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Post-sequelae one year after hospital discharge among older COVID-19 patients: A multi-center prospective cohort study

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SUMMARY

Background: To systematically evaluate the prevalence of post-sequelae and chronic obstructive pulmonary disease assessment test (CAT) scoring one year after hospital discharge among older COVID-19 patients, as well as potential risk factors.

Methods: A multi-center prospective cohort study involving 1,233 eligible older COVID-19 patients was conducted. All patients were followed-up between Mar 1, 2021 and Mar 20, 2021. CAT scoring was adopted to measure symptom burden in COVID-19 patients.

Results: Of the 1233 eligible cases, 630 (51.1%) reported at least one sequelae. The top six post-sequelae included fatigue (32.4%), sweating (20.0%), chest tightness (15.8%), anxiety (11.4%), myalgia (9.0%), and cough (5.8%). Severe patients had significantly higher percentage of fatigue, sweating, chest tightness, myalgia, and cough ($P<0.05$), while anxiety was universal in all subjects. Sweating, anxiety, palpitation, edema of lower limbs, smell reduction, and taste change were emerging sequelae. Disease severity during hospitalization (OR: 1.46, 95% CI: 1.15–1.84, $P=0.002$), and follow-up time (OR: 0.71, 95% CI: 0.50–0.99, $P=0.043$) were independently associated with risk of post-sequelae, while disease severity during hospitalization was significantly associated with increased risk of emerging sequelae (OR: 1.33, 95% CI: 1.03–1.71, $P=0.029$). The median of CAT score was 2 (0–5) in all patients, and a total of 120 patients (9.7%) had CAT scores $\geq$10. Disease severity during hospitalization (OR: 1.81, 95% CI: 1.23–2.67, $P=0.003$) and age (OR: 1.07, 95% CI: 1.04–1.09, $P<0.001$) were significantly associated with increased risk of CAT scores $\geq$10.

Conclusions: While the dramatic decline in the prevalence rate of persistent symptoms is reassuring, new sequelae among older COVID-19 patients cannot be ignored. Disease severity during hospitalization, age, and follow-up time contributed to the risk of post-sequelae and CAT scoring one year after hospital discharge among older COVID-19 patients. Our study provides valuable clues for long-term post-sequelae of the older COVID-19 patients, as well as their risk factors.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to pose a global threat.[1] As of August 2021, it has caused more than 109 million confirmed cases with more than 4.4 million deaths worldwide.[2] The coronavirus (including severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS])

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pandemic has caused long-term pulmonary, cardiovascular, neuropsychiatric and systemic sequelae in the affected patients.[3,4] Continued attention to global proliferation needs to be accompanied by systematic research on the long-term sequelae of COVID-19 recovery to establish an evidence-based system of prognostic assessment and health promotion.[5]

Both the occurrence and prognosis of COVID-19 were closely related to older age.[6-8] To date, series of studies have reported the potential short- to long-term sequelae of COVID-19 recovery, ranging from two months to one year.[9-25] However, the older patients have not attracted enough attention and no specific studies quantified the temporal trends and associated risk factors for sequelae of COVID-19 in older patients, especially long-term sequelae. In addition, although there were currently no agreed measures to assess the pulmonary burden of COVID-19, chronic obstructive pulmonary disease (COPD) assessment test (CAT), an eight-item questionnaire designed to quantify health status impairment in COPD patients, was adopted to measure pulmonary burden in COVID-19 patients and recognized by the scientific community.[26]

Here we systematically evaluated the post-sequelae one year after hospital discharge among older COVID-19 patients in a multicenter prospective cohort study, we also explored the risk factors of post-sequelae and CAT scoring one year after hospital discharge among older COVID-19 patients.

Materials and methods

Study design and patients

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was implemented to enhance the reporting quality of this manuscript. Totally included in this multi-center prospective cohort study were real-time reverse transcription polymerase chain reaction (RT-PCR)-confirmed older COVID-19 patients (age ≥ 60) who were discharged from Huoshenshan Hospital and Taikang-Tongji Hospital (both in Wuhan, China) between Feb 12 and Apr 10, 2020.[8] All discharged patients met the uniform discharge criteria of the World Health Organization interim guidance.[27] The follow-up was conducted between Mar 1, 2021 and Mar 20, 2021. Exclusion criteria included (1) participants who refused, (2) those who could not be contacted, and (3) those who died before the follow-up visit. This study was approved by the Daping Hospital of Army Medical University (Ethics number 202,153). Verbal informed consent was obtained from all patients or their legal guardians prior to the survey due to the telephone follow-up.

Definitions and data acquisition

The disease severity during hospitalization was defined by World Health Organization (WHO) guideline for COVID-19.[28] The severe refers to fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 ≤ 93% on room air.[28] Fever was defined as an axillary temperature of 37.3 °C or higher. The baseline characteristics, including demographic characteristics, coexisting disorders, and the clinical symptoms, were extracted from the electronic medical records using a uniformed questionnaire by two trained physicians, and validated by a telephone-interview. The one-year follow up was conducted via telephone interview by trained physicians using a uniformed questionnaire including self-reported symptoms, and CAT score items, of which ≥ 10 (the threshold for maintenance treatment in COPD) and >2 (the median value) were treated as categorical outcomes. Patients were asked to report any sustained, intermittent, and emerging symptoms, respectively. The patient's current symptoms were carefully documented and evaluated by specialists to distinguish from their pre-disease status or other underlying diseases that were not associated with COVID-19. All survey data was double entered and validated using EpiData (version 3.1, EpiData Association, Odense, Denmark) software, and disputes were arbitrated by the expert committees composed of experts of respiratory and critical care medicine, and epidemiology.

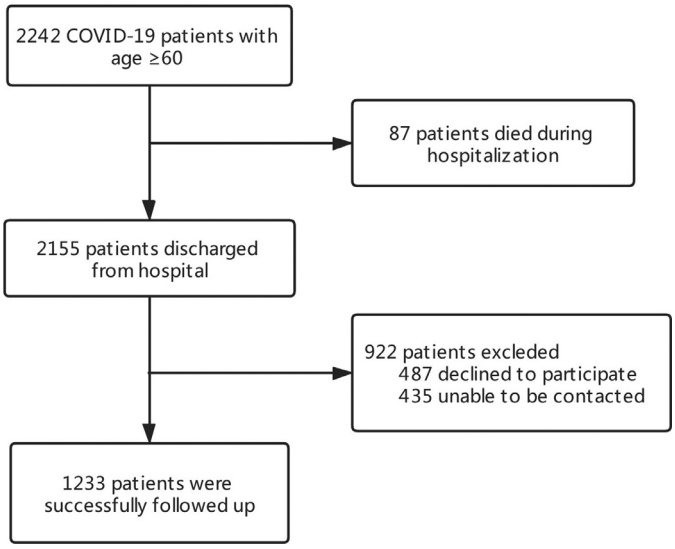

Fig. 1. flowchart of the inclusion of the older COVID-19 patients.

Statistical analyses

Categorical variables were described using frequency rates and percentages, while continuous variables were described using the median/interquartile range (IQR) values. Categorical variables were compared using the chi-squared test or fisher's exact test as appropriate, while continuous variables were compared using Manne-Whitney U test. The missing values of all potential predictors (missing rate of less than 5.0%) were imputed by expectation-maximization (EM) method. To test for the risk of bias due to the patients who were lost to follow-up, 1:1 propensity score-matching (PSM) between the lost to follow-up subpopulation and the enrolled subpopulation was carried out. Univariate logistic regression analysis was used to screen the potential risk factors which reached a P value of less than 0.1, and calculate their odds ratios (ORs) and corresponding confidence intervals (CIs). Then, the independent risk factors were derived from a stepdown selection process in multivariate logistic regression model. Multivariable adjusted logistic regression analysis was then used for exploring independent risk factors associated with any post-sequelae, CAT scores ≥10 or >2 (the median value). All statistical analyses were conducted using the R software version 4.0.0 (Institute for Statistics and Mathematics, Vienna, Austria). The reported statistical significance levels were all 2-sided, and a level of < 0.05 was considered statistically significant.

Results

Baseline characteristics of the older COVID-19 patients

Fig. 1 presented the flowchart of the inclusion procedure of the older COVID-19 patients. Totally 2242 COVID-19 patients with age ≥ 60 were admitted to these two hospitals, and 87 (3.88%) patients died during hospitalization. Of the remaining 2155 discharged patients, 1233 (57.2%) were available for one year follow-up (487 de-

Table 1
Demographic and clinical characteristics of the COVID-19 patients aged ≥60 years by disease severity during hospitalization.

Variables	Total patients (*N* = 1233)	Severe (*N* = 438)	Non-severe (*N* = 795)	P-value (Severe vs. Non-severe)
Gender, male	591(47.9%)	227(51.8%)	364(45.8%)	0.042
Age (Years), median (IQR)	68(64–73)	69.5(65–75)	67(64–72)	<0.001
60–69	716(58.1%)	219(50.0%)	497(62.5%)	<0.001
70–79	388(31.5%)	157(35.8)	231(29.1%)	
≥80	129(10.5%)	62(14.2%)	67(8.4%)	
Smoking				
Never	784(88.6%)	303(90.4%)	481(87.4%)	0.370
Former	18(2.0%)	5(1.5%)	13(2.4%)	
Active	83(9.4%)	27(8.1%)	56(10.2%)	
Coexisting disorders-no.(%)				
0	523(42.4%)	160(36.5%)	363(45.7%)	<0.001
1	340(27.6%)	118(27.0%)	222(27.9%)	
≥2	370(30.0%)	160(36.5%)	210(26.4%)	
Hypertension	516(41.8%)	212(48.4%)	304(38.2%)	0.001
Diabetes	234(19.0%)	96(21.9%)	138(17.4%)	0.051
Cardiovascular disease	169(13.7%)	78(17.8%)	91(11.4%)	0.002
Coronary heart disease	128(10.4%)	60(13.7%)	68(8.6%)	0.005
Cerebrovascular disease	72(5.8%)	32(7.3%)	40(5.0%)	0.103
Chronic liver disease	53(4.3%)	18(4.1%)	35(4.4%)	0.808
Chronic kidney disease	31(2.5%)	10(2.3%)	21(2.6%)	0.700
COPD	19(1.5%)	10(2.3%)	9(1.1%)	0.116
Tumor	32(2.6%)	15(3.4%)	17(2.1%)	0.174
Symptoms-no.(%)				
0	19(2.1%)	4(1.2%)	15(2.7%)	0.026
1–2	171(18.9%)	52(15.3%)	119(21.1%)	
>2	713(79.0%)	283(83.5%)	430(76.2%)	
Cough	849(68.9%)	326(74.6%)	523(65.8%)	0.001
Fever	699(77.3%)	279(82.3%)	420(74.3%)	0.006
Anorexia	663(53.8%)	243(55.5%)	420(52.9%)	0.384
Fatigue	721(58.5%)	270(61.8%)	451(56.7%)	0.085
Short breath	556(45.2%)	228(52.2%)	328(41.3%)	<0.001
Chest tightness	398(32.3%)	151(34.6%)	247(31.1%)	0.211
Myalgia	323(26.3%)	111(25.4%)	212(26.7%)	0.611
Expectoration	228(18.5%)	101(23.1%)	127(16.0%)	0.002
Dyspnea	111(9.0%)	69(15.8%)	42(5.3%)	<0.001
Diarrhea	78(6.3%)	22(5.0%)	56(7.1%)	0.164
Sore throat	71(5.8%)	21(4.8%)	50(6.3%)	0.285
Nausea	28(2.3%)	11(2.5%)	17(2.1%)	0.670
Vomiting	34(2.8%)	15(3.4%)	19(2.4%)	0.285
Dizziness	30(2.4%)	11(2.5%)	19(2.4%)	0.892
Chill	25(2.0%)	18(4.1%)	7(0.9%)	<0.001
Headache	27(2.2%)	8(1.8%)	19(2.4%)	0.519
Nasal congestion	9(0.7%)	6(1.4%)	3(0.4%)	0.076
Hemoptysis	7(0.6%)	4(0.9%)	3(0.4%)	0.253
Treatment approach				
ICU admission	40(3.2%)	35(8.0%)	5(0.6%)	<0.001
Mechanical Ventilation	17(1.4%)	15(3.4%)	2(0.3%)	<0.001
Corticosteroid-related therapy	103(8.4%)	63(14.4%)	40(5.0%)	<0.001
Length of hospital stay, days	15(10–22)	15.5(10–24)	15(10–21)	0.007
Time from discharge to follow-up, days	363(357–371)	360(356–368)	365(357–371)	<0.001

clined to participate and 435 were unable to be contacted). Baseline demographic and clinical characteristics were summarized in Table 1. In brief, the median age of the eligible patients was 68.0 (IQR: 64.0–73.0) years old, with 591 (47.9%) were male. A total of 438 (35.5%) patients were categorized as severe. The median duration of hospital stay was 15.0 (10.0–22.0) days and the median time from discharge to follow-up was 363.0 (357.0–371.0) days. During hospitalization, the most common symptoms were fever (77.3%), cough (68.9%), fatigue (58.5%), anorexia (53.8%), and short of breath (45.2%). Compared with non-severe cases, the severe were elder, more likely to be male, had more coexisting disorders, clinical symptoms, and receive more treatments.

Post-sequelae and CAT scoring one year after hospital discharge among older COVID-19 patients

Table 2 presented the post-sequelae and CAT scoring one year after hospital discharge, including systemic/general sequelae (34.6%), neurological sequelae (29.0%), cardiovascular sequelae (19.0%), respiratory sequelae (10.1%), and digestive system sequelae (1.9%). Of the 1233 eligible cases, 630 patients (51.1%) reported at least one sequelae at follow up, and the severe group had significantly higher percentage than the non-severe group (57.5% vs 47.5%, $P = 0.001$). The top six post-sequelae included fatigue (32.4%), sweating (20.0%), chest tightness (15.8%), anxiety (11.4%), myalgia (9.0%), and cough (5.8%). Severe patients had significantly higher percentage of fatigue, sweating, chest tightness, myalgia, and cough ($P<0.05$), while anxiety was universal in all subjects. Of them, fatigue, chest tightness, myalgia, and cough were sustained symptoms, although the prevalence rate dropped sharply (Fig. 2). Sweating, anxiety, palpitation, edema of lower limbs, smell reduction, and taste change were emerging sequelae (Fig. 2). The median of CAT score was 2 (0–5) in all patients, and the severe group had a significantly higher CAT score (3, IQR: 1–6) than the non-severe group (2, IQR: 0–5, $p<0.001$) (Table 2). A total of 120 patients (9.7%) had CAT scores ≥10, and 597 patients (48.4%) had

Table 2
Post-sequelae one year after hospital discharge among older COVID-19 patients by disease severity during hospitalization.

Post-sequelae	Total patients ($N=1233$)	Severe ($N=438$)	Non-severe ($N=795$)	P-value Severe vs. Non-severe
Any one of post-sequelae	630(51.1%)	252(57.5%)	378(47.5%)	0.001
Systemic/general sequelae	427(34.6%)	178(40.6%)	249(31.3%)	0.001
Fatigue	400(32.4%)	166(37.9%)	234(29.4%)	0.002
Myalgia	111(9.0%)	52(11.9%)	59(7.4%)	0.009
Chill	1(0.1%)	–	1(0.1%)	–
Respiratory sequelae	124(10.1%)	61(13.9%)	63(7.9%)	0.001
Dyspnea	44(3.6%)	22(5.0%)	22(2.8%)	0.041
Cough	71(5.8%)	34(7.8%)	37(4.7%)	0.025
Expectoration	53(4.3%)	26(5.9%)	27(3.4%)	0.035
Hemoptysis	1(0.1%)	–	1(0.1%)	–
Sore throat	12(1.0%)	7(1.6%)	5(0.6%)	0.129
Nasal congestion	2(0.2%)	1(0.2%)	1(0.1%)	–
Cardiovascular sequelae	234(19.0%)	111(25.3%)	123(15.5%)	<0.001
Edema of lower limbs	24(1.9%)	13(3.0%)	11(1.4%)	0.054
Chest tightness	195(15.8%)	94(21.5%)	101(12.7%)	<0.001
Short breath	53(4.3%)	30(6.8%)	23(2.9%)	0.001
Palpitation	66(5.4%)	29(0.6%)	37(4.7%)	0.142
Neurological sequelae	358(29.0%)	142(32.4%)	216(27.2%)	0.052
Dizziness	47(0.8%)	17(3.9%)	30(3.8%)	0.925
Headache	31(2.5%)	16(3.7%)	15(1.9%)	0.058
Anxiety	141(11.4%)	56(12.8%)	85(10.7%)	0.269
Sweating	246(20.0%)	105(24.0%)	141(17.7%)	0.009
Smell reduction	21(1.7%)	12(2.7%)	9(1.1%)	0.037
Taste change	23(1.9%)	11(2.5%)	12(1.5%)	0.213
Digestive system sequelae	24(1.9%)	9(2.1%)	15(1.9%)	0.838
Diarrhea	9(0.7%)	3(0.7%)	6(0.8%)	–
Nausea	1(0.1%)	–	1(0.1%)	–
Vomiting	1(0.1%)	–	1(0.1%)	–
Anorexia	13(1.1%)	6(1.4%)	7(0.9%)	0.561
CAT scores	2(0–5)	3(1–6)	2(0–5)	<0.001
0–10	1113(90.3%)	376(85.8%)	737(92.7%)	<0.001
10–20	100(8.1%)	47(10.7%)	53(6.7%)	
22–30	13(1.1%)	10(2.3%)	3(0.4%)	
30-	7(0.6%)	5(1.1%)	2(0.3%)	
CAT scores ≥ 10	120(9.7%)	62(14.2%)	58(7.3%)	<0.001
CAT scores > 2	597(48.4%)	235(53.7%)	362(45.5%)	0.006

CAT scores >2. The severe group had significantly higher proportion of patients with CAT score both ≥10 and >2 than the non-severe group ($P<0.001$).

As the patients lost to follow-up before were a little older than those enrolled (Supplementary Table 1), PSM was conducted to evaluate the lost to follow-up bias in the sensitivity analysis. Totally 843 patients in the enrolled population were matched successfully with those lost to follow-up, and the baseline characteristics were comparable (Supplementary Table 1). We then compared the post-sequelae one year after hospital discharge between totally enrolled patients ($n=1233$) and those selected by PSM ($n=843$) (Supplementary Table 2). Most symptoms were similar to those of totally enrolled patients (Supplementary Table 2, all $P>0.05$). This indicates the lost to follow-up bias was negligible, and the enrolled patients were representative.

Risk factors of post-sequelae one year after hospital discharge among older COVID-19 patients

Risk factors for post-sequelae one year after hospital discharge were evaluated for all older COVID-19 patients (Table 3-4, and Supplementary Table 3–6). Disease severity during hospitalization (OR: 1.46, 95% CI: 1.15–1.84, $P=0.002$), and follow-up time (OR: 0.71, 95% CI: 0.50–0.99, $P=0.043$) were independently associated with risk of post-sequelae (Table 3). Table 4 presents the risk factors for emerging sequelae. Disease severity during hospitalization (OR: 1.36, 95% CI: 1.06–1.75, $P=0.016$), and follow-up time (OR for per month: 0.68, 95% CI: 0.47–0.98, $P=0.038$) were individually associated with either increased or decreased risk of emerging sequelae. In multivariable model, Disease severity during hospitalization was significantly associated with increased risk of emerging sequelae (OR: 1.33, 95% CI: 1.03–1.71, $P=0.029$). We also explored risk factors for post-sequelae of each system, and disease severity during hospitalization, age, follow-up time, gender, and smoking were the main risk factors (Supplementary Table 3–6). Besides, our results revealed that corticosteroid-related therapy was associated with increased risk of both post-sequelae and emerging sequelae ($P<0.001$, Supplementary Table 7–8). To remove the potential confounding bias caused by disease severity during hospitalization, we also conducted stratified analyses of associations between any post-sequelae, emerging sequelae and corticosteroid-related therapy, and the results kept (Supplementary Table 7–8).

Risk factors of CAT scoring one year after hospital discharge among older COVID-19 patients

Risk factors for CAT scoring one year after hospital discharge were also evaluated for all older COVID-19 patients (Table 5-6). Disease severity during hospitalization (OR: 1.81, 95% CI: 1.23–2.67, $P=0.003$) and age (OR: 1.07, 95% CI: 1.04–1.09, $P<0.001$) were significantly associated with increased risk of CAT scores ≥10 (Table 5). Age (OR: 1.08, 95% CI: 1.06–1.10, $P<0.001$) was significantly associated with increased risk of CAT scores >2 (the median), while follow-up time (OR for per month: 0.66, 95% CI: 0.47–0.93, $P=0.017$) was inversely associated with increased risk of CAT scores >2 (Table 6).

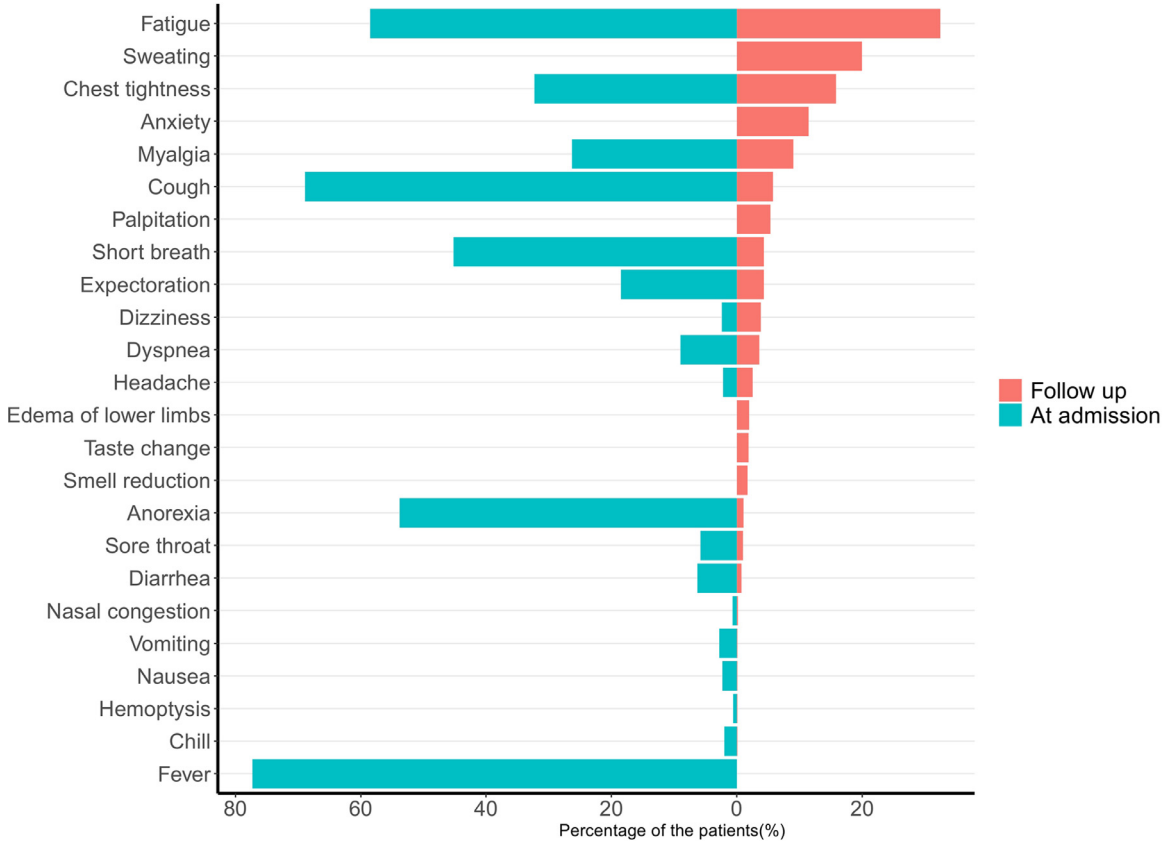

Fig. 2. Percentage of patients presenting with COVID-19-related sequelae during the acute phase of the disease (left) and at 1-year follow-up (right).

Table 3
Logistic regression models to evaluate the risk factors for any post-sequelae.

Variables	Univariate Logistic Analysis		Multivariate Logistic Analysis	
	HR (95%CI)	P-value	OR (95%CI)	P-value
Age, per year	1.01(0.99–1.02)	0.383		
Gender, male	0.89(0.71–1.11)	0.306		
Smoking	0.94(0.75–1.17)	0.560		
Severity during hospitalization	1.50(1.18–1.89)	0.001	1.46(1.15–1.84)	0.002
Coexisting disorders-no.(%)				
Hypertension	0.95(0.76–1.79)	0.673		
Diabetes	1.01(0.76–1.34)	0.949		
Cardiovascular disease	0.91(0.66–1.26)	0.579		
Coronary heart disease	1.10(0.76–1.58)	0.628		
Cerebrovascular disease	1.14(0.71–1.84)	0.591		
Chronic liver disease	0.92(0.53–1.59)	0.762		
Chronic kidney disease	0.69(0.33–1.41)	0.304		
COPD	0.55(0.22–1.42)	0.217		
Tumor	0.74(0.36–1.50)	0.401		
Time from discharge to follow-up, per month	0.67(0.78–0.93)	0.017	0.71(0.50–0.99)	0.043

Discussion

Age was an independent risk factor for the occurrence and prognosis of COVID-19, and older COVID-19 patients need more health monitoring and medical promotion. In the current study, we systematically evaluated the prevalence rate of post-sequelae and CAT scoring one year after hospital discharge among older COVID-19 patients, as well as the potential risk factors in a multi-center prospective cohort study. We revealed that more than half of the patients reported at least one sequelae one year after hospital discharge, and disease severity during hospitalization was independently associated with increased risk of post-sequelae and emerging sequelae. Totally 9.7% of patients had CAT scores ≥10, and 48.4% had CAT scores >2. Disease severity during hospitalization and age significantly associated with increased risk of CAT scores ≥10. Age was significantly associated with increased risk of CAT scores >2, while follow-up time was inversely associated with increased risk of CAT scores >2. To our knowledge, this should be the first study to focus on long-term post-sequelae of the older COVID-19 patients, as well as their risk factors.

Scientific and clinical evidence was evolving regarding the sub-acute and long-term effects of COVID-19, which may be caused by cellular damage, innate immune response and procoagulant state caused by SARS-CoV-2 infection.[29,30] A systematic review reported that the median proportion of individuals experiencing at least one short-term persistent symptom was 72.5% (IQR: 55.0%–80.0%),

Table 4
Logistic regression models to evaluate the risk factors for emerging sequelae.

Variables	Univariate Logistic Analysis		Multivariate Logistic Analysis	
	HR (95%CI)	P-value	OR (95%CI)	P-value
Age, per year	1.01(1.00–1.03)	0.141		
Gender, male	0.85(0.66–1.08)	0.188		
Smoking	0.94(0.73–1.20)	0.595		
Severity during hospitalization	1.36(1.06–1.75)	0.016	1.33(1.03–1.71)	0.029
Coexisting disorders-no.(%)				
Hypertension	0.82(0.64–1.05)	0.113		
Diabetes	1.09(0.80–1.48)	0.599		
Cardiovascular disease	0.86(0.59–1.23)	0.402		
Coronary heart disease	0.90(0.59–1.35)	0.597		
Cerebrovascular disease	0.86(0.50–1.47)	0.569		
Chronic liver disease	0.95(0.52–1.75)	0.863		
Chronic kidney disease	0.98(0.50–2.16)	0.968		
COPD	0.64(0.21–1.93)	0.427		
Tumor	1.67(0.82–3.42)	0.160		
Time from discharge to follow-up, per month	0.68(0.47–0.98)	0.038		

Table 5
Logistic regression models to evaluate the risk factors for CAT≥10.

Variables	Univariate Logistic Analysis		Multivariate Logistic Analysis	
	HR (95%CI)	P-value	OR (95%CI)	P-value
Age, per year	1.07(1.05–1.10)	<0.001	1.07(1.04–1.09)	<0.001
Gender, male	1.18(0.81–1.72)	0.389		
Smoking	0.99(0.69–1.41)	0.946		
Severity during hospitalization	2.10(1.43–3.06)	<0.001	1.81(1.23–2.67)	0.003
Coexisting disorders-no.(%)				
Hypertension	1.20(0.82–1.74)	0.352		
Diabetes	0.90(0.55–1.47)	0.664		
Cardiovascular disease	1.48(0.90–2.42)	0.123		
Coronary heart disease	1.38(0.78–2.41)	0.266		
Cerebrovascular disease	2.40(1.30–4.45)	0.005		
Chronic liver disease	1.19(0.50–2.85)	0.690		
Chronic kidney disease	0.99(0.30–3.32)	0.992		
COPD	1.09(0.25–4.79)	0.906		
Tumor	0.29(0.04–2.17)	0.229		
Time from discharge to follow-up, per month	0.99(0.97–1.01)	0.388		

Table 6
Logistic regression models to evaluate the risk factors for CAT > 2.

Variables	Univariate Logistic Analysis		Multivariate Logistic Analysis	
	HR (95%CI)	P-value	OR (95%CI)	P-value
Age	1.08(1.06–1.10)	<0.001	1.08 (1.06–1.10)	<0.001
Gender, male	0.96(0.77–1.20)	0.719		
Smoking	1.18(0.95–1.48)	0.141		
Severity during hospitalization	1.39(1.10–1.75)	0.006		
Coexisting disorders-no.(%)				
Hypertension	1.24(0.99–1.56)	0.062		
Diabetes	1.18(0.89–1.56)	0.263		
Cardiovascular disease	1.70(1.22–2.37)	0.002		
Coronary heart disease	1.70(1.17–2.47)	0.005		
Cerebrovascular disease	2.09(1.27–3.44)	0.004		
Chronic liver disease	1.11(0.64–1.93)	0.707		
Chronic kidney disease	1.30(0.64–2.67)	0.470		
COPD	0.96(0.39–2.38)	0.926		
Tumor	1.21(0.60–2.45)	0.590		
Time from discharge to follow-up, per month	0.61(0.44–0.85)	0.004	0.66(0.47–0.93)	0.017

which was higher than 51.1% in our study.[31] However, we didn't find significant difference between several medium-term reports and our results. [9,12,13,15,32] Consistent with previous studies, fatigue, which was common after acute lung injury and associated with severe impairment of physical function and quality of life, was the most common symptom.[33] Further, the emerging sequelae, including sweating, anxiety, palpitation, edema of lower limbs, smell reduction, and taste change, were all psychological responses and associated with posttraumatic stress disorder (PTSD).[34-36] In our results, anxiety was universal in all subjects, no matter the severe or the non-severe. This indicated that the psychological comfort after hospital discharge of COVID-19 should not be neglected.

As SARS-CoV-2 is an emerging virus, no effective treatment has yet been developed. Corticosteroids, which may reduce inflammatory-induced lung injury, were used frequently for the treatment of viral infections, since high amount of cytokines can be

induced by SARS-CoV,[37] MERS-CoV[38] and SARS-CoV-2 infections.[39] However, clinical evidence reveals that corticosteroids cause decreased clearance of SARS-CoV and MERS-CoV and increased complications among survivors.[40] In the recovery trial, the authors identified that dexamethasone reduced 28-day mortality among those receiving invasive mechanical ventilation or oxygen at randomization, but not among patients not receiving respiratory support.[41] Except for dexamethasone helping benefit patients during hospitalization, however, the conclusion above also reveals that use of steroids should be more precise. Here, our results indicated that usage of corticosteroid-related therapy was associated with increased risk of both post-sequelae and emerging sequelae, although this might be biased by the disease severity during hospitalization, detailed dose and duration information, and self-reporting symptoms. Taking evidence above together, we next should establish more precise guidelines of corticosteroids use, and strike a balance between saving patients' lives during hospitalization and long-term sequelae.

Study strength and limitations

The strength of the current study includes the large sample size, detailed questionnaire on sequelae and use of CAT scoring system, long-term follow-up period, and focus on the older population. However, the interpretation and generalizability of the findings in the current study were also affected by several limitations. First, similar to other follow-up studies, high rate of lost follow-up possibly caused by individual willingness of patients not to be continuously concerned might lead to underestimation of the incidence of post-sequelae. However, the PSM suggests this bias might be limited. Second, telephone follow-up relied on patient self-reported symptoms may affect the accuracy of the post-sequelae survey and CAT scoring, although we performed rigorous quality control and repeat surveys of partial samples. Third, the absence of a non-COVID-19 control group and the absence of a pre-COVID-19 CAT assessment of the same patients limited the possibility of a comparative study. Fourth, currently the disease severity during hospitalization was defined by World Health Organization (WHO) interim guideline for COVID-19. Further more precise severity markers are warranted to classify the patients and guide precise treatment.

Conclusions

Our study provides valuable clues for long-term post-sequelae of the older COVID-19 patients, as well as their risk factors. While the dramatic decline in the prevalence rate of persistent symptoms is reassuring, new sequelae cannot be ignored. Disease severity during hospitalization, age, and follow-up time contributed to the risk of long-term post-sequelae. Studies among different population and exploring relevant mechanisms are warranted to validate the results and popularize our findings.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Contributions

MX, LQ, CG and LL conceived and designed the study. MX, FX, MC, CY, and LQ drafted the paper and did the statistical analysis. FX, MC, CY, LH, ZK, YS, LL, CG collected the data. All authors approved the final draft of the manuscript for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.12.005.

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