the restrictions related to COVID-19 can make them more anxious than others. This study aims to determine the factors affecting the depression, stress, and anxiety levels of non-transplant HCC patients due to the fear of contracting COVID-19.

Patients and Methods

Type, Place, and Time of Research

This descriptive and survey-based cross-sectional study conducted at Inonu University (Liver Transplantation Institute), consisted of patients treated with non-transplant treatment options due to advanced HCC and those on the waiting list for an LT but had not had a chance to LT (DDLT or LDLT) until November 2021. Non- transplant treatment options consist of surgical resection, transarterial radioembolization (TARE), transarterial chemoembolization (TACE), microwave ablation (MWA), radiofrequency ablation (RFA), and systemic chemotherapy. Before starting the study, permission was obtained from the Directorate of Liver Transplantation Institute of Inonu University (2021/93882). Each participant gave consent before the questionnaire was distributed.

Study Protocol and Ethics Committee Approval

This study involving human participants followed the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was obtained from the Inonu University Institutional Review Board (IRB) for Non-Interventional Clinical Research (2021/2766). STROBE (Strengthening the reporting of observational studies in epidemiology) guideline was utilized for considering the checklist related to the current study[9].

Determination of the Research Population and Study Group

Based on the patient information and management system (HBYS-ENLIL) data used in our tertiary referral hospital, 126 HCC patients – who were under the follow-up of our Liver Transplant Institute as of November 2021 and were found to be alive on the specified date – were evaluated as the target population of this study. These patients either had advanced HCC disease and had received one of the non-transplant treatment options (resection, TARE, TACE, MWA, RFA) or were on the waiting list due to the absence of a donor despite surgical indication. Before starting this study, the patients' basic demographic data were examined and they were contacted by phone or WhatsApp. Eight patients who were not eligible to be included in the study for various reasons (communication disorder and inability to reach their phone) were excluded. The remaining 118 patients were included in this study. The current study evaluated the stress, depression, and anxiety levels of 118 HCC patients using standardized scales during the COVID-19 process. Whether there are any relationships between the scale scores, the demographic characteristics, and the status of COVID-19 exposure was determined. The minimum sample size required to detect a significant difference was calculated at 97, considering type I error (alpha) of 0.05, power (1-beta) of 0.8, an effect size of 0.29, and a two-sided alternative hypothesis. In the current study, 118 HCC patients were enrolled to increase the study's power, and the primary endpoint measure was the DASS-21 total score.

Inclusion and Exclusion Criteria

Since this study was questionnaire-based research, HCC patients who were aged $\geq$ 18 years old, who had sufficient Turkish language to read or understand the questionnaire questions, and who were in the routine follow-up protocol of our center were included. Patients who did not want to respond to the survey or did not respond to some of the questions were excluded from this study.

Variables and Scales Used in the Study

Demographic and social characteristics form

The questionnaire used in this study consisted of 26 questions and two scales. The sociodemographic and clinical characteristics in this study were briefly defined and recorded as follows: age, gender, height, weight, marital status, place of residence, education level, monthly income, cause of liver disease, presence of chronic disease [diabetes mellitus, hypertension, asthma, chronic obstructive pulmonary disease (COPD), cardiovascular disease], smoking, alcohol use, COVID-19 ex-

posure, antiviral drug use, hospitalization due to COVID-19 (service, intensive care, and intubation), COVID-19 vaccination status (Sinovac, BioNTech, and both), vaccine dose (one, two, three, and four doses), post-vaccine COVID-19 status, the vaccine hesitancy, belief in the protection of the vaccine, and legal obligation for the vaccination.

Coronavirus Anxiety Scale-Short Form (CAS-SF)

CAS-SF, which aims to determine the severity of anxiety caused by the COVID-19 pandemic in society, was first defined by Lee[10]. The factor loads of the items ranged from 0.81 to 0.88, and the Cronbach's alpha coefficient was calculated as 0.93. The validity and reliability tests of the Turkish version of this scale were performed by Biçer et al[11]. Biçer et al[11] demonstrated that the factor loads of the items in the Turkish version of the CAS-SF scale, which consisted of one dimension and five items, varied between 0.625 and 0.784. Biçer et al[11] calculated this scale's Cronbach's alpha coefficient as 0.832. The responses in the CAS-SF scale, which included five-point Likert-type questions, are listed as not at all (0 points), rare, less than one or two days (1 point), several days (2 points), more than seven days (3 points) and nearly every day over the last two weeks (4 points). The presence of anxiety related to COVID-19 was considered if the score was of 9 or above (min=0 and max=20). Lee[10] calculated an optimal cut-off point for anxiety (≥ 9 points) using ROC curve analysis and calculated the sensitivity and specificity values of this cut-off point as 90% and 85% (AUC: 0.94; $p<0.001$), respectively.

Depression, Stress and Anxiety Scale- Short Form (DASS-21)

The long form of the DASS scale, developed by a study in 1995[12], encapsulates 42 items and three sub-dimensions. The Cronbach's alpha internal consistency coefficients for the depression, anxiety, and stress sub-dimensions of the long version of the DASS scale were calculated as 0.91, 0.84, and 0.90, respectively. Henry and Crawford[13] designed a short version of the DASS scale based on the hypothesis that the short form of the DASS scale is also valid for the same measurement. The Cronbach's alpha reliability coefficient of the DASS-21 form was calculated as 0.93. Regarding sub-dimension analysis, Cronbach's alpha coefficients of depression, anxiety, and stress sub-dimensions of the DASS-21 were estimated to be 0.88, 0.82, and 0.90, respectively. The Turkish adaptation of the DASS-21 form was made by Yılmaz et al[14]. The DASS-21 scale, which consisted of four-Likert type questions, had choices as never (0 points; did not apply to me at all), sometimes (1 point; applied to me to some degree, or some of the time), often (2 point; applied to me to a considerable degree, or a good part of the time), almost always (3 point; applied to me very much, or most of the time). There are seven questions in each of the depression (3, 5, 10, 13, 16, 17, 21), anxiety (2, 4, 7, 9, 15, 19, 20) and stress (1, 6, 8, 11, 12, 14, 18) sub-dimensions. The Cronbach's alpha reliability and internal consistency coefficient of the DASS-21 scale was 0.87 reported by Yılmaz et al[14]. In terms of sub-dimensions analysis, Cronbach's alpha internal consistency coefficients of depression, anxiety, and stress were calculated as 0.819, 0.808, and 0.755, consecutively. There is no reverse-pointed item on the scale.

Statistical Analysis

Kolmogorov-Smirnov normality test was used to point out whether the variables had a normal distribution. Data were given as median (minimum-maximum) and number (percentage). Mann-Whitney U and Kruskal Wallis tests were used where appropriate for statistical analysis. Conover test was used for pairwise comparisons after the significant Kruskal Wallis test. Effect size is defined as the size of the difference between groups. For the Mann-Whitney U test, the effect size (Cohen d) is interpreted as a small effect between 0.20-0.50, a moderate effect between 0.50-0.80, and a large effect above 0.80. For the Kruskal Wallis test, the effect size (Cohen d) is commented as a small effect between 0.10 and 0.25, a moderate effect between 0.25 and 0.40, and a large effect with values above 0.40[15]. In the multilayer perceptron method (MLP), a feed-forward artificial neural network model from machine learning methods, COVID-19 exposure, gender, chronic illness, vaccination type, smoking, education level, and place of residence variables were taken as input variables, and DASS total variable was determined as output variable. Feature selection was not performed due to the potential clinical significance of the input variables included in the MLP model. Activation functions were hyperbolic tangent in the hidden layer(s) and identity in the output layer. The number of hidden layers and number of units in the hidden layer was 1, and the number of units and rescaling method for scale dependents was one and standardized, respectively. During the modeling phase, 70% of the data set was used as training and 30% as test data.

The sum of squares error and relative error were estimated to evaluate the model performance. A p <0.05 was considered statistically significant. SPSS Statistics 25.v0 program (IBM Corp., Armonk, NY, USA) was used in the analysis.

Results

Considering the inclusion and exclusion criteria, 118 HCC patients were included in the current study, with ages ranging from 20 to 80 years [median (IQR: 61.5)]. This study included 90 (76.27%) male and 28 (23.73%) female patients. The comparison results for the variables affecting the depression, stress, and anxiety levels caused by the fear of the COVID-19 exposure in patients treated with non-hepatic transplant options for HCC or who have not yet had the chance to be treated were given in Table I.

Table I shows statistically significant differences in DASS-21 depression, DASS-21 anxiety, and DASS-21 total scores for gender. In the analyses for gender, the effect sizes are small, and the difference in terms of gender categories is clinically significant. No significant difference was found for the DASS-21 stress score. There was a statistically significant difference in DASS-21 depression for education level. In the analyses for education level, the effect size (0.465) is large for DASS-21 depression, and the difference in terms of education level categories is clinically significant. There is a statistically significant difference in the DASS-21 depression and DASS-21 anxiety scores for chronic disease. However, no significant difference was found in DASS-21 stress and DASS-21 total scores. There was no statistically significant difference in the types of scores regarding COVID-19 exposure. In addition, no significant difference was found in the score types regarding the COVID-19 vaccine. While there was a statistically significant difference only for the DASS-21 anxiety score concerning vaccine hesitancy; no significant difference was identified in the other score types.

There is a statistically significant difference in the DASS-21 depression, DASS-21 anxiety, and DASS-21 total scores according to the vaccine's protectiveness. Pairwise comparisons showed a difference between the yes and no categories and the yes and no idea categories for the DASS-21 depression score. For the DASS-21 anxiety score, significant differences were observed between the yes and no idea categories and the no idea categories. The effect sizes concerning the vaccine protection for DASS-21 depression, DASS-21 anxiety, and DASS-21 total scores were 0.426 (large), 0.659 (large), and 0.451 (large), respectively. Finally, there was a difference between the yes and no categories for the DASS-21 total score. There was no statistically significant difference in the total score and sub-categories of the DASS-21 scale for the vaccine type. The comparison results of the CAS-SF scores of the variables are presented in Table II.

While there were significant differences in the categories of gender and hospitalization variables in the analyses for the CAS-SF scores, no statistically significant difference was found in the categories of other variables. The graphical architecture for the MLP algorithm is depicted in Figure 1.

According to the results from the MLP model's importance values of the input variables affecting the DASS-21 total score are given in Table III. Among the importance values, chronic disease was the most prominent factor. As a result of modeling, the sum of squares error was 18,457, and the relative error was 0.79.

Discussion

The present study investigates what factors may influence depression, stress, and anxiety in patients with advanced HCC treated with non-liver transplant options or who have not yet received a liver transplant while on the waiting list for one. To achieve this goal, DASS-21 scales were implemented on the patients to assess depressive, anxiety, and stress-related emotional states. According to the World Health Organization (WHO), a healthy individual is free of sickness or impairment and has a good psychological and physical condition. In accordance with the WHO, technical and medical success with transplantation does not necessarily reflect individual health; at the same time, patients should also be in an appropriate range of psychological state[16].

Depression, an important mental health problem frequently encountered worldwide, reduces the quality of life and causes workforce losses by preventing human functionality, creativity, happiness, and satisfaction[17]. The presence of physical illness is both a direct and indirect cause of depressive disorder. Diagnosis of a new illness can often initiate a depressive episode. Chronic diseases, on the other hand, are factors of depression due to their features such as accompanying chronic pain, becoming dependent on others, causing limitations in daily life, and reducing the quality of life. Furthermore, there is concern that the sickness would spread among patients, leading to addiction[18].

Table I. Comparison of DASS-21 scores according to total and sub-dimensions for the variables.

		DASS-21 Depression			DASS-21 Stress			DASS-21 Anxiety			DASS-21 Total		
		Median (Min-Max)	ES	*p*	Median (Min-Max)	ES	*p*	Median (Min-Max)	ES	*p*	Median (Min-Max)	ES	*p*
Gender	Female	2.5 (0-21)	0.466	**0.010***	5 (0-17)	0.28	0.128*	1.5 (0-13)	0.41	**0.010***	9 (0-43)	0.373	**0.046***
	Male	1 (0-26)			2 (0-13)			0 (0-10)			4 (0-33)		
Educational level	Illiterate	1 (0-26)	0.465	**0.044****	3 (0-13)	0.055	0.395	0 (0-13)	0.039	0.412**	5.5 (0-33)	0.313	0.153
	Primary school	2 (0-21)			3 (0-17)			0 (0-6)			6 (0-43)		
	Middle School	0 (0-6)			2 (0-8)			0 (0-9)			3 (0-19)		
	High school	0 (0-4)			1 (0-10)			0 (0-6)			1 (0-17)		
	≥ University	0 (0-14)			2 (0-11)			0 (0-10)			5 (0-32)		
Chronic disease?	Yes	1 (0-26)	0.375	**0.036***	4 (0-17)	0.284	0.124*	0 (0-13)	0.321	**0.043***	6 (0-43)	0.359	0.054*
	No	1 (0-14)			2 (0-15)			0 (0-7)			4 (0-32)		
Exposed to COVID-19?	Yes	1 (0-26)	0.041	0.817*	3 (0-11)	0.128	0.484*	0 (0-7)	0.002	0.991	6 (0-33)	0.009	0.962*
	No	1 (0-21)			3 (0-17)			0 (0-13)			5 (0-43)		
COVID-19 vaccine?	Yes	1 (0-0)	0.243	0.595*	3 (0-0)	0.248	0.583	0 (0-0)	0.323	0.223*	5 (0-0)	0.276	0.465
	No	1 (0-14)			3 (0-11)			0 (0-10)			7 (0-32)		
COVID-19 vaccine hesitancy	Yes	2 (0-26)	0.254	0.153*	3 (0-17)	0.21	0.239*	1 (0-10)	0.32	**0.043***	7 (1-43)	0.347	0.062*
	No	1 (0-16)			2 (0-15)			0 (0-13)			5 (0-32)		
Do you think the COVID-19 vaccine is protective?	Yes	1^{a} (0-14)	**0.426**	**0.030****	2^{a} (0-15)	0.084	0.333*	0 (0-13)^{a}	**0.659**	**0.001****	4 (0-32)^{a}	**0.451**	**0.023****
	No	4^{b} (0-21)			5^{a} (1-17)			5 (0-10)^{b}			22 (1-43)^{b}		
	No idea	2.5^{b} (0-26)			3.5^{a} (0-13)			0 (0-11)^{a}			7.5 (0-33)^{ab}		
Type of COVID-19 vaccine	Sinovac	1 (0-16)	0.25	0.173**	3 (0-15)	0.259	0.164*	0 (0-6)	0.213	0.212**	6 (0-27)	0.283	0.141**
	Biontech	1 (0-26)			2 (0-17)			0 (0-13)			5 (0-43)		
	Both	0 (0-14)			2 (0-14)			0 (0-11)			2 (0-31)		

The same letters (a or b letters) indicate no difference between groups, while different letters indicate statistical difference between groups. (Conover test; $p<0.05$); *: Mann-Whitney U test; **: Kruskal-Wallis test; ES: Effect size.

Table II. Comparison of CAS-SF total score for the variables.

Variable	Category	CAS Total	ES	p
Gender	Female	0 (0-4)	0.179	**0.044***
	Male	0 (0-6)		
Have you chronic disease?	Yes	0 (0-3)	0.017	0.845*
	No	0 (0-6)		
Have you been exposed to COVID-19?	Yes	0 (0-6)	0.115	0.196*
	No	0 (0-3)		
Have you had the COVID-19 vaccine?	Yes	0 (0-6)	**0.12**	**0.177***
	No	0 (0-0)		
Hospitalization due to COVID-19	Yes	0 (0-6)	0.571	0.014*
	No	0 (0-4)		
Type of vaccine	Sinovac	0 (0-6)	0.260	0.820**
	BioNTech	0 (0-4)		
	Both	0 (0-1)		
Vaccine dose	One	0 (0-0)	0.185	0.537**
	Two	0 (0-4)		
	Three	0 (0-6)		
	Four	0 (0-0)		
Post-vaccine COVID-19 status	Yes	0 (0-6)	0.116	0.192*
	No	0 (0-4)		
Have you hesitancy against the COVID-19 vaccine?	Yes	0 (0-6)	0.054	0.545**
	No	0 (0-4)		
Do you think the COVID-19 vaccine is protective?	Yes	0 (0-4)	0.365	0.058**
	No	0 (0-6)		
	No idea	0 (0-0)		
Should COVID-19 vaccine applications be made compulsory by law?	Yes	0 (0-4)	0.302	0.102**

*: Mann Whitney U test; **: Kruskal Wallis test; ES: Effect size.

Anxiety is a fear and worry that is difficult to define and can be in different intensities, ranging from a very mild feeling of uneasiness and tension to the degree of panic. Anxiety, fear, and panic are the most obvious reactions of individuals to the disease in general. These responses have been shown to impact patient recovery and behavior. The individual's reactions to the disease, such as anxiety and depression, directly affect the way and power of coping with the disease[19,20]. Patients with HCC who are treated with options other than liver transplantation or who have not yet had the chance to transplant have a mood disorder caused by the disease due to the difficulties of intensive treatments. In addition, the idea of the emergence of any other diseases in these patients may increase their mood disorder. In this case, individuals who are already sick may be exposed to new diseases and extreme situations. In the analyses for the DASS-21 scale and its sub-dimensions in the study, significant differences were observed for gender and vaccine protection for the other scales except for the DASS-21 stress scale. More anxiety and depression were observed in women than in men. Similarly, more anxiety and depression levels were observed in those who did not find the vaccine protective. In the CAS-SF scale score results, significant differences were found for the categories of gender and hospitalization variables.

According to the modeling results from the MLP model, chronic disease, gender, age, place of residence, smoking, and educational status are the most effective factors on the DASS-21 total score, respectively. Implementing the MLP is of clinical importance for predicting the DASS-21 total score associated with HCC during COVID-19. The current study enlights by applying the MLP model to explore the potential factors related to the score of DASS-21 total and presents the medical estimations from the clinical point of view.

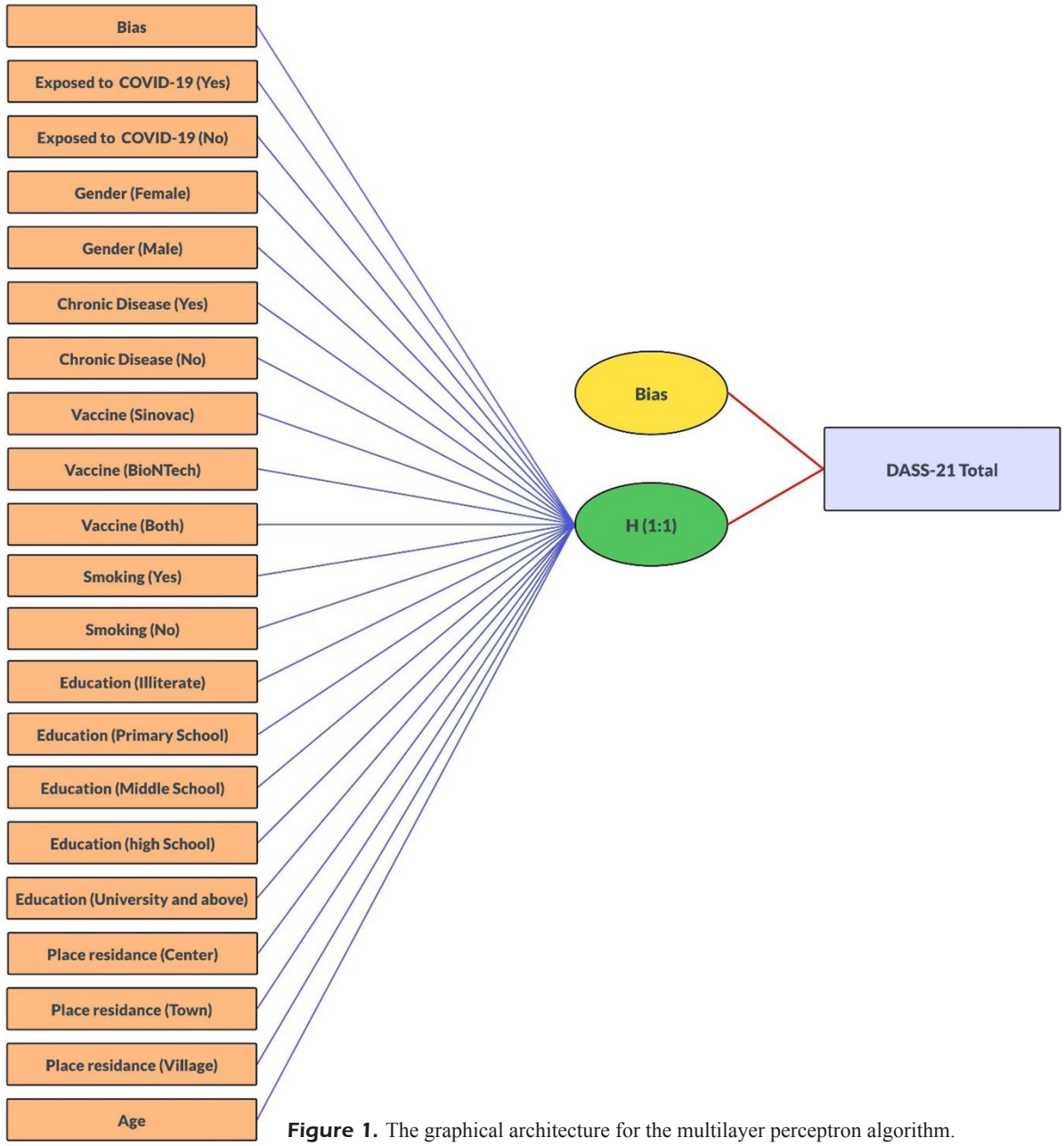

Figure 1. The graphical architecture for the multilayer perceptron algorithm.

Table III. Variable importance values for MLP model.

Variables	Importance
Have you been exposed to COVID-19?	0.021
Gender	0.202
Do you have chronic disease?	0.227
Type of vaccine	0.070
Smoking	0.111
Education level	0.100
Place of residence	0.120
Age	0.149

The psychological health of society is arguably a primary issue during such a crisis, and implementing mental health examination and support are important aims for coping with COVID-19's mental health effects[21].

Within the framework of this study, several clinical scales were considered to measure the anxiety, depression, and stress levels of HCC patients during COVID-19. Clinical research reports[22] increased anxiety and depression levels in people with chronic diseases, and the two conditions trigger each other. Similarly, in the current study, the

MLP model revealed that the patients with chronic diseases were the most emotionally affected. In a study, women observed an increase in anxiety levels compared to men in the case of chronic obstructive pulmonary disease. According to the study results, it can be inferred that women are more anxious and stressed than men in case of an illness[23]. Similar to the findings of the mentioned study, it was determined that women were affected more emotionally and increased their anxiety in the present study. Possible effects of the COVID-19 pandemic on anxiety, depression, and stress among patients who have advanced-stage HCC were evaluated with basic and sophisticated approaches (i.e., machine learning algorithm). Additionally,

Considering the outcomes of the DASS-21 scale, an important public health strategy can be developed collectively to evaluate and address the possible factors on the depression, anxiety, and stress states of HCC patients in the last stages of the COVID-19 pandemic.

A medical study[5] declares that education level reduces anxiety and depression, enhances the quality of life, and extends longevity in individuals with HCC who have had their tumor removed surgically. In the current study, education level was associated with the DASS-21 total score based on the outcome of the proposed MLP model. Based on the findings, it can be concluded that educational activities have positive effects on anxiety, stress, and depression.

Psychological aspects were found to be linked to cancer patient survival[24]. Depression, hopelessness, and emotional repression are all risk factors for cancer patients having a lower survival time and quality of life[25,26]. Studies[22-29] conducted during the COVID-19 process have shown that cancer patients have a greater fear of exposure to infection and that they experience anxiety and stress due to the risk of progression of their disease due to delays in their treatment. Exposure to COVID-19 was another key predictor in the proposed MLP model. In this context, it can be concluded that clinical improvement of depression, anxiety, and stress states is significant to increase the survival of advanced HCC patients.

Limitations

The present study may have some limitations. First, comprehensive inferences can be obtained by designing multicenter studies and with larger sample sizes. Second, precise estimates of the DASS-21 total score can be achieved by considering other demographic and clinical variables associated with HCC, and other machine learning models may be constructed.

Conclusions

To sum up, the MLP model revealed that chronic disease, gender, age, place of residence, smoking, type of vaccine, and the COVID-19 exposure were the most important predictors for the DASS-21 total score. Therefore, the crucial factors were clinically considered for managing depression, stress, and anxiety in HCC patients.

Authors' Contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Tamer M., Akyuz M., Saritas H., Bagci N., Ciftci F. and Akbulut M.S. Akbulut S., Yilmaz S., Kucukakcali Z. and Karabulut E. wrote the first draft of the manuscript, and all authors commented on previous versions. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflicts of interest regarding this manuscript.

Informed Consent

Each participant gave consent before the questionnaire was distributed.

Data Availability

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

Ethics Approval

Ethics Committee Approval was approved by the Inonu University Institutional Review Board (IRB) for non-interventional studies (Approval No: 2021/ 2766).

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