

The Relationship Between Benefit Finding and Quality of Life in Patients with Chronic Obstructive Pulmonary Disease: The Mediating Effects of Self-Management

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Objective: To explore the relationships among benefit finding (BF), self-management, and quality of life (QOL) among patients with COPD.

Methods: A total of 205 patients with COPD were selected via a convenient sampling method. BF refers to the ability to find meaning or benefit from difficult situations. The Benefit Finding Scale (BFS), self-management scale, and 36-item Short-Form Health Survey (MOS SF-36) were used to investigate BF, self-management and QOL (including a physical component summary (PCS) and a psychological component summary (MCS)). Structural equation modeling was used to examine the relationships among BF, self-management and QOL in patients with COPD and to analyze the effects of BF and self-management on QOL.

Results: The total QOL score of patients with COPD was 61.38 ± 21.15 , and the PCS and MCS scores were 57.67 ± 23.60 and 65.09 ± 21.24 , respectively. BF and self-management had positive predictive effects on both the PCS ($\beta_{BF} = 0.519$, $P_{BF} = 0.012$; $\beta_{self-management} = 0.473$, $P_{self-management} = 0.012$) and MCS ($\beta_{BF} = 0.425$, $P_{BF} = 0.013$; $\beta_{self-management} = 0.535$, $P_{self-management} = 0.016$) of patients with COPD, and self-management mediated the relationships of BF with the PCS ($\beta = 0.144$, $P = 0.008$) and MCS ($\beta = 0.162$, $P = 0.007$).

Conclusion: The QOL of patients with COPD needs to be improved, especially in terms of physical aspects. Helping COPD patients obtain better BF not only helps them improve their PCS and MCS directly but also indirectly through enhancing self-management to improve their PCS and MCS.

Keywords: COPD, benefit finding, self-management, quality of life

Introduction

Chronic obstructive pulmonary disease (COPD) is a common heterogeneous lung condition that often causes progressive airflow limitation with high morbidity and mortality.^{1,2} COPD is currently the third leading cause of death worldwide, following cardiovascular disease.³ In addition, there are nearly 100 million patients with COPD in China, and COPD is the third leading cause of death in China.⁴

COPD, a chronic disease, is accompanied by a series of symptoms of different severities (dyspnea, cough, sputum, wheezing, and chest tightness), which places a heavy burden on patients, has a negative impact on their physical and mental health, and seriously reduces their quality of life (QOL).⁵ QOL can also be called quality of health, which refers to individual satisfaction or well-being when the individual has a health condition or disease or is receiving a treatment, and quality of health includes physical and psychosocial aspects.⁶ A relevant study revealed that the QOL of patients

with COPD is much lower than that of patients without COPD.⁷ Therefore, research has focused on how to improve the QOL of patients with COPD.

Self-management refers to an individual's ability to manage their symptoms, treatment, physical and psychosocial responses, and inherent lifestyle changes; it is seen as an important factor affecting the QOL of people with chronic diseases.⁸ Previous studies have shown that patients with chronic diseases can continuously learn about and acquire disease-related knowledge during the disease treatment and rehabilitation process, enhance their self-management ability, and effectively manage their spontaneous symptoms and emotions, which can not only improve the treatment effect but also effectively improve their QOL.^{8–10} The study results of Benzo et al¹¹ also showed that self-management is a positive predictor of QOL among patients with COPD. Therefore, self-management is a nonnegligible factor in improving the QOL of patients with COPD.

In the field of positive psychology, benefit finding (BF) refers to a positive cognitive reorganization involving the ability to find meaning or benefit from difficult situations.^{12–15} According to cognitive adaptation theory, BF is developed from individual traumatic experiences (such as cancer and chronic diseases) that threaten health.¹⁶ The theory also suggests that BF is an important psychological resource for coping with traumatic and threatening events and a key factor for maintaining good mental or physical health in difficult situations.^{12,16} In addition, studies have suggested that BF helps individuals put the disease into perspective and explore their resources for fighting the disease, which are important factors for improving QOL.^{13,14}

Some studies on patients with chronic diseases have reported that when patients understand their illness, they can also engage in BF; their awareness of and responsibility for their own health increase, and they take the initiative to adjust their behavior and mindset to address the disease, thereby improving self-management.^{17–19} A study has shown that the BF ability of heart failure patients has a positive effect on their self-management ability.¹⁹ According to cognitive adaptation theory, the BF ability of individuals can enhance their resource integration ability and rebuild their sense of disease control, which can improve self-management of disease and thus enable the achievement of a good state of physical and mental health.^{16,18} Therefore, self-management might be a mediator between BF and QOL.

In summary, BF and self-management may be important factors for promoting individual QOL in patients with COPD. However, at present, there are few studies on the relationships among BF, self-management, and QOL in patients with chronic diseases, especially in patients with COPD. According to the health belief model (HBM), the best way to change the behavior of people is to change their cognition. BF is a positive cognition that may help us change the self-management behavior of patients with COPD and improve their QOL. However, the underlying mechanisms by which BF and self-management affect QOL among patients with COPD are still not clear. Therefore, we need to explore the direct/mediating effects of BF and self-management on QOL to better implement interventions to improve the QOL of patients with COPD. In this study, we propose the following hypothesis: patients with high levels of BF have better QOL, and this relationship might be mediated by self-management.

Materials and Methods

Participants

In this study, a convenience sampling method was used to select patients with COPD who were treated at the Fifth Affiliated Hospital of Sun Yat-sen University from January to December 2022; questionnaires were distributed to the selected patients. The inclusion criteria were as follows: aged ≥ 18 years, met the COPD diagnosis criteria,²⁰ and provided informed consent. The exclusion criteria were as follows: in the acute phase of COPD, other serious life-threatening diseases or psychological and cognitive disorders. In this study, a Structural Equation Model (SEM) was used for analysis. According to the statistical requirements of SEM, a sample size ≥ 200 was considered moderate, so at least 200 patients with COPD were included in this study.²¹ The study was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (2021K80-1).

Measurements

General Information Questionnaire

A custom-designed general information questionnaire was used to collect information on the sociodemographic characteristics of patients with COPD, including sex, age, monthly family income, smoking status and exercise (≥ 30 minutes).

The Chinese Version of the Benefit Finding Scale (BFS)

The BFS was translated into Chinese by Liu Huozhun et al,²² the Chinese version was adopted in this study. The BFS has 22 items in 6 dimensions: acceptance (AC), family relationships (FR), world view (WV), personal growth (PG), social relationships (SR) and health behavior (HB). Items are scored on a 5-point Likert scale. The total score ranges from 22 to 110. A lower total score indicates a lower BF ability. Cronbach's α was 0.949 in our study.

Self-Management Scale

The Self-Management Scale was developed by Caihong Zhang²³ and is used to measure the self-management ability of patients with COPD. The scale contains 51 items and 5 dimensions: symptom management (SM), daily life management (DLM), emotion management (EM), information management (IM) and self-efficacy (SE). The items are rated on a 5-point Likert scale. The total score ranges from 51 to 255, and the higher the score is, the stronger the self-management ability of patients with COPD. The Cronbach's α of the scale was 0.952 in this study.

The 36-Item Short-Form Health Survey (MOS SF-36)

The MOS-SF-36 consists of 36 items and is divided into 8 dimensions: physical function (PF), role-physicals (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). This scale can be divided into a physical component summary (PCS) (the first four dimensions) and a mental component summary (MCS) (the last 4 dimensions).²⁴ The scoring is as follows: (1) encode the scale items; (2) scale entries are scored; (3) standardized scores for each dimension, component summary and the total score of the scale range from 0 to 100, and the formula is as follows:
$$\frac{\text{Actual score} - \text{The lowest possible score in that area}}{\text{The highest possible score in this area} - \text{The lowest possible score in this area}} \times 100$$
, with higher scores indicating better QOL.²⁴ The Cronbach's α values of the PCS and MCS are 0.890 and 0.814, respectively.

Statistical Methods

After data collection and item-by-item verification, unified data were entered, and SPSS 25.0 and AMOS 21.0 were used to organize and analyze the data. The statistical analysis methods were as follows: (1) one-way ANOVA was used to examine the differences in QOL in participants with different ages or monthly family incomes, and independent-sample t tests were used to examine the differences in QOL in participants with different sex, smoking status and exercise; (2) Pearson correlation analyses were used to analyze the correlations among BF, self-management and QOL in participants; and (3) a structural equation model (SEM) (with maximum likelihood estimation and bootstrapping) was used to construct a mediation model including BF, self-management and QOL in participants and to analyze the predictive effects of BF and self-management on QOL. Comparing with the traditional regression model, SEM can reduce the standard error, and the data need not meet the normal distribution.²¹

Finally, we selected the ratio of χ^2 to its df ($\chi^2/\text{df} < 3$), the goodness-of-fit index (GFI > 0.9), the normed fit index (IFI > 0.9), the comparative fit index (CFI > 0.9), and the root mean square error (RMSEA < 0.08).²¹

Results

General Information of Patients with COPD

The average age of the 205 patients with COPD in this survey was 69.73 ± 9.72 years, and the QOL score significantly differed according to only age and exercise status (see Table 1).

QOL Status in Patients with COPD

In this study, the total QOL score of patients with COPD was 61.38 ± 21.15 , and the PCS and MCS scores were 57.67 ± 23.60 and 65.09 ± 21.24 , respectively. The RP, GH, PF and BP scores were 45.39 ± 44.88 , 47.25 ± 18.52 , 57.39 ± 32.06 , 80.65 ± 23.46 , respectively. Furthermore, the VT, SF, RE and MH scores were 59.78 ± 19.42 , 63.90 ± 25.62 , 64.88 ± 44.55 and 71.80 ± 16.24 , respectively.

Correlations of QOL, BF, and Self-Management in Patients with COPD

The QOL, PCS and MCS scores of patients with COPD were positively correlated with BF and self-management ($r = 0.476\sim 0.534$, $P < 0.05$), and BF was positively correlated with self-management ($r = 0.254$, $P < 0.05$). The correlation matrix of QOL, BF and self-management is shown in Table 2.

The Predictive Effects of BF and Self-Management on QOL in Patients with COPD

In this study, SEM was used to analyze the relationships among BF, self-management and PCS scores in patients with COPD, and Model 1 was constructed. The results of Model 1 showed that the model fit the data well. In Model 1, there were three significant direct effects: BF→self-management ($\beta = 0.304$, $P = 0.005$), self-management→PCS ($\beta = 0.473$, $P = 0.012$) and BF→PCS ($\beta = 0.519$, $P = 0.012$). Self-management also significantly partially mediated the relationship between BF and the PCS ($\beta = 0.519$, $P = 0.01$), and the effect size was 21.7% of the total effect ($\beta = 0.663$, $P = 0.011$) (see Figure 1 and Table 3).

Similarly, the relationships among BF, self-management and the MCS in patients with COPD were analyzed, and Model 2 was constructed. The results of Model 2 showed that the model fit the data well. In Model 2, there were also three significant direct effects: BF→self-management ($\beta = 0.304$, $P = 0.005$), self-management→MCS ($\beta = 0.535$, $P =$

Table 1 General Information and QOL Scores (N=205)

Variable	M±SD	N (%)	F/t	P
Age (years)			308.923	P<0.01
<60	89.92±5.18	29 (14.1%)		
60–70	75.74±7.63	67 (32.7%)		
70–80	50.41±10.73	78 (38.0%)		
≥80	31.25±9.67	31 (15.1%)		
Sex			1.290	0.214
Male	62.00±20.86	189 (92.2%)		
Female	54.08±23.79	16 (7.8%)		
Monthly family income			1.180	0.318
<3000	60.78±21.58	28 (13.7%)		
3000–5000	61.81±21.73	70 (34.1%)		
5000–8000	58.82±19.77	76 (37.1%)		
≥8000	67.22±22.51	31 (15.1%)		
Currently smoke			0.426	0.671
Yes	61.84±20.16	139 (67.8%)		
No	60.42±23.22	66 (32.2%)		
Regularly exercise			2.249	0.026
Yes	64.83±19.91	97 (47.3%)		
No	58.27±21.83	108 (52.7%)		

Abbreviation: QOL, quality of life.

Table 2 The Correlation Matrix Among the Variables of QOL, BF and Self-Management (N=205)

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. AC	I																		
2 FR	0.599**	I																	
3 WV	0.548**	0.516**	I																
4 PG	0.683**	0.582**	0.688**	I															
5 SR	0.538**	0.566**	0.618**	0.748**	I														
6 HB	0.584**	0.517**	0.539**	0.721**	0.635**	I													
7 SM	0.093	0.050	0.110	0.184**	0.120	0.185**	I												
8 DLM	0.121	0.108	0.221**	0.208**	0.192**	0.177*	0.538**	I											
9 EM	0.195**	0.208**	0.321**	0.338**	0.329**	0.285**	0.587**	0.803**	I										
10 IM	0.021	-0.011	0.103	0.093	0.110	0.051	0.583**	0.560**	0.655**	I									
11 SE	0.129	0.129	0.232**	0.240**	0.224**	0.222**	0.574**	0.853**	0.880**	0.622**	I								
12 PF	0.312**	0.327**	0.365**	0.491**	0.418**	0.388**	0.238**	0.336**	0.528**	0.255**	0.456**	I							
13 RP	0.256**	0.203**	0.330**	0.419**	0.356**	0.374**	0.228**	0.300**	0.488**	0.226**	0.449**	0.563**	I						
14 BP	0.265**	0.241**	0.272**	0.298**	0.358**	0.268**	0.235**	0.261**	0.413**	0.239**	0.354**	0.362**	0.397**	I					
15 GH	0.393**	0.378**	0.387**	0.493**	0.489**	0.379**	0.202**	0.344**	0.503**	0.180**	0.435**	0.614**	0.507**	0.463**	I				
16 VT	0.247**	0.341**	0.299**	0.382**	0.421**	0.287**	0.190**	0.340**	0.442**	0.198**	0.410**	0.556**	0.466**	0.276**	0.567**	I			
17 SF	0.336**	0.349**	0.396**	0.442**	0.378**	0.325**	0.345**	0.411**	0.523**	0.276**	0.479**	0.547**	0.611**	0.482**	0.617**	0.557**	I		
18 RE	0.237**	0.202**	0.295**	0.365**	0.395**	0.268**	0.221**	0.347**	0.576**	0.261**	0.482**	0.504**	0.613**	0.396**	0.564**	0.470**	0.583**	I	
19 MH	0.211**	0.203**	0.162*	0.269**	0.351**	0.157*	0.090	0.145*	0.260**	0.083	0.208**	0.378**	0.311**	0.175*	0.383**	0.694**	0.327**	0.367**	I

Note: *P<0.05, **P<0.01.

Abbreviations: AC, acceptance; FR, family relationship; WV, world view; PG, personal growth; SR, social relationship; HB, health behavior; SM, symptom management; DLM, daily life management; EM, emotion management; IM, information management; SE, self-efficacy; PF, physical function; RP, role-physics; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health.

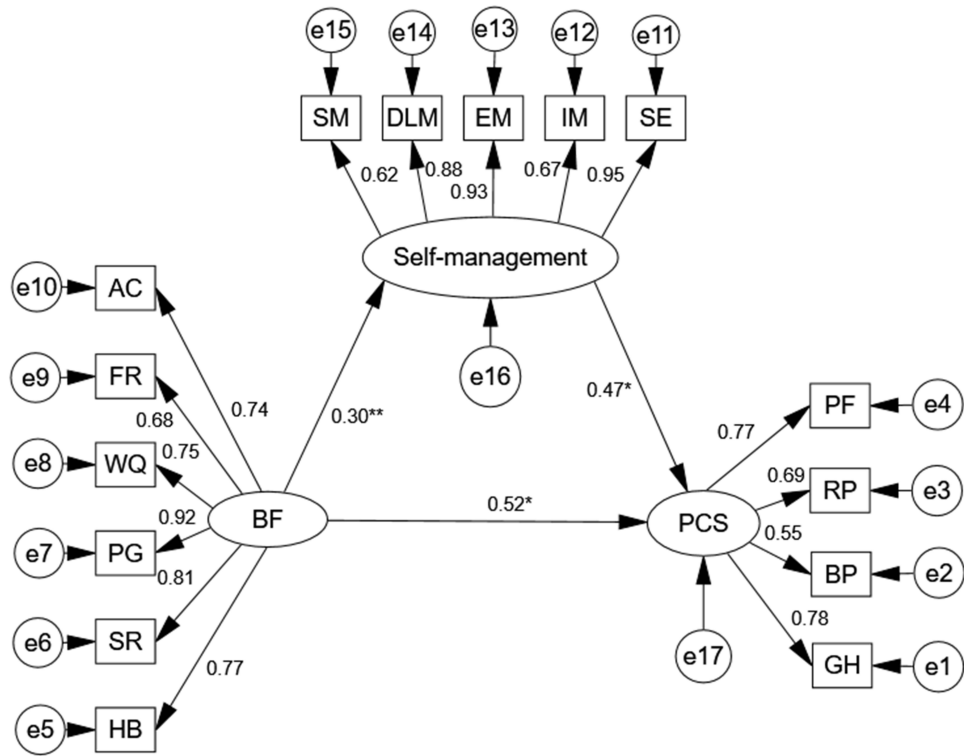


Figure 1 Model I, including self-management, BF and the PCS.
Notes: Model fit index: $\chi^2/df = 1.785$, GFI=0.911, NFI=0.924, CFI=0.965, RMSEA=0.062. * $P<0.05$, ** $P<0.01$.
Abbreviations: AC, acceptance; FR, family relationship; WQ, world view; PG, personal growth; SR, social relationship; HB, health behavior; BF, benefit finding; SM, symptom management; DLM, daily life management; EM, emotion management; IM, information management; SE, self-efficacy; PF, physical function; RP, role-physics; BP, bodily pain; GH, general health; PCS, physical component summary.

0.016) and BF→MCS ($\beta = 0.425$, $P = 0.013$). Self-management also significantly partially mediated the effect between BF and the MCS ($\beta = 0.162$, $P = 0.007$), and the effect size was 27.6% of the total effect ($\beta = 0.587$, $P = 0.013$) (see Figure 2 and Table 3).

Table 3 The Predictive Effects of BF and Self-Management on QOL (N=205)

Model Paths		β	95% CI	P
Model 1				
Direct effects	BF → Self-management	0.304	[0.190, 0.437]	0.005
	Self-management → PCS	0.473	[0.362, 0.572]	0.012
	BF → PCS	0.519	[0.417, 0.612]	0.012
Indirect effects	BF → Self-management → PCS	0.144	[0.078, 0.207]	0.008
Total effects	BF → PCS	0.663	[0.522, 0.750]	0.011
Model 2				
Direct effects	BF → Self-management	0.304	[0.190, 0.437]	0.005
	Self-management → MCS	0.535	[0.308, 0.530]	0.016
	BF → MCS	0.425	[0.415, 0.633]	0.013
Indirect effects	BF → Self-management → MCS	0.162	[0.092, 0.242]	0.007
Total effects	BF → MCS	0.587	[0.454, 0.688]	0.013

Abbreviations: BF, benefit finding; PCS, physical component summary; MCS, mental component summary.

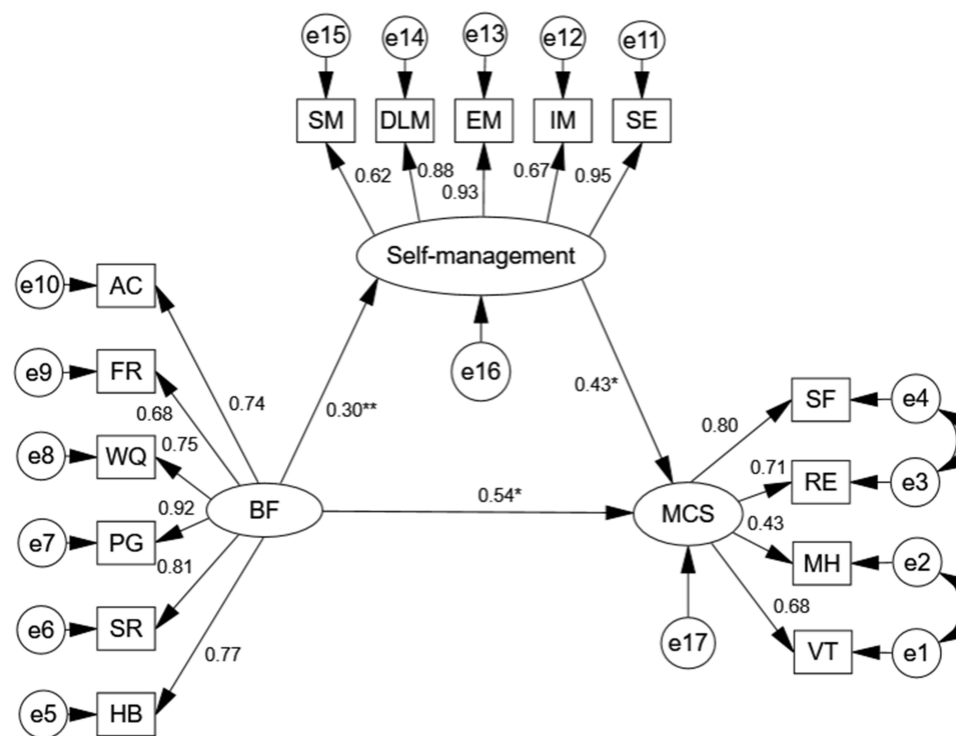


Figure 2 Model 2, which includes self-management, BF and the MCS.

Notes: Model fit index: $\chi^2/df = 2.079$, GFI=0.903, NFI=0.916, CFI=0.954, RMSEA=0.073. * $P < 0.05$, ** $P < 0.01$.

Abbreviations: AC, acceptance; FR, family relationship; WQ, world view; PG, personal growth; SR, social relationship; HB, health behavior; BF, benefit finding; SM, symptom management; DLM, daily life management; EM, emotion management; IM, information management; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; MCS, mental component summary.

Discussion

QOL in Patients with COPD

The results of this study revealed that older age is associated with worse QOL in patients with COPD. This may be because most patients with COPD are over 40 years old; with increasing age, physical function gradually declines, symptoms become more severe, and cognitive function and mental health worsen, with QOL decreasing accordingly.²⁵ In addition, the QOL of patients who exercised regularly (≥ 30 minutes) was greater than that of patients who did not exercise regularly, which is consistent with the findings of Qiu et al.²⁶ Exercise may partially restore cardiopulmonary fitness and reduce symptoms.

Moreover, the results of the present study revealed that the PCS score was lower than the MCS score in patients with COPD, which is consistent with the results of Jang et al.,²⁷ indicating that COPD is a chronic disease and that patients with COPD suffer more difficulties in physical health than in mental health. In addition, among the four dimensions of the PCS, the RP score was the lowest, and among the four dimensions of the MCS, the VT score was the lowest, which is consistent with the results of Camac et al.²⁸ This may be because the patients with COPD in our study were mostly men; given society's beliefs regarding masculinity, men may find it more difficult to accept physical limitations caused by illness and be more sensitive to feelings of reduced energy.

The Predictive Effects of BF and Self-Management on QOL in Patients with COPD

Predictive Effect of Self-Management and BF on the PCS Score

The results of Model 1 showed that the BF ability of patients with COPD had a positive predictive effect on their PCS score; that is, the higher the BF ability of patients was, the better their PCS score. Previous studies have also shown that BF is associated with several health outcomes because it reduces biomarkers of the physiological stress response.^{29,30} For example, Kaufhold et al.²⁹ reported that BF effectively reduced pain interference and intensity in patients with chronic

pain. These studies have shown that BF can help reduce the negative experience of physical symptoms caused by illness, thereby improving PCS scores.^{29,30}

In this model, the self-management ability of patients with COPD had a positive predictive effect on PCS scores, indicating that the better the self-management ability of patients with COPD was, the better their PCS scores. Previous studies have also shown that self-management and self-efficacy positively influence the PCS scores of patients with COPD.^{25,31,32} This may be because COPD is a chronic disease, and patients constantly experience physical symptoms, such as wheezing and dyspnea. Patients with greater self-management ability have a better understanding of the disease and management of symptoms, which can help them reduce the discomfort caused by some physical symptoms.^{9,25}

In addition, Model 1 revealed that self-management can have a partial mediating effect on the relationship between BF and PCS in patients with COPD. This finding is consistent with the study of An-kang et al, in which self-management also partially mediated the relationship between health literacy and QOL in patients with coronary heart disease.³³ In addition, in their study, the effect size of the mediating effect accounted for only approximately 10% of the total effect, whereas in this study, it accounted for approximately 21.7%, which indicates that the mediating effect of self-management in BF and QOL is more important.

According to protection motivation theory (PMT), proposed by Steven et al,³⁴ which led to behavior change theory, which is based on the health belief model, individuals' ability to exhibit healthy behaviors can improve their self-management ability, which leads to good health outcomes. In the disease process, BF is also the motivation for engaging in healthy behavior.^{30,35,36} Mao³⁷ also showed that helping patients with COPD correctly understand the disease and find benefits can enhance the initiation and continuity of self-management behaviors, thus improving QOL.

Predictive Effect of Self-Management and BF on the MCS Score

The results of Model 2 showed that the BF ability of patients with COPD also had a positive predictive effect on their MCS scores, which is consistent with the PCS results. According to positive psychology theory, BF is the process by which an individual perceives benefits in the face of illness, and it is often an important factor affecting mental health recovery.^{38,39} BF can enhance the positive emotions of patients and reduce their negative emotions to improve mental health.⁴⁰

In this model, the self-management ability of patients with COPD also had a positive predictive effect on the MCS score. This is consistent with the findings of Hernandez et al⁴⁰ that in patients with cancer, mental health can be effectively improved by providing patients with self-management education and improving their self-management ability. In addition, the stronger the self-management ability of patients is, the more motivation they may have in the treatment and rehabilitation of the disease and the better their self-confidence, thus improving their mental health.^{41,42}

In Model 2, the BF of patients with COPD also had a partial effect on self-management and the MCS. The effect size of the mediating effect accounted for only approximately 27.6% of the total effect but was greater than the mediating effect size of self-management in BF and PCS. Therefore, this result is inconsistent with the study of An-kang et al, in which self-management did not play a mediating role between health literacy and MCS.³³ This difference might suggest that interventions aimed at BF can better improve the PCS of patients with COPD.

Moreover, at present, few studies have investigated the mediating effect of BF on the relationship between self-management and mental health in patients with COPD. In a study of patients with type 2 diabetes, Zhang et al⁴³ found that self-efficacy, as a driving force that promotes the healthy behaviors of individuals, can improve their mental health by increasing their self-management behaviors. According to cognitive adaptation theory, individuals can enhance their self-management and sense of control through BF; ultimately, they can achieve a stable state of physical and mental health.¹⁶

Implications for Clinical Practice

These results suggest that the QOL of patients with COPD needs to be improved in terms of both physical and mental health aspects, especially in older patients or those who do not exercise regularly. These findings also suggest that helping patients with COPD improve their physiological and mental health, which is affected by the disease, can be achieved by enhancing their BF or self-management behaviors. In addition, our study revealed that helping patients with COPD

improve their PCS and MCS directly or indirectly by improving BF may be more helpful than helping patients only improve their self-management behaviors.

Strengths and Limitations

The limitations of this study are as follows: first, this study is a cross-sectional survey and cannot measure the dynamic changes in self-management, BF, and QOL. In the future, interventional or longitudinal studies should be designed to further explore the impact of BF and self-management on QOL, and changes in BF, self-management and QOL over time can also be explored through follow-up studies in patients with COPD. Second, this was a single-center study, and a multicenter large-sample study should be designed to improve the representativeness of the survey subjects in the future. Finally, the study relied on self-reports from patients, which are amenable to several biases, and we hope that there will be more objective measurement tools to ensure the accuracy of the measurement results.

Conclusion

The QOL of patients with COPD needs to be improved, especially in terms of mental health, and patients who are older and do not exercise regularly should receive more attention. In this study, we found that BF and self-management have direct effects on the PCS and MCS scores of patients with COPD and that self-management also acts as a partial mediator between BF and the PCS or MCS. These findings also suggest that there is a better way for patients with COPD to improve their self-management behaviors and achieve good PCS and MCS, which helps them gain positive cognition, such as BF, from their illness experience. Studies have shown that providing more social support from family and friends and helping patients understand their own condition correctly can help them increase their BF.^{44,45}

Ethics Approval and Informed Consent

The study complies with the Declaration of Helsinki. In addition, our study was approved by the Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University (2021K80-1).

Consent for Publication

All the authors would like to submit this manuscript for review to the International Journal of Chronic Obstructive Pulmonary Disease. The manuscript is original work and has not been submitted to, nor is it under consideration for publication in, another journal. The study complies with current ethical considerations. We also confirm that all the listed authors have actively participated in the study and have read and approved the submitted manuscript.

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Disclosure

Jiangping Zhang and Xinran Liu are co-first authors for this study. The authors declare that they have no conflicts of interest in this work.

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