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12-month risk factor evaluation for persistent pulmonary symptoms in long COVID-19 patients

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Abstract

Background Knowledge of the sequelae of new coronavirus disease 2019 (COVID-19) is still limited owing to the relative recent onset of the disease. However, the study of other different types of coronavirus infections prior to COVID-19 infection reports that the patients may experience persistent symptoms following the infection.

The aim of this study Assessment and follow-up of persistent respiratory symptoms in patients recovered from acute COVID-19 infection.

Methods In this prospective cohort study, COVID-19 patients diagnosed at Beni-Suef University hospital and followed up prospectively at 3, 6, and 12 months after discontinuation of quarantine. Patients were interviewed for persistent respiratory symptoms then underwent assessment by physical examination and routine labs.

Results Seventy-one patients were evaluated and participated in this study. The mean age of the patients was 47 years and 46 (64%) of them were females. After 3 months, 77.5% of the patients had persistent dyspnea, 57.7% persistent fatigue, 15.5% persistent cough, and 8.5% persistent chest pain. At the 6th month, dyspnea and fatigue persisted in 33.8% and 22.5% of cases respectively while at the 12th month dyspnea persisted in 22.5% of cases. Old age, smoking, diabetes mellitus, severity of the disease, and hypoxemia on admission were associated factors with persistent symptoms.

Conclusion Our result added to the growing evidence that there are pulmonary sequelae in COVID-19 survivors, which may become a significant chronic global pulmonary health problem.

Keywords COVID-19, Survivors, Pulmonary sequelae

Introduction

On 31 December 2019, the China Health government alerted the World Health Organization (WHO) to severe cases of pneumonia of unknown cause in Wuhan City [1]. On 7 January, a novel infection by coronavirus was detected, originally abbreviated as 2019-nCoV by WHO and identified from a throat swab sample of infected patient [2]. This virus then renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. On 11 March 2020, the WHO documented COVID-19 infection as pandemic [4]. Despite the majority of patients completely recovered, a significant proportion of the patients—including mild cases—still complaining of persistent symptoms as fatigue and exertional dyspnea up to 6 and even 12 months [5]. Post-viral syndromes are reported following other coronavirus infection outbreaks as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [6]. Persons who have recovered from COVID-19 but still have long-lasting consequences or who have experienced the

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usual symptoms but for longer duration than expected have acquired importance in recent scientific literature [7]. The long-term symptoms and how they influence the patient's quality of life are not yet understood. Several authors have documented lung injury, including fibrosis and pulmonary function impairment, as well as the persistence of respiratory symptoms up to months following release from COVID-19 infection [8]. Patient-reported outcomes, such as fatigue or dyspnea, are critical for enhancing healthcare delivery, increasing patient involvement, and ensuring that the treatment and research are oriented to this patient [9]. "Long COVID-19" patients, those with symptoms that persist after the acute viral illness has been subsided, are becoming well recognized [7]. There is a significant incidence of respiratory symptoms, including dyspnea, cough, and chest discomfort among the persistent symptoms [10]. One in three patients—those with or without comorbidities—has a worse quality of life as a result of the duration of these symptoms. Additionally, it might postpone a person's return to work [11].

The aim of the study

Assessment and follow-up of persistent pulmonary symptoms in long COVID-19 patients aiming to identify the clinical needs of COVID-19 survivors.

Methods

Study design and participants

A prospective observational (cohort) study was performed on adult patients infected with COVID-19 at Beni-Suef University hospital according to the illustrated flowchart (Fig. 1). Patients met the World Health Organization criteria for quarantine discontinuation (10 days after symptoms onset, not feverish for 3 additional days, and improvement in symptoms like cough, dyspnea, or fatigue) were followed up. This study was performed in the period between November 2020 and February 2022. The study was approved by the local ethical committee at Faculty of Medicine, Beni-Suef University (FMBSUREC/04102020/Ibrahim).

A written informed consent obtained from all study participants.

Procedures

Assessment was done including full history taking, physical examination, routine labs, measurement of peripheral oxygen saturation, and follow-up of persistent respiratory symptoms also identifying risk factors for persistent respiratory symptoms as age of the patients, DM, severity of hypoxemia, and smoking status. Symptoms were assessed at 3, 6, and 12 months after recovery.

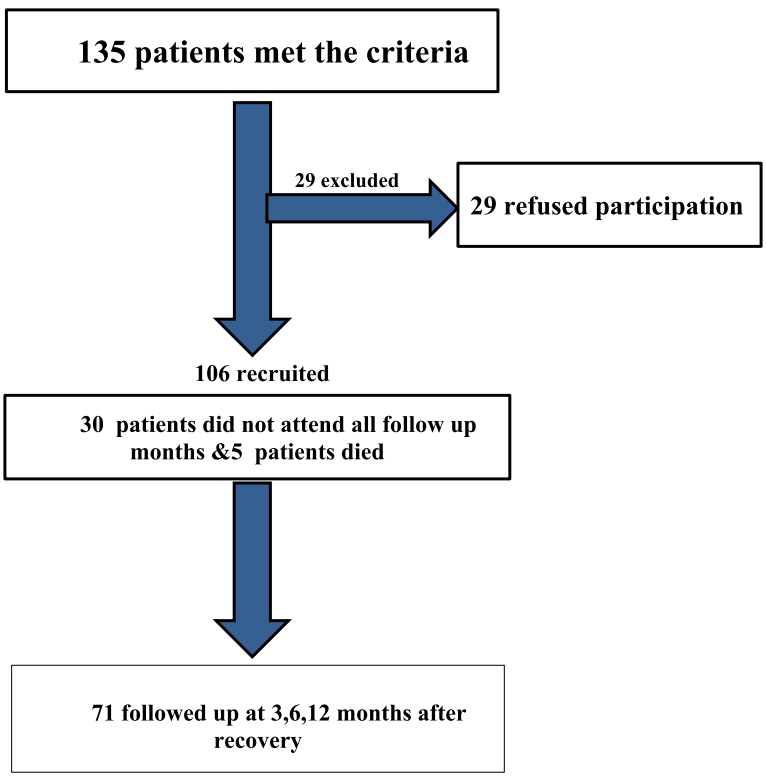

Fig. 1 Flowchart showing the patients' inclusion in the study

Dyspnea was assessed by a modified Medical Research Council dyspnea scale (mMRC scale) for measuring the degree of disability due to breathlessness that poses day-to-day activity on a scale from 0 to 4 [12].

Severity of the disease was classified according to the Egyptian management protocol of COVID-19 into:

1) Mild: mild symptoms, normal imaging
2) Moderate: pneumonia without hypoxia
3) Severe: pneumonia with hypoxia responding to oxygen therapy
4) Critical: pneumonia with hypoxia not responding to oxygen therapy and/or by organ dysfunction [13]

Statistical analysis

All data were collected then entered and coded into SPSS version 25 for Windows. Numeric variables expressed as mean, standard deviation, median, minimum, and maximum, while categorical variables expressed as number and percent.

McNemar test was used for follow-up of the symptoms between 3, 6, and 12 months. Pearson correlation was used to detect the correlation between length of hospital stay and different scale parameters.

Multivariable binary logistic regression analysis was conducted for assessment of the risk factors for residual symptoms at 3, 6, and 12 months.

*P value less than or equal 0.05 was considered as significant.

Results

The mean value for the age of the studied patients was 47 ± 15.6 years, most of them were females. Half of the participants were managed at home, 35.2% were managed in a hospital ward, and only 14.1% were managed in ICU (Table 1). Most of the studied patients had moderate to severe COVID-19 symptoms. The commonest management regimen based on diagnosis was steroids, parenteral antiviral, and parenteral anticoagulant regimen (Table 2).

Figure 2 shows that the most common persistent pulmonary symptom in the 3rd month of follow-up was dyspnea followed by fatigue then cough. In the 6th month, dyspnea and fatigue persisted in 33.8% and 22.5% of cases respectively while at the 12th month dyspnea and fatigue persisted in 22.5% of cases and 11.3% of cases, respectively (Table 3). There was a marked significant change in the proportion of patients who had dyspnea at 12-month follow-up after 6 months (Table 4). There was no significant change in patients who had cough at 12-month follow-up after 6 months (Tables 5 and 6). All cases of expectoration totally improved at 6 months (Table 7). Regarding fatigue showed that there was a statistically significant change in the patients who had fatigue at 6 months after 3 months (Table 8). There was no significant change in the patients who had chest pain at follow-up 6 months after 3 months; 4 of 6 patients became free at 6 months (Tables 9 and 10). All cases of other constitutional manifestations totally improved at 6 months (Tables 11 and 12). After adjustment for age, sex, presence of DM, HTN, smoking, chest problems, and oxygen saturation on admission to detect the associated risk factors for prediction of the probability of having symptoms persistent after 3 months, it was detected that every increase in age 1 year increased the probability of having symptoms persistent after 3 months about one time and half OR (95%CI for OR) was 1.4 (1.05 to 1.9) (Table 13). The probability of having symptoms persistent after 6 months, it was detected that smoking increased the probability of having symptoms persistent after 6 months OR (95%CI for OR) was 8.5 (1.3 to 58.2) and presence of diabetes also. In addition, it was found that every increase in oxygen saturation on admission one unit decreased the probability of having symptoms persistent after 6 months with about 13% OR (95%CI for OR) was 0.917 (0.863 to 0.974) (Table 14). Prediction of the probability of having symptoms persistent after 12 months, it was detected that smoking increased the probability of having symptoms persistent after 12 months OR (95%CI for OR) was 6.9 (1.04 to 45.9). In addition, increase in oxygen saturation one unit decreased the probability of having symptoms persistent after 12 months with about 13% OR (95%CI for OR) was 0.920 (0.868 to 0.976) (Table 15). Regarding Tables 13, 14, and 15, severity of the disease and site of care were excluded

Table 1 Characteristics of the studied patients

Characteristics	Number $N=71$	%
Age (mean ± SD)	47 ± 15.6	
Sex		
Males	25	35.2
Females	46	64.8
Comorbidities		
DM	13	18.3
HTN	19	26.8
Pulmonary comorbidities	10	14.1
Cardiac disease	3	4.2
Smoking	11	15.5
Site of care		
Home	36	50.7
Hospital ward	25	35.2
ICU	10	14.1

Table 2 Disease characteristics among the studied patients

Characteristics	Number	
	N **= 71**	**%**
COVID 19 clinical severity		
Mild cases	12	16.9
Moderate cases	22	31.0
Severe cases	28	39.4
Critical cases	9	12.7
Need for oxygen therapy		
No	34	47.9
Low flow	20	28.2
High flow	13	18.3
High flow NC	1	1.4
NIMV	3	4.2
Regimens on the acute stage		
Steroids, oral anti-viral, NEOACS, macrolide	22	31.0
Steroids, parenteral antiviral, parenteral anticoagulant	28	39.4
Steroids, parenteral antiviral, parenteral anticoagulant, anti-il6	5	7.0
Nonspecific or oral antiviral	14	19.7
Steroids, parenteral antiviral, parenteral anticoagulant, anti-fibrotic	2	2.8
Oxygen saturation baseline (mean ± SD)	85.6 ± 11.8	
Best oxygen saturation after recovery (mean ± SD)	95.9 ± 2.3	

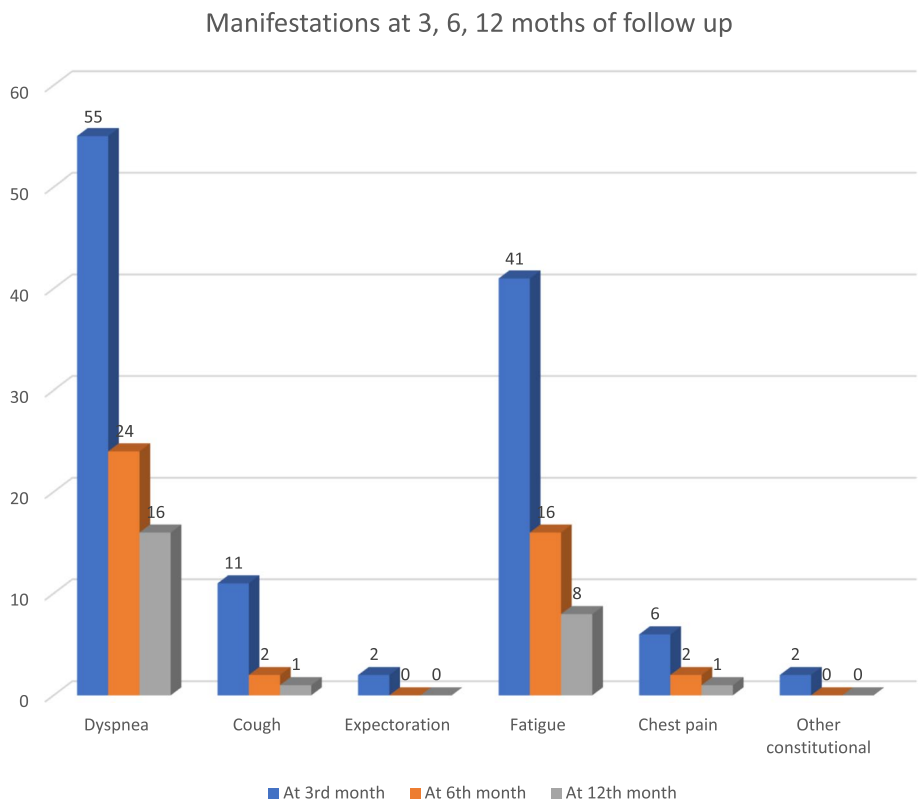

Fig. 2 Following up COVID 19 symptoms during the 1st year of infection

Table 3 Follow-up of dyspnea from 3 months till 6 months

Dyspnea 3 * dyspnea 6					
			Dyspnea 6		Total
			No	Yes	
Dyspnea 3	No	Count	16	0	16
		% within dyspnea 6	34.0%	0.0%	22.5%
	Yes	Count	31	24	55
		% within dyspnea 6	66.0%	100.0%	77.5%
Total		Count	47	24	71
		% within dyspnea 6	100.0%	100.0%	100.0%
P value of McNemar test			0.001*		

*significant difference

Table 4 Follow-up of dyspnea from 6 months till 12 months

Dyspnea 6 * dyspnea 12					
			Dyspnea 12		Total
			No	Yes	
Dyspnea 6	No	Count	47	0	47
		% within dyspnea 12	85.5%	0.0%	66.2%
	Yes	Count	8	16	24
		% within dyspnea 12	14.5%	100.0%	33.8%
Total		Count	55	16	71
		% within dyspnea 12	100.0%	100.0%	100.0%
P value of McNemar test			0.008*		

*significant difference

Table 5 Follow-up of cough from 3 months till 6 months

Cough 3 * cough 6					
			Cough 6		Total
			No	Yes	
Cough 3	No	Count	60	0	60
		% within cough 6	87.0%	0.0%	84.5%
	Yes	Count	9	2	11
		% within cough 6	13.0%	100.0%	15.5%
Total		Count	69	2	71
		% within cough 6	100.0%	100.0%	100.0%
P value of McNemar test			0.004*		

*significant difference

from the model as they were correlated with oxygen saturation on admission. There was a moderate linear positive correlation between the length of hospital stay and ferritin level on admission (Table 16, Figs. 3 and 4).

Discussion

The term "post-COVID 19 syndrome" includes persistent symptoms that may be caused by residual inflammation (convalescent phase), end organ damage, non-specific effects from hospital admission or prolonged mechanical ventilation, social isolation, or impact of pre-existing health problem [14].

Owing to the high number of patients infected by COVID-19 infection, and because it is important to detect the risk of persistent respiratory symptoms to plan management modalities for this the long COVID

Table 6 Follow-up of cough from 6 months till 12 months

Cough 6 * cough 12					
			Cough 12		Total
			No	Yes	
Cough 6	No	Count	69	0	69
		% within cough 12	98.6%	0.0%	97.2%
	Yes	Count	1	1	2
		% within cough 12	1.4%	100.0%	2.8%
Total		Count	70	1	71
		% within cough 12	100.0%	100.0%	100.0%
P value of McNemar test			0.999		

*significant difference

Table 7 Follow-up of expectoration from 3 months till 6 months

Expectoration 3 * expectoration 6				
			Expectoration 6	Total
			No	
Expectoration 3	No	Count	69	69
		% within expectoration 6	97.2%	97.2%
	Yes	Count	2	2
		% within expectoration 6	2.8%	2.8%
Total		Count	71	71
		% within expectoration 6	100.0%	100.0%
P value			–	

*significant difference

Table 8 Follow-up of fatigue from 3 months till 6 months

Fatigue 3 * fatigue 6					
			Fatigue 6		Total
			No	Yes	
Fatigue 3	No	Count	30	0	30
		% within fatigue 6	54.5%	0.0%	42.3%
	Yes	Count	25	16	41
		% within fatigue 6	45.5%	100.0%	57.7%
Total		Count	55	16	71
		% within fatigue 6	100.0%	100.0%	100.0%
P value of McNemar test			0.001*		

*significant difference

Table 9 Follow-up of fatigue from 6 months till 12 months

Fatigue 6 * fatigue 12					
			Fatigue 12		**Total**
			No	**Yes**	
Fatigue 6	No	Count	55	0	55
		% within fatigue 12	87.3%	0.0%	77.5%
	Yes	Count	8	8	16
		% within fatigue 12	12.7%	100.0%	22.5%
Total		Count	63	8	71
		% within fatigue 12	100.0%	100.0%	100.0%
P value of McNemar test			0.008*		

*significant difference

syndrome, this study was performed on 71 adult patients more than 18 years diagnosed with COVID-19 infection at Beni-Suef University hospital in the period between November 2020 and February 2022. Patients died or not attending the follow-up visits were excluded from the study. The most common persistent symptom in 3rd month of following-up was dyspnea followed by fatigue then cough. In the 6th month, dyspnea and fatigue persisted in 33.8% and 22.5% of cases respectively while at the 12th month dyspnea and fatigue persisted in 22.5% of cases and 11.3% of cases, respectively. There was a significant change in the percentage of the patients who had dyspnea at 6 months after 3 months and also at 12 months after 6 months. 15.5% of patients had cough at follow-up 3 months and 2.8% at follow-up 6 months with significant change. There was no significant change in the percentage of the patients who had cough at 12 months after 6 months. All cases of expectoration totally improved at 6-month follow-up. There was a significant change in the percentage of the patients who had fatigue at 6 months after 3 months. Follow-up of fatigue from 6 months till 12 months showed significant improvement. Smoking, diabetes mellitus, hypoxemia on admission, and severity of the disease were risk factors for persistent symptoms on follow-up. There was a moderate linear positive correlation between the length of hospital stay and ferritin level on admission. This study agrees with a study by Wu et al. who followed up patients at 3, 6, 9, and 12 months after hospital discharge. Dyspnea was very frequent in patients at 3 months. The number of patients significantly reduced at 6 months, 9 months, and 12 months [15]. Another study showed that the percentage of patients with at least one residual symptom

Table 10 Follow-up of chest pain from 3 months till 6 months

Chest pain 3 * chest pain 6					
			Chest pain 6		**Total**
			No	**Yes**	
Chest pain 3	No	Count	65	0	65
		% within chest pain 6	94.2%	0.0%	91.5%
	Yes	Count	4	2	6
		% within chest pain 6	5.8%	100.0%	8.5%
Total		Count	69	2	71
		% within chest pain 6	100.0%	100.0%	100.0%
P value of McNemar test			0.125		

*significant difference

Table 11 Follow-up of chest pain from 6 months till 12 months

Chest pain 6 * chest pain 12					
			Chest pain 12		**Total**
			No	**Yes**	
Chest pain 6	No	Count	69	0	69
		% within chest pain 12	98.6%	0.0%	97.2%
	Yes	Count	1	1	2
		% within chest pain 12	1.4%	100.0%	2.8%
Total		Count	70	1	71
		% within chest pain 12	100.0%	100.0%	100.0%
P value of McNemar test			0.999		

*significant difference

Table 12 Follow-up other constitutional manifestations from 3 months till 6 months

			Other constitutional 6	Total
			No	
Other constitutional 3	No	Count	69	69
		% within other constitutional 6	97.2%	97.2%
	Yes	Count	2	2
		% within other constitutional 6	2.8%	2.8%
Total		Count	71	71
		% within other constitutional 6	100.0%	100.0%
P value of McNemar			–	

Table 13 Binary logistic regression analysis for predicting associated risk factors with persistence of symptoms after 3 months of follow-up

Independent factors	*P* value	OR	95% C.I. for OR	
			Lower	Upper
Female sex	0.539	0.425	0.028	6.523
Age	0.020	1.423	1.058	1.914
Smoking	0.552	0.358	0.012	10.560
DM	0.266	0.001	0.000	183.071
HTN	0.674	0.093	0.000	5866.099
Chest problem	0.999	–	–	
O2 saturation at diagnosis	0.290	0.937	0.830	1.057

Table 14 Binary logistic regression analysis for predicting associated risk factors with persistence of symptoms after 6 months of follow-up

Independent factors	*P* value	OR	95% C.I. for OR	
			Lower	Upper
Female sex	0.902	1.085	0.297	3.963
Age	0.459	1.016	0.974	1.059
Smoking	0.028	8.594	1.269	58.211
DM	0.044	8.496	1.056	68.338
HTN	0.433	1.932	0.372	10.023
Chest problem	0.247	0.343	0.056	2.099
O2 saturation on diagnosis	0.005	0.917	0.863	0.974

Table 15 Binary logistic regression analysis for predicting associated risk factors with persistence of symptoms after 12 months of follow-up

Independent factors	*P* value	OR	95% C.I. for OR	
			Lower	Upper
Female sex	0.852	1.154	0.257	5.182
Age	0.282	1.027	0.979	1.077
Smoking	0.045	6.925	1.044	45.932
DM	0.107	0.181	0.022	1.450
HTN	0.358	2.229	0.403	12.332
Chest problem	0.441	0.458	0.063	3.330
O2 saturation on diagnosis	0.005	0.920	0.868	0.976

Table 16 Correlation between the length of hospital stay and different parameters among patients admitted to the hospital (ward or ICU)

		Length of stay
Age	*R* (correlation coefficient)	−0.156
	P value	0.478
O2 saturation on admission	*R* (correlation coefficient)	−0.359
	P value	0.093
Best SO2	*R* (correlation coefficient)	−0.092
	P value	0.676
Total leucocytic count	*R* (correlation coefficient)	0.037
	P value	0.867
C-reactive protein	*R* (correlation coefficient)	0.172
	P value	0.432
D-dimer	*R* (correlation coefficient)	0.282
	P value	0.193
Ferritin	*R* (correlation coefficient)	0.475*
	P value	0.022

*significant difference

decreased from 68% at follow-up 6 months to 49% at follow-up 12 months [16]. Lorent et al. [17] showed that about half of the studied patients detected fatigue, dyspnea, and/or cognitive impairment at follow-up 3 and 12 months, respectively.

Martino et al. [18] studied persistent symptoms after infection by COVID-19 at 12-month follow-up; the most common persistent symptoms were dyspnea (18.7%), then cough (6.2%), and finally fatigue (12.5%). Female sex and having underlying comorbidities were associated with fatigue [19]. Cirulli et al. [20] showed that severity

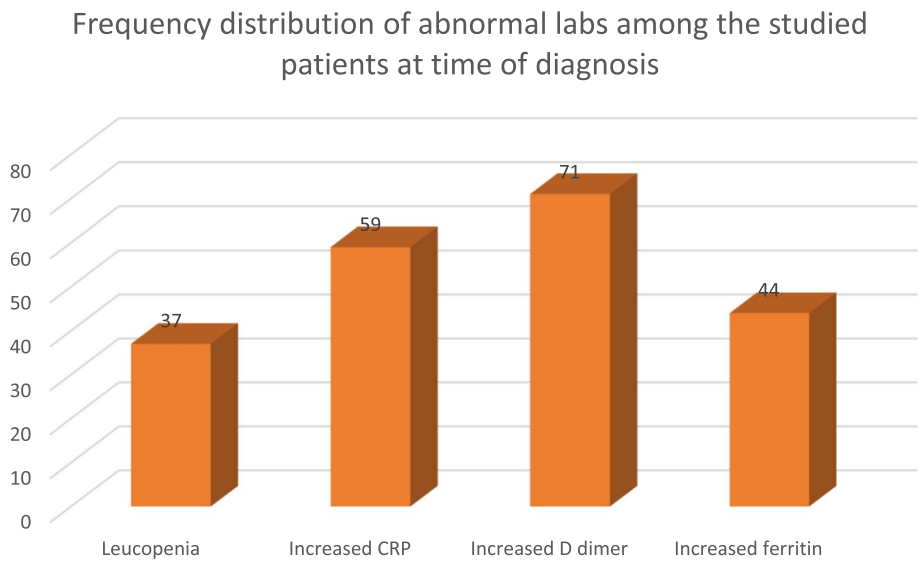

Fig. 3 Abnormal baseline labs

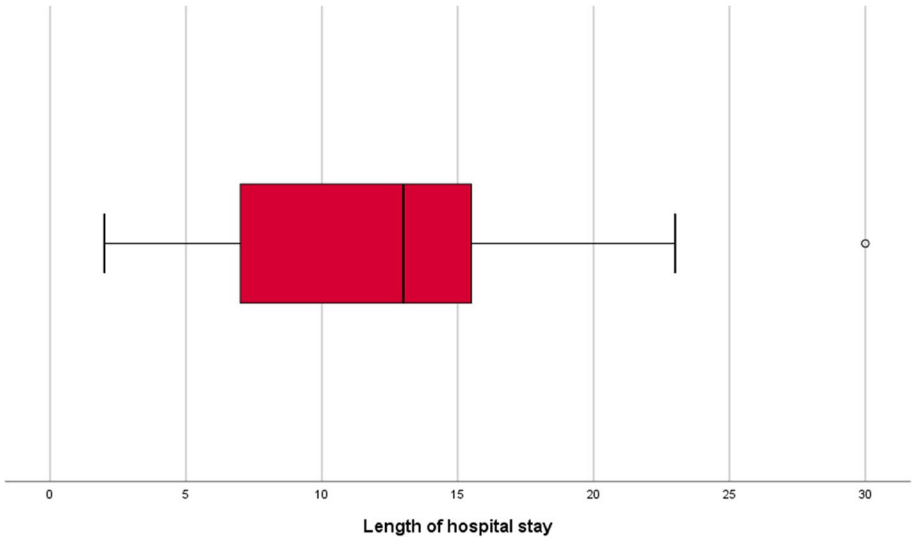

Fig. 4 Length of hospital stay in hospitalized patients (no = 35)

of the illness has a higher risk of long-term symptoms. Being current or ex-smoker, having diabetes mellitus, and having a longer length of hospital admission were risk factors with persistent pulmonary symptoms [21]. Martino et al. [18] reported that there is no influence of biological sex on persistent respiratory symptoms at all time points (6-month, 12-month follow-up). Huang et al. [16] showed that increasing age and severity of acute illness were positively associated with fatigue at follow-up. Pre-existing pulmonary comorbidity, type 2 diabetes mellitus, and malignancy were associated with persistent symptoms [22]. Elevated ferritin level was an associated factor with prolonged hospital stay [23]. The exact mechanisms that explain these chronic pulmonary symptoms after COVID-19 infection still not yet fully known. Added to the direct effects of SARS-CoV-2 infection, the host immune response to the virus may be responsible for the presence of these long-lasting symptoms, through facilitating an ongoing hyperinflammatory state [24]. Compared to the previous studies, the strength and novelty of our study consisted of a long-term follow-up, including a broad spectrum of different patient severity, as we included unselected COVID-19 patients with various comorbidities then analysis of the characteristics of acute

viral infection associated with persistent pulmonary symptoms.

Limitations of the study

The small sample size of the studied patients then including patients with severe cases may over estimate post-acute infectious sequelae or other comorbidity in patients with mild COVID-19. Also, we did not have data about the functional status of the studied patients before infection with COVID-19 also follow-up laboratory parameters as CRP, ferritin, and d-dimer not included in the study due to increasing number of variables of the study, number of vaccinated patient not included in the study as plan for this study was introduced for ethical committee approval in 2020 before obligation of COVID-19 vaccine in Egypt, and lastly, the lack of control group.

Conclusion

There is evidence that persistent symptoms are common after 1 year in patients recovered from COVID-19. Dyspnea and fatigue were the most common. Dyspnea and fatigue continued in 22.5% and 11.3% of cases respectively in the twelfth month of follow-up. It was detected that every increase in age 1 year increased the probability of having symptoms persistent after 3 months while increase in oxygen saturation on admission one unit decreased the probability of having symptoms persistent after 6 and 12 months but smoking increased the probability of having symptoms persistent after 6 and 12 months. Timely follow-up of survivors is recommended.

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NA.

Authors' contributions
EME collected the patients' data and performed the statistical component, ME conceived the publication design and prepared the manuscript, RS and LA revised the methods and results, and all authors have read and approved the final manuscript.

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Nil.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
This study was approved by the hospital research ethics board of Beni-Suef University, and a written informed consent was obtained from either patients themselves or their relatives. The study was approved by the local ethical committee at the Faculty of Medicine, Beni-Suef University (FMBSUREC/04102020/Ibrahim).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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