Quality of life of COVID-19 critically ill survivors after ICU discharge : 90 days follow-up

ICU-RER COVID-19 Collaboration

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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: 10.17632/5hxnf9s7rk.1

For the Finnish population please refer to Harri Sintonen (harri.sintonen@helsinki.fi)

Competing Interests

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

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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Introduction

The coronavirus disease (COVID-19) pandemic in Italy [1] rapidly induced an overburdening situation mostly due to a sudden increase of ICU admission [2–4] for respiratory and multiorgan [5] support.

COVID-19 related ARDS is an overwhelming disease that can require extended periods of invasive mechanical ventilation [6] and is characterized by a mortality rate that exceeds 50% in some reports [6–9].

Due to the magnitude of the pandemic, the evaluation of COVID-19 impact on ICU survivors could be useful to identify who may benefit for long term follow up and rehabilitation [10].

Several studies have been focused on the identification of tools able to recognize, define, and treat the long-term effects of ICU on quality of life. Post-intensive care syndrome (PICS) [11–13] is characterized by cognitive [14, 15], psychological and physical impairment that can affect ICU survivors [16]. Moreover, ARDS [17, 18], sepsis, delirium [19], and the need for invasive mechanical ventilation (IMV), which are common features in COVID-19 patients [5], are known risk factors for the development of this PICS syndrome.

Some registered ongoing trials aim to define the quality of life after COVID-19 infection (ClinicalTrials.gov NCT04375709, NCT04377464) but these studies do not focus on critically ill patients [20]. Notably, health-related quality of life (HRQoL) [12, 21] in "classical" ARDS survivors is impaired, as showed in previous studies. The primary aim of the present study was to evaluate the HRQoL at 90 days after ICU discharge in a cohort of critically ill COVID-19 patients who required invasive mechanical ventilation. Furthermore, we compared this population to an age and sex-matched sample of the general Italian and Finnish populations. The comparison with contemporary general Italian population had the objective to specifically assess the potential areas of intervention for the most affected HRQoL dimensions in COVID-19 survivors. On the other hand, in absence of previous Italian studies evaluating general population with the 15D instrument, a Finnish population sample from the 2011 National Finnish Health Survey data [22] was adopted as a pre-COVID western-type population for comparison. The secondary aim was to identify clinical, demographic, social factors than can play a role in the impairment of HRQoL.

Materials and Methods

This prospective multicenter observational study involved 16 Italian ICUs. Patients admitted in the ICU from the 22nd of February to the 4th of May 2020 (the end of lockdown in Italy) were screened for eligibility and followed up until 90 days after ICU discharge. The original study was registered in ClinicalTrials.gov (NCT04411459)

Inclusion, exclusion criteria and Ethical aspects

Inclusion criteria were: (a) age > 18 years; (b) admission to ICU due to respiratory failure determined by SARS-CoV-2 infection confirmed by real-time reverse transcription-polymerase chain reaction assays from either nasal swabs or lower respiratory tract sample; (c) need of invasive mechanical ventilation during ICU stay.

Exclusion criteria were: SARS-CoV2 positive patients admitted to the hospital for other reasons (i.e. trauma, stroke) b) refuse to participate to the study.

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 collected during ICU stay and/or follow-up according to the approval of the local Ethics committee. All data were analyzed anonymously.

Data Collection

Data were collected by one investigator from each hospital 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). Demographic data, clinical symptoms or signs at presentation, comorbidities, Sequential Organ Failure Assessment (SOFA) and Score and Simplified Acute Physiology Score (SAPS) II were collected at ICU admission. All the patients met the Berlin criteria definition for ARDS [23]. The need for renal replacement therapy, need of tracheostomy, duration of invasive mechanical ventilation, prone positioning, use of intravenous corticosteroids, use of a continuous infusion of neuromuscular blocking agents, use of vasoactive drugs, duration of ICU and hospital stay were also collected and included in the final analysis. Furthermore, the health-related quality of life was assessed using the 15D questionnaire at 90 days from ICU discharge by phone call. Social variables (marital status, occupational status and instruction degree) were collected during follow-up. In case of patients missed at follow up, we obtained these data from the medical records. Details of the other variables collected are available on clinicaltrials.gov (NCT04411459).

A sex and age-matched random sample from the general Italian population not affected by COVID-19 was interviewed in parallel to create a reference group. Moreover, as described above, in order to create a reference category for the pre-COVID-19 era, and due to the unavailability of Italian HRQoL data measured with the 15D instrument for that period, an equally sampled general Finnish population group was obtained from the 2011 National Finnish Health Survey data [22].

The 15D instrument

The 15D is a widely used, validated and standardized instrument that explores 15 dimensions (mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity). Five ordinal levels can be defined for each dimension, by which more or less of the attribute is distinguished. The respondent chooses from each dimension the level which best describes her/his present health status and a score between 1 (lower level) and 5 (upper level) is assigned [24].

The valuation system is based on the multiattribute utility theory. The single index score (15D score) represents the overall HRQoL on a 0-1 scale (1=full health, 0=being dead). The score of each dimension is 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. Moreover, 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 [25]. The 15D scores are shown to be highly reliable, sensitive and responsive to change, there is a considerable degree of agreement between health state evaluations from several European countries and these latter are generalizable at least in Western-type societies [24–26]. Moreover, the 15D instrument has already been applied in follow-up studies of ICU patients [27, 28].

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) and R Core Team 2020 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria URL https://www.R-project.org/).

Continuous variables were expressed as means and standard deviations or median and interquartile range (IQR) when appropriate, while categorical variables were expressed as numbers and percentages. Comparisons between continuous variables were performed with Student's t-test or Mann-Whitney U test; categorical variables were compared using Chi-square test. HRQoL values were expressed with the 15D instrument as means and standard deviations and t-test was used for comparisons, regardless from distribution.

Since the 15D value can be calculated only if all the 15 dimensions values are available, missing data on single dimensions of the 15D instrument were estimated using a multiple imputation technique when the missing data involved less than three dimensions [24].

Multiple univariate linear regression analyses were performed on the variables which could be rationally associated to 90-days HRQoL, and a multivariate model was computed using a least angle regression (LAR) selection [29] in order to select significant explanatory terms with respect to survivors' HRQoL.

P-values < 0.05 were considered statistically significant, and all tests were two-sided.

Results

Over the study period, 632 patients were screened for eligibility. Of these, 162 patients were excluded because they did not undergo invasive mechanical ventilation (n = 120) or because of missing data (n = 42). The remaining 470 patients were enrolled in the study. Two hundred and eighty-two patients out of 470 (60%) were discharged alive from the ICU and 4 of these died within 90 days after ICU discharge. Therefore, the final follow up cohort included a total of 278 patients. The flow-chart of the patients through the study is shown in Figure 1. Two hundred five out of 278 patients (73.7%) responded to the 15D questionnaire.

The main demographics, comorbidities, ICU- and hospital-related variables of the patients showed in Table 1. Overall, patients were predominantly male (74.1%), the median age was 64.5 years; the most frequent comorbidity was hypertension (51.8%). The majority of patients experienced a moderate ARDS (55%), a continuous infusion of neuromuscular blocking agents was used in 89.6% of cases, prone positioning was performed at least once in 62.9% of the patients and tracheostomy in 61.5% of them.

The median length of mechanical ventilation, ICU and hospital stay were, respectively, 16, 23 and 43 days.

Respondents were younger than non-respondents (63 vs 66 years), had a slightly lower SOFA score at ICU admission and needed less frequently renal replacement therapy; no differences were found for other variables.

Follow-up CT scans were available for 23 out of the 205 respondents and were performed at a median of 61 (35 - 99) days after ICU discharge (Supplement Table 1). Only two patients (8.7%) had a normal follow-up CT scan, while the other presented residual ground glass (65.2%), fibrosis (47.8%), consolidations (30.4%), pleural effusion (21.7%) or bronchiectasis (13%).

Missing data for the 15D instrument, that were replaced by multiple imputation technique, accounted for less than 0.3% of the cases in most of the dimensions, with exception for usual activities (0.5%), discomfort (1%), symptoms (1%) and sexual activity (13.4%).

The 15D score of the study population at 90 days after ICU discharge was significantly lower than the two matched controls of Italian and Finnish samples of general population, with a mean value of 0.850 vs 0.928 and 0.914,

respectively. Table 2 shows the mean values for the single dimensions and their comparisons. Figure 2 describes the 15D profiles of the three populations compared.

Considering the single dimensions of the 15D instrument, the mean values for mobility, breathing, eating, speech, usual activities, depression, vitality and sexual activity were significantly lower when compared both to the matched Italian and Finnish populations, while mental function resulted significantly lower only with respect to Italian population and distress only with respect to the Finnish population (Table 2).

The comparison of the matched samples of general Italian and Finnish populations revealed significant differences on most of the dimensions and on the total 15D score. However, despite the observed difference in the global 15D score was statistically significant, it did not reach the minimum value of ±0.015 that is the threshold value that most of the people need to feel such difference [25].

On the basis of univariate linear regression analyses, the variables age, number of comorbidities, ARDS class, SAPS II score, prone positioning, use of vasoactive drugs, duration of invasive mechanical ventilation, ICU length of stay, tracheostomy, need for renal replacement therapy, non-pulmonary complications of ICU stay and occupational status were significantly associated to 90-days HRQoL. The final model obtained after least angle regression selection demonstrated that female sex, increasing age, number of comorbidities, ARDS class, duration of mechanical ventilation and inability to return to work were significantly associated with a reduction in HRQoL. Table 3 shows the univariate regression analyses and the final multivariate model after the LAR selection of the variables included. The magnitude of potential changes in HRQoL demonstrated by the linear regression analysis is relevant from a clinical point of view because an increase of one comorbidity as well as ARDS class (severe vs moderate) or five adjunctive days of invasive mechanical ventilation can significantly worsen 90 days HRQoL of more than 0.015. For clarification, decreases of this entity are associated to a decrease in a subjective five-category global assessment scale evaluating HRQoL change of one or more classes (e.g., from "much the same" to "slightly worse" or "much worse") [25].

Discussion

In this study we used the 15D instrument to evaluate the HRQoL of COVID-19 critically ill survivors at 90 days after ICU discharge and compare it to two age and sex matched random populations. We found that a) the HRQoL of COVID-19 critically ill survivors was significantly lower than the HRQoL of both contemporary general Italian population and Finnish pre-COVID population and b) the most affected areas were mobility, breathing, eating, speech, usual activities, mental function, discomfort and symptoms, depression, vitality and sexual activity, c)

moreover, age, female sex, comorbidities, ARDS class, duration of invasive mechanical ventilation and occupational status were found to be significant determinants of 90 days HRQoL.

15D profile of the COVID-19 survivors

A high percentage of ARDS survivors experience cognitive impairment after ICU recovery [26, 27], ranging from almost 100% at hospital discharge to 80% at 1 year [28, 30, 31]. Moreover, a high rate of persistent psychological and physical disability, such as muscle weakness [31] and incomplete lung function recovery [32], can be frequently found. It is debated if COVID-19 related ARDS could be defined as "classical" ARDS [33, 34] from a pathophysiological point of view. However, in most of the COVID-19 cases admitted to the ICU, the disease evolution seems to be similar to the severe forms of classical ARDS, requiring endotracheal intubation and being characterized by a prolonged and difficult weaning and consequently a prolonged ICU stay. Indeed, the HRQoL profile observed in our cohort of COVID-19 ARDS patients is very similar to those observed in non-COVID ARDS survivors [35–37]. This cohort of COVID-19 ARDS patients revealed significantly lower scores in the motion and usual activities dimensions of the 15D instrument compared to both the contemporary Italian and the Finnish pre-COVID-19 populations. The reduction in terms of physical components of the HRQoL instruments is common in both ICU survivors [21] and non-COVID ARDS survivors [35, 38].

Critical illness acquired weakness (ICUAW) [39], compressive neuropathies and non-specific structural changes in muscle are the main causes of weakness and reduced exercise capacity in ARDS survivors [40]. Muscular wasting can be consequent to prolonged mechanical ventilation, exposure to sedatives, neuromuscular blocking agents and corticosteroids as well as malnutrition and hypercatabolic state [41, 42]. Recent reports in COVID-19 ARDS population highlighted an ICUAW incidence of 27% at ICU discharge [43], and this could have a central role in the significant deflection of the physical dimensions found using the 15D instrument.

The impairment in several pulmonary function tests has already been associated with worse scores in the physical components of HRQoL [44]. Indeed, we found a significant reduction of the breathing dimension in COVID-19 ARDS patients. Preliminary studies reported impaired pulmonary function tests in COVID-19 survivors, mostly in Carbon Monoxide Diffusing Capacity [34, 45]. Moreover, persistent weakness of the respiratory muscles and lung imaging abnormalities were reported mostly in the early post hospital discharge phase [46] and our data on follow up CT scans confirmed these results (see Supplement Table 1).

Tracheostomy is notoriously associated with swallowing and vocalization problems that need rehabilitation. Despite this variable was excluded from the final regression model during the stepwise selection, literature reports

a severe reduction in long term quality of life in tracheostomized general ICU patients [47]. The high prevalence of tracheostomies in the COVID-19 population could have contributed to the reduction on the eating and speech dimensions of the 15D instrument observed in our study population. Since tracheostomy is often a necessary procedure for the prolonged mechanical ventilation and the consequent difficult weaning process, optimal timing and vocal rehabilitation can be taken into consideration in order to try to improve HRQoL [48, 49].

In non-COVID-19 ARDS, a high prevalence of long-term cognitive impairment and psychiatric disorders has been described: depression, anxiety disorders and post-traumatic stress disorder (PTSD) [28, 36, 50]. Indeed, prolonged hypoxia, physical and psychic stressors related to the ICU experience could favor acute brain dysfunction and impair the coping mechanisms in response to stress events. COVID-19 patients, compared to previous cohorts of ARDS patients, experienced a profound social isolation during all the time of the hospital stay, in most of the cases more than a month. Indeed, in COVID-19 wards, no access was allowed to relatives or visitors and, moreover, these latter were frequently quarantined at home. Moreover, the need to wear full personal protective equipment by the healthcare personnel invariably complicated the communication processes and could have probably contributed to the social isolation described above.

The components of mental function and depression of the 15D instrument in COVID-19 ARDS survivors were significantly lower with respect to their matched Italian controls as already described for non-COVID-19 ARDS survivors. In a previous study on a large sample of general ICU patients with respiratory failure or shock [27], at three months after ICU discharge, 40% of them had global cognition scores that were worse than those typically seen in patients with moderate traumatic brain injury, and this impairment lasted at 1 year after ICU discharge in 34% of them. The occurrence of delirium during ICU stay and its duration were positively correlated with lower cognition scores after ICU discharge [27]. Recent reports evidenced a very high prevalence (84.3%) of delirium in the COVID-19 ICU population, that was also responsible for prolonged mechanical ventilation, another factor significantly associated to a reduced HRQoL in our population [51]. Therefore, this aspect needs attention during both ICU stay and after discharge for the development of rehabilitative programs.

Interestingly, the distress dimension values of COVID19 survivors were not significantly different from Italian general population but it was significantly lower than in the pre-COVID Finnish general population, while the sleeping dimension was not significantly affected with respect to general Italian and Finnish populations. The COVID-19 pandemics produced high levels of anxiety in the overall population of the most affected areas [52] and a recent cross-sectional study enrolling over 7000 self-selected Chinese volunteers reported a prevalence of

general anxiety disorder, depressive symptoms and bad quality of sleep of, respectively, 35.1%, 20.1% and 18.2% [53].

Italy, together with China, was one of the most affected countries during the first wave of the COVID-19 pandemic and the expected increase in terms of anxiety disorder and sleep disturbances could probably have partially smoothed the differences between the post-critical COVID-19 population and the general post COVID-19 Italian population in terms of distress and sleeping dimensions.

Factors associated with reduced HRQoL

Our study underlines that, in COVID-19 patients, ARDS class, prolonged mechanical ventilation, older age [54], female sex and comorbidities are associated with worse scores in HRQoL as already reported in "classical" ARDS survivors [35–37]. Moreover, ARDS severity resulted independently associated to HRQoL with a notably high β coefficient ($\beta = 0.040$ per class increase from severe as reference category). Few studies evaluated the potential impact of initial ARDS severity on reported HRQoL and our results could have been influenced by both the relatively short follow up time and the high homogeneity of the sample in terms of etiology, in fact, most of the other studies reporting HRQoL after ARDS had mixed etiology samples [37, 38, 55]. Female sex was also independently associated to worse HRQoL in the final multivariate model, this result is in contrast with the only other study evaluating this variable in non-COVID-19 respiratory failure [56], the relatively small sample of women in our series and the different reporting of symptoms between sexes could have had a role in determining this result. No other clinical variables investigated in the study, SAPS II score and SOFA score at ICU admission, resulted significantly associated with HRQoL, in line with available literature for non-COVID ARDS [35, 55].

In the COVID-19 ARDS cohort, the ability to return to work and the retiree status were significantly associated with better HRQoL with respect to the unemployed status. The ability to return to work is known to be positively associated with HRQoL and has been proposed as an outcome measure since it is considered a good operationalization for overcoming morbidity [57].

The marital status and degree of instruction were not significantly associated with HRQoL values and no other follow up studies on ARDS described these aspects. However, these social variables usually play a significant role in determining the quality of life in other cross-sectional studies. It is possible that, at 90 days from ICU discharge, the entity of disability related to clinical factors outweighs these social aspects in determining HRQoL.

Limitations

Our study has several limitations. First, the 15D instrument was originally developed to be self-administered, even if telephonic administration is possible. For this study, we administered the questionnaire using a telephonic interview mainly because of 1) the distance of patients that were transiently admitted to the study ICUs from other provinces, 2) the limitations related to the postal transmission of potentially infected documents and 3) the difficulty of older age patients to deal with eventual email transmission of the questionnaires.

Self-reporting questionnaires based on checklists of endorsed symptoms or severity scores could influence both the prevalence of symptoms investigated and the domain severity scores [58], however, this problem is common to all the other HRQoL instruments based on closed-ended questions.

Missing data for the 15D instrument were globally extremely low, with the exception of the sexual activity dimension that reached 13.4%, this percentage may be culture-dependent or related to the telephone interview that could have induced more reluctance to reply to this sensitive question if compared to self-administration.

A comparison between COVID-19 ARDS and non-COVID-19 ARDS would have been interesting, however, when this study was designed, it was not clear if COVID-19 pneumonia could be considered and ARDS form [59, 60] and, moreover, the number of non-COVID forms during the pandemic dramatically fell, therefore, it would have been impossible to build an adequate control group. Indeed, the use of data from patients experiencing ARDS before COVID-19 pandemic would have been biased by the absence of COVID-related restrictions (such as lockdown and limitations of the visits from relatives to ICU admitted patients, independently from their COVID-19 status).

The control population was built on the basis of an age and sex match; however, comorbidities were not taken into account and this could be another limitation in the interpretation of our results.

Ninety days are a short follow up for ARDS patients, but it could give early indication about the potential areas of intervention in these patients especially after hospital discharge.

Finally, most of the other studies about HRQoL in ARDS survivors used the SF-36 instrument thus leading to limited comparability of our results. However, the 15D instrument was chosen because it can simultaneously evaluate a wide range of dimensions. This can be an advantage in assessing a still not well categorized population. Moreover, the 15D instrument results demonstrated a good correlation with SF-36 and the majority of the other generic HRQoL measurement instruments [61].

Conclusions

COVID-19 related ARDS survivors at 90 days after ICU discharge present a significant reduction in both physical and psychological dimensions of HRQoL measured with the 15D instrument. The degree of reduction in HRQoL is mainly influenced by baseline clinical conditions, length of mechanical ventilation and social factors. Due to the complexity of these patients, a multidisciplinary approach, as well as social support, can be fundamental in granting an adequate recovery after COVID-19 critical illness.

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Figure Legends

Figure 1 – Patients flow through the study

Figure 2 – 15D profile of the COVID-19 related ARDS survivors compared with age and sex matched Italian and Finnish populations

Abbreviations

ICU – Intensive Care Unit

IMV – Invasive Mechanical Ventilation

LOS – Length of stay

PICS - Post-intensive care syndrome

IRB - Institutional Review Board

HRQoL - Health-related quality of life

ICUAW - ICU-Acquired Weakness

Demographics	Total population n = 278	Respondents n = 205	Non- Respondents n = 73	p
Age - years (IQR)	64.5 (57 - 70)	63 (55 - 70)	66 (61 - 71)	0.043
Sex - male - no (%)	206 (74.1%)	149 (72.7%)	57 (78.1%)	0.366
BMI - kg/m2 (IQR)	28 (26 - 31)	28 (26 - 31)	28 (26 - 31)	0.608
Comorbidities	n = 278	n = 205	n = 73	p
Hypertension - no (%)	144 (51.8%)	102 (49.8%)	42 (57.5%)	0.253
Chronic ischemic heart disease - no (%)	23 (8.3%)	14 (6.8%)	9 (12.3%)	0.143
Chronic kidney disease (CKD)	13 (4.7%)	7 (3.4%)	6 (8.2%)	0.110
COPD - no (%)	18 (6.5%)	15 (7.3%)	3 (4.1%)	0.418
Diabetes - no (%)	48 (17.3%)	34 (16.6%)	14 (19.2%)	0.615
Chronic liver disease (MELD > 10) - no (%)	1 (0.4%)	0 (0%)	1 (1.4%)	0.263
Active cancer - no (%)	1 (0.4%)	1 (0.5%)	0 (0%)	1.000
Number of comorbidities - no (%)				0.297
0	111 (39.9%)	87 (42.4%)	24 (32.9%)	
1	108 (38.8%)	78 (38%)	30 (41.1%)	
2	43 (15.5%)	30 (14.6%)	13 (17.8%)	
3	10 (3.6%)	5 (2.4%)	5 (6.8%)	
4	6 (2.2%)	5 (2.4%)	1 (1.4%)	
Intensive care and hospital stay	n = 278	n = 205	n = 73	p
SAPS II score (IQR)	35 (30 - 42)	35 (29 - 42)	35 (30 - 43)	0.644
SOFA score at ICU admission (IQR)	4 (3 - 6)	4 (3 - 6)	4 (3 - 7)	0.044
Intravenous corticosteroids	183 (65.8%)	140 (68.3%)	43 (58.9%)	0.146
Neuromuscular blocking agents continuous infusion	249 (89.6%)	186 (90.7%)	63 (86.3%)	0.288
Prone positioning	175 (62.9%)	130 (63.4%)	45 (61.6%)	0.780
Vasoactive drugs	171 (62%)	125 (61.3%)	46 (63.9%)	0.694
ARDS class - no (%)				0.234
mild (PaO2/FiO2 200 - 300)	14 (5%)	8 (3.9%)	6 (8.2%)	
moderate (PaO2/FiO2 100 - 200)	153 (55%)	111 (54.1%)	42 (57.5%)	
severe (PaO2/FiO2 < 100)	111 (40%)	86 (42%)	25 (34.2%)	
Tracheostomy - no (%)	171 (61.5%)	125 (61%)	46 (63%)	0.759
Renal replacement therapy – no (%)	29 (10.4%)	15 (7.3%)	14 (19.2%)	0.004
Length of invasive mechanical ventilation - d (IQR)	16 (10 - 28)	16 (10 - 27)	18 (11 - 35)	0.092
Length of ICU stay - d (IQR)	23 (15 - 38)	23 (15 - 35)	26 (14 - 46)	0.238
Length of hospital stay (n = 248)* - d (IQR)	43 (30 - 61)	42 (31 - 57)	55 (28 - 79.5)	0.142
Socioeconomic variables	n = 226*	n = 205	n = 21*	p
Marital status - married/cohabitee - no (%)	170 (75.2%)	156 (76.4%)	14 (66.7%)	0.340

Instruction degree - high school or higher - no (%)	147 (65.0%)	130 (63.4%)	17 (81%)	0.108
Actual occupational status				0.335
Employed - no (%)	113 (50.0%)	100 (48.8%)	13 (61.9%)	
Unemployed - no (%)	13 (5.8%)	13 (6.3%)	0 (0%)	
Retiree - no (%)	98 (44.2%)	92 (44.9%)	8 (38.1%)	

Table 1 - Characteristics of the patients enrolled in the study

Notes: * incomplete data due to the impossibility to contact the non-responders

Abbreviations: BMI – Body Mass Index; COPD – Chronic Obstructive Pulmonary Disease; MELD – Model for End stage Liver Disease; SAPS – Simplified Acute Physiology Score; SOFA – Sequential Organ Assessment Score; ICU – Intensive Care Unit; ARDS – Acute Respiratory Distress Syndrome

Health related Quality of Life	Respondents (n = 205)	General Italian population (n = 205)	General Finnish population (n = 4752)	p (respondents vs IT)	p (respondents vs FIN)	p (IT vs FIN)
Mobility	0.829 ± 0.262	0.975 ± 0.104	0.932 ± 0.140	< 0.001	< 0.001	< 0.001
Vision	0.933 ± 0.143	0.934 ± 0.114	0.958 ± 0.116	0.981	0.015	0.002
Hearing	0.972 ± 0.089	0.968 ± 0.115	0.937 ± 0.129	0.695	< 0.001	0.001
Breathing	0.730 ± 0.238	0.910 ± 0.148	0.935 ± 0.146	< 0.001	< 0.001	0.013
Sleeping	0.837 ± 0.226	0.843 ± 0.194	0.846 ± 0.171	0.780	0.571	0.830
Eating	0.945 ± 0.176	0.997 ± 0.040	0.997 ± 0.037	<0.001	< 0.001	0.744
Speech	0.959 ± 0.139	0.986 ± 0.064	0.982 ± 0.079	0.015	0.023	0.470
Excretion	0.918 ± 0.194	0.911 ± 0.173	0.890 ± 0.175	0.674	0.037	0.140
Usual activities	0.785 ± 0.283	0.958 ± 0.130	0.915 ± 0.167	< 0.001	< 0.001	< 0.001
Mental function	0.875 ± 0.201	0.934 ± 0.142	0.885 ± 0.180	0.001	0.486	< 0.001
Discomfort and symptoms	0.814 ± 0.239	0.936 ± 0.141	0.796 ± 0.197	< 0.001	0.271	< 0.001
Depression	0.828 ± 0.211	0.893 ± 0.169	0.940 ± 0.122	0.001	< 0.001	< 0.001
Distress	0.816 ± 0.223	0.811 ± 0.205	0.941 ± 0.129	0.816	< 0.001	< 0.001
Vitality	0.779 ± 0.230	0.880 ± 0.161	0.821 ± 0.145	< 0.001	< 0.001	0.247
Sexual activity	0.728 ± 0.301	0.866 ± 0.215	0.867 ± 0.224	< 0.001	< 0.001	0.691
15D	0.850 ± 0.143	0.929 ± 0.809	0.914 ± 0.084	< 0.001	< 0.001	0.030

Table 2 - Health-related quality of life dimensions of the respondents compared with age and sex matched Italian and Finnish populations.

Note: all the variables are expressed as mean ± SD. p values are referred to two-sided t test

Variable (N = 205)	Univariate analysis			Multivariate analysis		
	β	95% CI	p	β	95% CI	p
Gender (female)	-0.024	-0.069 ; 0.020	0.278	-0.043	-0.086 ; -0.001	0.045
Age (years)	-0.002	-0.004 ; 0.000	0.066	-0.004	-0.006 ; -0.001	0.003
BMI (Kg/m^2)	-0.002	-0.006 ; 0.002	0.410	-0.001	-0.005; 0.003	0.556
Number of comorbidities (n)	-0.031	-0.052 ; -0.010	0.004	-0.023	-0.043 ; -0.002	0.032
ARDS class[+] (reference class: severe)	0.030	-0.005 ; 0.065	0.065	0.040	0.007 ; 0.073	0.019
SAPS II score	-0.001	-0.003 ; 0.001	0.206			-
SOFA score at ICU admission	-0.001	-0.010 ; 0.009	0.908	0.008	-0.001 ; 0.017	0.073
Intravenous corticosteroids (yes)	0.014	-0.028 ; 0.057	0.504	0.020	-0.020 ; 0.060	0.330
Neuromuscular blocking agents continuous infusion (yes)	-0.002	-0.070 ; 0.066	0.952			-
Prone positioning (yes)	0.031	-0.010 ; 0.072	0.133	0.036	-0.003 ; 0.076	0.076
Vasoactive drugs (yes)	-0.052	-0.093 ; -0.013	0.010	-0.039	-0.079 ; 0.002	0.060
Duration of invasive mechanical ventilation (days)	-0.003	-0.004 ; -0.001	0.001	-0.003	-0.004 ; -0.001	0.001
Tracheostomy (yes)	-0.042	-0082 ; -0.002	0.039	-0.016	-0.058 ; 0.025	0.436
ICU length of stay (days)	-0.002	-0.003 ; -0.001	0.004			-
Renal replacement therapy (yes)	-0.047	-0.123 ; 0.029	0.221			-
ICU stay complications - non pulmonary (yes)	-0.022	-0.063 ; 0.018	0.278			-
ICU stay - infectious pulmonary complications (yes)	-0.007	-0.048 ; 0.033	0.720			-
Marital status - unmarried/non cohabitee	-0.013	-0.059 ; 0.034	0.597			-
Instruction degree - high school or higher	-0.004	-0.045 ; 0.037	0.850			-
Occupational status – employed*	0.146	0.065 ; 0.227	< 0.001	0.105	0.027 ; 0.184	0.009
Occupational status – retiree*	0.141	0.060 ; 0.223	0.001	0.175	0.094 ; 0.257	< 0.001

Table 3 – Linear regression analysis.

Notes: Dependant variable: 15D score. [+] per class increase, reference class: severe ARDS; * Reference category for occupational status: unemployed. Multiple R^2 for the model: 0.2503, Adjusted R^2: 0.1999

Abbreviations: Abbreviations: BMI – Body Mass Index; ARDS – Acute Respiratory Distress Syndrome; SAPS – Simplified Acute Physiology Score; SOFA – Sequential Organ Assessment Score; ICU – Intensive Care Unit

n = 162 patients excluded
- n = 120 only non invasive ventilation
- n = 42 missing data

n = 188 dead in ICU
n = 54 transferred to HDU
n = 182 transferred to medical ward
n = 15 direct transfer to rehabilitation
n = 31 transferred to another ICU out of the study

n = 4 dead at 90 days

n = 205 responded to the Health related quality of life questionnaire

n = 72 missed at follow up
n = 1 refused to respond

n = 632 patients screened for eligibility

n = 470 patients enrolled in the study

n = 282 patients discharged alive from ICU

n = 278 patients contacted 90 days after ICU discharge