Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Incidence and affecting factors of pulmonary diffusing capacity impairment with COVID-19 survivors 18 months after discharge in Wuhan, China

Dear editor,

Studies have showed that long-term sequelae from COVID-19 may affect human respiratory system, cardiovascular system, nervous system, immune system etc. with a negative impact on the patients' mental health, well-being and quality of life, but the lungs are the organ most likely to sustain serious impairment from COVID-19.[1] The convalescent patients with COVID-19 have manifested particularly noticeable pulmonary diffusing capacity impairment (PDCI).[2,3] However, the affecting factors for PDCI still remain undefined. We evaluated in this study PDCI of COVID-19 survivors after 18 months of recovery and its affecting factors, aiming to provide reference for treatment of the long COVID patients during the rehabilitation period.

During August to September 2021, we conducted a follow-up study on 221 COVID-19 survivors discharged from Wuhan, Hubei Province, China, who had been hospitalized from January 25 to February 29, 2020.

The inclusion criteria and severity of the disease are based on Chinese clinical guidelines. Clinical data of the survivors, including the demographic characteristics and clinical examinations, were collected by the trained physicians.

Patients underwent the chest HRCT examinations in the supine position and in the breath-holding manner following inspiration. Pulmonary function tests were performed using COSMED Italy under American Thoracic Society and European Respiratory Society guidelines.[4] All pulmonary function test measurements were the percentage of predicted normal values. Inadequate pulmonary diffusing capacity refers to carbon monoxide diffusing capacity of the lungs (DLCO) that is lower than 80% of the predicted values.

This study had been reviewed and approved by the Ethics Committee of Hubei Provincial Hospital of Integrated Traditional Chinese and Western Medicine (2,020,009). All participants provided their written or verbal consents before the study.

Totally, 221 COVID-19 survivors participated in this study (Table1). The patients' median age in this study is 58.2 [standard deviation (SD)= 12]. Among them, 104 survivors (47.06%) are male and 117 (52.94%) are female.

There were no significant differences in age, gender and BMI among the survivors before they were infected by COVID-19. This study showed that the PDCI incidence of COVID-19 survivors had reached 57.92% (128/221) and the most commonly-diagnosed complications of the patients were heart failure (3cases [1.36%]), anemia (3 cases [1.36%]) and chronic obstructive pulmonary disease (COPD) (1 case [0.45%]).

The univariate analysis as Table 1 showed that the two groups compared in terms of age, Hb, platelet (PLT), Cr, HbA1c, body mass index (BMI), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), maximal voluntary ventilation (MVV), CT score and severity of the disease, differences were statistically significant ($P < 0.05$) (Table 2).

The multivariate logistic regression analysis was performed by taking indexes with statistically significant differences in single factor as the independent variables, and whether survivors' DLCO was damaged as the dependent variable. The results manifested that females were more susceptible to DLCO impairment than males (odd ratio = 0.188, 95% CI 0.066–0.532, Wald x2 = 9.918, df = 1, $p = 0.002$). Compared with survivors with impaired DLCO, those with normal DLCO had higher Hb (odd ratio = 1.025, 95% CI 1.001–1.049, Wald x2 = 4.192, df = 1, $p = 0.041$) and higher MVV (odd ratio = 1.020, 95% CI 1.003–1.038, Wald x2 = 5.429, df = 1, $p = 0.020$). Also, survivors with impaired DLCO had higher PLT (odd ratio = 0.992, 95% CI 0.985–0.999, Wald x2 = 0.992, df = 1, $p = 0.031$). As the severity of the disease advanced, difficulty for COVID-19 survivors to recover from PDCI was increased (Grade Wald x2 = 8.796, df = 3, $p = 0.032$).

Studies have shown that a large proportion of COVID-19 patients' DLCO has been impaired, likely to associate with the damaged pulmonary interstitium or pulmonary blood vessels.[3] In our study, we reported the lung functions of the mild, moderate, severe and critical cases 18 months after discharge, approximately sixty percent discharged patients still manifested PDCI, although most survivors' vital capacity had been improved significantly or their CT images were normal.

In this study, we discovered the factors affecting COVID-19 patients' PDCI. The multivariate logistic regression analysis showed that gender, Hb, PLT, MVV and the disease severity levels were correlated with the declined pulmonary diffusing capacity. Furthermore, we found that the incidence of PDCI in female patients was significantly higher than that of males, which are in agreement with the previous studies on COVID-19 patients 1 year after discharge.[3,5]

In the acute phase, PLT activation and aggregation of COVID-19 patients were increased.[6,7] Histopathological assessment on the autopsy of COVID-19 cases revealed presence of PLT-involved inflammatory microvascular thrombosis in the patients' lungs, kidneys and hearts, confirming that respiratory failure of COVID-19 patients was connected with inflammatory thrombosis.[8–10] Our study also showed that pulmonary diffusing capacity was negatively correlated with PLT, that is, the diffusing capacity would be obviously impaired when PLTs were at the normal high value, and pulmonary diffusing capacity would be greatly improved when PLTs were at the normal low value.

Moreover, our findings exhibited that after the correction of hemoglobin that affected pulmonary diffusing capacity, the normal

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Table 1
Clinical characteristics of survivors with impaired and normal DLCO.

	All patientsM(P25,P75)	Patients with impaired DLCO	Patients withnormal DLCO	t or x^2	*P* value
Age	61(51,66)	62(51,67)	59(47.5,66.0)	-0.979	0.328
Gender					
Male (%)	104	42	62	24.114	0.000
Female (%)	117	86	31		
Severity					
mild	93	43	50	19.476	0.000
moderate	58	31	27		
severe	54	39	15		
critical	16	15	1		
WBC	5.640(4.810,6.530)	5.650(4.923,6.500)	5.695(4.810,6.450)	-0.366	0.714
Hb	135.000(127.000,145.000)	131.00(123.250,139.750)	139(132.000,151.000)	-5.200	0.000
PLT	184.000(158.000,219.000)	198.500(159.250,229.750)	179(156.000,209.750)	-2.545	0.011
N%	56.140(50.540,61.300)	56.600(52.685,62.075)	55.550(50.425,60.300)	-1.556	0.120
L%	32.400 ± 6.490	32.290 ± 6.415	32.618 ± 6.643	0.369	0.712
LY#	1.790(1.500,2.120)	1.790(1.493,2.063)	1.785(1.500,2.173)	-0.035	0.972
IgM	0.540(0.220,1.470)	0.500(0.220,1.518)	0.515(0.233,1.148)	-0.142	0.887
IgG	138.340(67.640,210.930)	146.100(73.298,217.485)	135.125(58.258,207.860)	-0.859	0.390
proBNP	105.300(81.250,169.200)	106.400(81.250,172.200)	103.340(80.633,166.075)	-0.213	0.831
ALT	13.000(10.000,21.000)	12.000(9.000,20.000)	13.000(10.000,21.000)	-1.774	0.081
AST	21.000(17.000,25.000)	20.500(17.000,25.750)	22.000(17.000,25.000)	-1.166	0.868
Alb	44.600(43.300,46.000)	44.500(43.425,45.875)	44.900(43.425,46.375)	-1.282	0.200
BUN	5.430(4.600,6.340)	5.525(4.760,6.345)	5.275(4.228,6.525)	-1.218	0.223
Cr	66.800(56.400,80.000)	63.950(54.100,78.650)	71.050(59.400,82.475)	-2.611	0.009
UA	343.700(289.600,409.000)	339.450(287.075,400.475)	368.450(289.625,416.800)	-1.697	0.090
HbA1c	5.500(5.200,5.900)	5.600(5.300,6.000)	5.400(5.100,5.900)	-2.199	0.028
FVC	100.280 ± 16.330	98.055 ± 16.615	103.520 ± 15.468	2.476	0.014
FEV1	101.470 ± 17.620	99.495 ± 18.569	104.361 ± 18.928	2.033	0.043
FEV1/FVC	83.800(79.000,89.320)	84.500(79.300,89.468)	82.650(78.100,89.315)	-0.971	0.332
MVV	93.520±24.800	88.013±25.142	101.278±22.311	4.032	0.000
BMI $kg•m^{-2}$	24.780(22.350,26.810)	24.140(21.915,26.583)	25.775(22.965,27.033)	-2.078	0.038
CT SCORE	2.000(1.000,3.000)	2.000(1.000,4.000)	2.000(0.000,3.000)	-2.439	0.015

Table 2
Multivariate logistic regression with DLCO as the dependent variable.

	Coefficients				OR	95.0% Confidence Interval for OR	
	B	Std. Error	Wald	*P* value		Lower Bound	Upper Bound
Hb	0.024	0.012	4.192	0.041	1.025	1.001	1.049
PLT	-0.008	0.004	4.667	0.031	0.992	0.985	0.999
Cr	-0.011	0.015	0.587	0.443	0.989	0.961	1.018
HbA1c	-0.158	0.153	1.063	0.303	0.854	0.633	1.152
BMI	0.099	0.054	3.406	0.065	1.104	0.994	1.227
CT Score	-0.161	0.101	2.558	0.110	0.851	0.699	1.037
FVC	0.027	0.019	1.916	0.166	1.027	0.989	1.067
FEV1	0.007	0.019	0.128	0.721	1.007	0.970	1.045
MVV	0.020	0.009	5.429	0.020	1.020	1.003	1.038
Gender	-1.673	0.531	9.918	0.002	0.188	0.066	0.532
Grade			8.796	0.032			
Grade(1)	-0.131	0.424	0.095	0.758	0.877	0.382	2.015
Grade(2)	-1.211	0.515	5.519	0.019	0.298	0.108	0.818
Grade(3)	-2.493	1.282	3.782	0.052	0.083	0.007	1.020

high value of hemoglobin was positively correlated with diffusing capacity of the lungs, which could be probably associated with the enhanced capacity of oxygen-carrying of hemoglobin when increased, and with the improved gas exchange in the lungs.

However, FVC and MVV of most COVID-19 survivors with PDCI were normal, which is consistent with other scholars' findings[2]. It should be noted that severity of the disease was closely linked to the survivors' PDCI as shown in Table 2.

As a cross-sectional study, limitations of this study still exist, and the baseline data are insufficient about the survivors' pulmonary functions prior to the onset of COVID-19.

In summary, our study revealed that 57.92% of COVID-19 patients had PDCI, which was correlated with gender, PLTs, hemoglobin, MVV and severity of COVID-19. The potential factors affecting pulmonary diffusing capacity of COVID-19 patients and the complicated mechanisms behind remain to be further investigated in the future.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Bo Xu: Data curation, Formal analysis, Writing – original draft, Formal analysis, Writing – review & editing. **Fu-qiang Ma:** Formal analysis, Writing – review & editing. **Cong He:** Data curation, Writing – review & editing. **Zi-qi Wu:** Writing – original draft, Formal analysis, Writing – review & editing. **Cun-yu Fan:** Writing – original draft, Formal analysis, Writing – review & editing. **He-rong Mao:** Writing – original draft, Formal analysis, Writing – review & editing. **Ji-xian Zhang:** Conceptualization, Formal analysis, Writing – review & editing. **Min Yang:** Conceptualization, Formal analysis, Writing – review & editing. **Zuo-wei Hu:** Conceptualization, Formal analysis, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.12.020.

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