Submitted: 10 February, 2022 Accepted: 23 March, 2022 Published: 08 March, 2023 DOI:10.22514/sv.2022.036

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ORIGINAL RESEARCH

One year health-related quality of life after discharge: a prospective cohort study among COVID-19 ICU survivors

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Abstract

Considering the paucity of data on long-term Health-Related Quality of Life (HRQoL) in coronavirus disease 2019 (COVID-19) intensive care unit (ICU) survivors, we present one-year follow-up results on patients' HRQoL and compare them with those of the already reported 6-month follow-up. We conducted a prospective cohort study of patients in COVID-19 ICU between March and June 2020. A HRQoL analysis was performed six months and 1 year after discharge by means of a short-form-36 (SF-36) questionnaire. Hospital mortality in 403 ICU COVID-19 patients was 44.9%; further 4.0% died between hospital discharge and 6-month follow-up and only 0.5% died in the next six months. The median physical component of HRQoL increased from 43.7 (interquartile range (IQR): 31.7–52.7) at 6 months to 46.0 (IQR: 38.0–53.0) 1 year after hospital discharge ($p = 0.007$). In multivariable regression analysis, age >50 (odds ratio (OR) 0.270) and female sex (OR 0.144) were independently associated with reduced physical HRQoL 1 year after discharge. The median mental component of HRQoL increased from 50.6 (IQR: 42.0–55.8) at 6 months to 53.0 (IQR: 47.0–56.0) 1 year after discharge ($p = 0.035$), with no significant predictors. Increased HRQoL was associated with an improvement in patients' physical status, role functioning, emotional well-being (all $p < 0.001$) and social functioning ($p = 0.007$). ICU COVID-19 patients' HRQoL slightly improved 1 year after discharge, when compared to results of the 6-month follow-up. Medications received during ICU stay had no effect on physical or mental HRQoL.

Keywords

COVID-19 survivors; Quality of life; SARS-CoV-2; SF-36 scale; Long-term outcome; Intensive care

1. Introduction

While the epidemiological and clinical features, pathogenesis, and complications of patients with Coronavirus Disease 2019 (COVID-19) are well known, the long-term consequences of this disease are still a matter of debate. Therefore, it is fundamental that, while prescribing different types of therapy, we should not only keep in mind the short-term consequences of the treatment, but also the long-term ones.

COVID-19 patients discharged from intensive care units (ICUs) are at high risk of developing the "post-intensive care syndrome (PICS)" [1–3], which consists of a mix of long-term somatic, psychological and cognitive impairments [4–6]. Few manuscripts described mid-term (4 months) consequences of COVID-19 with regards to Health-Related Quality of Life (HRQoL) [7–10]. According to the latest 1-year follow-up studies assessing the quality of life of COVID-19 patients, the main persistent complaints are fatigue, shortness of breath and neurological disorders [11]. Two manuscripts analyzed 1-year quality of life after discharge, identifying dyspnea and low exercise capacity as common complaints among survivors of severe COVID-19 [12, 13], who referred slow or no symptom improvement over time. One large case series reported 6-month and 1-year follow-up in hospital survivors with most patients having a good physical and functional recovery and being able to return to their original work and way of life [14, 15].

In our previous cohort study, which focused on 6-month follow-up after discharge, only one-third of ICU survivors did not report serious physical health concerns [16]. The aim of this prospective cohort study was to comprehensively compare health implications at 6 and 12 months after discharge among COVID-19 ICU survivors.

2. Methods

2.1 Study Design and Participants

This prospective cohort study included a convenience sample represented by all COVID-19 patients admitted to the ICU of a research hospital, which was adapted to become a COVID-19 center between March and June 2020. The exclusion criteria were: age <18 years, transfer to another hospital regardless of the cause (n = 88), a preliminary diagnosis of COVID-19 that was not confirmed after additional examination (n = 66) and nonfatal cardiac arrest before or at the time of admission to the ICU (n = 13). Criteria for ICU admission are specified in the Supplement (**Supplementary Table 1**).

Health-related quality of life at 1 year follow-up, starting from the day of patient hospital discharge, was designed as the primary endpoint. The secondary endpoints of the study were the components of the physical and mental quality of life (**Supplementary material**). The SF-36 was used to assess HRQoL [17]. A special electronic form was employed for the survey. The patient filled in the data on his/her own or with the help of a medical specialist (**Supplementary material**). Specially trained medical staff made up to three attempts to contact patients by telephone (six months and one year after patient discharge). After patients verbal consent to participate, a letter containing a login and password to access the survey was sent. Moreover, the authors attached an informed consent form to the letter, kindly requesting it to be completed and sent back. If it was not possible to contact the patient, it was marked off as "lost to follow-up".

2.2 Demographics and disease-related characteristics

The collected socio-demographic variables were age, sex, height, weight, and body mass index (BMI). Disease-related characteristics included comorbidities, need of mechanical ventilation, P/F ratio (PaO_2/FIO_2 ratio) and laboratory parameters at the time of ICU admission (**Supplementary Table 2**). Patient's condition at admission was assessed using the National Early Warning Score (NEWS) [18] and its latest version NEWS2 [19], as well as the Sequential Organ Failure Assessment (SOFA) score. The following comorbidities were recorded: Charlson comorbidity index [20] (**Supplementary material**); chronic obstructive pulmonary disease, cerebrovascular insufficiency, peripheral artery disease, diabetes, arterial hypertension, myocardial infarction, atrial fibrillation, coronary heart disease, congestive heart failure, chronic kidney disease, liver failure, diabetic organ damage, peptic ulcer, hemiplegia and cancer. The length of stay (LOS) in the hospital (total LOS and LOS before transfer to the ICU) and the ICU LOS were also assessed. Medical therapy in the ICU was collected: anticoagulant therapy (Enoxaparin or Unfractionated Heparin with the choice at the discretion of the attending physician), anticytokine therapy (Tocilizumab) as well as Hydroxychloroquine, antiviral therapy and antibiotic therapy. Additional information on prescribed regimens is provided in **Supplementary Table 3** and ICU complications are listed in **Supplementary Table 4**. Data were collected by trained research associates.

2.3 HRQoL assessment

HRQoL analysis was performed using the SF-36 Health Status Survey [17]. This is a standardized non-specific questionnaire, representing one of the most widely used indicators of health in Europe and the United States concerning human quality of life [21]. SF-36 consists of 11 questions and 36 items, combining 8 health areas (domains or subscales, see **Supplementary material**): Physical Functioning (PF), Role Limitations Due to Physical Problems (RP), Role Limitations Due to Emotional Problems (RE), Vitality (VT), Mental Health (MH), Social Functioning (SF), Bodily Pain (BP) and General Health (GH). Physical functioning, role limitations due to physical problems and bodily pain subscales contribute primarily to the physical component of HRQoL (physical health), while social functioning, emotional well-being and role limitations due to emotional problems affect the mental component of HRQoL (mental health) [22]. The two remaining domains, general health and vitality, are associated with both physical and mental components. The scores are expressed as a range from zero, when the respondent has the worst possible health, to 100, when the respondent is in the best possible health. The subscale scores are then converted by using Z-scores and weighted to obtain the values used to calculate the scores for the physical and mental components of health-related quality of life. Physical health and mental health are integral indicators, while each subscale allows for a more accurate characterization of individual elements of the patient's health-related quality of life. The reference level for all subscales, physical health and mental health is 50 points and is obtained in general population studies in the USA, Italy, Australia and France [21]. Subsequently, patients were divided into two groups depending on the physical and mental components as follows: (1) less than 50 points (reduced HRQoL) and (2) 50 or more points (normal HRQoL).

2.4 Statistical analysis

All quantitative values were presented as medians (interquartile range—IQR) for continuous variables and reported as absolute values along with percentages for categorical variables. Normality of data distribution was assessed using the Shapiro-Wilk test. To compare demographics, clinical characteristics and health-related quality of life parameters, the Wilcoxon rank-sum test (Mann-Whitney U-test for continuous variables, independent samples) or Wilcoxon signed-rank test (for continuous variables, related samples-comparison of HRQoL after 6 months and 1 year after discharge), as well as Fisher's exact test (for nominal data, independent samples) and McNemar's test (for nominal data, related samples) were adopted. The participants were divided into groups according to their health-related quality of life 1 year after discharge (reduced health-related quality of life on the SF-36 scale-physical or mental component <50; normal health-related quality of life—component values ≥50). Boxplot diagrams were used to graph the median and quartiles of HRQoL parameters for different groups. Spearman's rank correlation coefficient was used to assess the strength of the relationship between quantitative predictors (correlations were plotted and a "heatmap" diagram was created—the "Seaborn 0.11.1" library for "Python 3.7" in

the "PyCharm" environment was used for development).

Multivariable analysis based on binary logistic regression with an estimate of the adjusted odds ratio (adjusted OR) and its 95% confidence interval (CI) was used to determine independent predictors of patients' health-related quality of life in view of the presence of potential bias variables (severity of the condition, comorbidity, co-administration of drugs, *etc*.). A stepwise inverse method (likelihood ratio) was used to include predictors in the regression model. This method begins by fitting a model with all predictors and discarding the least significant factors at each stage until only significant independent predictors of outcome remain in the model. To assess the quality of the parameters as predictors of HRQoL, we used the receiver operating characteristic (ROC) analysis with the estimation of the area under curve (AUC) parameter and its 95% CI. For sensitivity investigation, we performed an analysis on outcomes of different cut-off values chosen to achieve the optimal sensitivity/specificity ratio according to the results of the ROC analysis (Youden's J statistic). Comparison of the predictive ability of quantitative parameters (comparison of AUCs) at 6 months and 1 year after discharge was carried out using the DeLong method with the assessment of the Z-test [23]. Positive and negative predictive values were also assessed for the selected cut-off point. If more than 10% of laboratory parameters were missing, an additional note was included in the data table.

All statistical analyses were performed using IBM SPSS Statistics for Windows® Software version 25 (IBM Corp., Armonk, NY, USA) and MedCalc® Statistical Software version 19.5.6 (MedCalc Software Ltd, Ostend, Belgium). The significance level was set at 0.05.

3. Results

3.1 Baseline characteristics

Overall, 222 out of 403 (55.1%) COVID-19 patients previously admitted to the ICU from March to June 2020 were discharged from the hospital: they were 62 ± 15.3 years old (range from 21 to 97) and 57% were men. Eighteen patients (18/403 = 4.5%) died after hospital discharge and within one year. 103 patients (65 men, 63.1%) agreed to take part in this research project and signed the informed consent 1 year after discharge, while the other 101 discharged patients either refused the survey (n = 47) or were lost for follow-up (n = 54) (Fig. 1).

To assess population representativeness, we performed a comparison of baseline characteristics and prescribed therapy in 103 patients who completed the SF-36 forms versus those 119 who did not (died, refused the survey or were lost to follow-up). In general, these groups were comparable in terms of baseline characteristics, severity of the condition upon admission to the ICU and length of stay (all $p > 0.05$), however, patients who did not complete the SF-36 formless frequently received Tocilizumab (19.3% *vs.* 40.8%, $p = 0.001$) and antiviral therapy (20.2% *vs.* 33.0%, $p = 0.03$) (Table 1).

3.2 HRQoL of overall group and its comparison to the general population

Overall, at 1 year follow-up, 62 patients (60.2%) had a reduced health-related quality of life with regards to the physical component (reduced physical health) while 36 patients (35.0%) had a reduced health-related quality of life as to the mental component (reduced mental health). Female gender was associated with a worse physical health status—the proportion of women in the cohort of patients with a normal physical component of HRQoL was only 12.2% (5/41) (Table 1). Patients that perceived reduced levels of the physical HRQoL component were significantly older—the percentage of patients in the 50+ category was 83.9% (52/62) in the group of patients with reduced physical health and 53.7% (22/41) in the group of patients with a normal health-related quality of life, Fisher's exact test: $p = 0.001$ (Table 1). Patients with normal and reduced physical and mental health were comparable in terms of other medical and demographic parameters, which included illness severity during hospitalization, length of stay in the hospital and in the ICU (Table 1), laboratory test results at the time of hospitalization (**Supplementary Table 3**) and incidence of complications in the ICU (**Supplementary Table 4**).

According to the results of univariate analysis, the prescription of low molecular weight heparin (LMWH), unfractionated heparin (UFH), interleukin-6 (IL-6) blockers, hydroxychloroquine, antiviral drugs and antibiotics was not associated with changes in physical and mental health 1 year after discharge (Table 1).

Patients with chronic obstructive pulmonary disease (COPD) (Fisher's exact test: $p = 0.025$), peripheral artery disease (Fisher's exact test: $p = 0.01$), and a history of hypertension (Fisher's exact test: $p = 0.014$) were more likely to perceive a reduced level of quality of life related to the physical component HRQoL at 1-year follow-up (Table 2). In addition, a higher Charlson comorbidity index was observed in patients with reduced physical health-2 (IQR: 1 to 4) versus 1 (IQR: 0 to 3), Mann-Whitney U test: $p = 0.024$. Comorbidities had no effect on the mental component of health (Table 2).

According to the results of the ROC analysis, the age of patients at the time of hospitalization was a significant predictor of reduced physical health (AUC: 0.72, 95% CI: 0.62 to 0.82, $p < 0.001$). The optimal cut-off point was set at 50.0 years (Sensitivity: 46.3%, 95% CI: 30.4% to 62.6%; Specificity: 83.9%, 95% CI: 72.3% to 92.0%, positive predictive value (PPV): 65.5%, 95% CI: 50.0% to 78.6%; negative predictive value (NPV): 70.3%, 95% CI: 63.5% to 76.2%) (Fig. 2).

3.3 HRQoL from six months to 1 year

The proportion of patients with a normal mental health increased 1 year after discharge, compared to the six-month period outcomes (McNemar's test: $p = 0.033$) (Table 3). At the same time, the proportion of patients with a normal physical health component did not change after 1 year (McNemar's test: $p = 0.3$).

One year after discharge, there was an increase in both physical health (46.0 (IQR: 38.0 to 53.0) versus 43.7 (IQR: 31.7 to 52.7), Wilcoxon signed-rank test: $p = 0.007$, Fig. 3A) and mental health (53.0 (IQR: 47.0 to 56.0) versus 50.6 (IQR:

TABLE 1. Descriptive statistics: patient characteristics and prescribed therapy in patients with normal/reduced quality of life 1 year after discharge.

Parameter	Completed SF-36 at 1 year	Did not complete SF-36 at 1 year	*p*-value, completed *vs.* lost	Patients with a reduced physical health	Patients with a normal physical health	*p*-value, physical health	Patients with a reduced mental health	Patients with a normal mental health	*p*-value, mental health
	N = 103	N = 119		N = 62	N = 41		N = 36	N = 67	
Medical and demographic parameters									
Sex F	38 (36.9%)	57 (47.9%)	0.8	33 (53.2%)	5 (12.2%)	<0.001	12 (33.3%)	26 (38.8%)	0.7
Age 50+ years	74 (71.8%)	84 (70.6%)	0.1	52 (83.9%)	22 (53.7%)	0.001	28 (77.8%)	46 (68.7%)	0.4
BMI, kg/m^2	28.0 (IQR: 25.7–33.0)	28.0 (IQR: 25.7–33.0)	0.3	28.0 (IQR: 25.7–35.4)	27.8 (IQR: 25.3–32.7)	0.7	31.0 (IQR: 25.8–35.4)	27.8 (IQR: 25.3–33.0)	0.3
Mechanical ventilation in ICU	5 (4.9%)	7 (5.9%)	0.8	2 (3.2%)	3 (7.3%)	0.4	1 (2.8%)	4 (6.0%)	0.7
*PaO_2/FiO_2 ratio on ICU admission	241 (IQR: 186–326)	325 (IQR: 300–380)	0.1	241 (IQR: 172–350)	245 (IQR: 182–296)	0.9	299 (IQR: 137–387)	207 (IQR: 186–285)	0.5
Characteristics of the severity of the condition upon admission									
SOFA, score	1.0 (IQR: 1.0–2.0)	1.0 (IQR: 1.0–2.0)	0.8	1.0 (IQR: 1.0–2.0)	1.0 (IQR: 1.0–2.0)	0.9	1.0 (IQR: 1.0–2.0)	1.0 (IQR: 1.0–2.0)	0.8
NEWS, score	7.0 (IQR: 5.0–9.0)	7.0 (IQR: 5.0–8.0)	0.5	7.0 (IQR: 5.5–9.0)	6.0 (IQR: 5.0–8.0)	0.2	7.5 (IQR: 5.0–8.0)	7.0 (IQR: 5.0–9.0)	0.8
NEWS2, score	9.0 (IQR: 7.0–10.0)	9.0 (IQR: 7.0–10.0)	0.8	9.0 (IQR: 7.0–10.0)	8.0 (IQR: 7.0–9.0)	0.1	8.0 (IQR: 7.0–10.0)	9.0 (IQR: 8.0–10.0)	0.5
Length of stay, days									
In hospital	16.0 (IQR: 13.0–21.0)	16.0 (IQR: 11.0–21.0)	0.4	16.0 (IQR: 12.0–21.0)	16.0 (IQR: 13.0–21.5)	0.7	17.5 (IQR: 12.3–22.8)	16.0 (IQR: 13.0–20.0)	0.5
In ICU	3.0 (IQR: 5.0–7.0)	4.0 (IQR: 3.0–7.0)	0.4	4.0 (IQR: 3.0–7.3)	6.0 (IQR: 3.0–7.5)	0.4	3.0 (IQR: 2.0–7.0)	6.0 (IQR: 3.0–8.0)	0.07
Hospital stay before ICU admission	2.0 (IQR: 0.0–4.0)	2.0 (IQR: 0.0–4.0)	0.3	2.0 (IQR: 0.0–4.3)	2.0 (IQR: 0.5–4.0)	0.9	2.5 (IQR: 0.0–5.0)	2.0 (IQR: 0.0–4.0)	0.5
Prescribed therapy									
Enoxaparin	67 (56.8%)	63 (61.2%)	0.6	37 (59.7%)	26 (63.4%)	0.8	18 (50.0%)	45 (67.2%)	0.1
Unfractionated Heparin	32 (26.9%)	31 (30.1%)	0.7	21 (33.9%)	10 (24.4%)	0.4	13 (36.1%)	18 (26.9%)	0.4
Tocilizumab	23 (19.3%)	42 (40.8%)	0.001	25 (40.3%)	17 (41.5%)	0.9	14 (38.9%)	28 (41.8%)	0.8
Hydroxychloroquine	68 (57.1%)	70 (68.0%)	0.1	39 (62.9%)	31 (75.6%)	0.2	23 (63.9%)	47 (70.1%)	0.5
Antiviral therapy	24 (20.2%)	34 (33.0%)	0.03	20 (32.3%)	14 (34.1%)	0.9	10 (27.8%)	24 (35.8%)	0.5
Antibiotics use	119 (100.0%)	102 (99.0%)	0.5	61 (98.4%)	41 (100.0%)	0.9	36 (100.0%)	66 (98.5%)	0.9

Abbreviations: ICU: intensive care unit, BMI: body mass index, IQR: interquartile range.
**missing values >10%.*

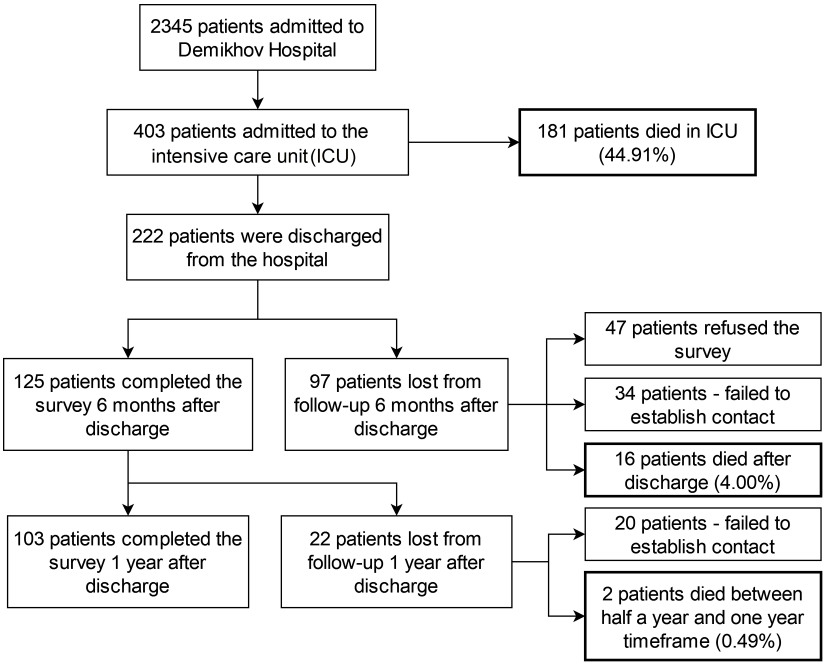


FIGURE 1. Flow chart of the study.

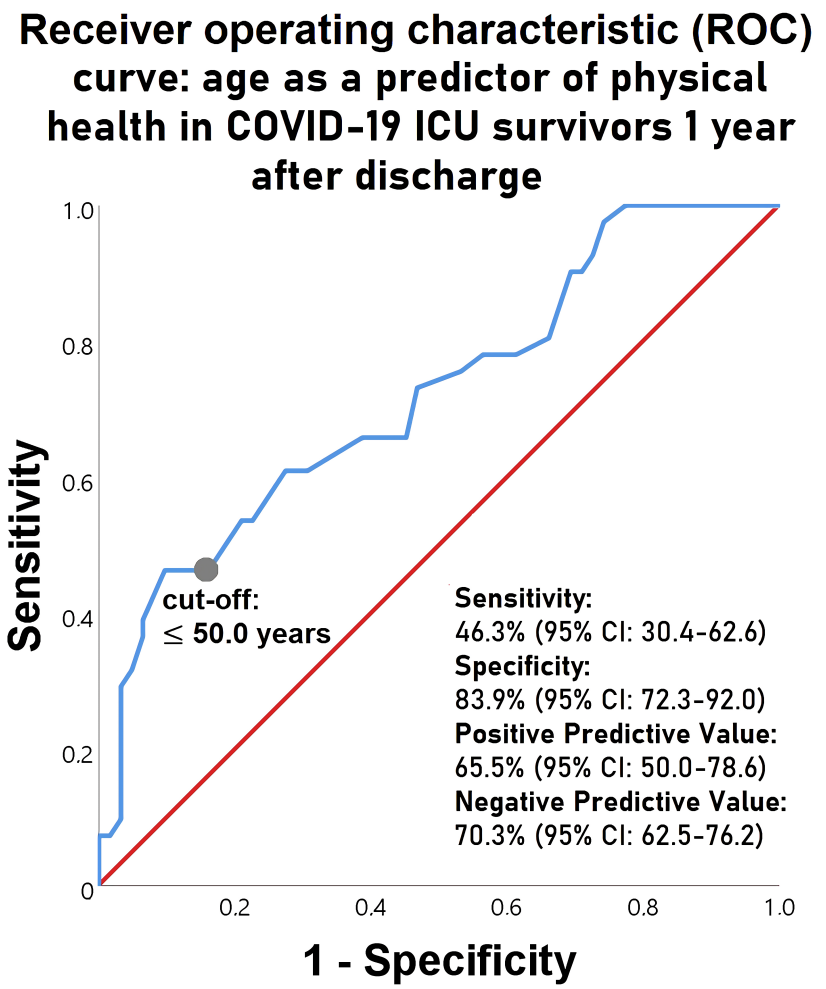


FIGURE 2. Roc-curve: age as a predictor of physical health in COVID-19 ICU survivors at 1 year after discharge.

42.0 to 55.8), Wilcoxon signed-rank test: $p = 0.035$, Fig. 3B) (Table 3).

We compared the median values of all eight SF-36 subscales at 6 months and 1 year follow-up to determine the main factors contributing to the positive changes in the patients' health-related quality of life 1 year after discharge. The increase

TABLE 2. Frequency of comorbid conditions in patients with normal/reduced health-related quality of life 1 year after discharge.

Comorbid condition	Patients with a reduced physical health	Patients with a normal physical health	*p*-value, physical health	Patients with a reduced mental health	Patients with a normal mental health	*p*-value, mental health
	N = 62	N = 41		N = 36	N = 67	
Chronic obstructive pulmonary disease	11 (17.7%)	1 (2.4%)	0.025	5 (13.9%)	7 (10.4%)	0.7
Cerebrovascular insufficiency	22 (35.5%)	9 (22.0%)	0.2	14 (38.9%)	17 (25.4%)	0.2
Peripheral arterial disease	48 (77.4%)	21 (51.2%)	0.01	26 (72.2%)	43 (64.2%)	0.5
Diabetes	13 (21.0%)	8 (19.5%)	0.9	9 (25.0%)	12 (17.9%)	0.4
Arterial hypertension	42 (67.7%)	17 (41.5%)	0.014	22 (61.1%)	37 (55.2%)	0.7
Myocardial infarction	11 (18.6%)	8 (21.1%)	0.3	5 (14.7%)	14 (22.2%)	0.4
Atrial fibrillation	5 (8.1%)	3 (7.3%)	0.3	3 (8.3%)	5 (7.5%)	0.9
Coronary heart disease	13 (21.0%)	7 (17.1%)	0.8	5 (13.9%)	15 (22.4%)	0.4
Congestive heart failure (1–4 Classes)	12 (19.4%)	5 (12.2%)	0.4	7 (19.4%)	10 (14.9%)	0.6
Congestive heart failure (Classes 3 and 4)	1 (1.6%)	3 (7.3%)	0.3	1 (2.8%)	3 (4.5%)	0.9
Chronic kidney disease	11 (17.7%)	6 (14.6%)	0.8	4 (11.1%)	13 (19.4%)	0.4
Liver failure	2 (3.2%)	0 (0.0%)	0.5	0 (0.0%)	2 (3.0%)	0.5
Diabetic organ damage	12 (19.4%)	6 (14.6%)	0.6	8 (22.2%)	10 (14.9%)	0.4
Peptic ulcer	4 (6.5%)	3 (7.3%)	0.9	2 (5.6%)	5 (7.5%)	0.9
Hemiplegia	3 (4.8%)	0 (0.0%)	0.3	3 (8.3%)	0 (0.0%)	0.1
Malignant neoplasms	7 (11.3%)	1 (2.4%)	0.1	2 (5.6%)	6 (9.0%)	0.7
Charlson comorbidity index	2 (IQR: 1–4)	1 (IQR: 0–3)	0.024	2 (IQR: 1–4)	2 (IQR: 1–4)	0.7

Abbreviations: IQR: interquartile range.

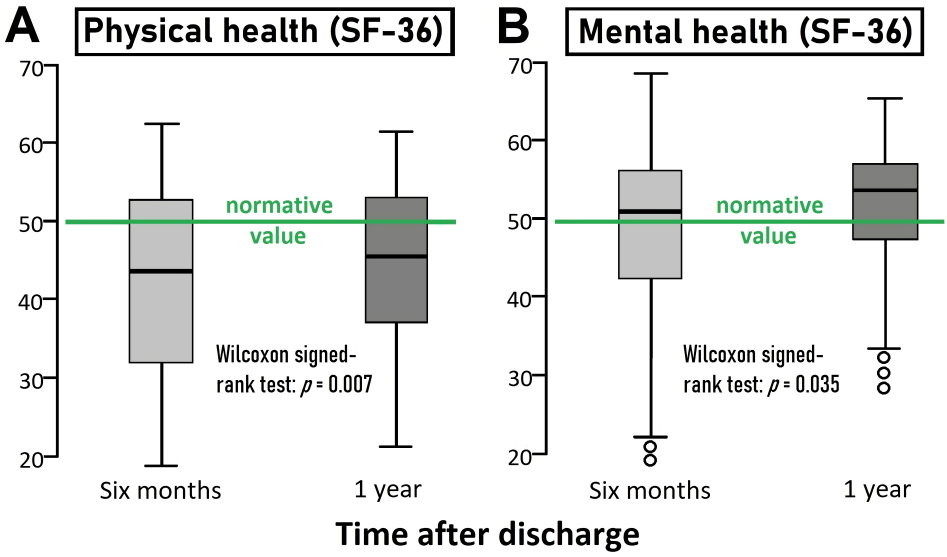


FIGURE 3. Comparative analysis of the physical. (A) and mental (B) Health-Related Quality of Life (SF-36 survey) in COVID-19 ICU survivors at 6 months and 1 year after discharge. Normative value is highlighted in green.

TABLE 3. Comparative analysis of multiple-item subscales of SF-36 in patients with COVID-19 six months and 1 year after discharge.

SF-36 subscales	All patients, 6 months after discharge	All patients, 1 year after discharge	*p*-value[a]	Men, 1 year after discharge	Women, 1 year after discharge	*p*-value[b]
	N = 125	N = 103		N = 65	N = 38	
Physical Functioning (PF)	70 (IQR: 35–85)	75 (IQR: 55–95)	<0.001	85 (IQR: 70–95)	58 (IQR: 30–75)	<0.001
Role Limitations Due To Physical Problems (RP)	50 (IQR: 0–100)	100 (IQR: 50–100)	<0.001	100 (IQR: 50–100)	50 (IQR: 25–100)	<0.001
Role Limitations Due To Emotional Problems (RE)	100 (IQR: 33–100)	100 (IQR: 33–100)	0.4	100 (IQR: 50–100)	100 (IQR: 33–100)	0.7
Vitality (VT)	75 (IQR: 60–85)	75 (IQR: 65–90)	0.1	80 (IQR: 70–90)	70 (IQR: 65–81)	0.1
Mental Health (MH)	64 (IQR: 48–72)	68 (IQR: 64–76)	<0.001	72 (IQR: 62–76)	68 (IQR: 64–76)	0.5
Social Functioning (SF)	75 (IQR: 56–100)	88 (IQR: 63–100)	0.007	88 (IQR: 75–100)	75 (IQR: 63–100)	0.2
Bodily pain (BP)	62 (IQR: 42–87)	62 (IQR: 51–84)	0.8	62 (IQR: 51–84)	62 (IQR: 41–90)	0.3
General Health (GH)	67 (IQR: 40–80)	70 (IQR: 47–85)	0.1	77 (IQR: 57–86)	52 (IQR: 42–73)	0.002
Physical component of HRQoL	43.7 (IQR: 31.7–52.7)	46.0 (IQR: 38.0–53.0)	0.007	51.0 (IQR: 45.0–55.5)	39.0 (IQR: 33.3–45.3)	<0.001
Mental component of HRQoL	50.6 (IQR: 42.0–55.8)	53.0 (IQR: 47.0–56.0)	0.035	52.0 (IQR: 46.0–56.0)	54.5 (IQR: 47.0–57.0)	0.2
Proportion of patients with normal physical health	40 (32.0%)	41 (39.8%)	0.3[c]	36 (55.4%)	5 (13.2%)	<0.001
Proportion of patients with normal mental health	65 (52.0%)	67 (65.0%)	0.033[c]	41 (63.1%)	26 (68.4%)	0.7

Abbreviations: HRQoL: health-related quality of life, IQR: interquartile range.
[a] *Wilcoxon signed-rank test;* [b] *Wilcoxon rank-sum test (Mann-Whitney U test);* [c] *McNemar's test.*

in COVID-19 patients' health-related quality of life was associated with: (1) improvement in the physical functioning of patients (PF), from 70 (IQR: 35 to 85) to 75 (IQR: 55 to 95; Wilcoxon signed-rank test: $p < 0.001$); (2) increased role functioning due to physical condition (RP), from 50 (IQR: 0 to 100) to 100 (IQR: 50 to 100; $p < 0.001$); (3) improved mental health (MH), from 64 (IQR: 48 to 72) to 68 (IQR: 64 to 76; $p < 0.001$); (4) improved social functioning (SF), from 75 (IQR : 56 to 100) to 88 (IQR: 63 to 100; $p = 0.007$) (Table 3).

Compared to females, males showed greater improvement in the physical performance and better general health, resulting in increased role functioning at 1 year follow-up. (Table 3).

3.4 Regression analysis

In multivariable regression analysis, age 50+ (adjusted OR: 0.270, 95% CI: 0.098 to 0.739, $p = 0.011$) and female sex (adjusted OR: 0.144, 95% CI: 0.048 to 0.437, $p = 0.001$) were independently associated with reduced physical health at the 1-year follow-up. The administration of anticoagulants and other drugs in the ICU did not affect 1-year HRQoL. Moreover, there were no significant predictors of mental health alterations 1 year after discharge.

3.5 Correlation analysis

Patients with an already high physical component of HRQoL 6 months after discharge presented with a further improvement in physical health after 1 year (Spearman r = 0.421, $p < 0.001$) (Fig. 4A). A similar but weaker relationship was observed for mental HRQoL (Spearman r = 0.222, $p = 0.024$) (Fig. 4B). A moderately strong negative correlation was found between age and physical functioning (PF, Spearman r = −0.52, $p < 0.001$), while a weak negative interaction was observed between age and role functioning due to physical condition (RP, Spearman r = −0.37, $p = 0.015$), age and physical pain (BP, Spearman r = −0.30, $p = 0.011$), age and general health (GH, Spearman r = −0.35, $p = 0.021$) (Fig. 5). Other correlations between health-

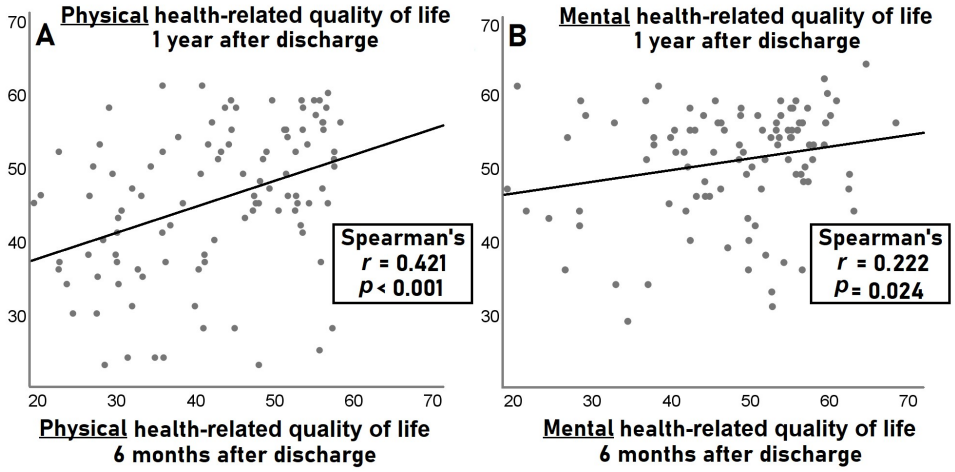


FIGURE 4. Scatter plot and linear regression: relationship of Health-Related Quality of Life at 6 months and 1 year after discharge. Fig. 4A: physical Health-Related Quality of Life. Fig. 4B: mental Health-Related Quality of Life.

related quality of life, medical-demographic characteristics, values of laboratory parameters and length of hospital and ICU stay are shown on the heat map (Fig. 5).

4. Discussion

The mortality of COVID-19 patients requiring ICU admission was 44.9% during the in-hospital period, 4.0% at 6-month follow-up and only 0.5% at 1-year from hospital discharge. Despite the slight improvement in physical and mental components of the health-related quality of life between the 6-month and the 1-year follow-up, the proportion of patients with poor physical (60.2%) and poor mental (35.0%) HRQoL was still high. We failed to identify predictors of HRQoL, except for age and sex which influenced the physical component.

Similar to other reports, even though some long-term consequences of COVID-19 were still present, a modest increase in patients' general health was evident after 1 year, compared to the 6-month follow-up data [16]. Lixue Huang *et al.* [15] observed a decrease in the proportion of patients complaining of fatigue or muscle weakness (52% (636/1230) versus (255/1272) ($p < 0.001$)) and an increment in anxiety or depression (23% (274/1187) versus 26% (331/1271), $p = 0.015$), when comparing reports from the 6-month follow-up to those from the 12-month follow-up. They also identified female sex to represent a risk factor for the development of fatigue and muscle weakness after 12 months, a data which is consistent with results of the current study, where female sex (adjusted OR: 0.144, 95% CI: 0.048 to 0.437, $p = 0.001$) was found to be independently associated with reduced physical HRQoL 1 year after discharge. However, it is complicated to make a precise comparison with our study, since different scales were used to assess health-related quality of life (SF-36 in our research *vs.* EuroQol in the aforementioned article).

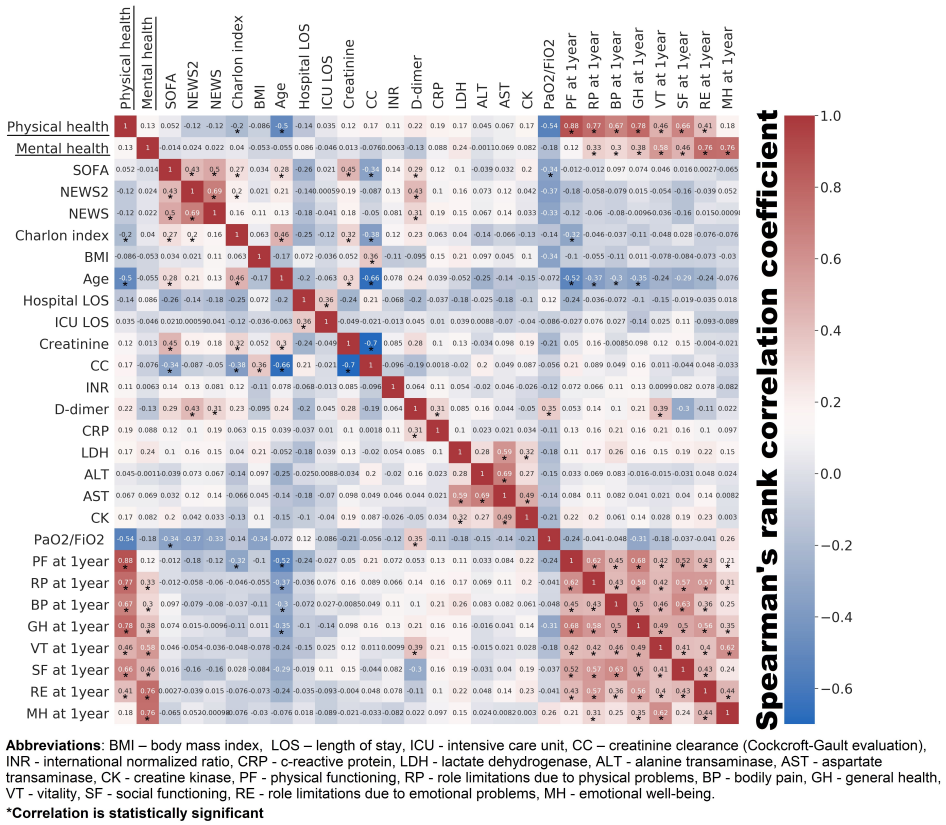
Aranda J *et al.* [24] described long-term outcomes of COVID-19 in patients with acute respiratory distress syndrome (ARDS) by means of a multivariable regression analysis. They showed that female sex, (adjusted OR: −9.80; 95% CI: −15.12 to −4.49), non-Caucasian race (adjusted OR: −6.51; 95% CI: −12.67 to −0.35) and a Charlson index >2 (adjusted OR: −10.52; 95% CI: −18.68 to −2.35) were independent risk factors for worsening of the mental health status, according the SF-36 scale. To the contrary, age (adjusted OR: 3.56; 95% CI: 0.61 to 6.52) was associated with a better prognosis. Furthermore, female gender (adjusted OR: −4.79; 95% CI: −9.15 to −0.42) and chronic obstructive pulmonary disease (adjusted OR: −5.78; 95% CI: −10.44 to −1.11) were independently associated with a decrease in physical health conditions [24].

In the current study we reported that, among men, high values of the HRQoL physical component 1 year after discharge were associated with improved physical performance ($p < 0.001$), increased role functioning due to the fitter physical condition ($p < 0.001$) and better general health ($p = 0.002$). The reason why female sex is associated with long-term poor HRQoL is still unclear and further investigations are needed to outline the actual relevance of this observation. Nevertheless, Seeßle J *et al.* [25] found that patients with antinuclear antibodies (ANA) titer elevations ≥1:160 at 12 months after acute infection had a significantly higher rate of several long-COVID symptoms. The authors concluded that post-COVID-19 syndromes may have an autoimmune component, including neurocognitive symptoms and dyspnea. More women showed ANA positivity with respect to men. The group of women with ANA titer elevations ≥1:160 displayed significantly higher symptom frequencies than the group of women with lower titers. As this observation was significant for female but not for male participants, autoimmune reactions might, in part, be responsible for the female predominance in the group of patients affected by long-COVID syndromes [25, 26].

Interestingly, among 21 studies included into the most recent review assessing HRQoL among COVID 19 patients after discharge or admission, only one showed that women had better HRQoL than men [27].

In the pre-Covid era, lower HRQoL in women was attributed with high levels of non-fatal disabling disorders and differences in health perception between sexes [28]. Taking into consideration all the reasons above, the results obtained in current study are not surprising.

Age 50+ (adjusted OR: 0.270, 95% CI: 0.098 to 0.739, p



Abbreviations: BMI – body mass index, LOS – length of stay, ICU - intensive care unit, CC – creatinine clearance (Cockcroft-Gault evaluation), INR - international normalized ratio, CRP - c-reactive protein, LDH - lactate dehydrogenase, ALT - alanine transaminase, AST - aspartate transaminase, CK - creatine kinase, PF - physical functioning, RP - role limitations due to physical problems, BP - bodily pain, GH - general health, VT - vitality, SF - social functioning, RE - role limitations due to emotional problems, MH - emotional well-being.

***Correlation is statistically significant**

FIGURE 5. "Heatmap" diagram of the correlation matrix (spearman's correlation coefficient): the relationship between health-related quality of life, medical and demographic parameters, characteristics of the condition upon admission, laboratory parameters and length of stay in hospital and ICU. Positive relationships are highlighted in red, negative ones in blue, the intensity of the color is related to the strength of the relationship.

= 0.011) was independently associated with reduced physical HRQoL 1 year after discharge in both our study and in the one carried out by Huang *et al.* [15]. Feng Pan *et al.* [29] evaluated the impact of CT changes 1 year after COVID-19 symptoms onset and reported that age ≥50 years, lymphopenia and severe/ARDS aggravation were independent risk factors for residual CT abnormalities at 1-year follow-up (odds ratios of 15.9, 18.9, and 43.9, respectively; $p < 0.001$, each). Older participants with severe COVID-19 or acute respiratory distress syndrome were more likely to develop lung sequelae persisting after 1 year.

Zangrillo *et al.* [30] recorded remarkable advancements in the quality of life of COVID-19 related-ARDS survivors at 1 year follow-up, with the vast majority of patients referring no difficulty in walking (82%), self-care (95%), or usual activities (84%), while only 8.9% of patients reporting severe anxiety/depression.

At our intermediate (6 months after discharge) survey, out of 125 patients, 85 (68%) complained of poor physical health and 60 (48.0%) of poor mental health [16]. When comparing the 6-month follow-up results to the 1-year after discharge data, a larger proportion of patients with normal mental health (65.0% *vs.* 52.0%, $p = 0.033$) and a slight increase in the proportion of patients with a normal physical health (39.8 *vs.* 32.0, $p = 0.3$) were observed. Age 52+ (adjusted OR: 0.223, 95% CI: 0.091 to 0.546, $p = 0.001$) and female gender (adjusted OR: 0.321, 95% CI: 0.123 to 0.824, $p = 0.020$) were independently associated with a decreased physical component of HRQoL [16]. LMWH prescription was a predictor of normal physical health (adjusted OR: 3.341, 95% CI: 1.298 to 8.599, $p = 0.012$). An independent predictor of a reduced mental quality component of HRQoL was the presence of cerebrovascular insufficiency (adjusted OR: 0.125, 95% CI: 0.033 to 0.465, $p = 0.002$). A predictor of normal mental health was BMI ≥27.6 kg/m^2 (adjusted OR: 7.466, 95% CI: 1.950 to 28.582, $p = 0.007$) [16]. The physical component of HRQoL lost its correlation with the prescription of LMWH 1 year after discharge, as well as the mental component of HRQoL was no longer associated with BMI and cerebrovascular insufficiency. We also found that prescribing unfractionated heparin (UFH), IL-6 blockers, hydroxychloroquine, antivirals, and antibiotics were not associated with changes in physical or mental HRQoL 1 year after discharge.

4.1 Strengths and limitations of the study

To our knowledge, this is the first study to present data on 1-year follow-up health-related quality of life of patients discharged from the ICU after COVID-19. The study, however, has some limitations: we acknowledge that this is a single center study with obvious external validity limitations and with some lack of follow-up data; moreover, we observed a relatively high hospital mortality rate, even considering that the cohort was limited to ICU patients; furthermore, we failed

to specifically identify the causes of death. Because of the significant number of patients who were lost to follow-up, the representativeness of the study population seems to be limited. We observed a difference in the number of patients receiving Tocilizumab and antiviral drugs in patients completing and not-completing the SF-36 forms.

4.2 Future studies and prospects

Future studies should be performed on larger samples and with higher adherence to confirm our findings that COVID-19 ICU survivors experience a health-related quality-of-life improvement between the 6-month and the 1-year follow-up after discharge.

In addition, clear guidelines should be developed for the assessment of the health status of patients with COVID-19 after discharge from the ICU.

Importantly, there is a much-needed comparison to the healthy population QoL standard, which would answer the question whether the changes after 1 year are only related to the ICU stay or other conditions (*e.g.* aging, comorbidities).

5. Conclusions

Mortality rate in COVID-19 ICU survivors was quite high in the first six months after hospital discharge, but then stabilized in the following six months. Despite the slow but steady improvement in the health-related quality of life, 60% of the patients perceived reduced level on HRQoL in terms of the physical component and 35% of with regards to the mental component still 1 year after discharge. Previously identified predictors of poor health-related quality of life one year after discharge lost their significance.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

All authors designed the research study. SP, NC, KK, LE, NM collected data and performed the follow up. MY, KK, LB, AK and AG analyzed the data. VL, GL, MT, MAB, VS wrote the manuscript. All authors read and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Federal Research and Clinical Center for Resuscitation and Rehabilitology Ethics Committee, Moscow, Russia (No. 2/21/1 dated 16 February 2021). All patients signed a written consent before answering the SF-36 questionnaire on quality of life.

ACKNOWLEDGMENT

We thank all colleagues and staff who took care of these patients.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Giovanni Landoni is serving as one of the Editorial Board members of this journal. We declare that Giovanni Landoni had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to GI.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1524317768091877376/attachment/Supplementary%20material.docx.

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How to cite this article: Likhvantsev V, Landoni G, Kuzovlev A, Perekhodov S, Chaus N, Tucci M, *et al*. One year health-related quality of life after discharge: a prospective cohort study among COVID-19 ICU survivors. Signa Vitae. 2023; 19(2): 55-65. doi: 10.22514/sv.2022.036.