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Long-term consequences in Covid-19 and Non-Covid-19 patients survivors of critical illness. A descriptive study

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Key words: *Coronavirus, Intensive Care Unit, post-Covid-19 syndrome, PICS, survey*
Parole chiave: *Coronavirus, Terapia Intensiva, Sindrome post-Covid-19, PICS, intervista*

Abstract

Background. *Critically ill patients may develop health problems related to their illness, injury, mechanical ventilation or other treatments. Such problems cannot be totally prevented and can continue after the patient leaves the hospital.*
Aim. *To explore the level of anxiety, depression, post-traumatic stress Intensive Care Unit and quality of life in Intensive Care Unit survivors. A comparison analysis between Covid-19 patients and Non-Covid-19 patients was conducted.*
Methods. *A prospective observational study exploring psychological, emotional, and behavioral difficulties experienced in patients admitted to Intensive Care Unit was performed. The study was conducted in an Italian adult 8-bed Intensive Care Unit, from July 2020 to April 2021, and followed-up until 25th May 2022. Data were collected during Intensive Care Unit stay (data collection of demographic and clinical characteristics) and 6 and 12 months after Intensive Care Unit discharge (interviews).*
Results. *A total of 143 patients participated in the study, of which 54 were admitted for Covid-19 (37.76%). Depression symptoms were observed more among Non-Covid-19 patients compared to Covid-19 patients at six months (p= .037) and 12 months (p< .001) after Intensive Care Unit discharge. The quality of life perceived by the Intensive Care Unit patients surveyed improved between 6 and 12 months after discharge (Eq-VAS mean=62.03, ± 11.2 vs Eq-VAS mean=66.6, ± 9.8) (p=.034). Six months after Intensive Care Unit discharge, the mean of the perception of quality of life, for Covid-19 patients was 63.91 (sd ± 9.30), greater than Non-Covid-19 patients of the same period, which was 60.18 (sd ± 8.63) (p= .038).*
Conclusions *Within 1 year from the acute infection, most hospital survivors of Covid-19 had good physical and functional recovery over time with better outcomes than other Intensive Care Unit patients and had returned to their original work and life.*

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Introduction

The impact of critical illness upon physical and mental health after Intensive Care Unit (ICU) admission has been well demonstrated. These critically ill patients may develop health problems related to their illness, injury, mechanical ventilation or other treatments. Such problems cannot be totally prevented and can continue after the patient leaves the hospital (1, 2). These problems can involve the patient's body, thoughts, feelings, or mind and may affect the family (3).

Problems known as post intensive care syndrome (PICS) (3), may show up as an easily noticed drawn-out muscle weakness, known as ICU-acquired weakness, as problems with thinking and judgment, called cognitive (brain) dysfunction and as other mental health problems (3-5).

PICS experienced by ICU survivors at home include decreased physical function (4), global cognitive impairment, especially for memory and executive function (5), emotional instability (6), anxiety and depression (7). Often patients face multiple health-related complications that, together or in unique combinations, add significant self-care complexity, worse quality of life and decrease their ability to return to work and social activities that subsequently affects the health in the long term (3).

Deficits in cognitive function are highly prevalent in acute respiratory distress syndrome (ARDS) survivors, with 30% to 46% of patients showing generalized cognitive decline at one year (8). In a mixed population of medical and surgical critically ill patients, respectively 26% and 40% of surviving patients assessed at three months had global cognition scores that were similar to scores for patients with mild Alzheimer's disease and moderate traumatic brain injury (8).

Since December 2019, when the first case of human transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan (China), more than a hundred million confirmed cases of coronavirus disease (Covid-19) have been described all over the planet (9). The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic disease to severe disease requiring hospitalization and admission to the ICU (9). The symptoms associated are relatively non-specific. Fever and lower respiratory tract symptoms, such as cough or breathlessness, are common in patients who require care in hospital, and radiological changes consistent with pneumonia are evident in up to 97 % of these patients (10).

In some people, Covid-19 can cause symptoms that last weeks or months after the infection has ended. This is sometimes called post-Covid-19 syndrome or "long Covid" (11).

It's necessary to monitor Covid-19 patients after discharge to understand the width and severity of long-term effects (12). This can be accomplished by repurposing or initiating large cohort studies focusing not only on the long-term consequences of SARS-CoV-2 infection, but also on the acquired immune function and on the impact of the disease on the psychophysical and psychosocial sphere of Covid-19 survivors.

Recently an Italian study assessed post-traumatic stress disorder, depression and anxiety symptoms in Covid-19 outpatients who had different levels of respiratory and ventilatory support in the acute phase at three months follow up. No statistically significant differences in terms of depression and anxiety were assessed among patients stratified by spontaneous breathing or ventilatory therapies. However significant higher levels of depression, anxiety and stress were measured in patients reporting Covid-19 disease as a traumatic experience after ICU stay (13).

It is also known how all critically ill patients may develop problems (3, 8).

Reminders of their illness may produce intense feelings or strong, clear images in their mind. Their reactions to these feelings may be physical or emotional. ICU survivors may feel depressed and anxious and may show symptoms of post-traumatic stress disorders (PTSD). These include having nightmares and unwanted memories besides their desire to avoid thinking or talking about their stay in the ICU (3, 8).

During Covid-19 outbreak, the aim of this study was to explore the level of anxiety, depression, PTSD and quality of life in ICU survivors 1 year after ICU discharge. In addition, a comparison analysis between Covid-19 patients and Non-Covid-19 patients admitted to the ICU was conducted to assess the impact of Covid-19 disease on long-term.

Methods

Study design

This study is reported following the Strengthening of Reporting in Observational studies in Epidemiology (STROBE) guidance (14). The EQUATOR Network website has been accessed. The EQUATOR Network website maintains a comprehensive, up-to-date list of guidelines (eg. STROBE) and a series of toolkits designed for authors, editors, developers, librarians, and teachers (15).

A prospective observational study exploring psychological, emotional, and behavioral difficulties experienced in adults with confirmed Covid-19 requiring ICU admission and a comparison with patients present in ICU for other admission diagnosis, were performed. For this study, a quantitative design was used for the prospective study (phase 1) and a qualitative design was used in the questionnaire study (phase 2).

A prospective study (phase 1) uses existing data that have been recorded for reasons other than research. A prospective case series is the description of a group of cases with a new or unusual disease or treatment.

A questionnaire study (phase 2) is a research consisting of a series of questions (or other types of prompts) for the purpose of gathering information from respondents. Although questionnaires are often designed for statistical analysis of the responses, this is not always the case. Surveys and questionnaires are the most common technique for collecting quantitative or qualitative data (16).

Patients received a letter introducing the study at their ICU discharge. The letter explained that they might receive a phone call from the study team and provided contact details for the study office. Written consent was obtained by the nursing staff at the time of discharge, or at the follow-up visit.

Setting and participant

The study was conducted in an Italian adult 8-bed ICU of a 850-bed second-level hospital. It included adult patients admitted to ICU from July 2020 to April 2021, and followed-up until 25th May 2022. Common conditions treated within ICU include acute respiratory distress syndrome (ARDS), post-operative surgical, trauma, multiple organ failure and sepsis.

During te Covid-19 outbreak, the unit (brought from 8 to 48 beds) was comprised of dedicated full-time intensivists (registered nurses and medical doctors) trained in adult multidisciplinary medicine; 56 registered nurses and 20 medical anesthesiologist doctors worked full-time in the department, (11 registered nurses on each shift, 5 medical anesthesiologist doctors morning-afternoon and 3 medical doctors on night shift). From July 2020 to April 2021, all consecutive patients with an ICU LOS> 72 hours admitted to the ICU were considered for inclusion.

Exclusion criteria were: 1) age < 18 years,

2) ICU length of stay (ICU LOS) < 72 hours, 3) hospital-acquired SARS-CoV-2 infection, 4) SARS-CoV-2 infection diagnosed > 48 h after hospital admission or 5) SARS-CoV-2 infection diagnosed > 48 h after ICU admission.

A total of 197 patients was initially considered eligible for the study. However, 54 patients (27.4%) were excluded from the final analysis: 23 patients (11.67%) were unable to respond to the phone-interview due to cognitive impairment, and 31 patients had died during the hospital stay (15.73%).

Data collection

The following outcomes were evaluated: Anxiety and Depression (17); Post-Traumatic Stress Disorders (PTSD) (18); Perceived quality of life (19, 20); Global disability and recovery after ICU stay (21- 23).

Data were collected at three separate time points over the 12-month of follow up: at baseline (during ICU stay) and 6 and 12 months after ICU discharge (during the follow-up visit).

During ICU stay (baseline), patients' socio-demographic and clinical data were obtained from electronic health records (Margherita3 2010 form). These included: patient age, APACHE II score, coexisting conditions at ICU admission, gender, ICU LOS, use of renal placement therapy, mechanical ventilation and severe sepsis, SARS-CoV-2 infection. At discharge, participants received a letter introducing the study.

All subjects willing to participate in the study completed a set of validated questionnaires which included: 1) the Hospital Anxiety and Depression Scale (HADS) for the assessment of anxiety and depression (17); 2) the Post-Traumatic Stress Disorder Check List Civilian (PCL-5) for the assessment of PTSD (18); 3) the Euroqol 5D instrument (EQ-5D short form) for the assessment of perceived quality of life (19); and 4) the Glasgow Outcome Scale-extended (GOS-E) to assess global disability and recovery after ICU stay (22, 23). These instruments can be both self-administered, administered in person or by phone.

During Covid-19 outbreak, the phone administration was chosen in order to increase the response rate. A short one-on-one phone interview including the aforementioned tools was designed for the purpose of addressing the first study aim. For each patient who decided to participate in the study, the phone interview was administered twice: six months after ICU discharge and 12 months after ICU discharge by an ICU health professional (physician or nurse) involved in the study.

Data source and measurement

All the validated tools adopted have specific cut-offs that indicate, based on the scores, the absence or presence of the assessed symptoms (eg. mild, moderate or severe/intense).

The HADS (17) is a 14-item scale designed to assess anxiety and depression, with emphasis on reducing the impact of physical illness on the total score. The Italian version of the HADS was carried out in 2011 (24) and recently updated in 2020 (25). The HADS comprises seven items related to anxiety and seven related to depression, resulting in two scales, one for anxiety (HADS–A) and one for depression (HADS–D). The items concerning the concept of depression tend to focus on the anhedonic symptoms of depression. Items are rated on a 4-point severity scale. Scores greater than or equal to 11 on either scale indicate a definitive case.

The PCL-5 is a 20-item self-report tool assessing the symptoms of PTSD (18, 26). Respondents are asked to rate how bothered they have been by each of the 20 items in the past month on a 5-point Likert scale ranging from 0 "not at all" to 4 "extremely". A total symptom severity score can be obtained by summing the scores for each of the 20 items

(range= 0-80). PTSD cut off score is set > 33 (18, 26).

The GOS-E (22, 23) is a global scale for functional outcome taking into account the following domains: consciousness, independence at home, independence outside, work, social and leisure activities, family and friendships, return to normal life. Patients' areas of functioning can be rated using eight categories: dead, vegetative state, severe disability (upper and lower), moderate disability (upper and lower) and good recovery (upper and lower). The GOS-E is an atypical form of assessment since it consists of a series of discrete categories arranged in a hierarchy and there is no sum score from individual items.

The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the five dimensions. The EqVAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled '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 (27-30). The EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (30). The EQ-5D-3L was introduced in 1990.

Study size

Study size was based on the total number of patients meeting inclusion criteria and admitted to the ICU from July 2020 to April 2021.

In the design phase, we have planned the duration of the study and enrolled all the patients treated within.

As a number of studies have suggested that the risk of developing Anxiety and/or Depression and PTSD after ICU discharge ranges from 1% to 62% (31-33), we needed at least 100 patients in total. Six months post ICU discharge, the sample provided sufficient patients to achieve this number, allowing for mortality and loss to follow-up. The number of patients we would assess at follow-up was known to us based on data collected from our ICU that has been doing follow-up since 2009. We knew that around 80-150 subjects would show up for an interview at six or 12 months after ICU discharge. The range of interviews carried out may vary each year based on the characteristics of the hospitalized patients and on the basis of the number of physician and nursing staff available to carry out the interviews.

Statistical significance for the identification of independent was set at < 0.05.

Statistical analysis

For normally distributed data, mean and standard deviation (SD) were applied, while median and interquartile range were used for data that did not exhibit normal distribution.

Comparison between groups of patients (Covid-19 and Non-Covid-19) were performed with the chi-square test for the categorical data and with Student's t-test for the continuous data. We used Student's t-test for paired samples.

Univariate and multivariate logistic regression analysis was used for investigation of possible associated outcomes and predictors of PICS acquisition. In both instances, a significance of $p < .05$ and a confidence interval (CI) of 95% were used.

Relative risk and the 95% confidence intervals were calculated for each variable analyzed.

No missing data and no sensitivity

analyses were addressed.

The Statistical Package for Social Sciences (SPSS) software version 21 (IBMCorp. Released 2015. IBM SPSS Statistics, Version 23.0. Armonk, NY: IBM Corp.) was used for analysis of patients' data.

Ethical approval

The study was approved by the Ethical Committee of the promoting center (Monza and Brianza; Italian registration number; Protocol: 3047).

Patients received a letter introducing the study at ICU discharge. The letter explained that they might receive an e-mail from the study team asking them to provide contact details for the study office. Participants provided their informed written consent to participate during their ICU stay, at the time of discharge. If patients were unable to give their consent due to sedation or intubation (eg. during ICU stay), the request was submitted to their relatives.

The dataset was pseudonymised before data analysis. The study protocol was in line with the Oviedo Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine (1996) and with the Declaration of Helsinki, as revised in 2013.

In addition, the authorization to access the data was given by the director and the manager of the ICU involved in the study.

Results

Participants

A total of 143 patients participated in the study: 54 of them were affected by Covid-19 (37.76%) (Table 1). The mean age of the study participants was 72.6 (sd ± 11.6), 68.83 years in Covid-19 (sd ± 10.34) and 75.62 in Non-Covid-19 (sd ± 6.43) ($p < .001$). According to the anthropometric data collected in the study, Covid-19 patients have a weight of 77.93 kg (sd ± 10.03) with a BMI of 28.58 (sd ± 4.09) and Non-Covid-19 patients a weight of 78.17 kg (sd ± 9.78) with a BMI of 27.79 (sd ± 3.80). The length of ICU stay was 27 days for Covid-19 patients (mean=27.57; sd ± 11.39) and 23 days for Non-Covid-19 patients (mean=23.03; sd ± 12.93) ($p= .038$). The mean of length of hospital stay post-ICU was 21 days for Covid-19 (mean=21.89; sd ± 10.86) and 18 days for Non-Covid-19 (mean=18.09; sd ± 8.16) ($p= .018$).

Among patients who died after ICU discharge, 8 (14.81%) were Covid-19 and 23 (25.84%) Non-Covid-19 ($p= .121$) (Table 1).

Long-term cognitive or physical impairment after ICU treatment

Over half of respondents declared at least one symptom of anxiety, depression or PTSD at 6 or 12 months (Table 2).

Anxiety-related symptoms were observed in 38/99 patients at 6 months (38.4%) and in 28/87 patients at 12 months (32.2%) (p=.409).

According to the HADS-anxiety scale (HADS-A), no significant differences in anxiety symptoms were observed at 6 and 12 months after ICU discharge among Non-Covid-19 patients compared to Covid-19 patients (Figure 1 A).

Depression-related symptoms were observed in 35/99 patients at 6 months (35.5%) and in 24/87 patients at 12 months (27.6%) (p=.256).

According to the HADS-depression scale (HADS-D), the absence of symptoms of depression (HADS-depression score: 0-7) was observed more among Covid-19 patients than Non-Covid-19 patients both at 6 months (n=34, 75.56% *vs* n=30, 55.56%; p= .038) and at 12 months (n=34, 85% *vs* n=27, 57.45%; p= .005) after ICU discharge. A significant difference in the mean score of the HADS-D was observed 12 months after ICU discharge among Non-Covid-19

Table 1 - Demographic and clinic characteristics of the studied population.

	Covid-19 (n=54)	Non-Covid-19 (n=89)	p.
Gender, n (%)			
Male	46 (85.19)	56 (62.92)	.043
Female	8 (14.81)	33 (37.08)	
Age in years, mean (sd)	68.83 (±10.34)	75.62 (±6.43)	.036
Marital status, n (%)			
married/engaged	45 (83.33)	66 (74.15)	.202
unmarried	6 (11.11)	11 (12.36)	
widower	3 (5.56)	12 (13.48)	
Anthropometric data, mean (sd)			
Weight in kg	77.93 (±10.03)	78.17 (±9.78)	.887
BMI	28.58 (±4.09)	27.92 (±3.80)	.894
ICU days, mean (sd)	27.57 (±11.93)	23.03 (±12.93)	.038
after ICU days, mean (sd)	21.89 (±10.86)	18.07 (±8.16)	.018
patients died in hospital, n (%)	8 (14.81)	23 (25.84)	.121
Anamnesis, n (%)			
diabetes	20 (37.03)	35 (39.33)	.785
hypertension	27 (50)	43 (48.31)	.845
heart attack	20 (37.03)	28 (31.46)	.494
heart failure	20 (37.03)	30 (33.71)	.686
kidney failure	28 (51.85)	46 (51.69)	.961
neurological pathologies	20 (37.03)	24 (26.97)	.206
oncological pathologies	14 (25.93)	22 (24.72)	.872
Clinical characteristics			
p/f entrance, median (IQR)	130.5 (62-408)	168 (96-408)	.016
ETT, n (%)	44 (81.48)	72 (80.90)	.931
ETT in hours, median (IQR)	355.5 (1-1152)	350.5 (1-1152)	.899
tracheostomy, n (%)	23 (42.59)	33 (37.08)	.513
tracheostomy in hours, median (IQR)	344.5 (23-1435)	344 (23-1435)	.921
hemodialysis, n (%)	9 (16.67)	10 (11.24)	.354
hemodialysis in hours, median (IQR)	260 (88-817)	370 (88-633)	.078
PiCCO, n (%)	13 (24.07)	20 (22.47)	.826
PiCCO in hours, median (IQR)	276 (28-558)	232.5 (28-558)	.066
Swan-Ganz, n (%)	3 (5,56)	2 (2.25)	.296
Swan-Ganz in hours, median (IQR)	34 (28-165)	1 (1-165)	.001

LEGEND: *BMI* - body mass index; *ICU* - intensive care unit; *p/f* - partial pressure of oxygen/fraction of inspired oxygen; *ETT* - endo-tracheal tube; *PiCCO* - pulse contour cardiac output

Table 2 - *Results of Covid-19 and Non-Covid-19 patients compared at 6 and 12 months after discharge*

	Scores at 6 months			Scores at 12 months		
	Covid-19 (n= 46)	Non-Covid-19 (n= 56)	p.	Covid-19 (n= 41)	Non-Covid-19 (n= 49)	p.
Eq-5D-3L mobility =1, n (%)	36 (78.26)	52 (92.86)	.033	41 (100)	47 (95.92)	.191
Eq-5D-3L mobility =2, n (%)	10 (21.74)	2 (3.57)	.005	0 (0)	2 (4.08)	.191
Eq-5D-3L mobility =3, n (%)	0 (0)	2 (3.57)	.196	0 (0)	0 (0)	
Eq-5D-3L self-care =1, n (%)	21 (45.65)	21 (37.50)	.405	21 (51.22)	29 (59.18)	.449
Eq-5D-3L self-care =2, n (%)	22 (47.82)	28 (50)	.827	20 (48.78)	20 (40.82)	.449
Eq-5D-3L self-care =3, n (%)	3 (6.52)	7 (12.50)	.312	0 (0)	0 (0)	
Eq-5D-3L usual activities =1, n (%)	17 (36.96)	19 (33.93)	.750	17 (41.46)	27 (55.10)	.197
Eq-5D-3L usual activities =2, n (%)	29 (63.04)	31 (55.36)	.433	24 (58.54)	22 (44.90)	.197
Eq-5D-3L usual activities =3, n (%)	0 (0)	6 (10.71)	.022	0 (0)	0 (0)	
Eq-5D-3L pain/discomfort =1, n (%)	22 (47.83)	26 (46.43)	.888	23 (56.10)	36 (73.47)	.084
Eq-5D-3L pain/discomfort =2, n (%)	24 (52.17)	24 (42.86)	.348	18 (43.90)	13 (26.53)	.084
Eq-5D-3L pain/discomfort =3, n (%)	0 (0)	6 (10.71)	.022	0 (0)	0 (0)	
Eq-5D-3L anxi./depress. =1, n (%)	32 (69.57)	38 (67.86)	.853	28 (68.29)	38 (77.55)	.323
Eq-5D-3L anxi./depress. =2, n (%)	14 (30.43)	16 (28.57)	.837	13 (31.70)	11 (22.45)	.323
Eq-5D-3L anxi./depress. =3, n (%)	0 (0)	2 (3.57)	.196	0 (0)	0 (0)	
Eq-VAS, mean (sd)	63.91 (±9.30)	60.18 (±8.63)	.038	68.54 (±8.23)	65.10 (±8.93)	.063
GOS-e, mean (sd)	6.90 (±1.67)	4.96 (±2.75)	<.001	7.09 (±1.97)	5.10 (±2.91)	<.001
PTSD median (IQR)	2 (0-56)	6.5 (0-60)		2 (0-51)	7 (0-60)	
PTSD <34, n (%)	38 (84.44)	38 (70.37)		36 (90)	40 (85.11)	
PTSD ≥34, n (%)	7 (15.56)	16 (29.63)	.099	4 (10)	7 (14.89)	.494
HADS - anxiety, median (IQR)	0 (0-21)	3 (0-21)		0 (0-21)	2 (0-21)	
HADS - anxiety 0-7, n (%)	30 (66.67)	31 (57.41)	.346	29 (72.50)	30 (63.83)	.295
HADS - anxiety 8-10, n (%)	2 (4.44)	2 (3.70)	.852	5 (12.50)	2 (4.26)	.159
HADS - anxiety 11-14, n (%)	0 (0)	3 (5.56)	.108	1 (2.50)	2 (4.26)	.655
HADS - anxiety 15-21, n (%)	13 (28.89)	18 (33.33)	.635	5 (12.50)	13 (27.66)	.082
HADS - depression, median (IQR)	0 (0-19)	5.5 (0-21)		0 (0-17)	5 (0-21)	
HADS - depression 0-7, n (%)	34 (75.56)	30 (55.56)	.038	34 (85)	27 (57.45)	.005
HADS - depression 8-10, n (%)	2 (4.44)	7 (12.96)	.142	3 (7.50)	8 (17.02)	.183
HADS - depression 11-14, n (%)	0 (0)	4 (7.41)	.099	0 (0)	2 (4.26)	.187
HADS - depression 15-21, n (%)	9 (20)	13 (24.07)	.627	3 (7.50)	10 (21.28)	.072

LEGEND: *Eq-5D-3L* - EuroQol-5Dimensions-3Levels; *Eq-VAS* - EuroQol visual analogue scale; *GOS-e* - Glasgow outcome scale extended; *PTS*D- post-traumatic stress disorder; *HADS* - hospital anxiety and depression scale.

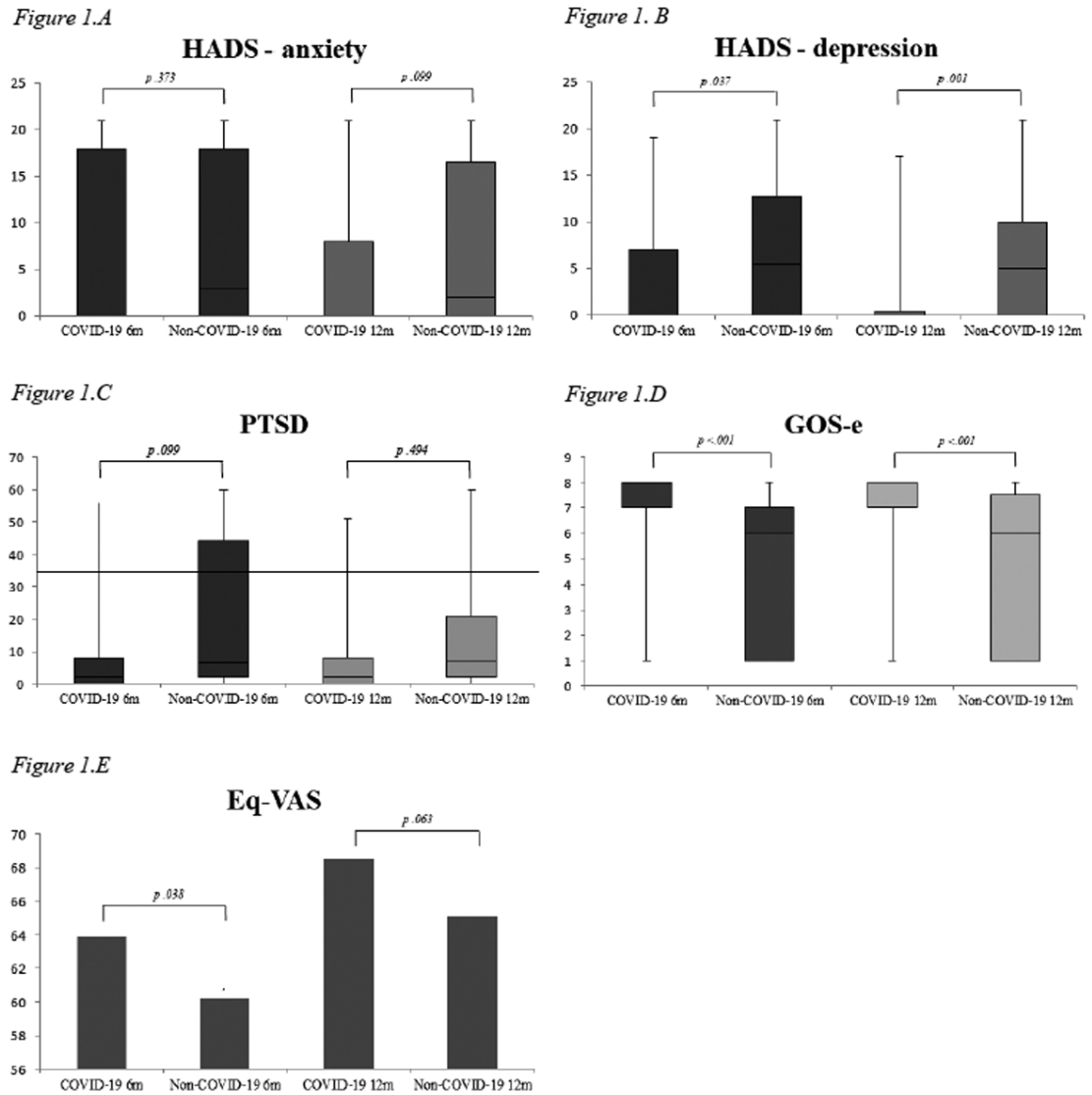

Figure 1 A-E - Results of follow-up scales

patients compared to Covid-19 patients ($p < .001$) (Figure 1 B).

PTSD-related symptoms were observed in 23/99 patients at 6 months (23.2%) and in 11/87 patients at 12 months (12.6%) ($p=.062$).

According to the PCL-5 scale no significant differences in PTSD symptoms were observed at 6 and 12 months after ICU discharge among Non-Covid-19 patients compared to Covid-19 patients (Figure 1 C).

According to the GOS-e scale, a better overall health index was observed between Covid-19 than Non-Covid-19. Indeed, the mean detected in Covid-19 patients at 6 months was 6.90 (sd ± 1.67), while it was 4.96 in Non-Covid-19 (sd ± 2.75) ($p< .001$) (Figure 1 D). At 12 months the mean for

Covid-19 patients was 7.09 (sd ± 1.97) better than Non-Covid-19 (mean=5.10; sd ± 2.91) (p < .001) (Figure 1 D).

Quality of life and index for activities of daily living

The quality of life perceived by the ICU patients surveyed improved between 6 and 12 months after discharge (Eq-VAS mean=62.03, ± 11.2; *vs* Eq-VAS mean=66.6, ± 9.8) (p= .034).

According to Eq-5D-3L - mobility, Covid-19 patients with mild problem detected at 6 months were 10 (21.74%), while in Non-Covid-19 they were only 2 (*p* = .005) (Table 2).

According to Eq-5D-3L - during usual activities no severe problem was detected in Covid-19 patients. However, severe problems in ordinary activities were identified in six (10.71%) of Non-Covid-19 patients (*p*= .022) (Table 2).

According to Eq-5D-3L - pain / discomfort at 6 months from ICU discharge, the Covid-19 patients with a mild problem were 24 (52.17%) and none of them had serious complications. In the same period, six (10.61%) Non-Covid-19 patients had serious problem (*p*= .022) (Table 2).

For the perception of quality of life, the mean of the Eq-VAS score for Covid-19 patients at 6 months after ICU discharge was 63.91 (sd ± 9.30) greater than Non-Covid-19 patients of the same period, which was 60.18 (sd ± 8.63) (p= .038) (Figure 1 E).

No significant differences were observed in the perception of quality of life at 12 months: mean of the Eq-VAS score for Covid-19 patients was 68.54 (±8.23) and in Non-Covid-19 patients of the same period 65.10 (±8.93) (*p*= .063) (Figure 1 E).

Discussion

The aim of this study was to explore the level of anxiety, depression, post-traumatic stress symptoms (PTSD) and quality of life in ICU survivors during Covid-19 outbreak. In addition, a comparison analysis between patients admitted to the ICU and patients admitted to the ICU for Covid-19 was conducted to assess the impact of Covid-19 on long-term.

A high burden post-ICU, affecting psychopathological issues, was reported in this study. Over half of respondents declared at least one symptom of anxiety, depression, or PTSD at 6 or 12 months. Worst outcomes seem to emerge among Non-Covid-19 patients one year after ICU discharge and these conditions are commonly observed in ICU survivors as long-term effects of intensive care treatment. Anxiety or depression were observed infrequently in patients at both six months and 12 months in line with the Huang et al. study that highlighted a prevalence at six months of 23% and at 12 months of 26% (34).

Our analysis showed that Covid-19 patients have fewer problems 6 and 12 months after discharge than Non-Covid-19. A simple explanation may be due to less comorbidity at the time of admission to intensive care in Covid-19 patients. In fact, during the Covid-19 outbreak, patients were managed in our operating unit with a lower age and with few comorbidities or chronic diseases at the admission.

After ICU discharge, discomfort experienced in the ICU and stressful memories of an ICU stay have been associated with the development of anxiety, depression, acute PTSD and impaired health-related quality of life (2). For some patients these symptoms are chronic and cause lasting personality changes. In past, other studies focused on outcomes such as functional status, ability to live at home, influence on the social network, and the burden on the family, all of which can, at times, be more important than the length of survival (6-8).

Long-term symptoms of PTSD, anxiety and depression, are common in the first five

years of ARDS. In-hospital screening for psychiatric history of patients after ICU discharge may help identify and predict those requiring structured psychiatric input to improve quality of life after critical illness (31-34).

In addition to an increase of psychiatric outcomes, Covid-19 survivors are also at risk to develop new-onset respiratory and cardiovascular disease during convalescence. Although the increased proportion in our cohort is relatively low, symptoms of anxiety and depression appear to increase over time and this is worrying. Our results are confirmed by other recent studies (35, 36).

A previous study of SARS has showed that the health status of survivors at one year after symptom onset was significantly lower than that of the general population (37) and lasted to two years (38). Fatigue was the most reported symptom of patients with SARS and could last as long as four years (39).

Most Covid-19 survivors had a good physical and functional recovery during one-year follow-up, had returned to their original work and life (34) in line with our results.

Despite our report, we underline an improvement in the perception of patients' quality of life and an improvement in functional recovery 12 months after ICU discharge. Indeed, patients' perception of quality of life appears to be positively correlated to functional, physical, or mental recovery, and not directly to observed cases of anxiety and depression.

The conditions that linger after recovery from Covid-19 are commonly referred to as the long-term effects of Covid-19 (long Covid). The risk for sequelae varies and seems to be associated with the severity of the initial acute SARS-CoV-2 infection. Our findings show that a substantial burden of health loss that spans pulmonary and several extrapulmonary organ systems is experienced by patients who survive after the acute phase of Covid-19 in line with a recent study (40).

Physical, cognitive, and mental impairments, persisting long after the Covid-19 disease onset, are common in ICU survivors. These results will help to inform health system planning and the development of multidisciplinary care strategies to reduce chronic health loss among individuals with Covid-19 (2, 41-43).

Recently, Al-Aly and colleagues reported that Covid-19 survivors had a high burden of incident use of bronchodilators, antitussives, expectorants, antidepressants, and anxiolytics after the cute stage (40). The chronic or late-onset psychological symptoms after Covid-19 could be driven by a direct effect of virus infection and might be explained by several hypotheses including aberrant immune response, hyperactivation of the immune system, or autoimmunity (40, 44). Additionally, indirect effects including reduced social contact, loneliness, incomplete recovery of physical health, and loss of employment could affect psychiatric symptoms.

The prevalence, severity, and duration of the various impairments in ICU survivors are weakly defined, and may reflect in the different studies, differences in the timing of assessment, the outcome measured, the instruments employed, and the thresholds adopted to establish the diagnosis, the qualification of personnel delivering the tests and the resource availability, as well as diversity in patients' characteristics (8).

Post-intensive care syndrome affects most patients discharged from intensive care units (3). Knowing this syndrome will help improve understanding and inform the design of preventative strategies to improve long-term consequences of an ICU stay. Future research and standardized instrument development will serve to better understand the scope and characteristics of this issue and inform about the development of possible preventative medical or nursing interventions.

Future longitudinal studies of adequate sample size with repeated assessments of validated outcomes and comparison with Non-Covid-19 patients are needed to fully explore the long-term outcome of ICU patients with Covid-19.

Finally, 23 patients exited the study because they were unable to answer at phone, due to cognitive impairment (11.67%). This data is in line with what emerges from the literature (45). Patients with recent SARS-CoV-2 infection appear to experience global cognitive impairment, attention and executive function, impairment in memory and in particular verbal fluency (45). Obviously, we must study larger samples, and we recommend physicians and nurses to evaluate the need for cognitive assessment of patients with a recent Covid-19, regardless the severity of the disease, the length of ICU stay, and the ICU treatment.

Limitations

The main limitation of this study is the loss of the 54/197 (27.4%) patients who were considered eligible and enrolled for the study but did not participate in the follow-up interviews (deaths, non-respondents, etc.). However, the limited response rate is predominantly a methodological limitation of undertaking a survey in a post critical illness population, already known in many follow-ups ICU studies (46, 2).

To the best of our knowledge, this work seems to be the first study that evaluated cognitive and/or physical impairment during the first year post-ICU discharge during Covid-19 outbreak. Therefore, it was difficult to conduct the study without reference data.

Even if the patients were enrolled consecutively, there were seven months where we did not enroll any cases. Inclusion of consecutive eligible patients was not feasible due to pandemic workload constraints. Apart from goodness-of-fit, we have not reported analysis of residuals for the regression models. In addition to the chi-square test for the categorical data, no Fishers exact test was used in the case one or more cells contained less than five cases.

This study had limited access to pre-morbid conditions, specifically pre-existing psychological and psychiatric conditions. People with pre-existing psychopathological conditions are at higher risk of both developing new symptoms and worsening existing problems following treatment in the ICU. In addition, it is possible that a phenotype exists where pre-morbid sufferers of anxiety/depression/PTSD are at a higher risk of developing critical illness. Future studies should collect pre-morbid psychological history, to explore this hypothesis further.

Finally, we do not know if between 6 and 12 months our cases have turned to specialized health personnel for the treatment/management of their cognitive and/or physical impairment. This piece of information could have been relevant to help us understand if our data overestimate or underestimate the real data.

Conclusion

Increasing numbers of survivors of critical illness are at risk for cognitive, physical and/or mental health impairments, that may persist for many years after ICU discharge.

The continuing spread of SARS-CoV-2 remains a public health emergency of international concern, resulting in an enormous global disease burden. As of early August 2021, more than 200 million Covid-19 cases have been confirmed globally, and more than 4·3 million people have died following SARS-CoV-2 infection (9, 47).

The ongoing effects of Covid-19 on patients, families, communities, organizations, health policies and systems are central features of many current and planned investigations.

The full range of long-term health consequences of Covid-19 in patients who are discharged from hospital is largely unclear. Despite overall 50% of ICU survivors suffer from new physical, mental, and/or cognitive problems at 1 year after ICU discharge (8, 48), our results show that functional and cognitive recovery improves between 6 and 12 months after discharge with a high perception of the patients' quality of life.

The study's findings can also be used to establish programs that can prevent the turnover of skilled physicians/nurses with experience in caring for Covid-19 patients.

Within one year of acute infection, most hospital survivors with Covid-19 had good physical and functional recovery over time with better outcomes than other ICU patients, and had returned to their original work and life. We suggest that multicenter follow-ups are needed in the future to better characterize the natural history and pathogenesis of the long-term health consequences of Covid-19 in ICU survivors.

Relevance to clinical practice

Our findings will help to inform health system planning and the development of multidisciplinary care strategies to reduce chronic health loss among individuals with Covid-19. In addition, these results can also be used to point towards areas of research interested in improving medicine or nursing. Health care workers are now actively involved in Covid-19 interventions, and they will remain key players in stopping the pandemic with adequate assistance in the short and long term.

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Riassunto

Conseguenze a lungo termine nei pazienti Covid-19 e Non-Covid-19 dimessi dalla Terapia Intensiva. Uno studio descrittivo.

Introduzione. I pazienti in condizioni critiche possono sviluppare problemi di salute legati alla loro malattia, alla degenza in Terapia Intensiva, alla ventilazione meccanica o ad altri trattamenti intensivi. Tali problemi non possono essere prevenuti del tutto e possono continuare anche dopo che il paziente ha lasciato l'ospedale.

Scopo. Esplorare il livello di ansia, depressione, sintomi da stress post-traumatico e qualità della vita nei pazienti dimessi da una terapia intensiva. In aggiunta, è stata condotta un'analisi di confronto tra pazienti Covid-19 e pazienti non Covid-19.

Metodi. È stato condotto uno studio osservazionale prospettico che ha esplorato le difficoltà psicologiche, emotive e comportamentali sperimentate dai pazienti ricoverati in terapia intensiva. Lo studio è stato condotto in una terapia intensiva italiana da 8 posti letto per adulti, da luglio 2020 ad aprile 2021, follow-up terminato il 25 maggio 2022. I dati sono stati raccolti durante la degenza in terapia intensiva (raccolta dati caratteristiche demografiche e cliniche) e 6 e 12 mesi dopo la dimissione (interviste).

Risultati. Hanno partecipato allo studio un totale di 143 pazienti, di cui 54 ricoverati per Covid-19 (37.76%). I sintomi di depressione sono stati osservati maggiormente tra i pazienti Non-Covid-19 rispetto ai pazienti Covid-19 a sei mesi (p=.037) e 12 mesi (p<.001) dalla dimissione dalla terapia intensiva.

La percezione della qualità della vita percepita tra i pazienti intervistati è migliorata tra I 6 e 12 mesi dopo la dimissione (media Eq-VAS= 62.03, $\pm$ 11,2; vs media Eq-VAS= 66.6, $\pm$ 9.8) (p=.034).

Sei mesi dopo la dimissione dalla terapia intensiva, la

percezione della qualità della vita, per i pazienti Covid-19 era 63.91 (sd ± 9.30) maggiore rispetto ai pazienti Non-Covid-19 dello stesso periodo che era 60.18 (sd ± 8.63) (p=.038).

Conclusione. Entro 1 anno dall'infezione acuta, la maggior parte dei sopravvissuti ospedalieri con Covid-19 ha avuto un buon recupero fisico e funzionale nel tempo con risultati migliori rispetto ad altri pazienti di terapia intensiva.

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