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AUTHORS: Zeynep KARAGÜN,Deniz ÇELIK,Mehmet Sinan AYDIN,Ibrahim GÜNDOGMUS,Yusuf Tugrul SIPIT

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Hidden face of chronic obstructive pulmonary disease: effects of patients' psychiatric symptoms on caregivers' burden and quality of life

Zeynep Karagün[1], Deniz Çelik[2], Mehmet Sinan Aydın[3], İbrahim Gündoğmuş[4], Yusuf Tuğrul Şipit[5]

[1]Department of Pulmonology, Sarıkamış State Hospital, Kars, Turkey; [2]Department of Pulmonology, Alanya Alaaddin Keykubat Univesity, Faculty of Medicine, Antalya, Turkey; [3]Department of Psychiatry, Ortaca State Hospital, Muğla, Turkey; [4]Department of Psychiatry, Kırıkkale Yüksek Ihtisas Hospital, Kırıkkale, Turkey; [5]Department of Pulmonology, University of Health Sciences, Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital, Ankara, Turkey

ABSTRACT

Objectives: Chronic Obstructive Pulmonary Disease (COPD) faces functional and physical limitations and often needs the help of others at certain times in their lives. Patients and caregivers can affect each other psychologically, physically, and socially. This study aims to examine the relationship between the demographic and clinical characteristics of COPD patients and the quality of life and burden of care of caregivers.
Methods: The study was carried out with 250 COPD patients who applied to the chest diseases hospital and their caregivers. Hospital Anxiety-Depression Scale (HADS), The Zarit Burden Interview (ZBI), and World Health Organization Quality of Life Scale Short Form (WHOQOL-BREF) scales were applied to the patients.
Results: The patients' gender, age, regular drug use, non-invasive mechanical ventilator use, emergency room admissions, number of hospitalizations, number of intensive care admissions, presence of comorbidities were found to be associated with HADS anxiety and depression scores, ZBI, and WHOQOL-BREF. According to the results of multiple linear regression analysis; it is seen that the patient's gender, NIV use, regular device use, presence of comorbidity, HADS anxiety score, and HADS depression score is an independent predictor of the caregiver's burden (ZBI score); and the patient's NIV use, regular device use, HADS anxiety score and HADS depression score is an independent predictor of the caregiver's WHOQOL-BREF score.
Conclusions: It is important to evaluate patients and caregivers in a holistic approach and to realize the factors that may negatively affect them in the early period to take the necessary therapeutic measures.

Keywords: COPD, caregiver, quality of life, caregivers' burden, psychiatry, inpatient

Chronic Obstructive Pulmonary Disease (COPD) is one of the most commonly seen causes of chronic respiratory failure worldwide [1, 2] . COPD, a major cause of mortality and morbidity, has negative effects on quality of life [1, 3]. COPD patients experience functional physical limitations over time and often need the help of others at certain times in their lives [1, 3]. This assistance is undertaken by the care-

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Address for correspondence: Deniz Çelik, MD., Associate Professor, Alanya Alaaddin Keykubat Univesity, Faculty of Medicine, Department of Pulmonology, Kestel Mah., Üniversite Cad., No: 80, 07425 Alanya, Antalya, Turkey. E-mail: drdenizcelik@hotmail.com, Phone: +90 242 510 61 35, Fax: +90 242 510 61 39

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info@prusamp.com

givers of the patients [4]. During the meeting of these needs, the multidimensional response of caregivers to stress caused by the care given to the patients is defined as the burden of care [5]. The burden of care may result in physical, emotional, and financial difficulties and quantitative and qualitative reduction of care provided [6, 7]. It can also lead to decreased quality of life, increased anxiety, and depressive symptoms for the caregiver [8-11]. Additionally, it is known that increasing the burden of care can negatively affect patient care and decreased communication and survival [12].

Timely determination of factors that increase the burden of care and negatively affect the quality of life of the caregiver will ensure that the physical and mental health of both the patient and the caregiver is maintained and thus their quality of life is improved [4, 13]. Studies have shown that the characteristics of caregivers such as age, gender, relationship, coping mechanisms, and social support have negative effects on the mental health of caregivers [14, 15]. Besides, some characteristics of patients such as gender, duration of care, relationship, the functionality of the patient, and tasks undertaken for care are expected to affect the burden of care and quality of life [16-18]. Little is known about the physical-social-psychological effects of patients who are followed up with COPD diagnosis on primary caregivers in Turkey. Furthermore, to the best of our knowledge, there is no study examining the relationship between the characteristics of COPD patients and the burden of care and quality of life of caregivers.

The current study aims to evaluate the relationship between the demographic, clinical, anxiety, and depressive characteristics of COPD patients and the quality of life and burden of care of caregivers.

METHODS

Patients who had hypoxic and/or hypercapnic respiratory failure due to COPD followed up in the inpatient or outpatient clinic between September 2019 and April 2020 in a tertiary chest diseases hospital, who received long-term oxygen therapy (LTOT) and/or non-invasive mechanical ventilation (NIV) at home with the diagnosis of chronic respiratory failure for at least one year, and those who provided care for these patients were included in this study. According to the criteria for inclusion and exclusion in the study, 250 patients and 250 relatives of patients (caregivers) were included. The following criteria were determined as the inclusion criteria in the study: (1) being diagnosed with hypoxic and/or hypercapnic respiratory failure; (2) receiving LTOT and/or NIV at home with a diagnosis of chronic respiratory failure for at least one year; (3) two or more exacerbations leading to hospitalizations per year with a respiratory complaint and/or admissions to emergency at least twice a year due to the same reasons; (4) having a first-degree family member who takes care of the patients included in the study; (5) being over 18 years of age; and (6) voluntary participation of the patient and the caregiver in the study.

The presence of an active psychiatric disorder of both the patient and caregiver or the presence of another chronic disease that may affect the burden of care other than COPD and respiratory failure were considered as criteria for exclusion.

The study was approved by the Ankara Keçiören Training and Research Hospital Clinical Research Ethics Committee with decision no. 1916 dated 28.08.2019. All patients and their relatives were asked to read and complete questionnaires after reading and signing the informed voluntary consent forms.

Evaluation of Patients

1. Anamnesis

Detailed anamnesis of all patients included in the study was taken by clinicians experienced in Pulmonology. Their demographic and clinical variables such as age, gender, smoking status, comorbidities, LTOT and/or NIV receiving durations at home, all hospital admissions, and hospitalizations in the last year were recorded. In the interview with the caregivers of the patients, it was questioned whether they were first-degree relatives and how long they were giving care.

2. Measuring tools

Both the patient and their relatives were allowed to complete the forms under the supervision of the researchers. Patients or their relatives who were not literate were expected to answer the question through an easy-to-understand reading of the items by the researcher.

Hospital Anxiety and Depression Scale (HADS)

It was developed in 1983 by Zigmond *et al*. [19] to assess the severity of symptoms of anxiety and depression in groups with a medical condition . The validity and reliability study of the scale was done in Turkey by Aydemir *et al*. [20]. 7 out of 14 questions in the 4-point Likert-type scale measure anxiety and 7 measure depression, and are scored between 0-3. The lowest score that patients can get from both subscales is 0 and the highest score is 21.

Turkish Version of the World Health Organization Quality of Life Scale Short Form (WHOQOL-BREF-TR)

The health-related quality of life scale was developed by the WHO, and the validation and reliability study was done by Eser *et al*. [21]. The scale consists of 27 items and evaluates the quality of life in five different dimensions. These are general health, physical health, social relations, environmental health, and psychological health.

Zarit Burden Inventory (ZBI)

This scale was first developed by Zarit [22], Reever, and Bach-Peterson in 1980 for caregivers of dementia patients. It is a 19-item 5-point Likert-type scale used to assess the difficulties and stress experienced by individuals giving care to patients. The validity and reliability study of the scale was carried out by Özlü *et al*. [23] in Turkey.

Statistical Analysis

The SPSS 22 package program was used in the

Table 1. Representation of sociodemographic and clinical characteristics of the participants included in the study

Patient's age (years) (mean ± SD)		69.84 ± 14.02
The Number of cigarettes smoked by the patient (pcs/day) (Mean ± SD)		28.23 ± 26.29
Number of emergency department admissions of the patient, (Mean ± SD)		5.52 ± 3.79
Number of hospitalizations of the patient (Mean ± SD)		2.90 ± 1.83
Number of intensive care hospitalizations of the patient (Mean ± SD)		1.70 ± 1.09
Patient's gender, n (%)	Male	164 (5.6)
	Female	86 (34.4)
Patient's use of LTOT, n (%)	Yes	250 (100)
	No	0 (0)
Patient's use of NIV, n (%)	Yes	85 (34)
	No	165 (66)
Patient's regular use of devices, n (%)	Yes	190 (76)
	No	60 (24)
The patient's presence of comorbidity, n (%)	Yes	214 (85.1)
	No	36 (14.4)
Psychiatric treatment status of the patient, n (%)	Yes	38 (15.2)
	No	212 (84.8)
The age of the caregiver (year) (Mean ± SD)		51.19 ± 11.64
Caretaking time (years) (Mean ± SD)		7.77 ± 6.39
The gender of the caregiver, n (%)	Male	71 (28.4)
	Female	179(71.6)

LTOT = Long-term oxygen therapy, NIV = Non-invasive mechanical ventilator, SD = standard deviation statistical analysis of the data. Descriptive analysis methods were applied after the sociodemographic and clinical characteristics of the participating patients and caregivers were duly recorded in the appropriate data set in order. Continuous variables were expressed as mean ± standard deviation and categorical variables as frequency (percentage). In the comparison of continuous variables, it was examined primarily whether they met the assumptions required for parametric tests. Student-T Test was used for those who met the assumptions for parametric tests. The Pearson correlation analysis was applied if they met the assumptions for parametric tests to examine the relationship between the two numerical variables. The Linear Regression analysis was applied to determine the predictors of the caregiving burden. In all statistical analyses, a p - value of ≤ 0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the participants are presented in Table 1. The mean age of COPD patients included in the study was 69.84 ± 14.02 years and 34.4% (n = 86) were female. The mean age of the caregivers was 51.19 ± 11.64 years, 71.6% (n = 179) were female and the mean caregiving period was 7.77 ± 6.39 years.

Comparison of WHOQOL-BREF and ABI scores of caregivers by gender and clinical variables of COPD patients is presented in Table 2. There was a statistical difference between General Health (p = 0.001), Psychological Health (p = 0.024), Social Relations (p = 0.018), WHOQOL-BREF Total (p = 0.005), and ZBI (p = 0.037) scores according to the comparison by the patient's gender. A statistically significant difference was found between General Health (p < 0.001), Physical Health (p = 0.045), Social relations (p < 0.001), Environmental Health (p < 0.001), WHOQOL-BREF Total (p < 0.001), and ZBI (p < 0.001) scores according to the comparison by regular LTOT and/or NIV device usage of the patient. Physical Health (p < 0.001), Environmental Health (p = 0.001), WHOQOL-BREF Total (p = 0.001), and ZBI (p = 0.001) scores were found to have a statistically significant difference according to the comparison by the NIV usage of the patient. There was a statistical difference in Psychological Health (p = 0.041) score according to the comparison by the presence of comorbid disease.

The relationship between the age and clinical variables of COPD patients and the WHOAOL-BREF and ZBI scores of the caregivers are presented in Table 3. There was a negative statistically significant relationship (r = -0.134) between the ZBI score and the age of the patient, and the HADS Anxiety subscale (r = -0.413), and a positive statistically significant relationship between the number of emergency admissions (r = 0.180), the number of hospitalizations (r = 0.214), the number of intensive care hospitalizations (r = 0.181) and the HADS (r = 0.176) Depression subscale. In addition, there was a positive statistically significant relationship between the WHOQOL-BREF score of the caregiver and the patient's age (r = 0.197), and the HADS Anxiety subscale (r = 0.325); and a negative statistically significant relationship between the number of hospitalizations (r = -0.179) and the number of intensive care hospitalizations of the patient (r = -0.131).

A significant relationship was found between the patient's age, gender, number of hospitalizations, NIV usage, regular device usage, presence of comorbidity, antidepressant use, which are thought to affect the caregiver's total scores of ZBI and WHOQOL-BREF, the variables as a result of multiple linear regression analyses to reveal the predictiveness of HADS anxiety and depression scores, and the ZBI score (R = 0.607, R2 = 0.369, F (9-240) = 15.594, p < 0.001); and a significant relationship with the WHOQOL-BREF total score (R = 0.480, R2= 0.230, F (9-240) = 7.980, p < 0.001). These variables explain 36% of the change in the ZBI scores. According to the model; patient's gender (p < 0.001), NIV use (p < 0.001), regular device usage (p < 0.001), presence of comorbidity (p = 0 .014), HADS anxiety score (p < 0.001), and HADS depression score (p < 0.001) are significant predictors of the caregiver's ZBI score. The variables included in the model explain 23% of the change in the WHOQOL-BREF total scores. According to the model; NIV usage (p < 0.001), regular device usage (p < 0.001), HADS anxiety score (p = 0.012), and HADS depression score (p < 0.001) are seen to be significant predictors of the caregiver's WHOQOL-BREF total score.

Table 2. Comparison of gender and clinical variables of COPD patients with caregivers' WHOQOL-BREF and Zarit Burden Inventory scores

	Caregiver's WHOQOL-BREF						Caregiver's Zarit Burden Inventory
	General Health	Physical Health	Psychological Health	Social Relations	Environmental Health	Total	
Patient's gender							
Male	52.99 ± 14.40	40.39 ± 12.67	49.00 ± 9.46	43.07 ± 14.43	58.31 ± 11.36	52.14 ± 9.77	59.37 ± 11.21
Female	39.03 ± 22.78	38.40 ± 12.01	45.39 ± 12.00	37.70 ± 16.69	56.52 ± 9.50	48.37 ± 9.42	62.85 ± 12.10
	t = 5.785 ***p* = 0.001**	t = 1.160 *p* = 0.247	t = 2.270 ***p* = 0.024**	t = 2.378 ***p* = 0.018**	t = 1.174 *p* = 0.243	t = 2.819 ***p* = 0.005**	t = -2.093 ***p* = 0.037**
Patient's status of regular device use							
Yes	46.57 ± 20.40	39.73 ± 12.78	47.19 ± 10.92	42.23 ± 15.96	58.60 ± 10.18	51.00 ± 9.72	59.82 ± 11.30
No	31.76 ± 21.76	36.54 ± 9.87	43.95 ± 12.70	29.72 ± 13.23	52.08 ± 7.94	44.52 ± 7.61	68.33 ± 11.67
	t = -4.855 ***p* < 0.001**	t = -2.023 ***p* = 0.045**	t = -1.920 *p* = 0.056	t = -5.501 ***p* < 0.001**	t = -5.156 ***p* < 0.001**	t = -5.359 ***p* < 0.001**	t = 5.047 ***p* < 0.001**
Patient's status of NIV use							
Yes	40.88 ± 19.03	34.95 ± 12.29	45.10 ± 10.74	36.96 ± 16.03	54.08 ± 9.33	46.65 ± 8.52	65.36 ± 10.63
No	44.09 ± 22.87	41.03 ± 11.67	47.04 ± 11.75	40.40 ± 16.27	58.56 ± 10.13	50.88 ± 9.91	60.05 ± 12.20
	t = 1.177 *p* = 0.241	t = 3.832 ***p* < 0.001**	t = 1.212 *p* = 0.227	t = 1.593 *p* = 0.112	t = 3.400 ***p* = 0.001**	t = 3.354 ***p* = 0.001**	t = -3.400 ***p* = 0.001**
Patient's comorbidity status							
Yes	43.69 ± 21.31	39.15 ± 12.15	47.02 ± 11.38	39.25 ± 15.65	56.57 ± 10.21	49.55 ± 9.58	61.26 ± 11.41
No	38.88 ± 23.38	37.89 ± 12.67	42.82 ± 11.25	39.12 ± 19.60	59.80 ± 8.87	48.83 ± 10.21	65.42 ± 14.38
	t = -1.232 *p* = 0.219	t = -0.570 *p* = 0.569	t = -2.050 ***p* = 0.041**	t = -0.038 *p* = 0.970	t = 1.792 *p* = 0.074	t = 0.409 *p* = 0.683	t = 1.942 *p* = 0.053
Patient's status of antidepressant use							
Yes	43.09 ± 20.89	37.96 ± 12.68	49.45 ± 10.07	40.57 ± 13.16	58.30 ± 7.34	50.47 ± 7.86	62.50 ± 11.99
No	42.98 ± 21.84	39.15 ± 12.14	45.87 ± 11.60	38.99 ± 16.74	56.81 ± 10.48	49.26 ± 9.95	61.75 ± 11.95
	t = 0.028 *p* = 0.977	t = 0.548 *p* = 0.584	t = 1.784 *p* = 0.076	t = 0.650 *p* = 0.518	t = 1.074 *p* = 0.287	t = 0.839 *p* = 0.405	t = 0.358 *p* = 0.721

COPD = Chronic Obstructive Pulmonary Disease, WHOQOL-BREF =World Health Organization Quality of Life Scale Short Form, NIV = Non-invasive mechanical ventilator

Table 3. Relationship between the age and clinical variables of COPD patients and WHOQOL-BREF and Zarit Burden Inventory scores

		Age	Number of Emergency Department Admissions	Number of Hospitalizations	Number of Intensive Care Hospitalizations	HADS Depression Subscale	HADS Anxiety Subscale
Caregiver's WHOQOL-BREF score							
General health	r	0.314^{**}	-0.180^{**}	$-.254^{**}$	-0.003	-0.181^{**}	0.476^{**}
	p value	**< 0.001**	**0.004**	**< 0.001**	0.959	**0.004**	**< 0.001**
Physical health	r	0.122	-0.072^{**}	-0.098^{**}	-0.159	0.091	0.205^{**}
	p value	0.054	0.257	0.122	**0.012**	0.154	**0.001**
Psychological health	r	0.154^{*}	-0.140	-0.071	-0.018	-0.036	0.171
	p value	**0.015**	**0.027**	0.261	0.779	0.575	**0.007**
Social relations	r	0.192	-0.168	-0.232	-0.196	-0.223	0.260^{*}
	p value	**0.002**	**0.008**	**< 0.001**	**0.001**	**< 0.001**	**< 0.001**
Environmental health	r	0.046	0.060	-0.087^{**}	-0.088^{**}	-0.040	0.193^{**}
	p value	0.465	0.342	0.169	0.163	0.528	**0.002**
Total	r	0.197^{**}	-0.112^{**}	-0.179	-0.131^{**}	-0.069	0.325^{**}
	p value	**0.002**	0.077	**0.005**	**0.038**	0.276	**< 0.001**
Caregiver's Zarit Burden Inventory Score	r	-0.134^{*}	0.180^{**}	0.214^{**}	0.181	0.176	-0.413^{**}
	p value	**0.034**	**0.004**	**0.001**	**0.004**	**0.005**	**< 0.001**

COPD = Chronic Obstructive Pulmonary Disease, WHOQOL-BREF = World Health Organization Quality of Life Scale Short Form, HADS = Hospital Anxiety and Depression Scale.
*< 0.05. **< 0.001.

DISCUSSION

This study evaluated the relationship between the demographic, clinical, anxiety, and depressive characteristics of COPD patients and the quality of life and the burden of caregivers. The most important finding of the current study is that the patients' gender, NIV usage, regular LTOT and/or NIV device usage, presence of comorbid diseases, anxiety, and depressive symptoms are independent predictors of the burden of caregivers; and that the patients' NIV use, regular LTOT and/or NIV usage, anxiety, and depressive symptoms are independent predictors of quality of life of caregivers. The results of our study reveal that the patients' factors affecting the caregiving burden and quality of life of caregivers and that it has the potential to be a roadmap for the measures to be taken.

It is natural for some characteristics of patients with COPD, which is one of the most important causes of chronic respiratory failure, to affect caregivers. Our study has shown that patients' regular usage of LTOT and/or NIV devices improves the quality of life of caregivers and reduces the burden of care. To the best of our knowledge, although there has been no previous study addressing this issue, it is a normal result that patients' regular use of their devices positively affects caregivers. The most likely reason for this result may be that regular device usage reduces the workload of caregivers as it reduces hospital admissions and hospitalizations of patients [2, 3]. On the other hand, the

Table 4. **The examination of the predictiveness of some demographic and clinical characteristics of COPD patients for the Zarit Burden Inventory WHOQOL-BREF scores of caregivers with the multiple linear regression analysis models**

	Zarit Burden Inventory	**WHOQOL-BREF**						
	Coefficient of regression (95%Cl)	**SE**	**t value**	***p value***	**Coefficient of regression (95%Cl)**	**SE**	**t value**	***p* value**
Age (year)	-0.075 (-0.169-0.020)	0.048	-1.553	0.122	0.061 (-0.022-0.145)	7.1940	1.4349	0.153
Gender (Female)	5.186 (2.582-7.789)	1.322	3.924	**< 0.001**	-2.317 (-4.642-0.008)	0.0429	-1.9629	0.051
Number of Hospitalizations (pcs)	-0.640 (-1.424-0.143)	0.398	-1.609	0.109	0.429 (-0.270-1.129)	1.1804	1.2083	0.228
Noninvasive mechanical ventilation (yes)	5.817 (3.160-8.473)	1.349	4.313	**< 0.001**	-4.472 (-6.845- -2.099)	0.3553	-3.7131	**< 0.001**
Regular device usage (yes)	-5.989 (-8.984- -2.995)	1.520	-3.940	**< 0.001**	4.702 (2.028-7.377)	1.2046	3.4640	**< 0.001**
Comorbidity (yes)	-4.568 (-8.187- -0.948)	1.837	-2.486	**0.014**	0.144 (-3.088-3.376)	1.3576	0.0878	0.930
Antidepressant use (yes)	-0.291 (-3.940-3.357)	1.852	-.157	0.875	2.290 (-0967-5.549)	1.6411	1.3849	0.167
HADS depression sub-scale score	1.787 (1.141-2.434)	0.328	5.444	**< 0.001**	-0.739 (-1.316- -0.161)	1.6542	-2.5200	**0.012**
HADS anxiety sub-scale score	-1.833 (-2.434- -1232)	0.305	-6.009	**< 0.001**	1.1587 (0.622-1.695)	0.2932	4.2534	**< 0.001**

COPD = Chronic Obstructive Pulmonary Disease, WHOQOL-BREF = World Health Organization Quality of Life Scale Short Form, HADS = Hospital Anxiety and Depression Scale fact that the devices are being used as recommended by the clinician, and that they reduce the risk of sudden mortality/morbidity of patients may have a positive effect on caregivers [17]. We believe that this result is important because it objectively demonstrates the need for patients to follow the advice given by their physician.

The patients and caregivers spend a significant part of their time together, it is expected that the mental state of the patients will affect their caregivers. In our study, we found that patients' severity of the depression symptoms negatively affects the burden of care and quality of life of the caregivers. In a study of patients with COPD, it was reported that the caregivers' burden of providing care to patients who were depressed with a comorbid disease, which supports our results [9, 15, 16, 24, 25]. Contrary to the literature, there is a linear relationship between the increased severity of anxiety symptoms of patients and the burden of caregivers [7]. This is most likely because patients are struggling to recover due to anxiety, thereby reducing the burden on the caregiver [26]. This situation needs to be investigated through in-depth studies in the future. We think that social-psychological support should be provided in the early period to prevent the negative effects of the burden of care on the mental state of the caregivers.

In our study, similar to studies in the literature, it was found that the patient's female gender increased the burden of care and led to a decrease in the quality of life of the caregiver [7]. This may be associated with the increased workload of caregivers due to higher emotional expressions of female patients [7, 27]. Female patients' greater focus on the physical symptoms thus increasing the number of hospital and emergency department admissions may also be another reason [28]. Another reason may be that it is harder to care for female patients than male patients.

A similar study about caregivers burden was published by Baha *et al*. in 2022. The patients with COPD which were symptomatic and had comorbidities were related to increased burden of caregivers [29]. COPD already itself is associated with comorbidities. The patients with advanced COPD likely had chronic hypoxemia and this is related with pulmonary vascular remodeling, leading to an increase in pulmonary artery pressure [30]. The clinical severity of COPD progresses, hypoxia increases, pulmonary hypertension appears and pathological changes occur in the right heart, which leads to atrial fibrillation as one of the main comorbidity [31]. Our results were supported by the previous data.

Another finding of our work is that patient's use of NIV negatively affects the burden of care and the quality of life of the caregiver. As far as we know, this is the first time this result has been presented in the literature. This is most probably because that the patient's use of NIV leads caregivers to consider that the patients' disease is in an advanced stage. On the other hand, the use of NIV may cause the presence of secondary negative consequences such as more hospitalization and comorbidity [26].

Limitations

We should evaluate the results of our study within some limitations. First of all, the sample of the study may not reflect all COPD patients as our study population was provided from a tertiary chest diseases hospital. Secondly, the fact that the data was collected through the scales applied to patients may provide a clear case for the manipulation of patients. Finally, there was no control group in our study. Future studies with a control group will ensure that possible errors are excluded.

CONCLUSION

The results of our study, which evaluated the patient characteristics affecting the burden of care and quality of life of caregivers, may support sustainable psychosocial support policies for patients and caregivers. A positive impact on the quality of life and burden of care of caregivers will indirectly positively affect patient care and reduce mortality/morbidity. We think that patients and caregivers should be evaluated with a holistic approach, risk factors that may affect them should be identified in the early period and measures should be taken to eliminate the risks. Both the patient and caregivers should be provided with psychological and social support and culture-based communication.

Authors' Contribution

Study Conception: ZK, DÇ, MSA, İG, YTŞ; Study Design: ZK, DÇ, MSA, İG, YTŞ; Supervision: ZK, DÇ, MSA, İG, YTŞ; Funding: ZK, DÇ, MSA, İG, YTŞ; Materials: ZK, DÇ, MSA, İG, YTŞ; Data Collection and/or Processing: ZK, DÇ, MSA, İG, YTŞ; Statistical Analysis and/or Data Interpretation: ZK, DÇ, MSA, İG, YTŞ; Literature Review: ZK, DÇ, MSA, İG, YTŞ; Manuscript Preparation: ZK, DÇ, MSA, İG, YTŞ and Critical Review: ZK, DÇ, MSA, İG, YTŞ.

Conflict of interest

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