

## RESEARCH ARTICLE

# Appetite loss, death anxiety and medical coping modes in COVID-19 patients: a cross-sectional study

Qiuxuan Zeng<sup>1</sup> | Huangliang Cao<sup>2</sup> | Qing Ma<sup>3</sup> | Jieya Chen<sup>1</sup> | Haixia Shi<sup>1</sup> | Jiaying Li<sup>4</sup> 

<sup>1</sup>Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

<sup>2</sup>Guangzhou Eighth People's Hospital, Guangzhou Medical University, Guangzhou, China

<sup>3</sup>School of Nursing, Guangzhou University of Chinese Medicine, Guangzhou, China

<sup>4</sup>School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

**Correspondence**

Jiaying Li, School of Nursing, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam Road, Hong Kong Special Administrative Region, China.  
Email: gaaiwing@connect.hku.hk

**Funding information**

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors

**Abstract**

**Aim:** This study aims to explore the current level and associated factors of appetite and death anxiety amongst COVID-19 patients and also to identify correlation between the two variables.

**Design:** A cross-sectional study.

**Methods:** Demographic and characteristic questionnaires, temper death anxiety scale, council on nutrition of appetite questionnaire and medical coping modes questionnaire were utilized.

**Results:** The average scores of appetite and death anxiety were 19.46 (4.09) and 6.58, (3.21) respectively. 76 patients (100%) suffered from appetite loss, whilst 27 (35.50%) patients suffered from severe death anxiety. Marital status, COVID-19 disease condition ranks, educational level and death anxiety were explained 55.20% of the total variance in the appetite regression model ( $F = 31.83, p < .001$ ), whilst the gender, avoidance coping strategy and appetite level were explained 49.80% of the total variance in death anxiety model ( $F = 17.80, p < .001$ ). A moderate negative correlation between appetite and death anxiety was also confirmed ( $r = -.55, p < .001$ ).

**KEYWORDS**

appetite level, associated factors, COVID-19, death anxiety, medical coping modes

## 1 | INTRODUCTION

COVID-19 has been known as a respiratory illness caused by severe acute respiratory syndrome, which has been threatening the health of the public around the world (Legido-Quigley et al. 2020; Li et al., 2020). Increasing evidence has proved it raises some digestive symptoms, such as anorexia, diarrhoea, nausea and vomiting, were found in patients diagnosed with COVID-19 (Richards & Andrews, 2004; Aguila et al., 2020; Ungaro et al., 2020). This was consistent

with what we were aware of when providing nursing care for patients with COVID-19. Some patients denied eating or had a lower level of appetite during their treatment. Because of this, there is a recognized need for managing their malnutrition that attributed to the alterations of smell and taste and lack of appetite (Lechien et al., 2020). Besides, this negative impact on food intake might also result in malnutrition and weight loss (Harris et al., 2017). As a result, this impaired appetite eventually appears to cause higher mortality (Barazzoni et al., 2020). Despite this, loss of appetite is a

Qiuxuan Zeng and Huangliang Cao made the same contribution to this paper.

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problem associated with more than physiological factors, and it is also related to a variety of cultural, psycho-social, and environmental factors (Donini et al., 2003). Consequently, understanding more factors associated with COVID-19 patients' appetite level is of great significance in dealing with patients' weight, nutrition and even their recovery.

Although the morbidity of COVID-19 is not as high as that of SARS, patients commonly suffering a certain degree of death anxiety that harmed their recovery (Dar et al., 2017; Huang et al., 2020; Sadri Damirchi et al., 2020; Xiang et al., 2020). A previous study reported psychological conditions impacted the patients' appetite and food intake in other disease (Fysekidis et al., 2018). Moreover, death anxiety, a negative psychological state, can suppress food intake. Accordingly, eating is an adaptive means for stress relief too (Epel et al., 2004; Oliver & Wardle, 1999; Stone & Brownell, 1994). However, no attempt was made to quantify the association between appetite and death anxiety in COVID-19 patients. Therefore, research to confirm the potential correlation is supposed to be an approach to address the patient's willingness to intake. Coping is considered as the active efforts, involving a series of cognitive and behavioural strategies, to manage, reduce, or demands generated by stress. It is generally manifested by confrontation, avoidance and resignation types. Previous has illustrated that it intermediates the external stress and individual psychological disorder outcome and also involved in the process of psychological stress (Joormann et al., 2006; Lazarus, 1993; Tuncay et al., 2008). To clarify the effect of medical coping model on patients' appetite and death anxiety also can help medical staff deal with this issue better.

Patients' appetite condition make an important contribution to the food intake and nutrition management in their treatment. What's more, it is also regarded as more than a physiological performance. The death anxiety and medical coping mode were assumed to correlate with appetite condition, which is unconfirmed by the previous study. Thus, in this study we aim to 1) firstly describe the appetite level, death anxiety of COVID-19 patients, 2) identify associated factors related to patients' appetite and death anxiety and 3) explore the relationship between appetite and death anxiety in patients affected with COVID-19.

## 2 | METHODS

### 2.1 | Design

A cross-sectional study was designed in this study.

### 2.2 | Participants

The convenience sampling method was utilized in this study, and the patients were recruited according to the following criteria: Inclusion criteria were as follows: (1) patients who have been diagnosed with

COVID-19 and has a positive nucleic acid test; (2) patients who are willing to participate in; and (3) patients who can read or understand the questionnaire. Exclusion criteria were as follows: (1) according to the principles of voluntary patients who refused to participate should be excluded from this study.

## 2.3 | Variables and measurements

### 2.3.1 | Demographic and characteristic questionnaire

The self-designed demographic and characteristic questionnaire consists of gender, marital status, census, income level, education level, COVID-19 disease condition ranks, and whether their relatives were diagnosed with COVID-19. Patients who met one of the following criteria were defined as severe type: (1) respiratory rate more than 30 breaths per minute; (2) pulse oxygen saturation (SpO<sub>2</sub>) less than 93% without oxygen support therapy; and (3) Oxygenation Index (arterial partial pressure of oxygen to fraction of inspiration oxygen [PaO<sub>2</sub>/FiO<sub>2</sub>]) less than 300 mmHg. Mild type was defined as the patient who did not meet any of the criteria for severe type mentioned above (Yang et al., 2020).

### 2.3.2 | Death anxiety

The death anxiety was accessed by Templer Death Anxiety Scale (T-DAS) developed with 15 items (Templer, 1970). The Chinese version of T-DAS was utilized in this study (Yang et al., 2013). The answers to each item were "yes" and "no," which means "1" and "0," respectively. A higher score indicates a higher level of death anxiety.

### 2.3.3 | Appetite

The assessment of the patients' extent of loss of appetite was according to the Council on Nutrition of Appetite Questionnaire (CNAQ) developed by Wilson et al., (2005). The scale contains 8 items scored on a 5-point Likert scale. The total score will range from 8–40. The lower score presents a lower level of appetite.

### 2.3.4 | Medical coping modes questionnaire (MCMQ)

The MCMQ was developed by Feifel et al., (1987), which has been widely used in patients with a life-threatening disease. The scale consists of confrontation (8 items), avoidance (7 items) and resignation (5 items) domains. All the items were rated by the 4-point Likert scale. The dimension with the highest cumulative score indicated the particular coping strategy the patients likely to use.

### 2.3.5 | Statistical methods

Data analysis was performed in IBM SPSS 23.0 (SPSS Inc., Chicago, IL, USA). The data of patients' demographic and characteristic information, level of patients' death anxiety and level of patients' appetite level were described by descriptive statistics. Specifically, continuous variables that meet with the normal distribution were reported by mean values (*M*) and standard deviations (*SD*), and categorical variables were described by frequency (rate). After finishing the normal check and normal transformation, *t* test, ANOVA analysis were utilized for confirming the group difference between independent variables. The significant-different variables were taken into the multiple linear stepwise regression analysis for building the prediction equation. The Pearson correlation coefficient method is used to detect the correlation between variables.

### 2.3.6 | Ethics consideration

This research has been approved by an ethics committee, and the approval number is 202119206. This study was performed according to the ethical principles as stated by the Declaration of Helsinki. An electronic questionnaire approach was utilized for the data collection. An instruction is annotated at the beginning of the questionnaire to let patients fully understand the aims, contents and procedure of the survey. We also set a question to let patients choose whether they want to answer this questionnaire or not. If they were unwilling to fill it, the electronic questionnaire will automatically end. Besides, patients completed the questionnaires anonymously, and data were used for research only and kept strictly confidential.

## 3 | RESULTS

### 3.1 | The demographic and characteristic information of the patients

A total of 76 patients diagnosed with COVID-19 were concluded in this study eventually, and all the patients came from Guangdong province. The patients' age is ranging from 24–71, with an average age of 41.62 (15.53). Of these 76 patients, 9 patients have diabetes, 2 patients have heart disease, and 1 patient has chronic respiratory diseases. Other demographic and characteristic details were given in Table 1.

### 3.2 | The current level and associated factors of appetite level in COVID-19 patients

#### 3.2.1 | The level of patients' appetite level

The Cronbach  $\alpha$  of the CNAQ in our study is 0.809, which is indicating a good internal consistency. The appetite level amongst patients

was ranging from 10–25, with an average of 19.46 (4.09). The score of each item is shown in Table 2. According to the standard that a lower score than 28 indicated an appetite loss, in this study 76 patients (100%) has this problem.

#### 3.2.2 | Univariate analyses of the factors associated with patients' appetite level

As present in Table 3, age ( $F = 8.90, p < .001$ ), marital status ( $t = -5.87, p < .001$ ), educational level ( $F = 5.88, p = .001$ ), monthly income ( $F = 3.53, p = .011$ ) and COVID-19 disease condition ranks ( $t = 3.82, p < .001$ ) had a significant impact on the level of patients' appetite level.

#### 3.2.3 | Multiple linear stepwise regression analyses on demographics and characteristics impacting patients' appetite level

In the appetite regression model, patients' demographics and characteristics information of participants were used as independent variables and appetite level as the dependent variable. Table 4 shows marital status, COVID-19 disease condition ranks, educational level and death anxiety were contained in this model, which explained 55.20% of the total variance ( $F = 31.83, p < .001$ ). Besides, the patient's education level and being unmarried were positive factors with appetite, whereas the severe type of COVID-19 and death anxiety were negative factors.

#### 3.2.4 | The current level and associated factors of death anxiety in COVID-19 patients

##### *The level of patients' death anxiety*

Amongst 76 patients, the death anxiety score is ranging from 1–13, with an average score of 6.58 (3.21). The score of each item is shown in Table 2. According to the standard that a higher score than 7 means severe death anxiety, in this study 27 (35.50%) patients suffered from death anxiety.

##### *Univariate analyses of the factors associated with patients' death anxiety*

As contained in Table 3, age ( $F = 6.00, p < .001$ ), gender ( $t = -3.67, p < .001$ ), an education level ( $F = 3.14, p = .031$ ), whether the relatives tested positive ( $t = 3.38, p = .001$ ), and coping strategy ( $F = 9.07, p < .001$ ) had a significant group difference in patients' death anxiety.

##### *Multiple linear stepwise regression analyses on demographics and characteristics impacting patients' death anxiety*

In the death anxiety model, COVID-19 disease condition ranks, gender, avoidance coping strategy and appetite level were the variables

**TABLE 1** The demographic and characteristic information of patients ( $n = 76$ )

Variables	Categories	$n$ (%)
Gender	Male	48 (63.20)
	Female	28 (36.80)
Age	Under 40 years old	44 (57.90)
	Between 40 and 60 years old	17 (22.40)
	Over 60 years old	15 (19.70)
Marital status	Married	51 (67.10)
	Unmarried	25 (32.90)
Educational level	Junior high school and below it	15 (19.70)
	High school or secondary school	35 (46.10)
	College degree	7 (9.20)
	Bachelor degree	19 (25.00)
	Master degree and above it	0 (0.00)
Census	Local	15 (19.70)
	Non-local	61 (80.30)
Monthly income	Less than 3,000	7 (9.20)
	3,000–6,000	26 (34.20)
	6,000–9,000	21 (27.60)
	9,000–12,000	15 (19.70)
	More than 120,000	7 (9.20)
Relatives tested positive	Yes	62 (81.60)
	No	14 (18.40)
COVID-19 Disease condition ranks	Mild type	56 (73.70)
	Severe type	20 (26.30)
Coping strategy	Confrontation	54 (71.10)
	Avoidance	18 (23.70)
	Resignation	4 (5.30)

contained in the equation, which can explain the 49.80% of the total variance ( $F = 17.80$ ,  $p < .001$ ). The details were contained in Table 4. Additionally, the education level and the avoidance coping strategy were the positive factors, whilst relatives have been tested positive was identified as the negative factor.

#### *The correlation between appetite and death anxiety*

There was a moderate negative correlation between appetite and death anxiety ( $r = -0.55$ ,  $p < .001$ ).

## 4 | DISCUSSION

Regarding appetite loss, when the CNAQ is lower than 28, there is a risk of significant weight loss for patients (Andreae et al., 2016). The average appetite score amongst patients was 19.46, and all the patients included in this study faced an appetite loss. Compared to other chronic diseases, the risk rate in patients diagnosed with COVID-19 was very high (Sieske et al., 2019). By far, this question has not been paid sufficient attention judging by the insufficient papers published on this issue. Lawrence et al. (2021) recent has pointed that 53% patient has appetite loss. However, only one

question to assess patients' loss of appetite by the subjective answer on 19 samples. Hence, assessment by scale, we recommended here, is more comprehensive, accurate and scientific. As we have demonstrated before, decreased appetite and inadequate food intake risk patients with malnutrition and a worsened prognosis (Landi et al., 2013; Malafarina et al., 2013). Efforts, which consist but are not limited to increasing the intake of energy and protein-rich food, nutritional supplements, dividing meals smaller and eating more frequently (Haehling & Anker, 2014), urgently needed to be made by health care professionals to address patients' impaired appetite. What's more, our study recommended that all the patients could be taken into these appetite-protect interventions without assessment work if there is a workforce shortage.

In terms of death anxiety, we can find that the death anxiety of patients diagnosed with COVID-19 (average score is 6.58) is very high according to the standard that a score of more than 7 is a sign of high-level anxiety death (Moradipour et al., 2019). Compared to the result of other studies conducted in the same period that the average anxiety death of a resident is about 2.77 (Sadri Damirchi et al., 2020), patients diagnosed with COVID-19 were suffering severe distress. Since a high level of death anxiety may result in negative physiological stress response and affect the recovery (Cicirelli, 2006),

**TABLE 2** The prevalence of patients' appetite loss and death anxiety ( $n = 76$ )

Scales and items	Min	Max	Mean (SD)
CNAQ (Council on Nutrition appetite questionnaire)	10	25	18.46 (4.09)
1. My appetite is(a. very poor; b. poor; c. average; d. good; e. very good;	1	3	1.61 (0.71)
2. When I eat (a. I feel full after eating only a few mouthfuls; b. I feel full after eating about a third of a meal; c. I feel full after eating over half a meal; d. I feel full after eating most of the meal; e. I hardly ever feel full)	1	4	2.22 (0.97)
3.I feel hungry (a. rarely; b. occasionally; c. some of the time; d. most of the time; e. all of the time)	1	3	1.46 (0.70)
4. Food tastes (a. very bad; b. bad; c. average; d. good; e. very good)	1	3	1.67 (0.64)
5. Compared to when I was younger, food tastes (a. much worse; b. worse; c. just as good; d. better; e. much better)	1	3	1.63 (0.73)
6. Normally I eat (a. less than one meal a day; b. one meal a day; c. two meals a day; d. three meals a day; e. more than three meals a day)	1	4	3.84 (0.61)
7.I feel sick or nauseated when I eat (a. most times; b. often; c. sometimes; d. rarely; e. never)	2	5	3.62 (0.99)
8. Most of the time my mood is (a. very sad; b. sad; c. neither sad nor happy; d. happy; e. very happy)	1	4	2.41 (0.80)
T-DAS (Templer Death Anxiety Scale)	1	13	6.58 (3.21)
1. I am very much afraid to die	0	1	0.34 (0.48)
*2. The thought of death seldom enters my mind	0	1	0.24 (0.43)
*3. It does not make me nervous when people talk about death	0	1	0.43 (0.50)
4. I dread to think about having to have an operation	0	1	0.75 (0.44)
*5. I am not at all afraid to die	0	1	0.39 (0.49)
*6. I am not particularly afraid of getting cancer	0	1	0.79 (0.41)
*7. The thought of death never bothers me	0	1	0.37 (0.49)
8. I am often distressed by the way time flies so very rapidly	0	1	0.11 (0.31)
9. I fear dying a painful death	0	1	0.80 (0.40)
10. The subject of life after death troubles me greatly	0	1	0.42 (0.50)
11. I am really scared of having a heart attack	0	1	0.68 (0.47)
12. I often think about how short life really is	0	1	0.20 (0.40)
13. I shudder when I hear people talking about a World War II	0	1	0.05 (0.23)
14. The sight of a dead body is horrifying to me	0	1	0.79 (0.41)
*15. I feel that the future holds nothing for me to fear	0	1	0.21 (0.41)

Note: The scoring methods of the two scales are as follows: in CNAQ Scale, a, b, c, d and e are equal to 1, 2, 3, 4 and 5 respectively, whilst in T-DAS Scale, "yes" = 1, "no" = 0. \* represents an item that is scored reversed. In this table, data of the revised score items have already been processed in reverse.

death anxiety should be regarded as another psycho-social problem for patients diagnosed with COVID-19.

As regards related factors of appetite, patients unmarried, with a mild type, with a higher education level, and who withstand less death anxiety have a higher appetite level. A handful of previous studies has found that marital status reflects patients' family support system, which was regarded as a significant sociodemographic determinant of food intakes (Anderson-Bill et al., 2011; Johnson, 2005). Consistent with Sieske et al. (2019), we confirmed that severe type patients had a lower level of appetite, which may ascribe to their more severe inflammation. Additionally, the educational level also has been proved as an associated factor in a previous study (Suma et al., 2018), which was also in line with our findings. In addition to the above-related factors, the loss of appetite is mainly caused by the disease of COVID-19 itself. Physiological-related factors

comprise loss of smell, loss of taste, flavour perception, fever, inflammation and gastrointestinal symptoms in some patients (Chaaban et al., 2021; Pan et al., 2020; Risso et al., 2020; Rothenberg, 2021).

In the case of factors that related to death anxiety, patients' older age, gender, severe type, avoidance coping strategy and the decreased appetite were associated factors with death anxiety. Although a previous study chose a different measurement tool with us, partial results of us were consistent with theirs. During the COVID-19 pandemic, those residences who are older or female have a higher level of death anxiety (Rababa et al., 2021). Females endorsed more severe death anxiety than males compared with previous studies (Harding et al., 2005; Russac et al., 2007). Male's unwillingness to disclose their fear of death and commonness of engaging in risk-taking behaviours might lead to gender difference (Mahlamäki, 2012; Sawyer et al., 2019). Since death anxiety is

**TABLE 3** Differences in mean of appetite level and death anxiety by characteristics of the patients ( $n = 76$ )

Variables	Categories	n	Appetite level		Death anxiety	
			Mean (SD)	t/F/p	Mean (SD)	t/F/p
Gender	Male	48	18.77 (3.95)	0.86/0.390	5.63 (3.06)	-3.67/<0.001
	Female	28	17.93 (4.35)		8.21 (2.81)	
Age	Under 40 years old	44	19.93(3.68)	8.90/<0.001	5.82(3.18)	6.00/0.004
	Between 40 and 60 years old	17	17.18(3.94)		6.47(2.85)	
	Over 60 years old	15	15.60(3.58)		8.93(2.63)	
Marital status	Married	51	16.92 (3.64)	-5.87/<0.001	7.00 (3.53)	1.92/0.059
	Unmarried	25	21.60 (3.07)		5.72 (2.23)	
Educational level	Junior high school and below it	15	15.80 (2.76)	5.88/0.001	8.00 (3.18)	3.14/0.031
	High school or secondary school	35	17.94 (4.32)		6.80 (3.61)	
	College degree	7	21.14 (2.97)		3.86 (1.95)	
	Bachelor degree	19	20.53 (3.45)		6.05 (2.01)	
	Master degree and above it	0	-		-	
Census	Local	15	17.27 (4.04)	-1.27/0.209	6.53 (2.95)	-0.06/0.951
	Non-local	61	18.75 (4.08)		6.59 (3.29)	
Monthly income	Less than 3,000	7	14.14 (1.35)	3.53/0.011	8.43 (4.35)	1.37/0.254
	3,000–6,000	26	19.73 (3.57)		5.88 (3.17)	
	6,000–9,000	21	18.86 (4.74)		6.81 (2.93)	
	9,000–12,000	15	17.20 (3.84)		7.20 (3.43)	
	More than 120,000	7	19.57 (3.21)		5.29 (1.60)	
Relatives tested positive	Yes	62	18.10 (4.22)	-1.65/0.103	6.94 (3.39)	3.38/0.001
	No	14	20.07 (3.10)		5.00 (1.41)	
COVID-19 disease condition ranks	Mild type	56	19.45 (3.96)	3.82/<0.001	6.48 (3.10)	-0.44/0.663
	Severe type	20	15.70 (3.11)		6.85 (3.56)	
Coping strategy	Confrontation	54	18.33 (4.30)	2.24/0.114	6.41 (3.02)	9.07/<0.001
	Avoidance	18	19.61 (3.33)		5.78 (2.78)	
	Resignation	4	15.00 (2.31)		12.50 (0.58)	

**TABLE 4** Regression analyses for demographics and characteristics and appetite level and death anxiety ( $n = 76$ )

Items	Appetite level					Death anxiety				
	B	SE	$\beta$	t	p	B	SE	$\beta$	t	p
Constant term	21.17	1.90	-	11.13	<.001	9.90	1.51	-	6.55	<.001
Marital status	1.89	0.91	0.22	2.08	.041	-	-	-	-	-
COVID-19 disease condition ranks	-2.82	0.84	-0.31	-3.37	.001	-	-	-	-	-
Educational level	0.85	0.37	0.22	2.31	.024	-	-	-	-	-
Gender	-	-	-	-	-	2.15	0.54	0.33	3.96	<.001
Avoidance (coping strategy)	-	-	-	-	-	4.66	1.19	0.33	3.91	<.001
Appetite level	-	-	-	-	-	-0.35	0.07	-0.45	-5.37	<.001
Death anxiety	-0.56	0.10	-0.44	-5.51	<.001	-	-	-	-	-

Note: Appetite level model:  $R = .759$ ,  $R^2 = .576$  Adjust  $R^2 = .552$ ,  $F = 31.83$ ,  $p < .001$ , death anxiety model:  $R = .720$ ,  $R^2 = .518$  Adjust  $R^2 = .498$ ,  $F = 17.80$ ,  $p < .001$ . Computed by multiple stepwise linear regression analysis. Marital status (married = 1, unmarried = 2), disease condition (mild type = 1, severe type = 2), educational level (junior school and below it = 1, high school and secondary school = 2, college degree = 3, bachelor degree = 4, master degree and above it = 5), gender (male = 1, female = 2), and avoidance (yes = 1, no = 0).

demonstrated as an understanding of danger to life in daily interactions (Lok et al., 2019), severe condition patients suffered more life-threatening symptoms, received advanced treatment and worn more supporting medical machines. Physical discomfort symptoms that are not merely limited to fever, fatigue, pain and dyspnoea, and psychological stress from more frequent treatment and ventilators made them experience more distress. It is worth mentioning that only patients who adopt the avoidance coping strategy have a lower appetite. A previous study has pointed out that fear of death leads to some maladaptive coping behaviours (Menzies & Menzies, 2020). Avoidance lead to detrimental consequences, such as anxiety disorders (Barlow, 2004; Hofmann, 2015). The patients who adopt avoidance mode are likely to have more severe pressure and need psychological intervention of medical staff.

Our study also found that there is a moderate negative correlation between appetite and death anxiety, which means the patients who endorse a higher level of death anxiety may have a lower level of appetite. Lasted studies revealed that the use of humoristic information about COVID-19 reduces anxiety of people infected with COVID-19 (Curşeu et al., 2021), which also can be an approach. Furthermore, nurses should provide patients adequate knowledge of the COVID-19 and treatment, which aims to let them have a better understanding of the disease, release their death anxiety and also improve their appetite.

## 5 | LIMITATIONS

Although this study has identified patients' decreased appetites, severe death anxiety, associated factors with them and the considerable negative correlation between them, several limitations should be taken into consideration when interpreting the findings. First, the sample size is limited and insufficient bought about by the close of the ward, which can hardly completely represent all the patients in other provinces or other countries. We encouraged future research carried out at several sites in multiple countries. Second, T-DAS, CNAQ and MCMQ scales were self-reported scales, which may rely on the accuracy of patients' responses. Third, we used a self-designed demographic and characteristic questionnaire for linear regression, which may bring limitations to the identification of potential factors that affect appetite and death anxiety. We expected future researches could identify more associated factors, to give healthcare professionals a better understanding of what can promote or hinders patients' appetite and death anxiety degree.

## 6 | CONCLUSION

Notwithstanding the above limitations, this study confirmed that currently almost every patient diagnosed with COVID-19 has a decreased appetite, a certain amount of them suffered severe death anxiety, several associated factors with appetite and death anxiety, and the negative correlation between appetite and death anxiety.

Our findings firstly highlight the importance of paying attention to patients' appetite. For nurses, we recommended they pay close attention to patients who were married, less educated, diagnosed with severe type, and have a higher level of death anxiety. Interventions for impaired appetite could be given with or without assessment.

## ACKNOWLEDGEMENT

The authors would like to thank Dr. Gong for her assistant in this paper writing.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTIONS

Qiuxuan Zeng and Huangliang Cao drafted the manuscript. Jiaying Li made the design of this study and also helps with the acquisition of data. Jieya Chen analysed the data. Haixia Shi, Qiuxuan Zeng, Qing Ma and Huangliang Cao helped Jiaying Li to collect data and also revised the manuscript critically.

## DATA AVAILABILITY STATEMENT

The data are available on request from the corresponding author.

## ORCID

Jiaying Li  <https://orcid.org/0000-0002-5473-4320>

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**How to cite this article:** Zeng, Q., Cao, H., Ma, Q., Chen, J., Shi, H., & Li, J. (2021). Appetite loss, death anxiety and medical coping modes in COVID-19 patients: a cross-sectional study. *Nursing Open, 8*, 3242–3250. <https://doi.org/10.1002/nop2.1037>