Alberto Preda[1*], Giorgio Fiore[1*], Carlo Gaspardone[1], Silvana Di Maio[1], Davide Romagnolo[1],
Lorenzo Rampa[1], Luigia Brugliera[2], Andrea Tettamanti[2], Carlo Meloni[2], Sandro Iannaccone[2]

[1]Clinical Cardiology Unit, IRCCS Ospedale San Raffaele, Milano, Italy
[2]IRCCS Ospedale San Raffaele, Milano, Italy
[*]A. Preda and G. Fiore equally contributed to this work and should be considered as shared first authors

Study on the utility and efficacy of clinical and instrumental tests in the follow-up of COVID-19 patients

Corresponding author:

Giorgio Fiore, Clinical Cardiology Unit,
IRCCS Ospedale San Raffaele, Milano,
Italy, e-mail: gio.fio@hotmail.it

ABSTRACT

Introduction: The disease caused by the SARS-CoV-2 virus (COVID-19) frequently leads to serious complications and prolonged hospitalizations requiring effective care after discharge.

Aim of the study: Aim of this study was to identify feasible and cost-effective predictors of outcome among clinical characteristics, functional status, laboratory, echocardiographic and lung ultrasound data of COVID-19 patients.

Material and methods: Patients affected by COVID-19 who experienced a prolonged hospitalization due to a severe form of the disease and that have been discharged from the COVID-19 rehabilitation unit (RU) were prospectively enrolled between April 6th and May 22nd, 2020. All the patients underwent a 6-minute walk test (6MWT) at the 30-day follow-up. Baseline characteristics, laboratory, functional exercise tests, echocardiographic and lung ultrasound (LUS) data collected between hospitalization, admission to RU, discharge from RU and follow-up were compared. Correlations with the predicted distance covered at the 6MWT (6MWD) were made.

Results: 40 patients met inclusion criteria and presented to follow-up (13 women [32.5%] and 27 men [67.5%]; mean age 66 ± 10 years). Among all variables analysed, only functional tests at discharge showed a remarkable correlation with the 6MWD. Significant improvement in lung ultrasound score (LUSS) was also observed however without correlation with 6MWD.

Conclusions: functional tests at discharge from RU identified patients with different 30-day outcomes that could deserve a stricter long-term follow-up. This may help in planning a personalized follow-up. The costs and effort were minimal. The severity of the acute phase did not significantly influence functional recovery. LUS was useful to identify subclinical lung damage and its evolution over time, however without clear functional correlation.

Key words: COVID-19, lung ultrasound, rehabilitation, SARS-CoV-2

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How these fit in:

— Little is known about the long-term functional status of discharged COVID-19 patients that experienced a severe disease needing rehabilitation.
— Given the variability of clinical pictures led by COVID-19 and the continuous increase of patients' discharge, cost-free and easy to use, efficient tools for planning the follow-up and stratify prognosis are needed.

— In a selected population of COVID-19 patients with loss of functional autonomy that required a rehabilitation period, commonest functional tests showed to correlate well with 6MWT performance at 30 days from discharge.
— Lung ultrasound sonography is a safe, feasible and cost-effective method to monitor lung damage over time.

Introduction

The coronavirus disease of 2019 (COVID-19) is a viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with large variability of clinical pictures [1]. Considering the high potential severity burden of long-term complications [2] and the need for prolonged hospitalizations [3], the establishment of rehabilitative departments dedicated to most compromised patients was deemed necessary [4–6]. In this context, an amount of literature discussing patient in-hospital management was published [7]. Nevertheless, remain a lack of evidence about adequate follow-up planning [8] because insight about the long-term clinical outcome and functional status is still missing [9, 10]. Considering the enormous number of outpatients to manage and the limited resources, the research should be oriented towards the identification of harmless, feasible and cost-effective tools that easily provide information on individual risk and help to select patients who need closer follow-up. Other than physiological characteristics, many laboratory and instrumental tests are used as risk predictors of mortality during hospitalization and at discharge [11], however without clear evidence of long-term benefit. Chest computed tomography (CT) is a critical tool for the diagnosis and inpatient management, with higher sensitivity than a swab sample [12] capable to identify lung alterations even at 60 days of follow-up [13] in asymptomatic individuals [14]. Despite this, it may not be a feasible method for the routine follow-up of discharged COVID-19 patients because of radiation exposure, costs, availability, and logistic issues. On the other hand, lung ultrasound sonography (LUS) appears to be a useful, rapid, harmless and low-cost alternative to CT, with similar sensitivity in COVID-19 [15, 16] and capable to identify subclinical residual lung damage in patients with severe COVID-19 that met discharge criteria [17]. Exercise tests and functional scales are quantitative validated tools to assess and train the functional reserve in several rehabilitation units, being useful to stratify patients risk according to their fitness. Among them, the 6 Minute Walk Test (6MWT) is a submaximal exercise test used to assess aerobic capacity and endurance, providing a measure of functional status and outcome in patients affected by different lung and cardiac diseases [18–20]. So far, the only test that found application in the context of the COVID-19 pandemic was the 6MWT, which demonstrated effectiveness in assessing oxygenation reserve in non-hypoxic patients at rest and help in looking for discharge preparedness [27, 28]. Moreover, in the largest cohort study with the longest follow-up available today, 6MWT at 6 months was decreased proportionally to the severity of illness [29]. This study aimed to identify feasible and cost-effective predictors of outcome among clinical characteristics, laboratory and functional tests, echocardiographic and LUS data in a selected high-risk cohort of COVID-19 patients who needed a rehabilitative recovery. This might help to identify frailer patients deserving a stricter follow-up strategy and to avoid the routine use, even during the acute phase of the disease, of useless laboratory and diagnostic tests with a huge waste of resources. The authors used the 6MWT as a functional endpoint, being this an effective, and easy to perform predictor of prognosis, largely validated in several lung and cardiac diseases [18, 19].

Material and methods

Study population

We prospectively enrolled consecutive COVID-19 patients who were hospitalized during the acute phase of the disease in the Emergency Room (ER), Intensive Care Units (ICU), Respiratory High Dependency Care Units (RHDCU) or Infectious Diseases units of the San Raffaele Hospital, that were subsequently admitted to a dedicated Rehabilitation Unit (RU) and underwent a 30-day post-discharge follow-up between April 6 and July 2, 2020. Criteria to admit COVID-19 patients in the RU were: positive swab for SARS-CoV-2, stable SatO$_2$ and respiratory rate, no need for respiratory assistance or no more than 2 l/min O$_2$, absence of fever, presence of areas of dependence at the FIM evaluation (FIM score < 100) [4]. For the present study, exclusion criteria were the presence of acute cardio-pulmonary or inflammatory conditions, not COVID-19 related (*i.e.,* acute heart failure, COPD exacerbation, pulmonary embolism), concurrent condition influencing functional tests (i.e., traumatic injury), patient refusal or loss at the 30-day follow-up and death. All patients gave their informed consent, and the study was approved by the local Ethics Committee.

Laboratory tests

Based on the reported haematological findings of COVID-19 patients, the following inflammatory indexes were considered: white blood cells (WBCs) and subtypes counts, C-reactive protein (CRP), serum ferritin, and D-dimer [30]. The N-terminal pro-brain natriuretic peptide (NT-proBNP) level was also assessed, which is an independent risk factor for in-hospital death in patients with severe COVID-19 [31]. Laboratory data were assessed during the hospitalization (acute phase of the disease) before admission to the RU and were part of the COVID-BioB Study [32].

Transthoracic echocardiography

Wide spectrum cardio-pulmonary involvement is common in COVID-19 [33]. Transthoracic echocardiography at discharge from RU and follow-up was performed by a trained cardiologist blinded to the patient's clinical characteristics, aimed at identifying signs of right ventricle (RV) dysfunction and/or pressure overload. The authors evaluated RV longitudinal systolic function by tricuspid annular plane systolic excursion (TAPSE) and lateral tricuspid annular tissue Doppler imaging (S' TDI). Pulmonary artery systolic pressure (PASP) was estimated by a sum of tricuspid regurgitation jet gradient and estimated right atrial pressure derived from analysis of the inferior vena cava (IVC) dimensions and response to inspiration. Images were obtained with GE VividS60 (GE-Healthcare, Chicago, Illinois) equipped with a 3Sc-RS sector transducer probe.

Lung US (LUS)

Lung US at admission and discharge from the RU and at 30-day follow-up was performed with the patient in a sitting position by a single trained operator blinded to the patient's clinical characteristics. Findings were classified according to a validated quantitative LUS Score (LUSS) [34]. Three areas per hemithorax were identified (anterior, lateral, and posterior) by using the anterior and posterior axillary lines as anatomical landmarks. Each area was then divided into two, superior and inferior [35]. Therefore, a total of 12 thoracic areas was considered. Each area was given a score from 0 to 3 according to the following criteria: 0, normal aeration; 1, more than 2 B-lines occupying 50% of the pleura or less; 2, more than 2 B-lines occupying greater than 50% of the pleura; and 3, tissue-like pattern. Therefore, the total LUSS ranged from 0 to 36. Lung US images were obtained with a Prosound α6 system (Hitachi Aloka Medical Systems, Tokyo, Japan) equipped with a UST-9123 convex transducer.

Functional evaluation

Functional status and independence in daily living activities were assessed at the admission of the RU, discharge from RU and 30-day follow-up with tests used in Rehabilitation Units and selected for this kind of patient [6]: 6MWT [36], TUG [21] and 30CST [23]. Timed up and go test (TUG) [21] is a measure of functional mobility validated in patients affected by chronic obstructive pulmonary disease and pulmonary arterial hypertension [22]. It evaluates the time a patient takes to rise from a chair, walk three meters, turn around, walk back to the chair and sit down. The Thirty-second chair-stand test (30CST) evaluates leg strength and endurance in older adults assessing the number of stands that a person can complete in 30 seconds [23, 24]. Activities of daily living (ADL) is commonly assessed using the Functional Independence Measure (FIM) scale, an 18-item measurement tool that explores the level of a patient's disability and indicates how much assistance is required for the individual to perform daily living activities [25]. By adding the points for each item (1 = total assist and 7 = complete independence), the level of independence ranges from 18 (lowest) to 126 (highest) [26]. The 6MWT can be expressed as absolute distance and percentage of the predicted 6-minutes walking distance (6MWD). A validated reference equation was used for the prediction of the total distance walked during six minutes for healthy adults [38]. The distance covered over a time of 6 minutes is used to compare changes in performance capacity.

Statistical analysis

For each continuous variable, normal distribution by the Shapiro-Wilk test was verified. Normally distributed variables were described as mean ± standard deviation while non-normally distributed ones were described as medians (interquartile range). The comparisons between groups were performed using t-tests or Wilcoxon sum-rank tests, as appropriate.

The categorical variables were described as frequencies (percentages) and compared by Chi-squared tests. The relationship between variables was exhibited by using the Spearman Rank Correlation coefficient. A two-sided P value < 0.05 was required for statistical significance. Data were analysed with R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Forty patients (13 women [32.5%] and 27 men [67.5%]; mean age 66 ± 10 years) met inclusion criteria and presented to the follow-up (Fig. 1). Baseline demographic and clinical characteristics of the population are reported in Table 1. Eighteen patients (45%) required ventilatory support during the acute disease phase. Comorbidities were present in 57.5% of patients, with hypertension being the most prevalent one (50%). 36 patients (90%) received at least 1 antimicrobial or immunosuppressant COVID-19 treatment, with hydroxychloroquine being the most frequent one (77.5%). Patients baseline characteristics, treatment during the acute phase (hospitalization), laboratory findings, functional tests, echocardiographic data and LUSS at discharge from RU were correlated with the distance covered at the 6MWT at the 30-day follow-up.
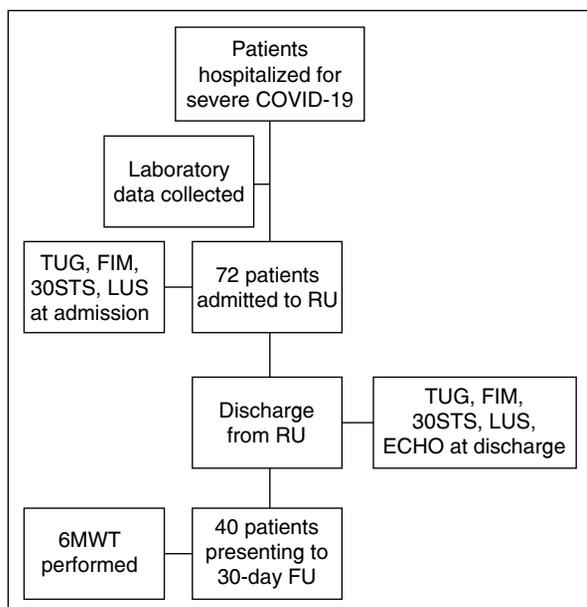
Figure 1. Flow diagram of study structure.
30 STS — 30 seconds sit-to-stand; TUG — time up-and-go; FIM — functional independence measure; LUS — lung ultrasound; ECHO — transthoracic echocardiography; RU — rehabilitation unit; FU — follow-up

(Tab. 3). Considering comorbidities, diabetes was associated with the worst performance at 6MWT (p = 0.02). Patients treated with lopinavir-ritonavir combination or IL-6 inhibitors performed significantly better at the 6MWT at follow-up. No difference was observed between patients treated with other drugs. Eighteen patients (45%) scored a 6MWT lower than the predicted for age, weight and height. Interestingly, a patient needing ventilatory support during the acute phase did not perform worse at the 30-day 6MWT (p = 0.399). Regarding functional evaluation, this analysis showed that all TUG, FIM and 30CTS at discharge from RU significantly correlated to the 6MWD at follow-up (Tab. 3, Fig. 2) and markedly improved throughout the observation period from discharge from RU to the 30-day follow-up (Tab. 2). No correlation was found between laboratory tests, echocardiographic parameters at discharge from RU and follow-up and the distance covered at the 6MWT.

Similarly, no correlation was observed between LUSS at discharge from RU, LUSS at follow-up and 6MWT. About Lung US findings, median LUSS at follow-up was significantly lower when compared with LUSS at discharge from RU (8.0 *vs.* 3.0, p < 0.001; Tab. 2). The same trend was observed both in patients that needed ventilatory support during the acute phase of the disease (8.0 *vs.* 4.0 p < 0.001) and those who did not (2.5 *vs.* 0.0 p = 0.05) and it was significantly higher in the first group at discharge from RU and follow-up

Table 1. Baseline demographic and clinical characteristics of the population

Variable	
No. Patients, n	40
Age, mean ± DS	66 ± 10
Female, n (%)	13/40 (32.5%)
Body mass index, Kg/m2 ± DS	25.7 ± 4.9
Current smoking status, n (%)	3/40 (7.5%)
Need for endotracheal intubation (n%)	18/40 (45%)
6MWT lower than the predicted	18/40 (45%)
Comorbidities, n (%)	
Hypertension	20/40 (50%)
Diabetes	9/40 (22.5%)
Chronic obstructive lung disease	2/40 (5%)
Coronary artery disease	5/40 (12.5%)
Chronic kidney disease	5/40 (12.5%)
Chronic therapy with ACE-i or ARBs	16/40 (40%)
COVID-19 treatment, n (%)	
Hydroxychloroquine	31/40 (77.5%)
Antibiotics (Azithromycin)	20/40 (50.5%)
Antiviral drugs (Lopinavir — Ritonavir)	26/40 (65%)
IL-1 inhibitor (Anakinra)	4/40 (10%)
IL-6 inhibitors (Tocilizumab, Sarilumab)	7/70 (10%)
Laboratory findings at discharge, median (IQR)	
White blood cell count, ×109/L	5.7 (2.7)
Lymphocyte count, ×109/L	1.7 (1.0)
C-reactive protein, mg/L	5.95 (7.7)
Serum ferritin, μg/L	401.50 (650)
D-dimer, μg/L	0.42 (0.305)
NT-pro-BNP, pg/mL	167 (461)

ACE-I — Angiotensin-converting enzyme inhibitors; ARBs — Angiotensin II receptor blockers; COVID-19 — coronavirus disease 2019; IL — Interleuchine

(Fig. 3). A positive trend from admission to RU (median 8, IQR 9) to discharge from RU (median 8, IQR 8, p = 0.0413) was also found.

Discussion

Summary

Our study led to the following results: 1) Among a variety of clinical, laboratory and instrumental data in a selected population of Covid-19 patients with loss of

Table 2. LUSS, echocardiography and functional test findings of patients at discharge from COVID-19 Rehabilitation Unit and after 30 days

Variable	Discharge	Follow-up	P-value
Lung ultrasound, median (IQR)			
LUS score, points	8 (8)	3 (5.75)	< 0.001
Transthoracic echocardiography of the RV, mean ± DS			
Estimated PASP, mmHg	28.9 ± 4.8	27.2 ± 8.0	0.328
TAPSE, mm	23.3 ± 4.6	21.5 ± 4.6	0.092
Lateral tricuspid S' TDI, cm/s	17.5 ± 4.5	14.8 ± 4.4	0.008
Functional Tests, median (IQR)			
30 STS test, No. of repetitions	10.5 (5)	12 (6)	0.0036
TUG test, seconds	11 (5)	9 (5)	0.00038
FIM scale, points	110 (14.5)	125 (7.75)	< 0.00001

Bold for statistically significant values at p < 0.05. IQR — interquartile range; LUS — lung ultrasound; RV — right ventricle; PASP — pulmonary arterial systolic pressure; TAPSE — tricuspid annular plane systolic excursion; TDI — tissue doppler imaging 30 STS, 30 seconds sit-to-stand; TUG — time up-and-go; FIM — functional independence measure

functional autonomy that required a rehabilitation period only functional evaluation through TUG, FIM and 30CTS showed to correlate well with the prognosis evaluated by 6MWT at 30 days from discharge; 2) the severity of the acute phase of the disease did not influence functional recovery; 3) LUSS significantly improved from admission to RU to discharge form RU and 30-day follow-up, however without functional correlation at the 6MWT.

Follow-up and long-term outcome of severe COVID-19 patients

Nowadays there is a poorness of shared strategies for the follow-up of patients that suffered from severe COVID-19 requiring strict monitoring. There is also little knowledge about functional long-term outcomes, the presence of residual lung damage and its clinical correlation. In this pilot single-centre study, even limited by low sample size and a short-term follow-up, it was looked for a correlation between a variety of clinical and functional tests, evaluated before discharge from the rehabilitation unit of the hospital, and the functional outcome using the 6MWT, a simple, economic, reproducible and largely validated prognostic predictive test. In a population of patients that presented with clinical indications for functional rehabilitation (FIM < 100) shortly after the onset of the disease and immediately after the acute phase of the infection, this analysis showed that functional tests performed at discharge (TUG, 30-CTS, FIM) positively correlated with the distance covered at the 6MWT at the follow-up, helping to identify frailer patients needing a stricter and personalized follow-up strategy after discharge. On the other hand, no laboratory test before discharge (white blood cell and subtype counts, C-reactive protein, serum ferritin, D-dimer and

N-terminal pro-brain natriuretic peptide) nor echocardiographic parameters (right ventricular function, PASP) correlates with 6MWD at the 30-day follow-up.

Ventilatory support and functional recovery

An interesting aspect that emerged from this analysis is that patients that needed ventilatory support during the acute phase of the disease, experiencing a more severe pulmonary involvement also confirmed by higher LUSS, performed worse at the 30-CTS test before discharge, but no difference emerged at the 30-day follow-up. Similarly, there was no difference between the two groups and the 6MWT performance at the 30-day follow-up. This result may signify that the severity of the acute phase, once discharge criteria are met, does not influence the functional long-term outcome. This data is in line with a recent study that highlighted the incongruity between the severity of respiratory disease and cognitive outcome [38]. The authors hope that this notable acknowledgement would be confirmed in larger population observational studies.

Lung ultrasound in the follow-up of discharged patients

Lung ultrasound is a central tool for the diagnosis and management of hospitalised COVID-19 patients, owning several advantages in terms of safety, costs, comfort and availability in respect to radiological instruments [6, 26, 27]. In the present study, the 30-day LUSS was significantly lower compared to LUSS at discharge. Thus, there was a clear reduction of parenchymal involvement within 30 days both in the group of patients that needed mechanical ventilation and those who did not. Furthermore, patients experiencing a more severe

Table 3. Correlations between variables in the study and the percentage of the predicted value of 6 minutes walking test

Qualitative Variables	P-value
Need for endotracheal intubation	0.399
Current smoking status	0.082
Chronic therapy with RAAS Inhibitors	0.98
Comorbidities	
Hypertension	0.37
Diabetes	0.02
Chronic obstructive lung disease	0.91
Coronary artery disease	0.09
COVID-19 treatment	
Hydroxychloroquine	0.36
Antibiotics (Azithromycin)	0.31
Antiviral drugs (Lopinavir–Ritonavir)	0.059
IL-1 inhibitor (Anakinra)	0.82
IL-6 inhibitors (Tocilizumab, Sarilumab)	0.027
Quantitative Variables	**r coefficient**
Body mass index	0.4
Laboratory findings at discharge	
White blood cell count	–0.2
Lymphocyte	–0.2
C-reactive protein	–0.14
D-dimer	–0.04
Serum ferritin	0.004
NT-pro-BNP	–0.21
Lung Ultrasound	
LUSS at discharge	–0.04
LUSS at follow-up	–0.14
Echocardiography of the RV at discharge	
Estimated PASP	0.52
TAPSE	0.24
Lateral tricuspid S' TDI	0.04
Echocardiography of the RV at Follow-up	
Estimated PASP	–0.16
TAPSE	0.22
Lateral tricuspid S' TDI	0.37
Functional Tests at discharge	
30 STS test	0.58 (95CI 0.25–0.79; p = 0.002)
TUG test	–0.66 (95CI 0.42–0.82; p < 0.001)
FIM scale	0.57 (95CI 0.30–0.75; p < 0.001)
Functional Tests at follow-up	
30 STS test	0.65
TUG test	–0.55
FIM scale	0.48

Discharge refers to discharge from the rehabilitation unit. Bold for statistically significant values at p < 0.05. RAAS — Renin Angiotensin Aldosterone System; COVID-19 — coronavirus disease 2019; IL — Interleuchine; LUS — lung ultrasound; RV — right ventricle; PASP — pulmonary arterial systolic pressure; TAPSE — tricuspid annular plane systolic excursion; TDI — tissue doppler imaging; 30 STS — 30 seconds sit-to-stand; TUG — time up-and-go; FIM — functional independence measure

$p < .001$
$R = -0.75$
$R^2 = 0.56$
$y = 185 - 46x$
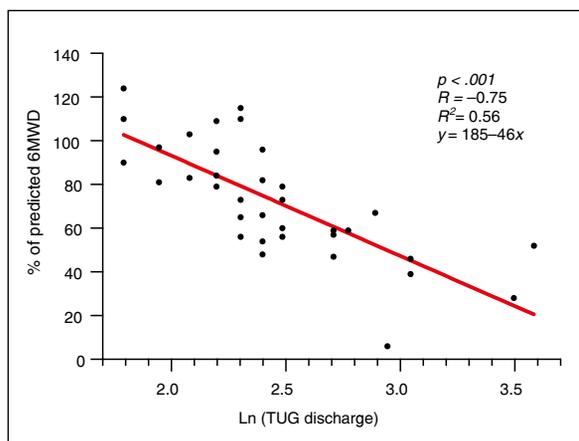
Figure 2. Correlation between TUG (values expressed as natural logarithm) and the distance covered at 6MWT
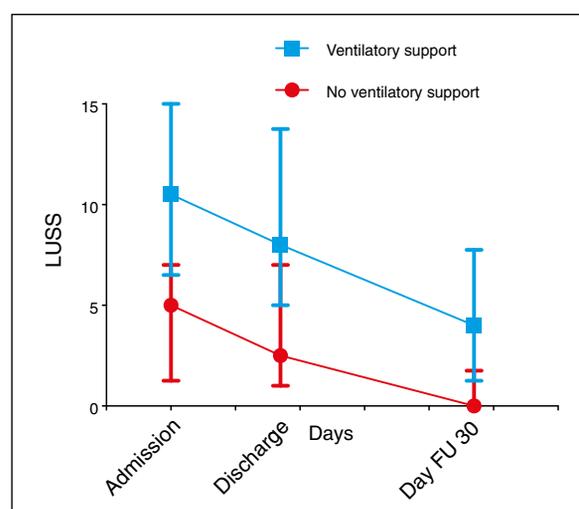
Figure 3. Median LUSS from admission to discharge and follow-up in patients needing and not needing ventilatory support during the acute phase of the disease. The median LUSS was higher in patients needing ventilatory support ($p < 0.05$)

disease (needing ventilatory support) had a higher LUSS at the admission of the RU, discharge from RU and 30-day follow-up. However, no correlation was found between LUSS at discharge, LUSS at follow-up and 6MWT. This interesting result may be explained by the high sensitivity of the method, revealing residual lung involvement even without clinical and/or functional correlation.

Implications for research and/or practice

Most of the tests commonly used to predict outcome in COVID-19 during the acute phase failed in predicting

the long-term outcome availed at the follow-up by the 6MWT, a well-validated predictor of mortality. Therefore, new risk predictors to consider for customized follow-up planning aimed at the optimization of available resources may be needed. Routine use of instrumental or expensive tests (i.e., pro-BNP, echocardiography, contrast-enhanced CT, LUS etc.) in the absence of specific condition (i.e., heart failure, signs of pulmonary hypertension, pulmonary embolism) should be avoided, as they failed to correlate with the clinical and functional outcome of the patient and, as in the case of echocardiogram, may raise the risk of infection spread among healthcare professionals. On the contrary, all the functional tests that were considered (TUG, 30CTS, FIM) seemed to be the most useful and strongest predictors of outcome at 30-day.

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