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DECLARATIONS

Ethics approval and consent to participate

The study was approved by the Institutional Review Board (IRB) of the study coordinator centre (Maggiore Hospital, Bologna, Italy, approval number: 273/2020/OSS/AUSLBO) and by each institutional review committee of the participating hospitals. Informed consent was waived for unconscious patients while it was acquired for conscious patients or after liberation from mechanical ventilation or at the time of follow-up. The researchers analysed anonymized individual data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets related to the Italian population used and/or analysed during the current study are available at doi: 10.17632/krvnn6dzjx.1

Competing Interests

Harri Sintonen is the developer of the 15D and obtains royalties from its electronic versions. The other Authors have nothing to disclose

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Authors Contributions

LG, SS, GZ, CC, EG and CAM conceptualized and designed the work. DC, TT, VA, FB, GM, IC, FD, MF, GG, CL, MCL, ML, AM, RP, AP, JM, ST, MM, AFF, RN, VMR, ER acquired and interpreted the data.

DA and LG performed the statistical analysis. LG, CAM and IP drafted the article. HS, SS, GS and CAV substantively revised the article.

The ICU-RER COVID-19 collaboration was involved in data collection (see acknowledgements)

All the Authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved.

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Abstract

Background

Health-related quality of life (HRQoL) impairment is often reported among COVID-19 ICU survivors, and little is known about their long-term outcomes.

We evaluated the HRQoL trajectories between 3 months and 1 year after ICU discharge, the factors influencing these trajectories and the presence of clusters of HRQoL profiles in a population of COVID-19 patients who underwent invasive mechanical ventilation (IMV). Moreover, pathophysiological correlations of residual dyspnea were tested.

Methods

We followed up 178 survivors from 16 Italian ICUs up to one year after ICU discharge. HRQoL was investigated through the 15D instrument. Available pulmonary function tests (PFTs) and chest CT scans at 1 year were also collected. A linear mixed-effects model was adopted to identify factors associated with different HRQoL trajectories and a two-step cluster analysis was performed to identify HRQoL clusters.

Results

We found that HRQoL increased during the study period, especially for the significant increase of the physical dimensions, while the mental dimensions and dyspnea remained substantially unchanged. Four main 15D profiles were identified: full recovery (47.2%), bad recovery (5.1%) and two partial recovery clusters with mostly physical (9.6%) or mental (38.2%) dimensions affected. Gender, duration of IMV and number of comorbidities significantly influenced HRQoL trajectories. Persistent dyspnea was reported in 58.4% of patients, and weakly, but significantly, correlated with both DLCO and length of IMV.

Conclusions

HRQoL impairment is frequent 1 year after ICU discharge, and the lowest recovery is found in the mental dimensions. Persistent dyspnea is often reported and weakly correlated with PFTs alterations.

Highlights

- Little is know about HRQoL long term evolution in COVID-19.
- In COVID-19 patients requiring ICU, HRQoL is impaired 1 year after acute phase;
- the lowest recovery 1 year after COVID-19 emerged in mental dimensions;
- persistent dyspnea is reported in more than 50% of patients 1 year after COVID-19.
- Impairment in pulmonary function weakly explains the entity of dyspnea complained.

MAIN TEXT

Introduction

As of the end of August 2021, the COVID-19 pandemic resulted in more than 4 million deaths worldwide [1], and it considerably increased the need for healthcare resources dedicated to the acute phase of the syndrome, posing a hard challenge to the national health systems [2].

A series of somatic and psychological consequences are described among survivors, including pulmonary function impairment, such as a reduction in forced vital capacity (FVC) and diffusion capacity of lungs for carbon monoxide (DLCO) [3], neuropsychiatric disorders [4], and cardiac sequelae [5]. The most frequently complained persistent symptoms are dyspnea [6,7] and fatigue, as well as anxiety, depression, and sleep problems, which could significantly undermine the health-related quality of life (HRQoL) of these patients, and together identify the so-called long-COVID syndrome [4,8].

Moreover, patients who underwent ICU admission for COVID-19 related ARDS (C-ARDS) may also experience post-intensive care syndrome (PICS), which eventually overlaps other symptoms related to COVID-19 itself [9].

Little is known about the long-term HRQoL of patients who underwent invasive mechanical ventilation (IMV) for COVID-19 pneumonia, and no studies have yet investigated if the persistence of symptoms is associated with long-term pulmonary function impairment in this particular population.

This study reports the results of the second follow-up (1 year) of a population of C-ARDS survivors who required ICU admission, intubation, and IMV [10], and who were previously evaluated at 3 months after ICU discharge [11]. The primary objective of this study was to describe the HRQoL trajectories between 3 months and 1 year after ICU discharge. Moreover, we defined clusters of patients based on their HRQoL profiles at 1 year and investigated the factors influencing the recovery trajectories of the survivors.

Finally, a subgroup analysis was performed for patients having pulmonary function tests available between 9 and 12 months after ICU discharge to evaluate the relationship between the persistence and entity of dyspnea and pulmonary function.

Material and methods

This prospective multicenter observational study involved 16 Italian ICUs. Patients admitted to the participating ICUs from 22nd February through 4th May 2020 (the end of lockdown in Italy), who survived hospital discharge were subsequently followed up until one year after ICU discharge.

The study was approved by the Institutional Review Board (IRB) of the study coordinator centre (Maggiore Hospital, Bologna, Italy) and by each institutional review committee of the participating hospitals. Informed consent was asked at the time of the first follow-up if not obtained during ICU stay according to the approval of the local Ethics committee, and researchers analyzed anonymized data. The study was registered in ClinicalTrials.gov (NCT04411459).

Data Collection

Data were collected in an electronic case report form developed by YGHEA, CRO division of Ecol Studio SPA (Bologna Operational Headquarters), and hosted by Actide Nubilaria (Novara, Italy). Collected data comprised demographic data, comorbidities, and ICU-related variables such as SAPS II and SOFA score at ICU admission and the severity of ARDS following the Berlin criteria [12]. Social related variables recorded were: marital status, occupational status, and instruction degree. Residual symptoms at 1 year evaluated were: dyspnea measured with the modified Medical Research Council (mMRC) scale [13], arthromyalgia, palpitations, cough.

Follow-up pulmonary function tests (PFTs) data were collected for tests performed between 9 and 12 months after ICU discharge and consisted of: forced expiratory volume in the first second (FEV_1), FVC, FEV_1/FVC ratio, and DLCO. Follow-up CT scan data between 9 and 12 months after ICU discharge were also recorded, in particular concerning the presence of signs of fibrosis, residual ground glass, and atelectasis.

HRQoL was measured at 3 months and 1 year by telephonic interview and administration of the 15D instrument.

The 15D instrument

The 15D instrument (http://www.15d-instrument.net/15d/) is a generic, 15-dimensional multiutility instrument assessing different aspects of HRQoL (including mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity).

The respondents are required to answer about their state of health at the moment of the interview, and each answer is scored on a 5 points scale, with 1 being the best value and 5 being the worst [14]. The valuation system is based on an application of the multiattribute utility theory. The single index score (15D score), representing the overall HRQoL on a 0-1 scale (1=full health, 0=being dead) and the dimension level values, reflecting the goodness of the levels relative to no problems on the dimension (=1) and to being dead (=0), are calculated from the health state descriptive system using a set of population-based preference or utility weights. Mean dimension level values are used to draw 15D profiles for groups. The minimum clinically important change or difference in the 15D score has been estimated to be ± 0.015 on the basis that people can on average feel such a difference [15].

The 15D scores are shown to be highly reliable, sensitive and responsive to change, there is a considerable degree of agreement between health state valuations from several European countries [11], and these latter are generalizable at least in Western-type societies [14,16].

Statistical Analysis

Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range (IQR) when appropriate, and comparisons were performed with Student's t-test or Mann-Whitney U test when

appropriate. One way analysis of variance (ANOVA) and Kruskal-Wallis ANOVA were used to compare means and medians in the multiple HRQoL clusters. Categorical variables were expressed as numbers and percentages and compared using the Chi-square test or Fisher exact test. To evaluate the modifications of the 15D score and its dimensions throughout the study period, a paired-samples t-test was adopted.

Since the 15D value can be calculated only if all the 15 dimensions values are available, patients with three or more missing dimensions were excluded from the analysis while a multiple imputation technique was adopted when information regarding less than three dimensions was missing [14].

Two-Step cluster analysis, an exploratory tool designed to reveal natural groupings (clusters) within a dataset, was adopted to define the presence and number of HRQoL profile clusters one year after ICU discharge. This selection procedure allows both categorical and standardized continuous variables and it is fairly robust even when the assumptions of independence and normality of distribution of the variables are violated [17]. To determine the best number of clusters automatically, the indicators BIC (Schwarz's Bayesian Information Criterion) or AIC (Akaike's Information Criterion) are calculated for each number of clusters from a specified range. Automatic clustering was performed based on the 15 dimensions of the 15D instrument, the distance between clusters was calculated using the log-likelihood distance and both AIC and BIC were used to evaluate the best number of clusters.

A linear mixed-effects model was used to determine which factors predicted changes in HRQoL between 3 months and 1 year after ICU discharge using different demographic, ICU-related, and social variables as fixed effects and subject-level random effects while 15D score measured at 3 months and 1 year was the dependent variable. Fixed effects associated with 15D score change with a $p < 0.2$ in the univariate analyses were introduced in the final multivariate model.

Finally, to assess eventual correlations between the 15D breathing score and mMRC scale with pulmonary function tests and ICU stay-related variables, bivariate Spearman correlation tests were performed.

P-values < 0.05 were considered statistically significant, and all tests were two-sided. All data were analyzed using SPSS Statistics 26 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.) and RStudio (RStudio Team 2020. RStudio: Integrated Development for R. RStudio, PBC, Boston, MA).

Results

Of the 470 patients initially enrolled in the study, 282 (60%) were discharged alive from the ICU and 205 (43.6%) were followed up at 3 months after ICU discharge.

Four (2%) out of the 205 patients who were initially interviewed, died between three months and 1 year after ICU discharge, while another 23 (11.2%) were lost to follow-up, therefore, the final follow-up cohort was represented by 178 patients (86.8%). The main characteristics of the study population are described in Table 1, while supplement figure 1 shows the flow of patients throughout the study.

Globally, patients were mostly males (n=129, 72.5%), and had a median age of 64 years (IQR 55-70), the median number of comorbidities was one (IQR 0 - 1) and the most frequent were hypertension (n=88, 49.4%),

and diabetes (n=28, 15.7%). The median length of invasive mechanical ventilation was 16 (IQR 10 - 27) days, and the median ICU stay was 23 (IQR 15 - 35) days.

The multiple imputation technique was adopted only for replacing missing values in the sleeping (n = 2, 1.1%) and sexual activity (n = 37, 20.8%) dimensions.

Table 2 shows the mean values for each of the 15D dimensions at 1 year. Globally, the 15D score significantly increased during the study period, with mean values increasing from 0.857 to 0.880 (p = 0.006). The change was clinically important since it is above the threshold of ± 0.015 [15].

Most of the increase in HRQoL between 3 months and 1 year was related to physical dimensions (mobility, eating, excretion, usual activities, and sexual activity), while the psychological and breathing dimensions were substantially unchanged (Figure 1).

The two-step cluster analysis identified three different clusters based on BIC and four different clusters based on AIC (see supplement tables 1 and 2). Based on the clinical relevance of the clustering process, AIC-based clustering was chosen. Figure 2 shows the 15D dimensions values among the four different clusters, 84 patients (47.2%) were classified in the "full recovery" group (15D score = 0.964 ± 0.033), and 9 patients (5.1%) were classified in the "bad recovery" group (15D score = 0.572 ± 0.112).

Finally, two different clusters of intermediate recovery were distinguished: 68 patients (38.2%) were classified in a cluster of "partial recovery with mental dimensions most affected" while 17 patients (9.6%) were grouped in a cluster of "partial recovery with physical dimensions most affected". These two intermediate clusters did not significantly differ in terms of absolute 15D score, but only in terms of 15D profiles. The partial recovery-physical cluster indeed demonstrated significantly lower mean values in the hearing and excretion dimensions but higher values for sleep, discomfort, depression, and distress values. Patients grouped into the four clusters demonstrated different characteristics concerning age, the median number of comorbidities and prevalence of hypertension, and diabetes (Table 2), with those in the partial and bad recovery clusters being older and affected by more comorbidities.

Most of the patients reported persistent symptoms 1 year after ICU discharge, of which dyspnea (n=104, 58.4%) and arthromyalgia (n=62, 34.8%) were the most frequent. The prevalence of symptoms and the severity of dyspnea measured with the mMRC scale demonstrated significant differences in distribution across the four clusters, with the bad recovery and partial recovery demonstrating a significantly higher prevalence of persistent symptoms and more severe dyspnea.

Univariate linear mixed-effects model analyses selected sex, age, BMI, number of comorbidities, duration of IMV, and tracheostomy for introduction in the multivariate model. The final multivariate model demonstrated that the male gender was associated with a higher increase in HRQoL from 3 to 12 months after ICU discharge while the increase in the duration of IMV and number of comorbidities were negatively associated with HRQoL change (Table 3).

Pulmonary function tests at 1 year were available for 68 patients (Table 4), 35 of these (51.5%) had a reduction in DLCO values (DLCO lower than 80% of the predicted), while 12 out of 68 (17.6%) showed a restrictive

ventilatory defect (FVC lower than 80% of the predicted). Only 2 patients (0.5%) showed an obstructive ventilatory impairment ($FEV_1/FVC < 0.7$).

Median PaO_2/FiO_2 ratio nadir during the first five days of IMV was significantly lower in patients showing restrictive ventilatory abnormality (81, IQR 69 - 108 vs 112 IQR 83 - 150, p = 0.020), while this difference was not observed about DLCO. On the other hand, DLCO impairment was more frequent in the subgroup with partial or bad recovery compared with the subgroup reporting good recovery (Table 4), and the mean 15D score was significantly lower among those patients showing DLCO impairment (0.881± 0.105 vs 0.933± 0.075, p=0.022).

Finally, bivariate Spearman correlations showed that the 15D breathing dimension at one year after ICU discharge was significantly correlated with both DLCO and duration of IMV, even if the strength of these associations was low ($\rho = 0.244$ and -0.162, respectively), while the degree of dyspnea measured with mMRC scale was significantly correlated only with the duration of IMV ($\rho = 0.204$).

Only 37 out of 178 patients had a chest CT scan performed within 9 months and 1 year after ICU discharge, therefore data are only reported in supplement table 3, pulmonary fibrosis signs were observed in 26 (70.3%) of the available CT scans, while non-fibrosing signs such as persistent ground-glass opacities or consolidations in 15 (40.5%) patients.

Discussion

Approximately half of the mechanically ventilated ICU patients subsequently develop PICS [18], a multidimensional syndrome that concerns both the physical and psychological traits of the survivors. Signs of persistent impairment in these traits could be found up to two years after ICU discharge among ARDS patients [19,20]. The COVID-19 pandemic produced waves of ICU survivors at risk of developing both PICS and long-COVID syndrome, moreover, these patients experienced ICU stay in a healthcare system sustaining profound structural and organizational changes in response to the pandemic.

In this cohort of COVID-19 survivors who underwent ICU admission and IMV, we found that: a) HRQoL significantly increased from 3 months to 1 year after ICU discharge; b) this increase was mainly due to an increase in physical dimensions scores, while mental and breathing dimensions scores remained substantially unchanged; c) four main clusters of HRQoL profiles could be identified, two groups at the extremities of the sample showing good and bad recovery and two distinct groups with partial recovery, a larger one showing more severe alterations in mental dimensions, and a smaller group with alterations in physical dimensions; d) factors influencing HRQoL trajectories between 3 months and 1 year were: sex, duration of IMV and number of comorbidities; e) dyspnea remains the most reported symptom in ICU survivors and it is only partially explained by pulmonary function tests.

Health-related quality of life trajectories

Due to the lack of long-term information about COVID-19 sequelae, there is currently no consensus about follow-up measures after hospital discharge for COVID-19 patients [21]. Moreover, the follow-up of these

patients could be furtherly complicated by the health systems overload due to the repeated pandemic waves and by the need to recover ordinary activity for non-COVID diseases [22]. A recent online survey evidenced both physical and mental sequelae one year after COVID-19 syndrome for both survivors and their relatives, with age, sex, distance from COVID-19 diagnosis, and length of hospital stay being significant predictors of HRQoL impairment [23].

This is the first literature report specifically focusing on ICU survivors who required IMV and our results strengthen the information that more than half of C-ARDS survivors report significant impairment in HRQoL and persistent symptoms, in particular dyspnea, at 1 year after ICU discharge. In fact, despite a significant increase in HRQoL from 3 months to 1 year after ICU discharge being evidenced, only 47.2% of the patients showed a complete recovery at 1 year after ICU discharge with 15D values comparable to those of the general population [11,24].

We have to underline that only physical functioning dimensions showed a significant improvement in this time frame, while mental dimensions remained substantially unchanged. This aspect is confirmed by previous literature about ARDS survivors demonstrating a slower recovery in psychological dimensions [25,26]. Therefore, a significant proportion of patients (38.2%) with partial recovery showed a long-lasting impairment in mental dimensions. Specific COVID-19 ICU policies about isolation and visits from relatives, in particular for patients admitted during the first wave, could have had a role in worsening this aspect, and this should probably demand different visiting policies and psychological support during hospital stay [27].

Several factors influenced the slope of HRQoL trajectories. In our previous study at 3 months after ICU discharge [11], we found that increasing age resulted negatively associated with HRQoL scores. Indeed, in the current follow-up, the "bad recovery" cluster showed a higher median age (Table 1). Older age, however, did not significantly influence the entity of HRQoL change towards the study period, which was instead significantly affected by the number of comorbidities and duration of IMV, like in available follow-up literature for other diseases [28]. Male sex was associated with a greater increase in HRQoL over time, this is possibly related to gender-based different shapes of the HRQoL trajectories already reported in the literature [29].

The absence of association between young age and HRQoL trajectories is another clinically relevant aspect because it underlines that even young patients, often missed at follow-up, could have significantly hampered recovery trajectories and could benefit from a longer follow-up and specific interventions. Finally, the impairment in mental dimensions has been demonstrated to be significant and long-lasting [30], therefore, psychological advice may be considered when planning the follow-up. Moreover, a not negligible fraction of patients reported dyspnea and a variable degree of impairment in pulmonary function tests that should be furtherly discussed.

Persistent dyspnea and pulmonary function tests

We reported a very high prevalence (58.4%) of persistent dyspnea at 1 year after ICU discharge in comparison to that reported from papers, this phenomenon could be explained by the fact that our population was made by critically ill patients (ICU survivors) and not by a mixed population of critical and non-critical COVID-19 patients [3]. Analogously, the 15-D breathing dimension score significantly contributed to the reduction in HRQoL at 3 months, and it did not significantly improve during the study period (see Figure 1 and Table 2).

Most of the survivors showed some kind of impairment in both DLCO (51.5%) and FVC (17.6%) values, in line with previous literature about ARDS survivors patients [31]. In particular, in our study, reduction of FVC was significantly more frequent in patients experiencing more severe forms of ARDS (Table 4). According to actual literature [3,30], respiratory functional impairment after COVID-19 pneumonia is associated with persistent pulmonary radiological abnormalities so that PFTs may therefore represent a marker of radiological sequelae of severe COVID-19.

On the other hand, in our study population DLCO impairment degree, which is the most reported respiratory functional impairment in post-COVID syndrome, was not associated with ARDS severity. Even if potentially controversial, this result confirms that COVID-19 patients requiring intensive care and IMV can fully recover [32,33].

Interestingly, the presence and severity of dyspnea, measured by the mMRC scale, was correlated with IMV length and not with DLCO and FVC values, while the 15D breathing dimension was correlated to both IMV length and DLCO (Table 4).

According to our results, pulmonary function tests alterations do not completely explain the persistence of dyspnea, so that the perceived breathing impairment complained by patients after COVID-19 may not be fully related to pulmonary function impairment [34,35]. Other clinical and neuro-psychological aspects such as experiences of anxiety and pain, the sedative regimens, and mechanical ventilation settings during ICU stay [36,37], could play a role in determining the presence and entity of dyspnea among survivors.

Dyspnea is defined as a subjective perception of uncomfortable breathing and could be determined by complex and multiple mechanisms including social, psychological, and physical conditions [38], and it is one of the major components of the post-COVID syndrome [39]. This study evaluated a population made of critically ill patients, which could be also affected by the so-called post-intensive care syndrome (PICS), a multisystemic syndrome characterized by new or worsening physical, mental and neurocognitive disorders [40,41], that could overlap post-COVID syndrome manifestations.

It is impossible to precisely estimate the proportion of mental and physical components potentially responsible for dyspnea as well as the relative roles of PICS and post-COVID syndrome from the available data in our population. However, the very high prevalence of psychological consequences, together with the only partial concordance between dyspnea and pulmonary functional impairment (especially DLCO), may suggest a cardinal role of neuropsychological mechanisms at the root of this symptom.

Exploring this topic in larger studies could be helpful to better understand an important aspect of both PICS and post-COVID syndrome, and to foster their management in a multidisciplinary approach.

Limitations

Several limitations should be discussed: first, we adopted the telephonic interview rather than follow-up visits, this was chosen to reach the maximum number of patients taking into account the travel restrictions due to the second and third waves of the COVID-19 pandemic. Other limitations are also represented by the small proportion of patients with available PFTs at 1-year, so that the prevalence of functional impairment could be biased. Moreover, the lack of association with lung radiological data at 1-year due to data unavailability and the absence of baseline PFTs information prevented us from deriving clinical-radiological correlations and carrying out pre-post analyses.

Missing data for the sexual activity dimension exceeded 20%, despite this aspect is in line with our previous follow-up [11] and data substitution was obtained with the multiple imputation technique, cautious interpretation of these data should be warranted.

Finally, among ICU survivors significant modifications in HRQoL dimensions were reported up to ten years after discharge [42], therefore, longer follow-up times could help in better defining the HRQoL trajectories and the effects of eventual interventions [43].

Conclusions

COVID-19 survivors who needed IMV reported a significant HRQoL impairment at 1 year after ICU discharge in most of the cases. Despite a trend towards an increase in HRQoL being detected during the first year after ICU discharge, mental dimensions did not significantly improve and dyspnea proved to be the most frequent symptom reported 1 year after ICU discharge. Pulmonary function tests alterations, in particular concerning DLCO, only partially explained the entity of this symptom and other physiological and psychological causes should be investigated.

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Figures

Figure 1 – Health-related quality of life profiles at 3 months and 1 year after ICU discharge

Notes: asterisks highlight the dimensions significantly different between 3 months and 1 year

Abbreviations: Move – mobility; See – vision; Hear – hearing; Breath – breathing; Sleep – sleeping; Eat – eating; Speech – speech; Excret – excretion; Uact – usual activities; Mental – mental function; Disco – discomfort; Depr – depression; Distr – distress; Vital – Vitality; Sex – sexual activity

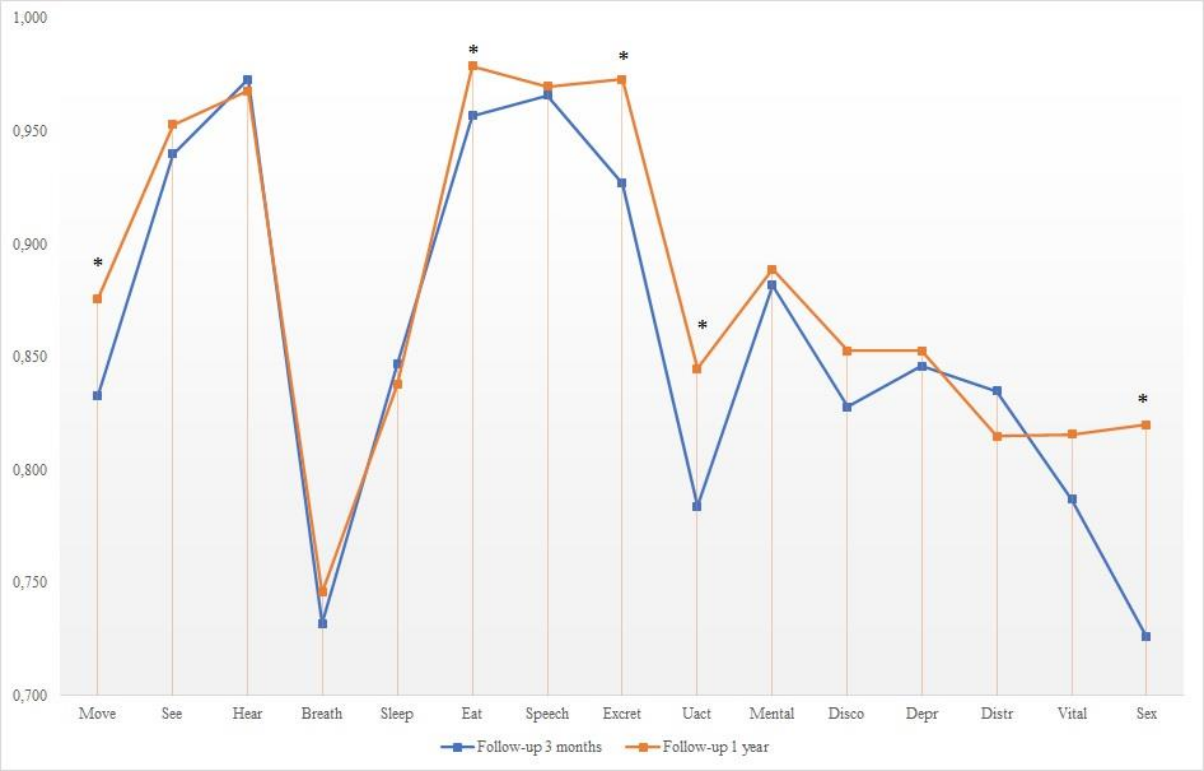
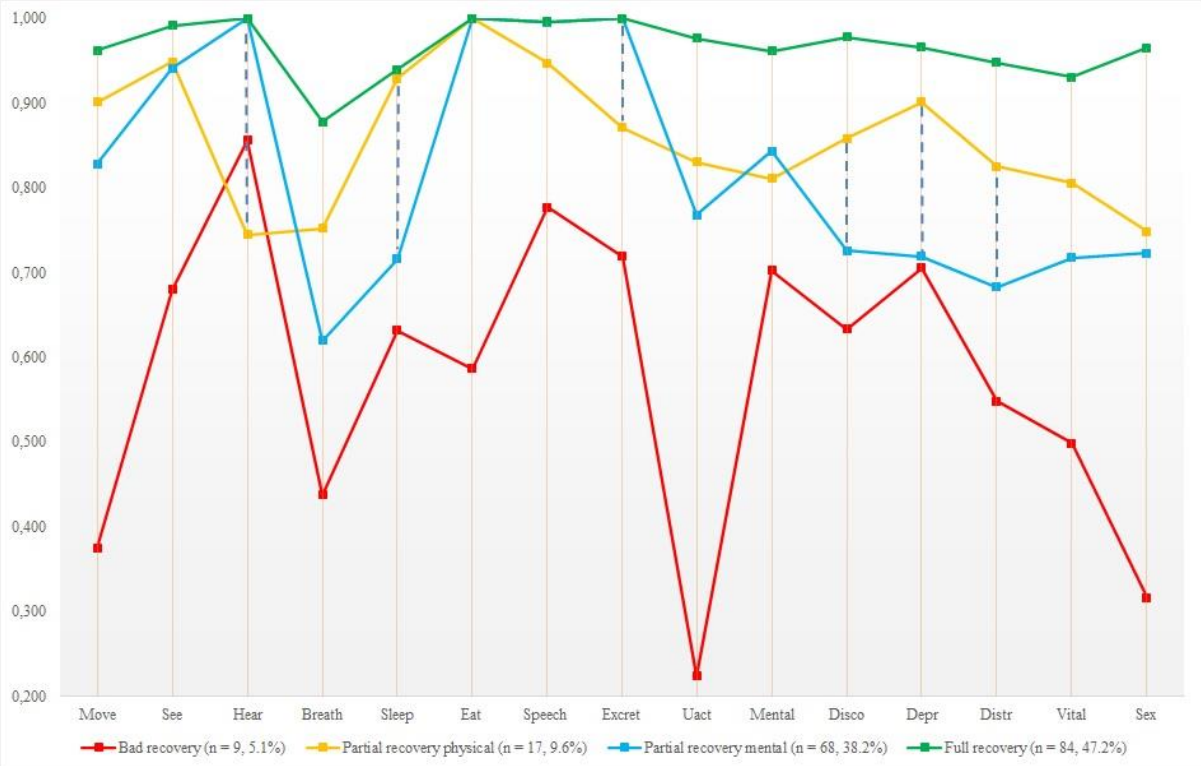


Figure 2 - Comparison of the 1-year health-related quality of life profiles clusters

Notes: the blue dashed lines highlight the significant differences between the partial recovery-mental and the partial recovery-physical groups

Abbreviations: Move – mobility; See – vision; Hear – hearing; Breath – breathing; Sleep – sleeping; Eat – eating; Speech – speech; Excret – excretion; Uact – usual activities; Mental – mental function; Disco – discomfort; Depr – depression; Distr – distress; Vital – Vitality; Sex – sexual activity



Supplement figure 1 – Patients' flow throughout the study

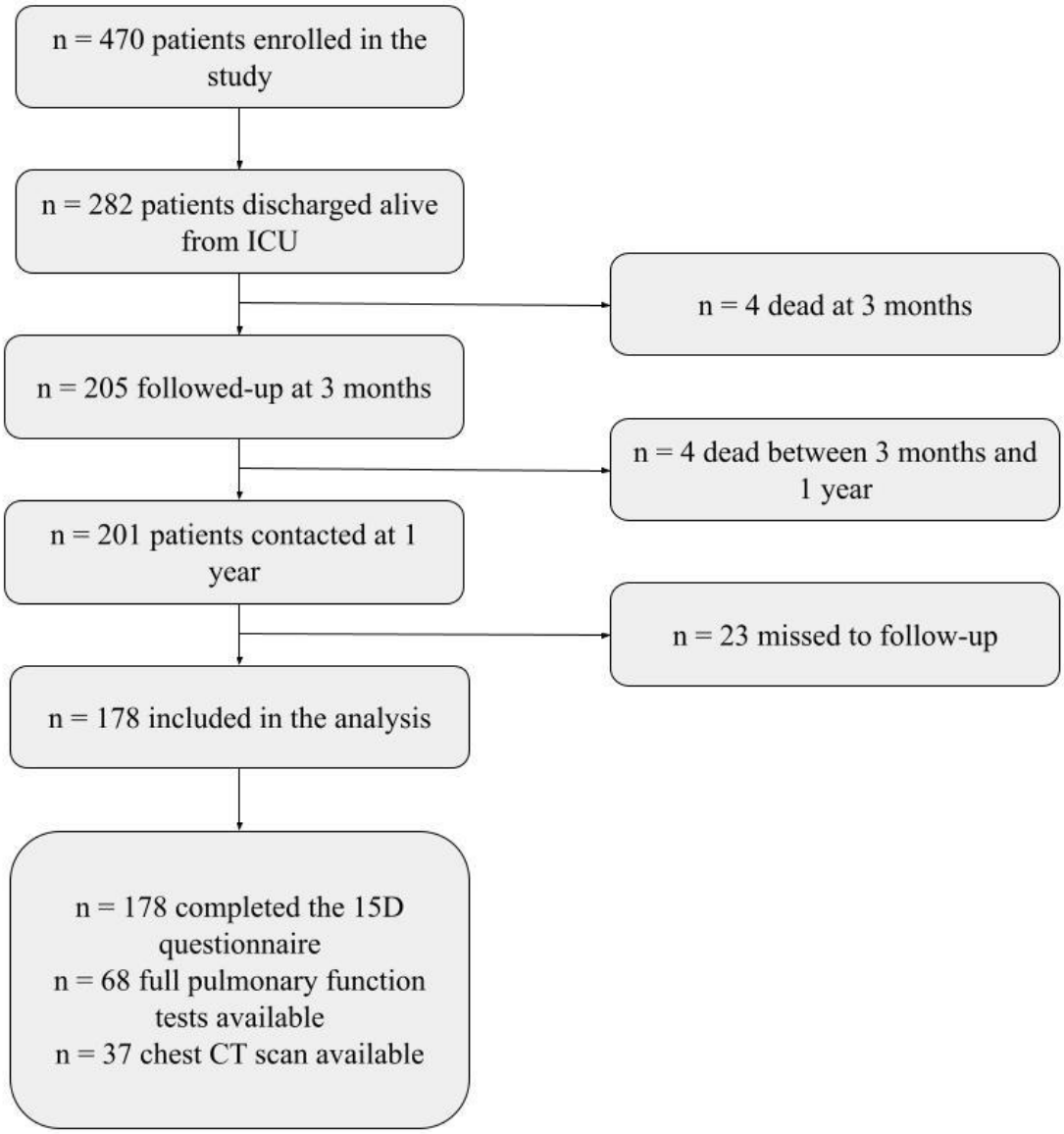


Table 1 – General characteristics of the study population and the recovery clusters based on the 15D dimensions

	Total population n = 178	Full recovery n = 84	Partial recovery Mental n = 68	Partial recovery Physical n = 17	Bad recovery n = 9	p
Age - years (IQR)	64 (55 - 70)	60 (52 - 68)	66 (57 - 71)	69 (55 - 75)	66 (60 - 74)	**0.011**
Sex - male - no (%)	129 (72.5%)	67 (79.8%)	46 (67.6%)	11 (64.7%)	5 (55.6%)	0.184
BMI - kg/m2 (IQR)	28 (26 - 31)	28 (26 - 31)	28 (26 - 31)	27 (25 - 29)	32 (27 - 35)	0.116
Comorbidities						
Hypertension - no (%)	88 (49.4%)	36 (42.9%)	36 (52.9%)	9 (52.9%)	7 (77.8%)	0.190
Chronic ischemic heart disease - no (%)	13 (7.3%)	3 (3.6%)	7 (10.3%)	2 (11.8%)	1 (11.1%)	0.345
Chronic kidney disease - no (%)	6 (3.4%)	2 (2.4%)	2 (2.9%)	0 (0%)	2 (22.2%)	**0.013**
COPD - no (%)	13 (7.3%)	4 (4.8%)	7 (10.3%)	0 (0%)	2 (22.2%)	0.112
Diabetes - no (%)	28 (15.7%)	9 (10.7%)	11 (16.2%)	2 (11.8%)	6 (66.7%)	**< 0.001**
Number of comorbidities - (IQR)	1 (0 - 1)	0 (0 - 1)	1 (0 - 1)	1 (0 - 2)	2 (1 - 3)	**0.001**
Intensive care and hospital stay						
ARDS class - no (%)						0.745*
mild (PaO_2/FiO_2 200 - 300)	7 (3.9%)	4 (4.8%)	3 (4.4%)	0 (0%)	0 (0%)	
moderate (PaO_2/FiO_2 100 - 200)	93 (52.2%)	47 (56.0%)	35 (51.5%)	7 (41.2%)	4 (44.4%)	
severe (PaO_2/FiO_2 < 100)	78 (43.8%)	33 (39.3%)	30 (44.1%)	10 (58.8%)	5 (55.6%)	
SAPS II score (IQR)	35 (29 - 42)	34 (28 - 40)	38 (29 - 42)	38 (32 - 42)	38 (31 - 49)	0.431
SOFA score at ICU admission (IQR)	4 (3 - 6)	4 (3 - 6)	4 (3 - 6)	5 (4 - 7)	3 (3 - 5)	0.182
Tracheostomy - no (%)	110 (61.8%)	53 (63.1%)	43 (63.2%)	10 (58.8%)	4 (44.4%)	0.722
Length of invasive mechanical ventilation - d (IQR)	16 (10 - 27)	14 (9 - 26)	18 (13 - 26)	18 (9 - 32)	20 (11 - 33)	0.499
Length of ICU stay - d (IQR)	23 (15 - 35)	19 (14 - 35)	24 (17 - 36)	25 (13 - 37)	29 (13 - 55)	0.671
Socioeconomic variables						
Marital status - married/cohabitee - no (%)	135 (75.8%)	62 (73.8%)	52 (75.6%)	14 (82.4%)	7 (77.8%)	0.893
Instruction degree - high school or higher - no (%)	113 (63.5%)	58 (69.0%)	39 (57.4%)	11 (64.7%)	5 (55.6%)	0.479
Actual occupational status						0.594*
Employed - no (%)	87 (48.9%)	47 (56.0%)	28 (41.2%)	7 (41.2%)	5 (55.6%)	

Unemployed - no (%)	10 (5.6%)	4 (4.8%)	4 (5.9%)	1 (5.9%)	1 (11.1%)	
Retiree - no (%)	81 (45.5%)	33 (39.3%)	36 (52.9%)	9 (52.9%)	3 (33.3%)	

Abbreviations: IQR – interquartile range; BMI – body mass index; COPD – chronic obstructive pulmonary disease; ARDS – acute respiratory distress syndrome; SAPS – simplified acute physiology score; SOFA – sequential organ failure assessment; ICU – intensive care unit. Notes: significant p values for differences among the recovery clusters are evidenced in bold. * p-value referred to the Chi-square test for the whole contingency table.

Table 2 – Quality of life and reported symptoms details of the study population and the recovery clusters based on the 15D dimensions

Health related Quality of Life	Respondents (n = 178)	Full recovery n = 84	Partial recovery Mental n = 68	Partial recovery Physical n = 17	Bad recovery n = 9	p
15D score 3 months - mean ± SD	0.857 ± 0.133	0.927 ± 0.061	0.800 ± 0.135	0.853 ± 0.114	0.637 ± 0.204	< **0.001**
15D score 1 year - mean ± SD	0.880 ± 0.115	0.964 ± 0.033	0.820 ± 0.068	0.866 ± 0.088	0.572 ± 0.112	< **0.001**
Mobility - mean ± SD	0.876 ± 0.207	0.963 ± 0.104	0.828 ± 0.191	0.901 ± 0.166	0.375 ± 0.298	< **0.001**
Vision - mean ± SD	0.953 ± 0.119	0.992 ± 0.040	0.942 ± 0.108	0.949 ± 0.094	0.681 ± 0.280	< **0.001**
Hearing - mean ± SD	0.968 ± 0.098	1.000 ± 0.000	1.000 ± 0.000	0.745 ± 0.135	0.857 ± 0.192	< **0.001**
Breathing - mean ± SD	0.746 ± 0.238	0.879 ± 0.154	0.620 ± 0.227	0.753 ± 0.223	0.438 ± 0.238	< **0.001**
Sleeping - mean ± SD	0.838 ± 0.238	0.940 ± 0.135	0.716 ± 0.274	0.929 ± 0.142	0.632 ± 0.312	< **0.001**
Eating - mean ± SD	0.979 ± 0.102	1.000 ± 0.000	1 .000 ± 0.000	1.000 ± 0.000	0.587 ± 0.221	< **0.001**
Speech - mean ± SD	0.980 ± 0.090	0.996 ± 0.032	0.996 ± 0.036	0.948 ± 0.117	0.777 ± 0.276	< **0.001**
Excretion - mean ± SD	0.974 ± 0.110	1.000 ± 0.000	1.000 ± 0.000	0.872 ± 0.191	0.720 ± 0.292	< **0.001**
Usual activities - mean ± SD	0.845 ± 0.234	0.977 ± 0.078	0.768 ± 0.211	0.831 ± 0.231	0.224 ± 0.085	< **0.001**
Mental function - mean ± SD	0.889 ± 0.174	0.962 ± 0.111	0.844 ± 0.185	0.811 ± 0.183	0.903 ± 0.248	< **0.001**
Discomfort - mean ± SD	0.853 ± 0.206	0.979 ± 0.077	0.726 ± 0.214	0.859 ± 0.216	0.633 ± 0.202	< **0.001**
Depression - mean ± SD	0.853 ± 0.203	0.966 ± 0.091	0.719 ± 0.220	0.901 ± 0.172	0.706 ± 0.203	< **0.001**
Distress - mean ± SD	0.815 ± 0.210	0.949 ± 0.128	0.683 ± 0.184	0.825 ± 0.186	0.549 ± 0.201	< **0.001**
Vitality - mean ± SD	0.816 ± 0.196	0.931 ± 0.125	0.718 ± 0.160	0.806 ± 0.227	0.499 ± 0.185	< **0.001**
Sexual activity - mean ± SD	0.820 ± 0.235	0.966 ± 0.103	0.723 ± 0.215	0.749 ± 0.219	0.317 ± 0.185	< **0.001**
Reported symptoms at 1 year						
Cough - n (%)	18 (10.1%)	2 (2.4%)	13 (19.1%)	1 (5.9%)	2 (22.2%)	**0.004**
Arthromialgia - n (%)	62 (34.8%)	15 (17.9%)	33 (48.5%)	7 (41.7%)	7 (77.8%)	< **0.001**
Palpitations - n (%)	12 (6.7%)	1 (1.2%)	8 (11.2%)	2 (11.8%)	1 (11.1%)	0.050
Dyspnoea (mMRC ≥ 1) - n (%)	104 (58.4%)	32 (38.1%)	51 (75.0%)	13 (76.5%)	8 (88.9%)	< **0.001**
Dyspnoea mMRC scale - (IQR)	0 (0 - 2)	0 (0 - 0)	1 (0 - 2)	1 (0 - 2)	3 (2 - 4)	< **0.001**

Abbreviations: mMRC - modified Medical Research Council dyspnoea scale

Notes: significant p values for differences among the recovery clusters are evidenced in bold

Table 3 – Univariate and multivariate analysis for the general mixed model

	Univariate analysis			Multivariate analysis		
Variable	**β**	95% CI	p	**β**	95% CI	p
Gender (male)	0.031	-0.005 : 0.068	0.092	0.038	0.004 : 0.073	**0.030**
Age (years)	-0.001	-0.003 : 0.001	0.097	- 0.001	-0.002 : 0.001	0.606
BMI	-0.003	-0.006 : 0.001	0.098	-0.003	-0.006 : 0.001	0.118
Number of comorbidities	-0.036	-0.053 : -0.019	<0.001	-0.033	-0.051 : -0.015	< **0.001**
ARDS class (per class increase)*	0.011	-0.018 : 0.040	0.467			
SAPS II score	-0.001	-0.002 : 0.001	0.315			
SOFA score at ICU admission	0.002	-0.005 : 0.009	0.597			
Duration of invasive mechanical ventilation	-0.002	-0.003 : -0.001	0.001	-0.002	-0.003 : -0.001	**0.004**
Tracheostomy	-0.026	-0.060 : 0.007	0.129	0.003	-0.032 : 0.039	0.857
Marital status - married/cohabitee	-0.004	-0.042 : 0.035	0.840			
Instruction degree - high school or higher	0.005	-0.029 : 0.039	0.767			
Occupational status - unemployed*	0.015	-0.058 : 0.088	0.680			
Occupational status - retiree*	0.004	-0.030 : 0.037	0.837			

Abbreviations: BMI – body mass index; ARDS – acute respiratory distress syndrome; SAPS – simplified acute physiology score; SOFA – sequential organ failure assessment; ICU – intensive care unit.

Notes: significant p values are evidenced in bold; *reference class: severe ARDS; * reference class: employed

Table 4 – Pulmonary function tests and health-related quality of life correlations

	Total population n = 68	DLCO < 80% n = 35	DLCO > 80% n = 33	p	FVC < 80% n = 12	FVC > 80% n = 56	p
Age - years (IQR)	62 (54 - 71)	65 (57 - 71)	59 (52 - 68)	0.077	60 (57 - 66)	64 (54 - 71)	0.705
Sex - male - no (%)	6 (9%)	22 (62.9%)	29 (87.9%)	**0.017**	11 (91.7%)	40 (71.4%)	0.269
BMI - kg/m2 (IQR)	28 (25 - 30)	28 (25 - 31)	28 (25 - 29)	0.598	28 (26 - 37)	28 (25 - 30)	0.292
COPD - no (%)	6 (8.8%)	2 (5.7%)	4 (12.1%)	0.667	0 (0%)	6 (10.7%)	0.581
Number of comorbidities - (IQR)	1 (0 - 1)	1 (0 - 1)	0 (0 - 1)	0.203	0 (0 - 1)	1 (0 - 1)	0.505
Intensive Care Unit stay related variables							
SAPS II score (IQR)	35 (27 - 43)	38 (29 - 49)	34 (27 - 42)	0.161	35 (27 - 40)	35 (29 - 44)	0.384
SOFA score at ICU admission (IQR)	4 (3 - 7)	6 (3 - 7)	4 (3 - 6)	0.053	4 (3 - 5)	5 (3 - 7)	0.128
Worst PaO2/FiO2 5d - (IQR)	105 (80 - 149)	118 (82 - 146)	90 (80 - 150)	0.165	81 (69 - 108)	112 (83 - 150)	**0.020**
Worst respiratory system compliance 5d - IQR	40 (32 - 49)	37 (31 - 46)	40 (33 - 50)	0.299	34 (30 - 49)	40 (33 - 49)	0.380
Length of invasive mechanical ventilation - d (IQR)	14 (8 - 21)	15 (9 - 28)	14 (8 - 18)	0.140	16 (7 - 23)	14 (9 - 21)	0.942
Length of ICU stay - d (IQR)	19 (14 - 33)	22 (15 - 42)	19 (13 - 29)	0.100	32 (15 - 42)	19 (14 - 29)	0.102
Pulmonary function tests at 1 year after ICU discharge							
FEV 1 - % of predicted - mean ± SD	99.7 ± 17.4	85.5 ± 14.5	86.7 ± 14.5	0.195	77.2 ± 11.0	104.6 ± 14.6	< **0.001**
FVC - % of predicted - mean ± SD	97.3 ± 18.5	95.0 ± 22.6	99.7 ± 12.7	0.293	70.3 ± 8.7	103.0 ± 14.5	< **0.001**
FEV/FVC - % of predicted - mean ± SD	86.1 ± 14.6	85.5 ± 14.9	86.7 ± 14.5	0.729	95.4 ± 21.8	84.1 ± 11.9	0.105
DLCO - % of predicted - mean ± SD	77.6 ± 21.6	63.6 ± 11.9	92.6 ± 19.5	< **0.001**	68.2 ± 17.6	79.7 ± 22.0	0.096
Health-related quality of life and dyspnoea							
Outcome cluster				**0.039**•			0.122•
Bad recovery – n (%)	1 (1.5%)	1 (100%)	0 (0%)		0 (0%)	1 (100%)	
Partial recovery physical – n (%)	9 (13.2%)	4 (44.4%)	5 (55.6%)		0 (0%)	9 (100%)	
Partial recovery mental – n (%)	20 (29.4%)	15 (75%)	5 (25.0%)		6 (30%)	14 (70%)	
Good recovery – n (%)	38 (55.9%)	15 (39.5%)	23 (60.5%)		6 (15.8%)	32 (84.2%)	
15D score 1 year - mean ± SD	0.906 ± 0.095	0.881 ± 0.105	0.933 ± 0.075	**0.022**	0.886 ± 0.078	0.911 ± 0.098	0.413
15D - Breathing - mean ± SD	0.768 ± 0.215	0.731 ± 0.189	0.807 ± 0.236	0.150	0.711 ± 0.159	0.780 ± 0.225	0.223
mMRC grade of dyspnea - (IQR)	0 (0 - 1)	1 (0 - 1)	0 (0 - 1)	0.061	1 (0 - 1)	0 (0 - 1)	0.251
Bivariate correlations*							

	PaO2/FiO2	C_{RS}	DLCO	FVC	FEV1	FEV/FVC	MV length
15D - breathing (ρ)	- 0.029	- 0.071	**0.244**	0.109	0.159	0.133	**- 0.162**
mMRC grade of dyspnea (ρ)	- 0.105	0.066	- 0.196	- 0.068	- 0.191	- 0.137	**0.204**

Abbreviations: IQR – interquartile range; COPD – chronic obstructive pulmonary disease; ARDS – acute respiratory distress syndrome; SAPS – simplified acute physiology score; SOFA – sequential organ failure assessment; ICU – intensive care unit; mMRC modified Medical Research Council; C_{RS} Respiratory system compliance; DLCO – diffusion capacity of lungs for carbon monoxide, FVC - forced vital capacity; FEV1 – forced expiratory volume in the first second; MV - mechanical ventilation

Notes: significant p values are evidenced in bold, as well as the rho (ρ) values of significant bivariate Spearman correlations. ˙ p values referred to the likelihood ratio of the Chi-square test. * bivariate correlations are calculated with a pairwise exclusion of missing data