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Residual clinical damage after COVID-19: A retrospective and prospective observational cohort study

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Abstract

Data on residual clinical damage after Coronavirus disease-2019 (COVID-19) are lacking. The aims of this study were to investigate whether COVID-19 leaves behind residual dysfunction, and identify patients who might benefit from post-discharge monitoring. All patients aged ≥18 years admitted to the Emergency Department (ED) for COVID-19, and evaluated at post-discharge follow-up between 7 April and 7 May, 2020, were enrolled. Primary outcome was *need of follow-up*, defined as the presence at follow-up of at least one among: respiratory rate (RR) >20 breaths/min, uncontrolled blood pressure (BP) requiring therapeutic change, moderate to very severe dyspnoea, malnutrition, or new-onset cognitive impairment, according to validated scores. Post-traumatic stress disorder (PTSD) served as secondary outcome. 185 patients were included. Median [interquartile range] time from hospital discharge to follow-up was 23 [20–29] days. 109 (58.9%) patients needed follow-up. At follow-up evaluation, 58 (31.3%) patients were dyspnoeic, 41 (22.2%) tachypnoeic, 10 (5.4%) malnourished, 106 (57.3%) at risk for malnutrition. Forty (21.6%) patients had uncontrolled BP requiring therapeutic change, and 47 (25.4%) new-onset cognitive impairment. PTSD was observed in 41 (22.2%) patients. At regression tree analysis, the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) and body mass index (BMI) at ED presentation, and age emerged as independent predictors of the *need of follow-up*. Patients with PaO_2/FiO_2 <324 and BMI ≥33 Kg/m^2 had the highest odds to require follow-up. Among hospitalised patients, age ≥63 years, or age <63 plus non-invasive ventilation or diabetes identified those with the highest probability to need follow-up. PTSD was independently predicted by female gender and hospitalisation, the latter being protective (odds ratio, OR, 4.03, 95% confidence interval, CI, 1.76 to 9.47, p 0.0011; OR 0.37, 95% CI

0.14 to 0.92, p 0.033, respectively). COVID-19 leaves behind physical and psychological dysfunctions. Follow-up programmes should be implemented for selected patients.

Introduction

Since the identification of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) as the causative agent of Coronavirus disease-2019 (COVID-19), more than four million cases were reported worldwide, mortality reaching 6.68% as of the 20th of May 2020 [1]. The majority of affected patients manage to overcome the acute phase of the disease and appear to achieve clinical recovery [2]. Knowledge of early disease characteristics accumulates rapidly. However, *sequelae* of COVID-19 remain unexplored. It seems, therefore, reasonable to question whether it is safe to lower the guard. Monitoring recovered patients over time might be revelatory of what comes next, maximizing preparedness and optimizing medical care.

Persistent radiological lung abnormalities and breathing difficulties were reported in patients recovered from previous coronavirus diseases [3, 4]. The applicability of these observations to SARS-CoV-2-infected patients is unknown [5, 6]. Inflammation is a recognized promoter of tissue fibrosis [7]. As such, the burden of pulmonary dysfunction after COVID-19 recovery may be substantial. The suggested neurotropism of SARS-CoV-2 might entail neurocognitive *sequelae* of COVID-19 [8], and the persistence of other disease features cannot be excluded [9, 10]. Psychological health in convalescent patients is also a matter of concern. Fear of infection-associated complications, prohibition of human contact, and uncertainty about reacceptance in society may jeopardize mental well-being and influence quality of life, prompting to the need of adequate mental counselling.

Alertness and awareness of what to expect are crucial not to underestimate health problems and to guarantee timely interventions. This would aid in preventing national health care systems from being overwhelmed by the sudden surge of conditions requiring medical assistance.

With the belief that hospital discharge is far from being the endpoint of monitoring and precautionary measures, we set up a COVID-19 follow-up outpatient clinic to longitudinally follow patients recovered from COVID-19. Here, we report a first assessment of the information gathered on COVID-19 *sequelae* and propose strategies to identify patients who may benefit from continued monitoring.

Methods

Design and study population

This is a retrospective and prospective cohort study included in an extensive monocentric observational investigation, the COVID-BioB study, implemented at San Raffaele University Hospital in Milan, Italy. All patients aged 18 years or older, admitted to San Raffaele University Hospital from 25 February 2020 with confirmed SARS-CoV-2 infection were consecutively enrolled in the COVID-BioB study. Confirmed infection was defined as positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal and/or throat swab. Patients with clinical and radiological findings suggestive of COVID-19 pneumonia were selected for follow-up evaluation after hospital discharge at the COVID-19 Follow-up Outpatient Clinic of San Raffaele University Hospital. Patients evaluated since the start of the Clinic (7 April 2020) up to 7 May 2020 were included for the present analysis. Patients admitted for reasons other than COVID-19 who subsequently tested positive for SARS-CoV-2 at routine screening were excluded.

The COVID-BioB study protocol conforms to the declaration of Helsinki, was approved by the Hospital Ethics Committee, namely *Comitato Etico Ospedale San Raffaele* (*CE-OSR*, protocol no. 34/int/2020), and registered on ClinicalTrials.gov (NCT04318366). For patients able to provide a signed informed consent (IC) at the time of hospital admission, written IC was obtained prior to data collection. Otherwise, patients were consented as soon as they were able to sign. This study is reported in compliance with the STROBE statement [11].

Follow-up evaluation

A comprehensive evaluation of physical, neurological, cognitive and mental health was performed by a multidisciplinary team consisting of internists, nutritionists, neurologists, and psychiatrists (Fig 1). Data about the initial presentation of COVID-19 and the disease course were retrospectively scrutinized from medical records in the presence of the patient during follow-up evaluation and collected. Complete physical examination and vital sign assessment were integrated with detailed patient medical history. The modified Medical Research Council (mMRC) scale for dyspnoea was used to quantify residual shortness of breath [12], and a visuo-analog scale (VAS) for self-rated health status [13]. Percent of body weight change and the Mini Nutritional Assessment (MNA) screening tool served as indicators of nutritional status [14]. The MNA screening tool was initially developed for detecting undernutrition in the elderly, but it has subsequently been adopted in several clinical settings and patient populations [15–17]. The tool identifies individuals at risk of malnutrition or malnourished based on the presence of reduction in food intake (due to loss of appetite, digestive problems, chewing or swallowing difficulties), disease burden (psychological stress or acute disease in the previous 3 months or presence of neuropsychological problems), weight loss, body mass index or reduced mobility. An MNA value ≤ 7 indicates malnutrition and a score between 8 and 11 identifies patients at risk of malnutrition [14]. Complete neurological examination was performed to investigate neurological *sequelae*. Cognitive function was assessed through the Montreal Cognitive Assessment (MoCA) score [18], and cognitive impairment was defined by a score <24 in the absence of known history of neurocognitive disease.
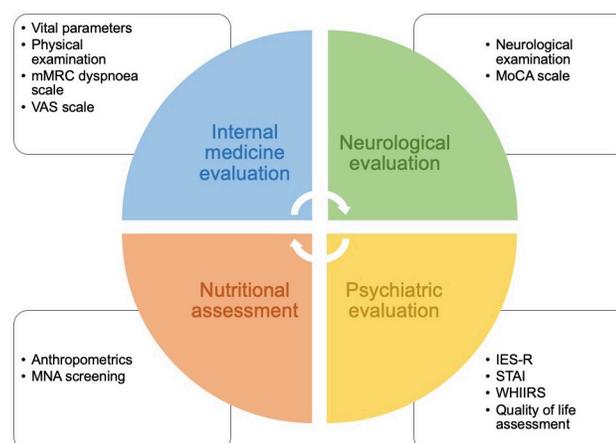
Fig 1. Multidisciplinary organisation and assessment measures of the COVID-19 Follow-up Outpatient Clinic at San Raffaele University Hospital. mMRC, modified Medical Research Council. VAS, visuo-analog scale. MoCA, Montreal Cognitive Assessment. MNA, Mini Nutritional Assessment. IES-R, Impact of Event Scale-Revised. STAI-Y, State-Trait Anxiety Inventory form Y. WHIIRS, Women's Health Initiative Insomnia Rating Scale.

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Psychiatric unstructured clinical interview was conducted to investigate the presence of a current major psychiatric disorder (depressive disorders, bipolar and related disorders, anxiety disorders, psychotic disorders, eating disorders, and trauma-related disorders) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Validated self-report questionnaires were used to assess quality of life through the World Health Organization Quality of Life (WHOQOL-BREF), post-traumatic stress disorder (PTSD) through the Impact of Events Scale-Revised (IES-R), anxiety through the State-Trait Anxiety Inventory form Y (STAI-Y), and insomnia through the Women's Health Initiative Insomnia Rating Scale (WHIIRS) [19–22].

Variables

Demographical data (i.e. age, gender, and ethnicity), comorbidities (i.e. hypertension, HTN, coronary artery disease, CAD, diabetes mellitus, DM, chronic obstructive pulmonary disease, COPD, chronic kidney disease, CKD, active cancer, and current psychiatric disorder according to DSM-5), as well as body mass index (BMI), axillary body temperature, and laboratory values (i.e. the ratio of arterial oxygen partial pressure, PaO_2 in mmHg, to fractional inspired oxygen, FiO_2, expressed as a fraction, PaO_2/FiO_2, white blood cell count, WBC, neutrophil to lymphocyte ratio, NLR, liver enzymes, lactate dehydrogenase, LDH, C-reactive protein, CRP, estimated glomerular filtration rate, eGFR using the CKD-EPI equation) at ED presentation were extracted for all patients. Acute respiratory distress syndrome (ARDS) was defined as PaO_2/FiO_2 <300 [23]. For hospitalised patients, length of stay (LoS), transfer to the intensive care unit (ICU), and non-invasive ventilation (NIV) administration were also recorded.

Data collected at the follow-up visit included vital parameters, percent of body weight change from hospital admission, mMRC for dyspnoea, MNA, VAS and WHOQOL scores, and the presence of cognitive impairment, PTSD, anxiety, and insomnia according to the generally accepted cut-off scores (MoCA <24, IES-R ≥33, STAI-state ≥40, STAI-trait ≥40, and WHIIRS ≥9, respectively). Previous need for psychiatric interventions and previous or current intake of psychotropic drugs were also collected. Tachypnoea was defined as respiratory rate (RR) >20 breaths/min [24], measured by counting respiratory chest movements of over a period of 60 seconds.

Prior to analysis, data were cross-checked with medical charts and verified by data managers and clinicians for accuracy.

Outcomes

To investigate the relevance of the follow-up visit, we created a composite dichotomous variable, i.e. *need of follow-up*, which identified patients requiring medical advice after COVID-19 recovery. Accordingly, the *need of follow-up* was defined by the presence of at least one of the following: *i)* tachypnoea, *ii)* mMRC for dyspnoea score ≥2, *iii)* uncontrolled blood pressure requiring a change in therapy (increase in dose or new prescription of at least one anti-hypertensive drug, i.e. diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers), *iv)* MNA score ≤7, *v)* presence of cognitive impairment. The *need of follow-up* variable represented the primary outcome. Psychiatric disturbances were not included in the primary outcome for the purpose of the analysis, and PTSD was used as secondary outcome.

Statistical analyses

Descriptive statistical analyses were performed for all variables. Dichotomous variables were expressed as absolute frequencies (percentage), and continuous variables as medians [IQR].

Group comparisons were performed using the χ2 test or Fisher's exact test for categorical variables, and the Mann-Whitney U test for continuous variables.

To investigate the impact of individual variables on the *need of follow-up*, we performed univariable and multivariable logistic regression analyses both for the entire cohort and for hospitalised patients only. We subsequently employed a regression tree (RT) algorithm to identify risk groups based on the *need of follow-up*, within the entire cohort (RT 1) and the hospitalised population (RT 2). The RT algorithm uses recursive partitioning to sequentially split a cluster of patients into increasingly homogeneous sub-groups based on several independent variables, selecting the optimal sequence of classifications as defined by a hierarchy of prognostic factors and associated cut-points [25]. Demographical data, comorbidities, BMI, clinical and laboratory features at ED presentation, and hospitalisation due to COVID-19 were included as predictors in RT 1. LoS, NIV administration, and transfer to ICU, together with demographical data and comorbidities, were used as covariates in RT 2. The results of these analyses were graphically represented. The area under the receiver operating characteristic (ROC) curve (ROC_{AUC}) was used as a quality metric of the regression trees.

Univariable and multivariable logistic regression analyses were employed to identify predictors of PTSD among age, gender, BMI at ED presentation, comorbidities, hospitalisation, and ARDS.

Missing data was not imputed.

All statistical analyses were performed using R statistical package (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria), with a two-sided significance level set at p <0.05.

Patient and public involvement

As the study addresses an urgent unmet clinical need in response to a global public health emergency, patients and members of the public were not directly involved in the design, conduct, or reporting of this research.

Results

Patient characteristics at baseline and at follow-up

From 7 April to 7 May 2020, a total of 195 COVID-19 patients were evaluated at the COVID-19 Follow-up Outpatient Clinic of San Raffaele University Hospital. Of these, 10 had been admitted for reasons other than COVID-19 and were therefore excluded for the present analysis. All patients included (n = 185) had a positive SARS-CoV-2 RT-PCR test result from a nasopharyngeal and/or throat swab. Characteristics at disease onset and follow-up assessment measures of the cohort are reported in Tables 1 and 2, respectively. Of the 185 patients included in the analysis, 68.1% had been hospitalised, while the rest were discharged from the ED. Most inpatients received hydroxychloroquine in conjunction with lopinavir/ritonavir, which was the standard therapy for COVID-19 at our Institution at the time patients included in the study were admitted to hospital. Additional treatments were prescribed based on the severity of the clinical picture. Patients managed at home were prescribed symptomatic treatments. Patients were assessed after a median [interquartile range, IQR] time from hospital discharge of 23 [20–29] days.

Hospitalised patients were older than patients discharged from the ED, more commonly males and white. The two populations did not differ in terms of BMI at hospital admission and medical history, with the exception of HTN, which was more frequent in hospitalised patients. Laboratory findings at ED presentation of hospitalised and non-hospitalised patients are presented in Table 1.

Table 1. General features of COVID-19 patients.

Variable	All Cohort	Discharged from ED	Hospitalised	P
No. of patients	185 (100)	59 (31.9)	126 (68.1)	
Age (years)	57 (48; 67)	50 (40.5; 57.7)	61 (51.2; 69)	<0.0001
Female gender	62 (33.5)	28 (47.5)	34 (27)	0.0098
Ethnicity				0.029
European (Eastern/Western)	168 (90.8)	49 (83.1)	119 (94.4)	
Hispanic (South America)	16 (8.6)	9 (15.3)	7 (5.6)	
African-American (Black)	1 (0.5)	1 (1.7)	0 (0)	
BMI (Kg/m^2)	27.2 (24.7; 30.5)	26.2 (24.1; 30.7)	27.8 (25.4; 30.5)	0.12
Comorbidities				
HTN	70 (37.8)	15 (25.4)	55 (43.7)	0.029
CAD	12 (6.5)	5 (8.5)	7 (5.6)	0.65
DM	21 (11.4)	4 (6.8)	17 (13.5)	0.28
COPD	2 (1.1)	0 (0)	2 (1.6)	0.84
CKD	3 (1.6)	0 (0)	3 (2.4)	0.58
Active cancer	3 (1.6)	1 (1.7)	2 (1.6)	1.00
Psychiatric disorder	40 (21.6)	15 (25.4)	25 (19.8)	0.77
At ED presentation				
PaO$_2$/FiO$_2$	314.8 (263.8; 357.6)	371.4 (333.8; 409.5)	296.4 (249.6; 330.7)	<0.0001
Body temperature (˚C)	37.8 (37; 38.3)	37.5 (36.6; 38)	37.9 (37.1; 38.5)	0.0088
WBC (x10^9/L)	6 (4.8; 7.9)	5.5 (4.2; 6.6)	6.3 (4.9; 8.3)	0.017
NLR	3.5 (2; 6.3)	2.7 (1.9; 3.9)	4.4 (2.2; 7.3)	0.0018
AST (U/L)	39 (27; 55.2)	27 (24; 47)	44 (32; 58.5)	<0.0001
ALT (U/L)	35 (22.8; 55)	27 (21; 48)	38 (24; 58)	0.058
LDH (U/L)	330 (248; 409.5)	249 (208; 340)	362.5 (281.2; 426)	<0.0001
CRP (mg/dL)	46.7 (14.8; 100.8)	12.3 (4.9; 48.8)	67.2 (29; 120.2)	<0.0001
eGFR (mL/min)	85.5 (68.3; 97.2)	92.8 (76.2; 105.8)	79.8 (66.4; 92.4)	0.0001
LoS	9.5 (6; 15)	-	9.5 (6; 15)	-
Transfer to ICU	4 (2.2)	-	4 (3.2)	-
NIV	32 (17.3)	-	32 (25.4)	-

Dichotomous variables were expressed as count (percentage) and continuous variables as median (interquartile range).

Abbreviations: BMI, body mass index; ED, Emergency Department; PaO$_2$/FiO$_2$, arterial oxygen partial pressure/fractional inspired oxygen; WBC, white blood cell count; NLR, neutrophil to lymphocyte ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HTN, arterial hypertension; CAD, coronary artery disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; LoS, length of stay; ICU, intensive care unit; NIV, non-invasive ventilation.

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At follow-up evaluation, 54 (29.2%) patients had shortness of breath or were tachypnoeic. 116 (62.7%) patients were malnourished or at risk for malnutrition, and approximately one quarter of patients achieved MoCA scores compatible with cognitive impairment, despite no known history of cognitive disorders. Psychiatric disturbances including anxiety, insomnia, or PTSD were observed in 83 (44.9%) patients (Table 2).

Hospitalised patients had a tendency towards a more important weight loss during disease and towards higher RR values, compared with patients discharged from the ED. Conversely, patients discharged from the ED had lower WHOQOL scores, reflecting a decreased quality of life, especially in the psychological domain. Anxiety and PTSD were more frequent among patients discharged from the ED (Table 2).

Table 2. Features at follow-up of COVID-19 patients.

Variable	All Cohort	Discharged from ED	Hospitalised	P
Time from hospital discharge to follow-up visit (days)	23 (20; 29)	26 (22; 33.5)	21.5 (19; 26.8)	0.00011
SBP (mmHg)	132.5 (123; 144.8)	130 (120; 141)	134 (125; 145)	0.17
DBP (mmHg)	78 (70; 85)	75 (70; 86)	80 (70; 85)	0.99
HR (bpm/min)	79 (70; 90)	80 (70.2; 91)	78 (70; 88)	0.43
RR (breaths/min)	16 (14; 20)	16 (14; 18)	18 (15; 20)	0.052
SpO$_2$ (%)	98 (97; 99)	98.5 (97.2; 99)	98 (97; 99)	0.016
Weight change (%)	-1.3 (-5; 1.4)	0 (-3.3; 2.1)	-2 (-5; 1.2)	0.074
Risk of malnutrition	106 (57.3)	25 (42.4)	81 (64.3)	0.008
Malnutrition	10 (5.4)	5 (8.5)	5 (4)	0.36
mMNA score	11 (9–12)	11 (8.5–12.5)	11 (9–12)	0.88
mMRC for dyspnoea scale				0.72
Mild dyspnoea	42 (22.7)	11 (18.6)	31 (24.6)	
Moderate dyspnoea	8 (4.3)	4 (6.8)	4 (3.2)	
Severe dyspnoea	5 (2.7)	2 (3.4)	3 (2.4)	
Very severe dyspnoea	3 (1.6)	1 (1.7)	2 (1.6)	
Tachypnoea	41 (22.2)	8 (13.6)	33 (26.2)	0.051
Uncontrolled BP requiring therapeutic change	40 (21.6)	14 (23.7)	26 (20.6)	0.78
WHOQOL				
Total	99 (90; 107.2)	93 (85; 105.5)	100 (92; 109)	0.081
Physical health/Level of independence	16 (13.7; 17.1)	14.9 (13.4; 17.1)	16 (13.7; 17.1)	0.47
Psychological	14.7 (13.3; 16.7)	13.3 (12; 16)	15.3 (13.3; 16.7)	0.0084
Social relations	16 (14.7; 17.3)	16 (13.3; 17.3)	16 (14.7; 17.3)	0.42
Environment	15 (13.5; 17)	14 (13; 16.5)	15 (13.5; 17)	0.32
VAS pain	77.5 (75; 90)	75 (75; 90)	80 (75; 95)	0.68
Cognitive impairment	47 (25.4)	11 (18.6)	36 (28.6)	0.26
Insomnia	51 (27.6)	20 (33.9)	31 (24.6)	0.32
Anxiety	55 (29.7)	23 (39)	32 (25.4)	0.046
PTSD	41 (22.2)	23 (39)	18 (14.3)	0.00054

Dichotomous variables were expressed as count (percentage) and continuous variables as median (interquartile range).

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SpO$_2$, peripheral oxygen saturation; mMNA, mini nutritional assessment; mMRC, modified Medical Research Council; WHOQOL, World Health Organization quality of life; VAS, visuo-analog scale; PTSD, post-traumatic stress disorder.

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Need of follow-up

The *need of follow-up*, defined as the presence at follow-up evaluation of at least one among RR >20 breaths/min, uncontrolled blood pressure requiring therapeutic change, moderate to very severe dyspnoea, malnutrition, or new-onset cognitive impairment, was present in 109 (58.9%) patients (Fig 2). This number rose to 126 (68.1%) when including PTSD. No significant difference in the *need of follow-up* was found between hospitalised patients (75 of 126, 59.5%) and patients discharged from the ED (34 of 59, 57.6%). Age predicted the *need of follow-up* at regression analyses in the entire cohort. Specifically, for each additional year of age, the odds of requiring post-discharge monitoring increased by 4% (Table 3). Univariable and multivariable regression analyses predicting the *need of follow-up* within the hospitalised population are described in Table 4.

RT analysis identified three variables, namely PaO$_2$/FiO$_2$ and BMI at ED presentation, and age, that robustly classified patients into risk groups for the *need of follow-up* after discharge,
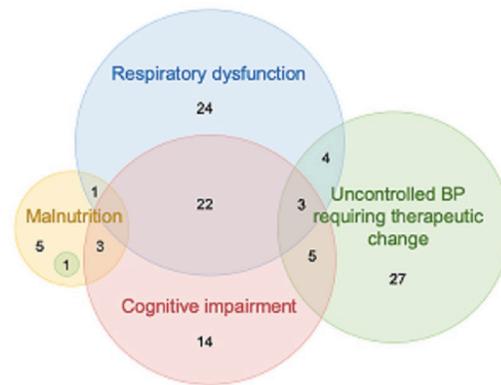
Fig 2. Prevalence of the main follow-up assessment measures. Respiratory dysfunction was defined as respiratory rate >20 breaths/min or modified Medical Council Research scale for dyspnoea ≥2. Depicted numbers indicate the absolute counts of patients in each set. One malnourished patient had uncontrolled blood pressure levels requiring a change in therapy. BP, blood pressure.

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Table 3. Univariable and multivariable logistic regression analyses predicting the *need of follow-up* within the entire cohort (n = 185).

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age (years)	1.040	1.013 to 1.061	0.0031	1.033	1.003 to 1.067	0.037
Female gender	1.76	0.94 to 3.37	0.085			
Ethnicity	1.42	0.61 to 3.95	0.45			
BMI (Kg/m^2)	1.033	0.97 to 1.10	0.30			
Comorbidities						
HTN	1.18	0.64 to 2.17	0.60			
CAD	0.68	0.20 to 2.25	0.51			
DM	1.15	0.46 to 3.04	0.78			
CKD	1.41	0.13 to 30.66	0.78			
Active cancer	0.35	0.016 to 3.67	0.39			
Psychiatric disorder	1.27	0.62 to 2.70	0.52			
At ED presentation						
PaO$_2$/FiO$_2$	0.99	0.98 to 0.99	0.002	0.99	0.99 to 0.99	0.054
Body temperature (°C)	1.12	0.81 to 1.55	0.50			
WBC	0.96	0.87 to 1.07	0.48			
NLR	1.026	0.96 to 1.011	0.48			
AST	1.00	0.99 to 1.01	0.73			
ALT	1.00	0.99 to 1.01	0.57			
LDH	1.00	1.0004 to 1.01	0.030	1.00	0.99 to 1.00	0.95
PCR	1.00	0.99 to 1.01	0.19			
eGFR	0.99	0.97 to 1.00	0.11			
Hospitalisation	1.081	0.57 to 2.02	0.81			

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; HTN, arterial hypertension; CAD, coronary artery disease; DM, diabetes mellitus; CKD, chronic kidney disease; ED, Emergency Department; PaO$_2$/FiO$_2$, ratio of arterial oxygen partial pressure to fractional inspired oxygen; WBC, white blood cell count; NLR, neutrophil to lymphocyte ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactic dehydrogenase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

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Table 4. Univariable and multivariable logistic regression analyses predicting the *need of follow-up* within the hospitalised cohort (n = 126).

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Age (years)	1.043	1.01 to 1.978	0.012	1.038	1.00 to 1.08	0.055
Female gender	1.61	0.71 to 3.79	0.26			
Ethnicity	0.90	0.19 to 4.74	0.90			
Comorbidities						
HTN	1.51	0.73 to 3.15	0.27			
CAD	0.88	0.19 to 4.65	0.87			
DM	1.26	0.45 to 3.89	0.67			
CKD	1.34	0.13 to 29.35	0.81			
Psychiatric disorder	1.25	0.50 to 3.27	0.64			
NIV	2.064	0.89 to 5.15	0.10			
Transfer to ICU	0.67	0.078 to 5.75	0.70			
LoS	1.017	0.97 to 1.074	0.53			

Abbreviations: OR, odds ratio; CI, confidence interval; HTN, arterial hypertension; CAD, coronary artery disease; DM, diabetes mellitus; CKD, chronic kidney disease; NIV, non-invasive ventilation; ICU, intensive care unit; LoS, length of stay.

and indicated the cut-offs that maximized the separation among the resulting patient clusters (RT 1, Fig 3). The three groups were: *low probability of need* ($PaO_2/FiO_2 \geq 324$ and age <63 years), *intermediate probability of need* ($PaO_2/FiO_2 <324$ and BMI lower than 33 Kg/m^2 or $PaO_2/FiO_2 \geq 324$ and age ≥ 63 years), and *high probability of need* ($PaO_2/FiO_2 <324$ and BMI ≥ 33 Kg/m^2). The ROC_{AUC} for RT 1 was 0.85. Most patients in the *low probability of need* group (65.5%) were discharged from the ED. The fraction of patients that had been hospitalised was higher in the other groups, reaching the totality of patients in the *high probability of need* group.
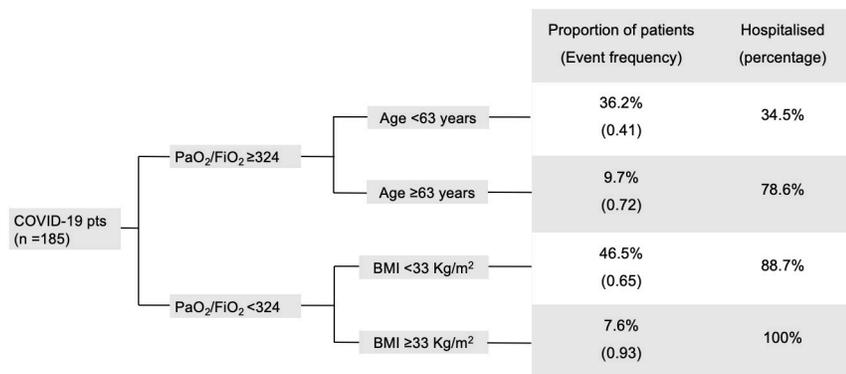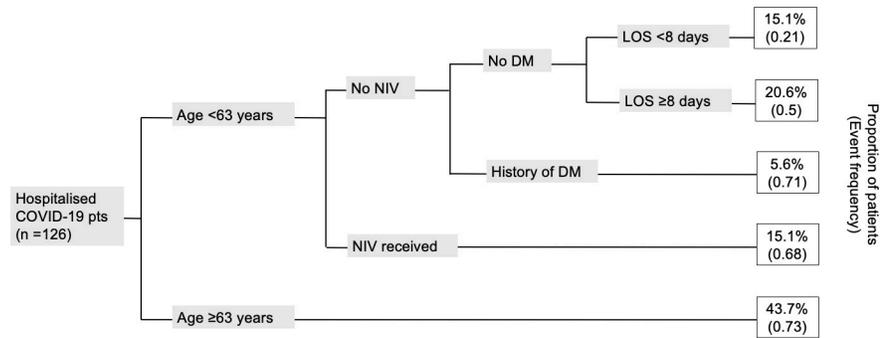

Fig 3. Regression tree analysis (RT 1) to predict the need of post-discharge follow-up among patients recovered from COVID-19. Event frequency defines the proportion of patients needing follow-up. The prevalence of hospitalisation in the obtained groups is depicted. Age, gender, ethnicity, history of hypertension, coronary artery disease, chronic kidney disease, diabetes mellitus, body mass index (BMI), axillary body temperature, ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2), aspartate transaminase, lactic dehydrogenase, and C-reactive protein at Emergency department presentation, and hospitalisation were included in RT 1 analysis. PaO_2/FiO_2 was available for 155 patients. BMI was available for 160 patients. Pts, patients. PaO_2/FiO_2, ratio of arterial oxygen partial pressure to fractional inspired oxygen. BMI, body mass index.

Fig 4. Regression tree analysis (RT 2) to predict the need of post-discharge follow-up among hospitalised patients recovered from COVID-19. Event frequency defines the proportion of patients needing follow-up. Age, gender, ethnicity, history of hypertension, coronary artery disease, chronic kidney disease, diabetes mellitus, administration of non-invasive ventilation, length of stay, and transfer to intensive care unit were included in RT 2 analysis. Pts, patients. NIV, non-invasive ventilation. LoS, length of stay.

When RT analysis was restricted to hospitalised patients (n = 126), four variables emerged as strong predictors of the *need of follow-up* (RT 2, Fig 4). Age, NIV administration, history of DM, and LoS stratified patients into three groups: *low probability of need* (age <63 years, no NIV administration, no history of DM and LoS <8 days), *intermediate probability of need* (age <63 years, no NIV administration, no history of DM and LoS ≥8 days), and *high probability of need* (age <63 years plus NIV or history of DM, or age ≥63 years). The ROC_{AUC} for RT 2 was 0.69.

PTSD

Decreasing age, female gender and positive psychiatric history were significantly associated with the risk of developing PTSD after COVID-19. Hospitalisation, instead, emerged as protective (Table 5). At multivariable analysis, only female gender and hospitalisation survived as independent predictors of PTSD occurrence. No significant impact was observed for BMI or other comorbidities on PTSD development (Table 5).

Table 5. Univariable and multivariable logistic regression analyses predicting PTSD within the entire cohort (n = 185).

	Univariate			Multivariate		
	OR	**95% CI**	**P**	**OR**	**95% CI**	**P**
Age (years)	0.97	0.94 to 0.99	0.041	0.98	0.95 to 1.02	0.39
Female gender	4.88	2.29 to 10.78	0.0001	4.03	1.76 to 9.47	0.0011
BMI (Kg/m²)	1.035	0.96 to 1.12	0.38			
Comorbidities						
HTN	0.48	0.20 to 1.05	0.075			
CAD	1.30	0.26 to 5.19	0.72			
DM	1.82	0.57 to 5.45	0.29			
Psychiatric disorder	2.34	1.04 to 5.26	0.039	2.14	0.86 to 5.28	0.098
Hospitalisation	0.25	0.11 to 0.53	0.0004	0.37	0.14 to 0.92	0.033
ARDS	0.49	0.21 to 1.10	0.09			

Abbreviations: PTSD, post-traumatic stress disorder; OR, odds ratio; CI, confidence interval; BMI, body mass index; HTN, arterial hypertension; CAD, coronary artery disease; DM, diabetes mellitus; ARDS, acute respiratory distress syndrome.

Discussion

Here, we present an early analysis of a multidisciplinary follow-up of patients recovered from COVID-19. Between 7 April and 7 May, 2020, 185 patients previously referred to our Institution for COVID-19 were evaluated. Patient characteristics at disease onset were faithful to previously described data [26–28].

Our analysis reveals that many patients, despite apparent clinical recovery at discharge, had clinically relevant medical problems when evaluated after approximately 3 to 4 weeks. For example, one third of them complained of dyspnoea, and 22.2% had a RR >20 breaths/min. Radiological signs of interstitial pneumonia have been described in COVID-19 [29]. Whether these alterations will persist remains to be established. Indeed, viral eradication does not preclude progression to parenchymal fibrosis, and data on pulmonary function after clinical recovery are urgently needed. Uncontrolled HTN was also highly prevalent in our cohort. This is consistent with the hypothesis that SARS-CoV-2 infection may be associated with chronic cardiovascular damage [30], and highlights the need of cardiovascular care in the management of COVID-19 patients.

As high as 68.3% of hospitalised patients were malnourished or at risk of malnutrition, as were 51.0% of patients managed at home. Malnutrition has been reported in hospitalised COVID-19 patients [31], and is likely due to systemic inflammation-related hypercatabolism [32]. ARDS survivors lose lean body mass during acute illness but gain fat mass in the first year after recovery, which may adversely affect functional outcomes [33]. Nutritional assessment and counselling are crucial to these patients. The finding that even patients managed at home were at risk of malnutrition is novel and warrants further investigation. Gastrointestinal symptoms [34] and smell and taste disturbances [35] associated with SARS-CoV-2 infection are possible mechanisms underlying this phenomenon.

We observed cognitive impairment in a quarter of our patients, despite no history of cognitive disorder. Cognitive *sequelae* of COVID-19 might be due to direct viral pathogenicity or immune-mediated mechanisms [8]. In line with a previous study [36], 22.2% of patients developed PTSD. Independent predictors were female gender, in agreement with the prevalence of the disorder in the general population [37], and hospitalisation, which had a protective effect. This might be due to psychosocial stressors such as lockdown and isolation at home, secluded from caregivers, and to a higher vulnerability to inflammation-induced mood and behavioural changes in women [38]. COVID-19 follow-up cannot be separated from an accurate cognitive and psychological monitoring [39].

To set up a follow-up outpatient clinic in times of emergency may be arduous. Apart from logistic difficulties, careful monitoring programs are energy- and time-consuming, and selection of patients who most likely benefit from follow-up programmes may be necessary. We found that older age is a strong predictor of the need of follow-up in both patients who were hospitalised and those who were discharged from the ED. Through recursive partitioning analysis, we identified a hierarchy of independent predictors able to estimate the odds of requiring follow-up after COVID-19. Accordingly, within the entire patient cohort, in addition to older age, lower PaO_2/FiO_2 values at ED presentation and obesity discriminated patients not to be lost at hospital discharge. Among hospitalised patients, priority should be given to patients older than 63 years, or to younger patients receiving NIV or with a history of DM, the latter being a known predictor of severity in viral infections, including COVID-19 [40]. In line with our results, age emerged as being an independent predictor of ARDS development in a previous report on severe acute respiratory syndrome (SARS) patients [41]. Likewise, metabolic syndrome-related conditions including obesity and diabetes were found to increase the risk of developing severe illness in patients with Middle East respiratory syndrome coronavirus

(MERS-CoV) infection [42, 43]. Although proving causality may be challenging, our findings reinforce the hypothesis that systemic metabolic derangement may precipitate coronavirus diseases, owing to the need of post-recovery monitoring. Potential mechanisms may include endothelial dysfunction, the proinflammatory state, as well as the dysfunctional innate immune response common to both metabolic and viral disorders [43–46].

A main limitation of our study is that instrumental exams were not included in patient monitoring. Nevertheless, clinical measures may be informative surrogates in times of crisis. Our Follow-up COVID-19 Outpatient Clinic was recently upgraded by adding spirometry, electrocardiography, and lung ultrasound in routine evaluations. Patients will be subsequently evaluated at 3 and 6 months from hospital discharge [47]. Another potential limitation is the lack of external validation of our regression tree models. On the other hand, the inclusion of a well characterized population monitored using uniform standards of care, and with the same healthcare access, minimizes the risk of ascertainment bias. Although information on treatment received during the acute phase was not available for all COVID-19 survivors, treatments in the outpatient setting were quite homogenous, whereas in the inpatient setting treatments other than those specifically used for COVID-19 were driven by illness severity, which in our analysis was accounted for by including variables such as administration of non-invasive ventilation, length of stay, and transfer to intensive care unit.

Our study suggests that COVID-19 may leave behind physical and psychological dysfunctions, whose underestimation may be costly in terms of long-term morbidity and mortality. Multidisciplinary follow-up of these patients is therefore crucial to avoid a second wave of late health problems associated with this pandemic. In this sense, selected patient subgroups should be prioritised.

Supporting information

S1 Dataset. The dataset employed for this manuscript.
(XLSX)

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