

Health-related Quality of Life, Social and Economic Consequences of COVID-19 in Critically Ill Survivors at 6-months Follow-up

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Research

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Abstract

Introduction

Limited evidence exists on the health-related quality of life and the socio-economic impact of disease in critically-ill, COVID-19 survivors. Aims of this study were to: assess the quality of life of survivors after ICU discharge; identify social and disease-related risk factors for long-term health consequences; recognize changes in relational, work and economic skills.

Methods

Critically ill ARDS survivors were followed up 6 months after ICU discharge. Quality of life was assessed using validated tools (SF-36 and EuroQol EQ-5D-5L), and the socio-economic burden of COVID-19 was evaluated with a specifically-translated questionnaire. Independent sample analysis and regression analysis were performed to evaluate the associations between the evaluated factor and the quality of life.

Results

79 survivors were enrolled (age 63 [57-71], 84% male). 38.4% report worsened social relations after ICU discharge; 15.4% required health support, 42% had a change in their employment status and 18% had an income reduction. The average physical and mental SF-36 summary scores were 43.6 [34.4-50.2] and 52.1 [44.5-57.0]. The average EQ VAS quality of life score was 80 [60-89]. Reduced quality of life was found in patients with more than one comorbidity, decreased $\text{PaO}_2/\text{FiO}_2$ (≤ 150) and increased SAPS II score (>25) on ICU admission, and prolonged hospital length of stay (LOS) > 4 weeks. The univariate analysis identified hospital LOS, SAPS II, age and two or more comorbidities as factors associated with reduced quality of life.

Conclusions

COVID-19 survivors have a reduced quality of life, due to an impaired physical and cognitive functioning, while anxiety and depression are less frequent. A significant proportion of patients report worsened social relations, employment changes and income reduction, and require health and financial support. People with previous comorbidities, most severe respiratory failure and prolonged hospital and ICU stay are at higher risk of health-related problems, while the level of education and the premorbid income have no impact in this cohort.

Introduction

Ever since its first description in late 2019, the global pandemic caused by the new SARS-COV-2 virus and the associated COVID-19 disease has caused > 200 million confirmed cases and > 4 million deaths. The clinical spectrum of COVID-19 ranges from asymptomatic cases to highly aggressive respiratory failure, which often leads to rapid and unexpected deterioration and significant mortality even in previously healthy and fully active people [1, 2].

It is increasingly acknowledged how patients who survive critical illness commonly report persistent adverse effects on their health-related quality of life (HR-QoL) in terms both of physical and cognitive impairment, a reduced ability to care for themselves, to perform usual activities of daily living and to participate in social roles as compared to an age and gender-matched population [3–5]. In spite of a huge amount of research on the pathophysiology and management of critically ill patients with COVID-19, only a few studies have assessed post-intensive care discharge persistent symptoms and health-related quality of life [6–10].

All-cause ARDS survivors demonstrated a marked reduction in nearly all physical and mental domains of quality-of-life assessments in the post-discharge period compared with a reference population [11, 12]. Previous data after the Middle East Respiratory Syndrome (MERS) outbreak found that neither physical nor mental component quality of life scores were different between patients with MERS and non-MERS acute respiratory failure; however, critically ill MERS survivors reported lower quality of life than survivors who had not been admitted to the ICU [13]. A recent telephone, follow-up study on 120 COVID-19 patients (of whom only 24 were admitted to an ICU) showed that most patients had persistent symptoms at 4 months after being

discharged, especially fatigue and dyspnea [8]. In the largest cohort study (n = 1733) with the longest (6 months) follow-up, up to three quarters of COVID-19 survivors reported at least one symptom, mainly fatigue or muscle weakness, sleep difficulties, and anxiety or depression, as well as a reduction in the overall quality of life [9].

Besides the effects of critical illness on the perceived physical and mental health, also the socioeconomic determinants and consequences of critical illness have to be considered. A recent exploratory study identified a significant socioeconomic burden following critical illness: a cohort of critical illness survivors showed functional disabilities, faced a negative impact on employment and commonly had a care requirement after discharge from hospital, with a corresponding reduction in their level of income [14].

Indeed, limited attention has been paid on the extent to which the socioeconomic status is linked to the health conditions and the outcomes of COVID-19. According to the extensive literature on the social shaping of health and disease, patients with reduced economic, social, and cultural resources are more likely to experience worse health conditions and lower quality of life, as health is not exclusively the product of individual characteristics, but also the outcome of the contextual dimension in which people are embedded [15, 16], and patients with a higher socioeconomic status show a greater functional recovery after critical illness [17]. During the COVID-19 outbreak in the United Kingdom, morbidity and mortality were found to be related to the socioeconomic characteristics of local areas [18]. Similarly, socioeconomic factors such as being unmarried, not having a computer, or being unemployed were associated with COVID-19 prevalence and/or fatality in the 50 largest American cities [19]. After correcting for age, sex, country of birth, and pre-existing health conditions, socioeconomic indicators such as the educational disadvantage, unemployment, housing crowding, mobility, and population density were significantly associated with the incidence and outcome of COVID-19 in Northern Italy, suggesting a pattern of socioeconomic inequalities in the outbreak [20].

The aim of this study is to: 1) assess the quality of life in a cohort of patients with COVID-19 critical illness and ARDS (i.e. CARDS) 6 months after intensive care discharge and identify long-lasting physical and psychological symptoms impairing normal daily activities; 2) identify social and disease-related risk factors for long-term health consequences; and 3) recognize changes in relational, work and economic skills, quantify any unrecognized need for health and assess the responses of the national health service.

Materials And Methods

Participants

All Covid-19 ICU survivors admitted to two distinct referral hospitals in the Northern Italy region Trentino (S. Chiara Hospital-Trento and S. Maria del Carmine Hospital-Rovereto) between March 5th and April 30th, 2020 were screened for enrolment in this prospective cohort study. The study was approved by the local ethics committee as part of a follow up study on Covid-19 survivors (Azienda Provinciale per i Servizi Sanitari della Provincia di Trento; Protocol number 1/2021). Patients were firstly contacted through an informative phone call, asked for oral or email consent to participate to the study and appointed for a telephone interview at least 6 months after ICU discharge by an ICU physician (AS, SM). Written informed consent was next obtained at an outpatient follow-up visit. At the time of the structured interview patients were administered a set of four questionnaires including EQ-5D-5L, EuroQol Visual Analogue Scale (EQ VAS) Short Form, SF-36 Version 2 (SF-36v2) and a novel question set designed to determine changes in family circumstances, socio-economic stability and care requirements. Patients who refused to participate or were lost at follow up had been excluded. A flow chart of the study is shown in Fig. 1S.

Study design and materials

This study was conducted by a group of ICU physician directly involved in the management of COVID-19 patients during the pandemic surge and interested in understanding the long-term consequences concerning patient quality of life and the socio-economic-relational impact on patients and their families. Expert ICU physicians conducted a structured interview using four different tools. The survey questionnaires included: 1) a multiple choice questionnaire to evaluate the socio-economic-relational

impact on patients and families, previously used in general intensive care survivors in the UK and subsequently adapted to the Italian context with the help of a health sociologist (prof. Annamaria Perino, Department of Sociology and Social Research, University of Trento, Italy), who validated the socio-economic question set [14]. In particular, we collected: demographic and socio-economic data about patients and family; economic and socio-relational impact of the disease and the ICU stay, information on health service utilization and need for care after ICU discharge and observed possible stigmatization processes of the survivor and of their families; 2) The EQ-5D-5L scale; 3) the EQ VAS; and 4) the SF-36v2 scale to assess quality of life.

The EQ-5D-5L scale describes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression [21]. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. A 5L evaluation study has not been conducted in Italy yet. Therefore, neither a crosswalk nor a directly elicited value set is available.

The SF-36 is a 36-item questionnaire frequently used to describe quality of life after ICU care [22, 23], through the investigation of eight health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. For the 36-item questionnaire estimates scores were calculated as recommended in the specific manual and interpretation guide. We also scored Physical (PCS) and Mental (MCS) Component Summary measures using US norms.

Epidemiological and clinical information about ICU stay, severity scores and laboratory data were manually or digitally extracted and recorded from our electronic system. All data were anonymized and saved in Microsoft Excel files. Education levels were classified according to the International Standard Classification of Education (ISCED). ISCED 0: Early childhood education ('less than primary' for educational attainment), ISCED 1: Primary education, ISCED 2: Lower secondary education, ISCED 3: Upper secondary education, ISCED 4: Post-secondary non-tertiary education, ISCED 5: Short-cycle tertiary education, ISCED 6: Bachelor's or equivalent level, ISCED 7: Master's or equivalent level, ISCED 8: Doctoral or equivalent level.

Statistical analysis

Descriptive results for continuous variables are reported as mean (SD) if normally distributed, or median [25th -75th percentiles] otherwise, and as number and percentages when indicated. Eight clinically and epidemiologically relevant variables (i.e. age, education, income, comorbidities, worst PaO₂ to FiO₂ ratio on first day of ICU admission, SAPS, days of mechanical ventilations, length of hospital stay) were selected a priori and dichotomized using meaningful reference values, as relevant to COVID-19 [24] and to grade disease severity, as performed in previous ARDS studies [25], when applicable. Each of the EQ-5D-5L dimensions were grouped in two categories: "no problems" and "some problems", this latter including slight, moderate, severe and extreme problems, if applicable.

Mann Whitney U-test was used for comparisons of non-normally distributed continuous variables. Chi-square test was used when appropriate. Univariate logistic regression analysis with Wald test was used for exploring factors (covariates) associated with problems in each of the EQ-5D-5L domains (dependent variable): pain, mobility, usual activity, self-care problems and anxiety and depression. Reference value for the dependent variables were set as: no problems vs. some problems. Continuous variables were transformed as follows: age/10; PaO₂/FiO₂/100; SAPSII/5; duration of mechanical ventilation(days)/10; hospital length of stay(days)/10. Categorical variables were dichotomized as previously described. Statistical analysis was performed with Jamovi (The jamovi project 2012; version 1.6). For all the comparison, $p < 0.05$ was considered statistically significant.

Results

Of the 93 potentially recruitable patients 6 months after ICU discharge, 79 were included in the study; the others were lost at follow up or denied consent (Fig. 1S). Clinic and demographic data are described in Table 1. In particular, patients were generally highly educated with 51 (64.5%) having an ISCED level > 2; most of the patients lived in small towns (with < 15.000 inhabitants)

and this reflects the geographical composition of our rural territory. All patients suffered acute respiratory failure and ARDS, according to the Berlin definition [26]. 69 patients (87.3%) required mechanical ventilation, whereas 10 (12.7%) received non-invasive ventilation with helmet CPAP only. The median duration of symptom before hospitalization was 7 (5–10) days. Laboratory data and information about ICU treatments are summarized in Table 1.

Table 1

Demographic, socio-economic and clinical characteristics of critically ill COVID-19 survivors responding at follow up

Demographic characteristics	
Number of patients	79
Age (years)	63 (57–71)
Sex N	
Male	66 (83.5%)
Female	13 (16.5%)
Socio-economic characteristics	
Family unit composition	
single	9 (11.4%)
≥ two people	70 (88.6%)
Population of the municipality of residence	
< 15.000	66 (83.5%)
> 100.000	13 (16.4%)
Employment status ^a	
Active worker	33 (41.8%)
Retired	43 (54.4%)
Monthly Income (€)	
<500	4 (5.0%)
500–1000	15 (18.9%)
1000–1500	22 (27.8%)
1500–2000	12 (15.2%)
2000–2500	13 (16.5%)
2500–3000	3 (3.8%)
> 3000	8 (10.1%)
Education	
ISCED 0–2	27 (34.2%)
ISCED > 2	51 (64.5%)

Values are presented as median (25–75% interquartile range) or if categorical as number and percentage. ^aHouswives excluded (N = 3)

BMI, Body Mass Index; SOFA, Sequential Organ Failure Assessment Score; SAPS II; Simplified Acute Physiology Score; RRT, renal replacement therapy; ICU; intensive care unit; LOS, length of stay

ISCED, International Standard Classification of Education. ISCED 0: Early childhood education ('less than primary' for educational attainment), ISCED 1: Primary education, ISCED 2: Lower secondary education, ISCED 3: Upper secondary education, ISCED 4: Post-secondary non-tertiary education, ISCED 5: Short-cycle tertiary education, ISCED 6: Bachelor's or equivalent level, ISCED 7: Master's or equivalent level, ISCED 8: Doctoral or equivalent level

WBC: White Blood Cells; CRP: C-Reactive Protein.

Demographic characteristics	
Clinic characteristics	
Comorbidities	
Hypertension	30 (37.9%)
Diabetes	7 (8.8%)
Chronic liver or kidney disease	0
Ischemic heart disease	6 (7.6%)
Neoplasm	3 (3.8%)
Immunocompromised	0
Asthma and/or COPD	10 (12.7%)
BMI (kg/m ²)	27 (25–29)
Time from symptoms to hospital admission (days)	7 (5–10)
SOFA score on ICU admission	6 (4–7)
SAPS II score on ICU admission	27 (24–33)
PaO ₂ /FiO ₂ on ICU admission (worst)	160 (114–225)
Renal replacement therapy (N)	31 (39.2%)
Prone positioning (N)	35 (44.3%)
Hydroxychloroquine (N)	76 (97.4%)
Steroids (N)	37 (46.8%)
Tocilizumab (N)	16 (20.3%)
Tracheostomy (N)	22(28.2%)
Duration of mechanical ventilation (days)	16 (12–25)
ICU LOS (days)	20 (13–28)
Hospital LOS (days)	40 (29–49)
Laboratory data in the ICU	
Creatinine on admission (mg/dl)	0.92 ± 0.38
Creatinine max (mg/dl)	2.00 ± 2.15
D dimer on admission (µg/mL)	2407 ± 5892

Values are presented as median (25–75% interquartile range) or if categorical as number and percentage. ^aHouswives excluded (N = 3)

BMI, Body Mass Index; SOFA, Sequential Organ Failure Assessment Score; SAPS II; Simplified Acute Physiology Score; RRT, renal replacement therapy; ICU; intensive care unit; LOS, length of stay

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WBC: White Blood Cells; CRP: C-Reactive Protein.

Demographic characteristics	
D dimer max ($\mu\text{g/mL}$)	5821 \pm 9694
WBC on admission ($10^3/\text{mL}$)	9.47 \pm 4.42
WBC max ($10^3/\text{mL}$)	17.28 \pm 7.6
CRP on admission (mg/dl)	113 \pm 81
CRP max (mg/dl)	234 \pm 114
Values are presented as median (25–75% interquartile range) or if categorical as number and percentage. ^a Houswives excluded (N = 3)	
BMI, Body Mass Index; SOFA, Sequential Organ Failure Assessment Score; SAPS II; Simplified Acute Physiology Score; RRT, renal replacement therapy; ICU; intensive care unit; LOS, length of stay	
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WBC: White Blood Cells; CRP: C-Reactive Protein.	

Social and relational life were affected by COVID-19 in a significant proportion of subjects. Table 2 describes the social and relational impact of COVID-19 and the requirement of care after ICU discharge and in the follow-up phase among survivors. Figure 1 shows the economic impact. Description and distribution of met and unmet health professionals needs in critically ill, COVID-19 survivors is shown in Additional file : Fig. 2S.

Table 2
Impact on social relation and requirement of care in critically ill,
COVID-19 survivors at follow up

Social-relational impact	
Worsening of social relation after your return home	
No	48 (61.6%)
yes	30 (38.4%)
If yes (N = 30), have been turned away by	
family members	5 (16.6%)
friends and acquaintances	25 (83.3%)
Requirement of care	
Need for health support	
No	66 (84.6%)
Yes	12 (15.4%)
Need for social support	
No	76 (97.5%)
Yes	2 (2.5%)
Health/personal care need at home	
No need / autonomy	57 (73.1%)
< 20 hours (weekly)	18 (23%)
20–50 hours (weekly)	1 (1.3%)
> 50 hours (weekly)	2 (2.6%)

Health-related quality of life

SF-36

In this cohort of ICU survivors, SF-36 data show a marked reduction in the majority of the domain scores, except for pain and emotional domains, when compared with previously published Italian norms [23] (Additional file 1: Table 1S). Independent samples analysis showed several significantly reduced SF-36 domain scores, both emotional and physical, in patients with comorbidities (more than one) compared to those with no or only one comorbidity, in patients with PaO₂/FiO₂ less or equals to 150, SAPS II score greater than 25 on ICU admission, and with longer hospital stay (longer than 4 weeks), as summarized in Table 3. Notably, patients with a high burden of comorbidities had significantly reduced scores in almost all SF-36 domains (seven out of eight); significant deficits were found in four out of eight domains in patients with worse gas exchanges on admission or prolonged hospital stay; in patients with higher SAPS II, only two out of eight domains were significantly reduced (Table 3).

Table 3

SF-36 domain scores according to demographics, socio-economic and clinical characteristics in critically ill, COVID-19 survivors at follow up

		N = 79	Physical Function	Physical Health	Emotional Problems	Energy Fatigue	Emotional Well Being	Social Function	Pain	General Health
Age (yrs)	≤ 65	43	90	75	100	65	80	75	90	40
			(80-97.5)	(0-100)	(67-100)	(53-70)	(70-88)	(50-88)	(68-100)	(25-60)
	> 65	36	85	12.5	100	55	78	62.5	77.5	48
			(64-95)	(0-100)	(67-100)	(40-71)	(56-88)	(25-100)	(45-100)	(20-70)
	<i>p</i>		<i>p</i> = 0.2158	<i>p</i> = 0.5171	<i>p</i> = 0.9152	<i>p</i> = 0.3882	<i>p</i> = 0.5626	<i>p</i> = 0.4159	<i>p</i> = 0.1615	<i>p</i> = 0.6715
Education (ISCED)	0-2	27	85	50	100	60	84	87.5	90	50
			(80-98)	(0-100)	(100-100)	(45-78)	(64-92)	(50-100)	(68-100)	(20-70)
	> 2	51	85	25	100	55	76	62.5	77.5	45
			(63-95)	(0-100)	(33-100)	(45-70)	(64-88)	(25-88)	(45-100)	(25-60)
	<i>p</i>		<i>p</i> = 0.3815	<i>p</i> = 0.9121	<i>p</i> = 0.1990	<i>p</i> = 0.5873	<i>p</i> = 0.2109	<i>p</i> = 0.1362	<i>p</i> = 0.0920	0.4841
Monthly Income €	≤ 1500	41	85	0	100	55	80	62.5	87.5	45
			(80-95)	(0-100)	(67-100)	(45-70)	(68-88)	(25-88)	(50-100)	(25-60)
	> 1500	35	90	100	100	65	80	75	77.5	50
			(70-98)	(0-100)	(83-100)	(50-70)	(64-88)	(56-100)	(55-100)	(20-75)
	<i>p</i>		<i>p</i> = 0.7281	<i>p</i> = 0.1537	<i>p</i> = 0.7816	<i>p</i> = 0.3575	<i>p</i> = 1.000	<i>p</i> = 0.1844	<i>p</i> = 0.8466	0.2239
Comorbidities	0-1	61	90	50	100	65	80	88	90	50
			(80-100)	(0-100)	(100-100)	(50-75)	(68-88)	(50-100)	(68-100)	(30-70)
	> 1	18	70	0	0	45	62	31	50	15
			(41-90)	(0-100)	(0-100)	(26-55)	(45-80)	(13-75)	(25-85)	(5-45)
	<i>p</i>		<i>p</i> = 0.0037	<i>p</i> = 0.2446	<i>p</i> < 0.0001	<i>p</i> = 0.0010	<i>P</i> = 0.0017	<i>P</i> = 0.0021	<i>P</i> = 0.0018	<i>P</i> = 0.0004
PaO ₂ /FiO ₂ on ICU	≤ 150	34	82.5	0	100	55	80	56	78	33

Data are expressed as median (25th -75th percentile) of transformed SF-36 domains. Data are analyzed with Mann-Whitney U test. P values < 0.05, were considered significant.

ISCED, International Standard Classification of Education. ISCED 0: Early childhood education ('less than primary' for educational attainment), ISCED 1: Primary education, ISCED 2: Lower secondary education, ISCED 3: Upper secondary education, ISCED 4: Post-secondary non-tertiary education, ISCED 5: Short-cycle tertiary education, ISCED 6: Bachelor's or equivalent level, ISCED 7: Master's or equivalent level, ISCED 8: Doctoral or equivalent level; ICU: intensive care unit; SAPS II: Simplified Acute Physiology Score; LOS: length of stay; M: Mechanical Ventilation: duration of mechanical ventilation; LOS: length of stay.

		N = 79	Physical Function	Physical Health	Emotional Problems	Energy Fatigue	Emotional Well Being	Social Function	Pain	General Health
			(65–95)	(0-100)	(0-100)	(41–69)	(58–88)	(25–88)	(38–100)	(16–58)
	> 150	44	90	100	100	60	76	88	90	48
			(80–96)	(0-100)	(0-100)	(50–71)	(64–88)	(50–100)	(55–100)	(29–71)
	<i>p</i>		<i>p</i> = 0.1007	<i>P</i> = 0.0388	<i>p</i> = 0.0330	<i>p</i> = 0.1276	<i>p</i> = 0.4059	<i>P</i> = 0.0225	<i>P</i> = 0.0529	<i>p</i> = 0.0313
SAPS II	≤ 25	28	90	75	100	62.5	78	75	90	37.5
			(85–100)	(0-100)	(67–100)	(55–73.8)	(62–88)	(50–87.5)	(67.5–100)	(16–54)
	> 25	51	85	25	100	55	80	75	77.5	50
			(65–95)	(0-100)	(67–100)	(45–70)	(64–88)	(25–100)	(45–100)	(25–70)
	<i>p</i>		<i>p</i> = 0.0202	<i>p</i> = 0.2835	<i>p</i> = 0.4662	<i>p</i> = 0.1268	<i>p</i> = 0.5614	<i>p</i> = 0.1481	<i>p</i> = 0.0363	0.9283
M ventilation (days)	≤ 15	34	90	50	100	60	78	75	90	40
			(75–99)	(0-100)	(100–100)	(46–70)	(60–88)	(41–88)	(55–100)	(20–69)
	> 15	44	85	38	100	60	80	69	78	45
			(65–95)	(0-100)	(67–100)	(45–70)	(68–88)	(38–100)	(54–100)	(25–61)
	<i>p</i>		<i>p</i> = 0.4920	<i>p</i> = 0.6844	<i>p</i> = 0.3814	<i>p</i> = 0.8595	<i>p</i> = 0.7883	<i>p</i> = 0.8460	<i>p</i> = 0.6661	<i>p</i> = 0.7352
Hospital LOS (weeks)	≤ 4	23	90	100	100	60	84	88	100	45
			(85–100)	(0-100)	(100–100)	(55–80)	(70–88)	(50–100)	(89–100)	(20–63)
	> 4	56	85	0	100	58	76	75	73	45
			(64–95)	(0-100)	(33–100)	(40–70)	(59–88)	(25–88)	(45–100)	(20–65)
	<i>p</i>		<i>p</i> = 0.0344	<i>p</i> = 0.0112	<i>p</i> = 0.0806	<i>p</i> = 0.0411	<i>p</i> = 0.1061	<i>p</i> = 0.0945	<i>p</i> = 0.0025	<i>p</i> = 0.4634

Data are expressed as median (25th -75th percentile) of transformed SF-36 domains. Data are analyzed with Mann-Whitney U test. P values < 0.05, were considered significant.

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No differences were found in regard to age, sex, education family income, and utilization of rescue therapies such as prone positioning, laboratory data (i.e. CRP) or renal replacement therapies (data not shown).

EQ-5D-5L

Health-related quality of life after hospitalization for COVID-19 as assessed by the EQ-5D-5L in ICU survivors in each of the five domains is summarized in Fig. 2. Among the different dimensions, the most reported problems were primarily in pain (49%), mobility (46%) and usual activities of daily life (44%). Less reported problems were anxiety and depression (33%) and difficulties with personal care (22%). The majority of subjects reported slight or moderate problems, from 19% up to 40%, whereas the proportion of subjects reporting most severe health impairments (i.e. not able to do things) in any of the domains ranged from 3 to 11% (Fig. 2A). The proportion of patients reporting full health (no problems in any domain) was 24%, those reporting problems in one or two domains was 26.6% and 13.9%, respectively, those reporting worse health conditions with problems in three, four or all five domains were 11.4%, 16.5% and 7.6% respectively (Fig. 2B). The proportion of patients reporting problems of any severity, was significantly increased in COVID-19 survivors compared to Italian people (norm data) in all domains, except for anxiety and depression (Additional file 1:Table 2S) [27].

A univariate analysis identified factors associated with the occurrence of problems in each of the five EQ-5D-5L domains, as summarized in Fig. 3. Length of hospital stay was significantly associated with an increased risk of problems in four out of five domains (pain and discomfort, mobility, usual activities and self-care). Increased SAPS II was associated with significant problems in three out of five domains, i.e. mobility and usual activities and self care. Age was also associated with an increased risk of problems in two domains (i.e. usual activities and self-care), such as presence of two or more comorbidities (i.e. anxiety and depression and self care).

Summary SF-36 scores and EQ-5D-5L VAS

The average SF-36 physical and mental component summary scores were 43.6 [34.4–50.2] and 52.1 [44.5–57.0]. The average EQ VAS score for overall quality of life was 80 [60–89]. In patients with a high burden of comorbidity, both the SF-36 mental and physical summary scores, and the EQ VAS score were significantly reduced compared to patients with better premorbid status. Worse gas exchange on ICU admission and prolonged hospital stay were associated with significantly reduced physical SF-36 summary score and EQ VAS (Fig. 4 and Additional file 1: Table 3S).

Discussion

The main findings of the present study are: 1) a majority of patients requiring ICU care for COVID-19 critical disease report physical or psychological health-related problems at 6 months after being discharged, such as pain, mobility limitation and impairment in the activities of daily life, while anxiety and depression symptoms were less frequently reported; 2) two well validated and internationally used, different sets of health-related quality of life questionnaires, the SF-36 and EQ-5D-5L, gave similar results; 3) a significant proportion of patients reported a worsening of their social relations, experienced employment changes and income reduction, required health and financial support; 4) the risks of developing health-related problems at 6 months after ICU discharge raised significantly among people with previous comorbidities, most severe disease and respiratory failure and with prolonged hospital and ICU stay, while the level of education and the premorbid income had no impact.

Long-term consequences of COVID-19

In the last decade, an increased awareness towards the long-term consequences of critical illness has been developed, as ensuring good long-term quality of life, rather than simply survive the acute event, has become the main aim of intensive care medicine. Indeed, up to 30% of critical illness survivors develop cognitive, physical, and psychological sequelae, independently of the reason for ICU admission, with a significant burden and costs for patients, caregivers, and society [28]. Follow-up of critical illness survivors has been suggested to facilitate prompt recognition and treatment of such symptoms and improve long-term physical, psychological, and cognitive outcomes [29].

Four out of five ARDS survivors experience some degree of cognitive impairment after ICU recovery [30–32], as well as a high rate of persistent psychological and physical disability, such as muscle weakness and incomplete lung function recovery, chronic fatigue [33] and a reduced quality of life [34]. Moreover, it has been known for a long time that viral infections are characterized by several long-term manifestations [35]. Long-term follow-up of SARS and MERS survivors showed a 30–40% prevalence of post-traumatic stress disorder, depression, anxiety, decrement in mental health, chronic fatigue and reduced

quality of life [36–38]. Similar to other post-acute viral syndromes, emerging literature suggests persistent and prolonged effects after acute COVID-19 [39]. A survey on > 3500 respondents from 56 countries found that systemic and neurological symptoms such as fatigue, cognitive dysfunction, post-exertional malaise, headache, memory troubles, sleep disorders, dizziness and chest tightness were common and persisting at 6 months after virological recovery [40]. While still not entirely understood, the underlying mechanism of the long-term neurocognitive consequences of COVID-19 is likely to be multifactorial and might include the direct effects of viral infection, the immunological response, corticosteroid therapy, ICU stay, social isolation, and stigma [41].

Health-related quality of life after COVID-19

We found that at 6 months after ICU discharge, critically ill survivors of COVID-19 reported significantly lower HR-QoL domain scores compared to population norms, with the exception of pain and emotional problems. Anxiety and depression symptoms were also not significantly different compared to population norms, when using EQ-5D-5L as evaluation tool. It is debated if COVID-19-related acute respiratory failure could be defined as a classic form of ARDS from a pathophysiological point of view [42]. However, in terms of supportive therapy, the disease seems to be similar to the severe forms of classic ARDS, requiring endotracheal intubation, deep sedation, prolonged mechanical ventilation and ICU stay. Indeed, the HR-QoL profile observed in our cohort of patients is not dissimilar to those observed in non-COVID ARDS survivors [43, 44] or in survivors of ARDS due to other viral infections [45].

As a matter of fact, the physical and psychological sequelae of COVID-19 may even be more frequent than classic ARDS, because of the restriction of visitation and the limitations to social and rehabilitation supports. Of note, only few other studies assessed the health-related quality of life in follow-up studies after severe cases of COVID-19. A preliminary report of a 3-month, French follow-up study on 54 ICU survivors found that all patients reported an impaired quality of life, and up to 80% described pain or discomfort in their daily life, almost half complained about mental health disturbances and worsened mobility due to muscular weakness [46]. Garrigues et al. compared patients managed in hospital wards, with those who were transferred to the ICU, and found that most patients report persistent symptoms after 4 months from hospital discharge, especially fatigue and dyspnea, and except for pain and discomfort, there was no significant difference regarding persistent symptoms and HR-QoL between ward and ICU patients [8]. Monti et al. performed a 2-months follow-up in a small cohort of 39 consecutive COVID-19 invasively ventilated patients; they found that the overall quality of life was reduced to a similar extent as we found, with cognitive and psychological scales showing no impairment, and the most affected dimensions being self-care, usual activities and pain [47]. In a cohort of 205 mechanically-ventilated critically ill COVID-19 patients from 16 ICUs, the HR-QoL at 90 days after ICU discharge was significantly lower than sex and age-matched random sample population not affected by COVID-19 in both physical (mobility, ability to speak, ability to eat) and mental (discomfort, depression, vitality, sexual activity) dimensions [48]. In a three-month follow-up study, about three out of four C-ARDS survivors showed pulmonary structural abnormalities at chest CT-scan and a reduced lung diffusing capacity, together with symptoms of dyspnea and cough and a reduced self-reported physical and mental quality of life [10]. In the largest cohort study with the longest follow-up duration assessing the health consequences of adult COVID-19 patients discharged from hospital, at 6 months after symptom onset, most patients reported at least one symptom, particularly fatigue or muscle weakness, sleep difficulties, and anxiety or depression, with more severely ill patients having an increased risk of fatigue or muscle weakness, anxiety or depression [9].

At variance with other studies, anxiety and depression were far less frequently reported in our cohort of survivors. We wonder whether this might depend on the relatively younger age or prevalent male sex of the patients we enrolled [49], or the peculiar characteristic of the national and regional social support system. As a matter of fact, the Autonomous Province of Trento has shown that it also mobilizes social services in the emergency and in the actions to combat the spread of the virus, providing support to people and communities. The project ""#Restaacasapassoio" is an example. Involving the territorial network of volunteers, it tried to provide answers both to basic needs (food, medicines, connections for computer, transport of medical devices, etc.), as well as to emotional-psychological needs, offering relational support at a distance [50].

Social and economic burden of recovery after COVID-19 critical illness

To the best of our knowledge, this is the first study to investigate the socio-economic impact of COVID-19-related critical illness. More than one third of the patients who were discharged from our ICU report a worsening of their social relations after returning home and about 15% require some form of health support during the first 6 months after discharge. About 40% of the patients did not return to their previous employment, and about one in 5 suffered from an income reduction. This is not unexpected, as a recent systematic review found that about two-thirds of previously employed intensive care unit survivors are jobless up to 3 months following hospital discharge, while those returning to work often experience job loss, occupation change or worse employment status [51].

As for care received by COVID-19 survivors, this was mainly provided by family members; moreover, about one out of four caregivers reported a change in their employment status. In a UK study, Griffiths and coll. found that one quarter of patients followed up after ICU discharge reported themselves in need of assistance with care at 6 months; reduction in employment and disruption in lifestyle were common in the caregivers, and a negative impact on employment and on reported family earning sources and income was experienced by about 20% of respondents [14]. This is also underlined by a recent research conducted in Italy, which identified economic and food support as the most urgent needs to which social services must respond. The massive use by the Municipalities of the Fund established by the Civil Protection for the food emergency highlighted the connection between the request for food support and the loss of work due to the lockdown or for having contracted the virus [52].

Determinants of health-related quality of life

We found that the number of comorbidities, the severity of gas exchange impairment at ICU admission, the duration of mechanical ventilation and of hospital stay were associated with a lower perceived quality of life in ICU survivors. ARDS class, prolonged mechanical ventilation and comorbidities are known to be associated with worse scores in HR-QoL in “classical” ARDS survivors [43, 44]. In a recent study, the HR-QoL of severe COVID-19 ICU survivors was significantly associated with age, sex, number of comorbidities, the severity of ARDS, duration of invasive mechanical ventilation, and occupational status, while the marital status and degree of instruction were not [48]. A recent prospective cross-sectional global online survey using social media assessed > 700 COVID-19 survivors and their caregivers’ health-related quality of life, and found how survivors who were hospitalized for COVID-19 or who had existing health conditions reported significantly more problems on their physical and psychosocial health [53]. Hypertension and diabetes mellitus are among the most prevalent comorbidities in COVID-19 patients and often coexist as multiple comorbidities, as in our cohort. Age was only marginally associated with worse ICU outcome in this cohort, however age is embedded within the critical illness severity scoring systems such as SAPSII, which was found significantly associated with several reduced HR-QoL domains.

Quite unexpectedly, neither the education status nor the monthly income were found to be associated with any health-related quality of life domain. However, these social variables are known to play a significant role in determining the quality of life [54], and a recent French investigation found that long-term physical recovery appeared to be poorer prolonged psychiatric symptoms were common in the socially deprived ICU survivors [17]. On the one hand, a number of studies have identified factors such as material living conditions (housing and neighborhood), health behaviors, early childhood conditions and psychosocial stress as important factors underlying the association between social status and health [55]. On the other side it is also possible that, at 6 months from ICU discharge, the entity of disability related to clinical factors still outweighs the social aspects in determining HR-QoL. Another possible explanation to these apparently conflicting results is that the Italian context (and even more the Autonomous Province of Trento), as compared to that of the other studies, despite worse job indicators and lower average incomes, is characterized by a higher degree of social and family support, a better work-life balance and an easier access to the health care system, with a lower influence of the education level on life expectancy [56]. This might have counterbalanced the baseline inequality in patient income or education level [57, 58].

Limitations

Several limitations of this study need to be acknowledged: as with any follow-up study the loss-to-follow-up rate may limit the generalizability of the results; this phenomenon was however comparable to other studies [8, 14, 46, 47]. The patient cohort was relatively small, but homogeneous. This can be considered a limitation, or more likely, a positive aspect. Moreover, we had

limited medical information on potential predictors that may have influenced the reported HR-QoL, such as the dose and the duration of sedatives and neuromuscular blocking agents that have been shown to affect long-term outcomes. Eventually, we were not able to evaluate the impact on patient relatives and caregivers. At variance with the majority of the studies dealing with this topic, patient follow up was performed by a telephone interview conducted by a physician previously involved in patient management.

Conclusion

At 6 months after ICU discharge, a high proportion of patients who had recovered from COVID-19-related critical illness report a reduced quality of life, due to an impaired physical and cognitive functioning and a delay or inability to return to work; people with previous comorbidities, most severe respiratory failure and with prolonged hospital and ICU stay are at higher risk of experiencing health-related problems.

These results suggest that patients with severe disease or more comorbidities may need post-discharge care. While we wait for longer follow-up studies in a larger population, which are necessary to understand the full spectrum and the duration of health consequences from COVID-19, we highlight the need for a multidisciplinary follow-up, involving different healthcare (such as physiotherapists) and social sector professionals (in particular social workers, who played an active role in the management of social fragilities highlighted by the health emergency) [59], able to give integrated answers that are fundamental for an adequate recovery and rehabilitation after COVID-19 critical illness. SF-36 and EQ-5D-5L questionnaire may be both valid and complementary tools to identify COVID-19 ICU survivors with persistent symptoms of Long COVID-19 and reduced quality of life.

Because of the scale of this pandemic, disability related to COVID-19 may represent the next public health crisis and both healthcare professionals and decision-makers should focus on this still unrecognized and underdiagnosed burden and find reliable and cost-effective strategies to screen patients for selective rehabilitative interventions.

Abbreviations

COVID-19: coronavirus disease 2019

ICU: Intensive Care Unit

ARDS: Acute Respiratory Distress Disease

SF-36: 36-item Short Form health survey

EuroQoL: European Health-Related Quality of Life

HR-QoL: Health-Related Quality of Life

EQ-5D-5L: five levels five dimensions EuroQoL

EQ VAS: EuroQoL-Visual Analog Scale

SAPS II: Simplified Acute Physiology Score

PaO₂: Partial Pressure of arterial oxygen

FiO₂: Inspired Fraction of Oxygen

Declarations

Ethics approval and consent to participate

Consent was waived for the initial admission data, while it was acquired at the time of follow-up. The study was approved by the the ethics committee (Azienda Provinciale per i Servizi Sanitari della Provincia di Trento) as part of a follow up study on Covid-19 survivors (Protocol number 1/2021).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests in this section.

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Authors' contributions

Study design and data collection: AS, SMI, EB, SL

Writing original draft: MU, SM

Data analysis: SM, AC

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Figures

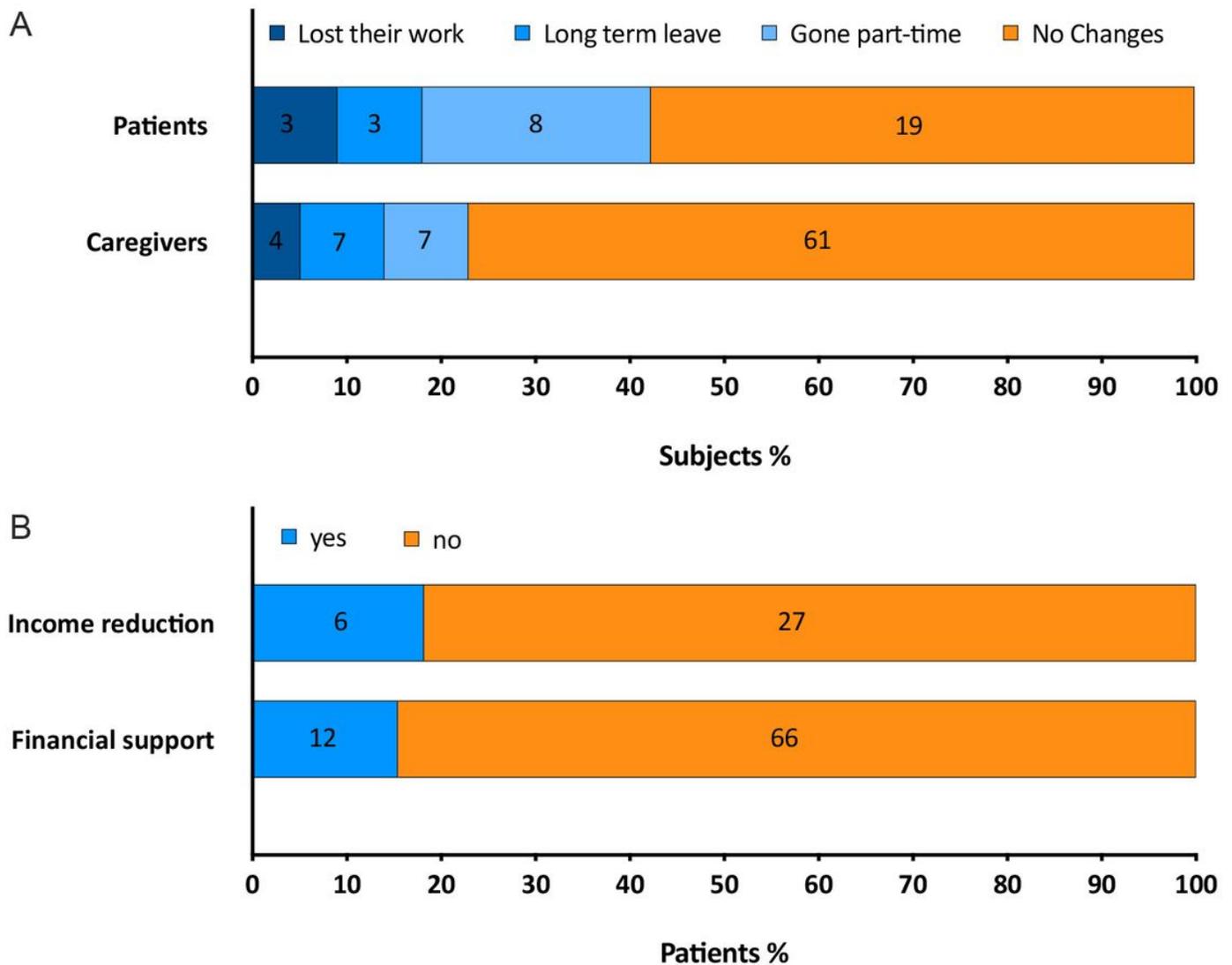


Figure 1

Economic impact in critically ill COVID-19 survivors at follow up. A) Employment changes in active working patients (N =33) and caregivers (N=79). B) Proportion of active working patients (N=33) experiencing an income reduction and proportion of patients (all) receiving financial support. Numbers on the bars are the subjects numbers.

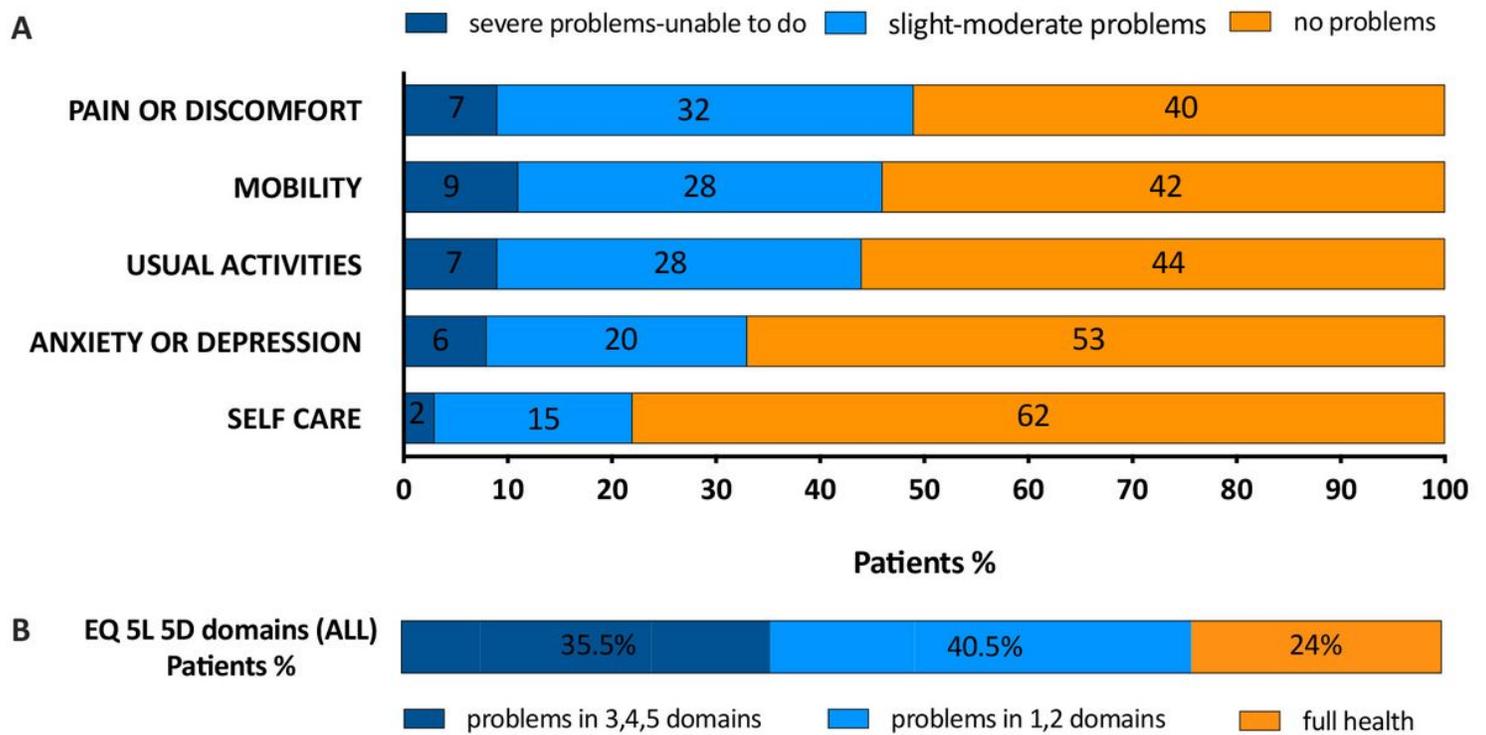


Figure 2

Health-related quality of life scale (EQ-5D-5L) in critically ill COVID-19 survivors at follow up. The figure represents the A) frequency distribution of the EQ-5D-5L scores in each of the five domains (pain or discomfort; mobility; usual activities; anxiety and depression; self care). Each domain is scored on a 5-point scale: 1 no problems, 2 slight problems, 3 moderate problems, 4 severe problems, 5 unable to do. In the figure scores are grouped in three classes: no problems; slight to moderate problems; severe problems or unable to do. Numbers on the bars are the patients numbers. B) frequency distribution of of the EQ-5D-5L scores among patients grouped as: full health=no problems in any domain; problems in 1 or 2 domains; problems in 3 up to 5 domains.

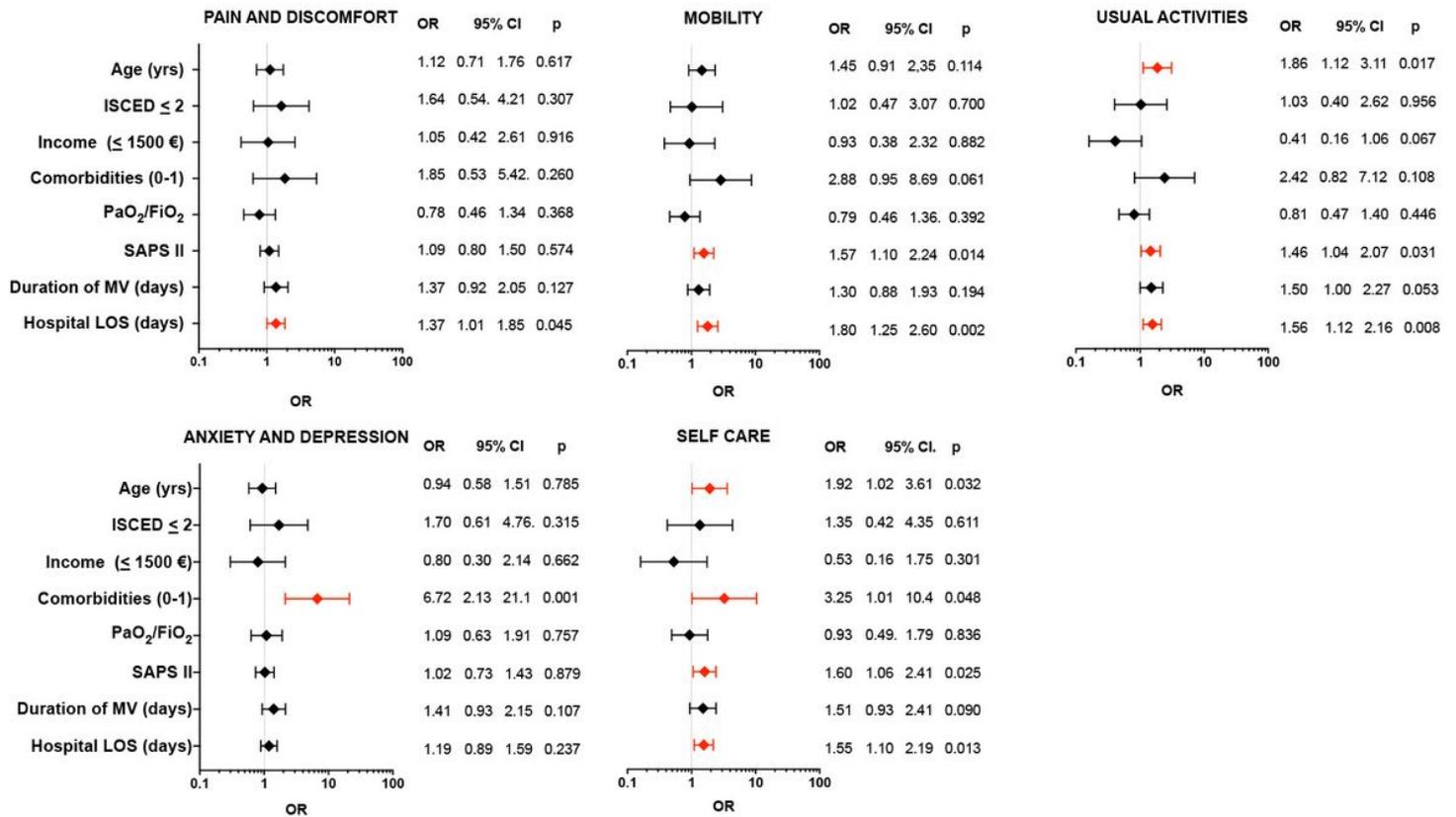


Figure 3

Univariate analysis of demographics, socio-economic and clinical factors associated with Health-related quality of life (EQ-5D-5L) in critically ill COVID-19 survivors at follow up. The figure shows the results of the univariate analysis of factors associated with problems (of any severity) in each of the five EQ-5D-5L domains (dependent variable) and the correspondent forest plots. In red, variables significantly associated with the occurrence of problems in each single domain. Reference value for the dependent variable: no problems vs some problems. Covariate values are on the y axis, with reference values and/or unit of measure in brackets when applicable (factors). Variables were transformed as follows: age/10; PaO₂ to FiO₂/100; SAPS II/5; duration of mechanical ventilation (days)/10; hospital LOS (days)/10. SAPS II: Simplified Acute Physiology Score; MV: mechanical ventilation; LOS: length of stay.

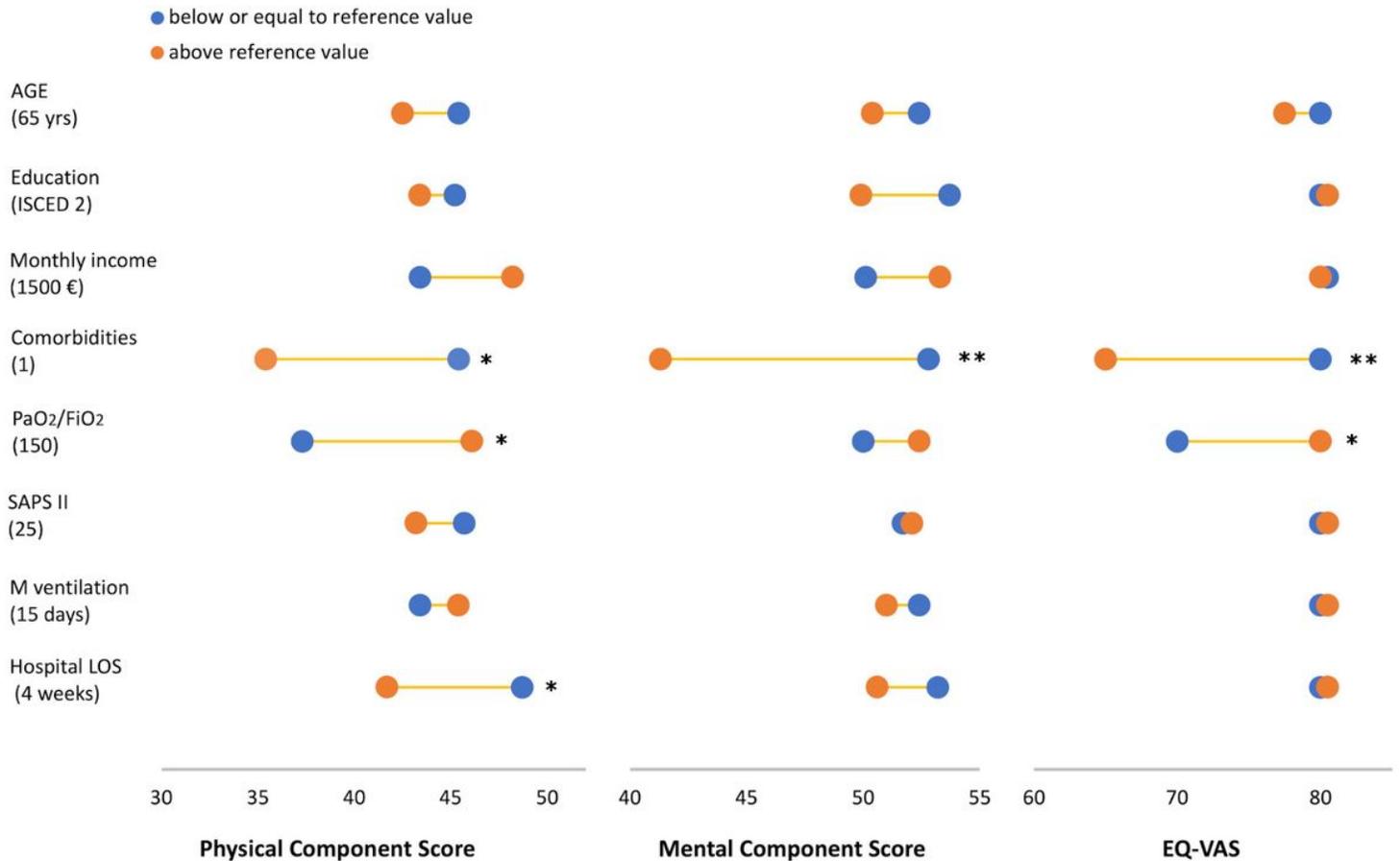


Figure 4

Physical and mental component score of SF-36 and EQ-5D-5L visual analogue scale score (EQ-VAS) according to demographics, socio-economic and clinical characteristics in critically ill COVID-19 survivors at follow up. Lolly plot graph showing the differences between median values of the calculated physical and mental scores of SF-36 and EQ-VAS (EQ-5D-5L visual analogue scale) among dichotomized variables. Reference values are shown in brackets on the Y axes. Variables associated with significantly different physical, mental SF-36 scores and EQ-VAS, analyzed by Mann-Whitney U test (details and numbers are reported in Additional file 1:Table 3S). *indicates $p < 0.05$, **indicates $p < 0.01$.

Supplementary Files

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