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The impact of Mindfulness-based stress reduction on Covid-19 survivors. A randomized controlled trial

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Key words: Mindfulness-Based Stress Reduction; Intensive Care Unit; Long-COVID
Parole chiave: Riduzione dello stress basata sulla consapevolezza; Terapia Intensiva Long-Covid

Abstract

Introduction. *Long-COVID represents a clinical condition characterized by the inability of the patient who survived COVID-19 to regain the same state of health prior to the acute infection. Mindfulness-based stress reduction focuses on increasing awareness and acceptance of moment-to-moment experiences including difficult emotions and physical discomfort.*
Objective. To examine the effects of a Mindfulness-based stress reduction intervention on the functional and psychosocial outcomes of Long-COVID patients
Design. *A two-arm randomized controlled trial with repeated-measures design.*
Setting. *Department of Anesthesia and critical care.*
Participants. COVID-19 survivors (105 patients).
Methods. *The patients were randomly allocated to either psychoeducation (intervention group) or usual care (control group) (53 vs 52 patients per group). A Mindfulnes program was implemented in the intervention group included an 8-week Mindfulnes-program (2 hours per week) in a group format. Study outcomes included Chronic pain (pain intensity and pain interference) assessed with Brief Pain Inventory (primary outcomes), Anxiety and Depression assessed with Hospital anxiety and depression scale, Insomnia assessed with the Insomnia Severity Index. Data were collected at 6 month and 12 months after Mindfulness-program.*
Results. *A reduction in pain intensity and pain interference on some activities of daily living were observed 6 and 12 months after intervention. A statistically significant difference emerged in the mean score of symptoms of anxiety in favor of the intervention group (11.28 vs 13.15, t= -3.636, p< .001) at 6 month and at 12 months (10.88 vs 13.41, t= -5.167, p< .001) and in the mean score of the symptoms of depression in favor of the intervention group (9.95 vs 11.23, t= -2.823, p= .007) at 6 month and at 12 months (9.67 vs 10.69, t= -2.458, p= .018). Symptoms of insomnia were statistically reduced 6 months after the Mindfulness-program (score: 53.2 vs 30.4, x= 4.944, p= .026).*
Conclusions. *In light of what emerged from our study, we suggest a Mindfulness program in addition to drug therapy to be carried out once a year on patients with consequences of COVID-19. Studies with larger sample sizes that attempt to test a Mindfulness-program twice a year are needed.*

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Introduction

The SARS-CoV-2 pandemic has affected and continues to affect a very large number of individuals, with an enormous burden of disease and mortality (1). Although the clinical manifestations of the acute phase symptoms of the infection are relatively well defined, we observed the emergence, in an increasingly clear way, that the infection, after the end of the acute phase, can determine a heterogeneous complex of acute and chronic clinical manifestations that preclude a full return to the previous state of health (1).

The symptoms attributed to this condition are numerous and heterogeneous, they can concern subjects of any age, and with varying severity of the acute phase of the disease. The lack of a precise definition of this condition and the breadth of the symptoms' spectrum make epidemiological evaluation difficult (2). In fact, to define the epidemiology of the condition there is a need for a common definition to establish incidence, prevalence and risk factors and sociodemographic and clinical data to identify favorable factors and exclude confounding ones (3). However, it appears clear that, due to the unusual spread of the pandemic and the enormous number of people suffering from the acute infection, the persistence of significant symptoms, even if they affect only one part of the subjects suffering COVID-19, acquires great public health relevance in terms of number of patients and their care.

This need for assistance and treatment has been addressed in various ways, both from the point of view of clinical and instrumental diagnosis and from a management point of view, with the prompt creation in various locations of "post-COVID" clinics and clinics directly linked to varying degrees with general medicine and the hospital (4). The variety of symptoms and the age range of the affected population have clearly indicated the need for an integrated and multidisciplinary approach.

Long-COVID represents a clinical condition characterized by the failure of the patient to return to the same state of health enjoied prior to the acute infection (1). The mechanisms by which the infection determines Long-COVID have not yet been fully understood and defined. There is growing evidence that supports the hypothesis of a genesis caused by direct organ damage by the virus, but an innate immune response with release of cytokines could also involve inflammatory conditions or the development of a pro-coagulative state. The reasons why only some patients develop Long-COVID are currently unknown, although age advanced, female sex and hospitalization appear to be favorable factors (5). Even children, though rarely, may present sequelae of COVID-19 disease (6). Although there is no single symptom or test to diagnose Long-COVID, many patients complain profound asthenia, and a range of clinical symptoms that highlight the possible involvement of the majority of the body systems. For working people, Long-COVID can make it difficult to return to work, with obvious economic consequences and loss of working days (1). For older people the Long-COVID can have a significant impact on functional status and reduce their independence in carrying out daily activities (7).

The management of people with Long-COVID must be multidisciplinary to respond to the different clinical, functional, cognitive, psychological and nutritional manifestations. This approach must be personalized, modulated and adapted taking into account the variety of conditions that arise in the single patient. It is important to define timely and personalized follow-ups based on the characteristics and needs of each patient in order to re-evaluate the general conditions and plan new interventions, if necessary.

Non-pharmacological treatments for these symptoms are poorly understood.

Mindfulness Based Stress Reduction (MBSR) program is a Non-pharmacological treatment developed by Dr. Jon Kabat-Zinn in 1979 with some updates in recent years (8). Indeed, although initially developed for stress management, it has evolved to encompass the treatment of a variety of health related disorders such as anxiety, depression, skin diseases, pain, hypertension, diabetes and immune disorders (9). It employs mindfulness meditation to alleviate suffering associated with psychosomatic, psychiatric and physical disorders. Several specialized centers across the world offer MBSR as an alternative treatment option to patients. The MBSR programs include 2.5 hour/week, 8-weeks course with a 1-day retreat (8). Participants receive training in formal mindfulness meditation techniques involving simple stretches and postures.

An advantage of MBSR program is that these interventions have little risk and can increase the capability of patients to have control over their pain, mood swings and lives, as well as enhance quality of their life (9). Researches are warranted for investigation of the mechanism through which MBSR facilitates patients with chronic illnesses. This will lead to a better understanding of the applications of MBSR.

Aim

This Randomized Controlled Trial compared MBSR with usual care among patients who survived the acute phase of a SARS-COV-2 infection.

We hypothesized that adults with long-term consequence of COVID-19, randomized to receive MBSR, would show greater short- and long-term improvement in Long-Covid–related pain, anxiety, depression and insomnia - than those randomized to usual care.

Methods

Trial design

A two-arm randomized controlled trial, with repeated-measures design, was conducted from April 2023 to July 2024 (Figure 1). This study was prospectively registered at ClinicalTrials.gov (ClinicalTrials.gov ID: NCT05815693).

Participants

The study sample was recruited from one General Hospitals (Department of anesthesia) in Lecco, Italy from April 2023 to July 2024 (1 or 2 year after ICU discharged).

To identify eligible participants, the principal researcher examined the reasons for admission to the intensive care unit and approached potential patients for further assessment according to the study inclusion and exclusion criteria.

During the first interview the patients were asked: Do you remember suffering from problems such as anxiety, depression, chronic pain or insomnia before your admission to the Intensive Care Unit due to a SARS-COV-2 infection?

If patients being enrolled reported that they were suffering from pain, anxiety, depression and insomnia both before exposure to a SARS-COV-2 infection and after admission to the Intensive Care Unit they were not considered Long-COVID patients.

The inclusion criteria for Long-COVID patients was as follows: 1) patients with anxiety, depression, insomnia symptoms in drug therapy after ICU discharged; 2) patients with chronic pain on current drug therapy; 3) patients hospitalized in intensive care units in the years 2021-2022 for a Sars-CoV-2 infection; 4) patients older than 18 years; and 5) patients who, during enrollment, reported that they suffered from pain, anxiety, depression and insomnia only after SARS-COV-2 infection and after admission to the Intensive Care Unit.

Patients were excluded if 1) undergoing cognitive behavioral therapy before the COVID-19 event; 2) under 18 years of age; 3) affected with chronic

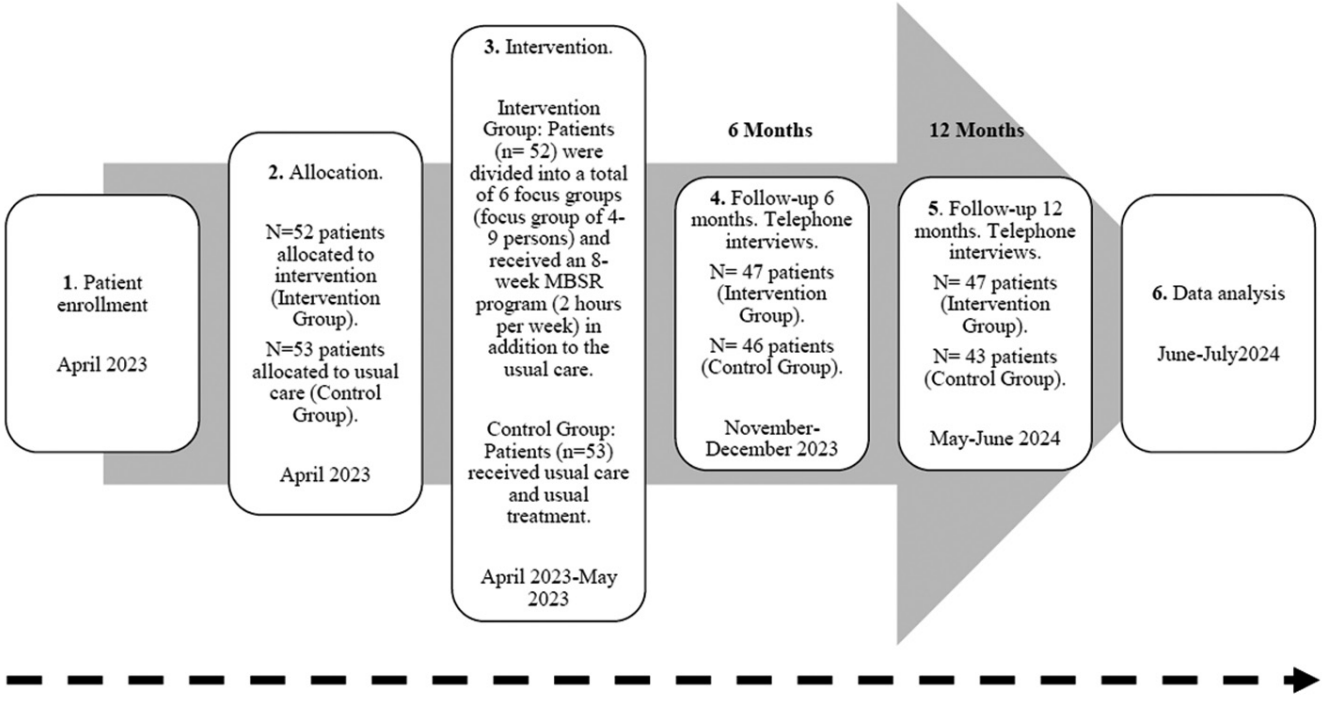

Figure 1 - Timeline for Study implementation and Mindfulness-Based Stress Reduction program.

cancer pain; 4) without current drug therapy; and 5) who reported during enrollment that they suffered from pain, anxiety, depression and insomnia prior to SARS-COV-2 infection and admission to the Intensive Care Unit.

Moreover, patients were required to demonstrate understanding of the study protocol and the ability to follow the instructions for the interventions and for filling questionnaires.

Experienced clinical nurses carefully referred those who met the criteria to the research staff and assessed patients. The participants who met the clinical criteria for this study were informed about the study and a written informed consent was obtained from each participant. Then the trained researchers presented participants with detailed information, and if the participant agreed to participate, an informed consent form was signed.

Sample Size

A priori estimation of sample size was based on the effect sizes calculated according to the similar clinical trials of MBSR approaches to patients (10).

In addition, we used our similar research to define the prevalence of symptoms in COVID-19 survivors after intensive care (11). One hundred and six (51.2%) patients between 6 and 12 months after ICU discharge reported at least one physical or cognitive impairment (7, 11).

We assumed a statistically difference by at least 5 % points in each issues (eg. reduction on the number of patients with anxiety, depression, insomnia) of BPI-pain intensity (four-items) between the MBSR and control groups at 12 months from enrollment.

Assuming to find 106 patients divided into 53 patients per arm, but assuming a hypothetical 18% dropout rate (n = 19), we aimed to recruit 125 participants (intervention group n = 63 vs control group n= 62). As the dropout rate was lower than expected, we stopped recruiting at 105.

Randomization

A randomisation sequence was generated, using an online programme (https://www.sealedenvelope.com/simple-randomiser/v1/lists), by a nurse who was not involved in the participant recruitment, intervention implementation, or outcome assessments of the present study. In each block, the two letters 'A' and 'B' indicated the intervention and control group, respectively.

The randomization was minimized, taking into account the imbalance between the groups over a number of prognostic clinical and demographic factors. With minimization, the treatment allocated to the next participant enrolled in the trial depends on the characteristics of those participants already enrolled.

Intervention

Introduction of the MBSR program among ICU patients was supported by ICU's staff after ICU's discharge.

The MBSR protocol is a structured and systematic program that uses mindfulness meditation as a central element to teach people to take better care of themselves and live a healthier and more adaptive life (8). The official MBSR protocol was developed by Jon Kabat-Zinn at the Center for Mindfulness at the University of Massachusetts and was created with the aim of facilitating stress reduction. Therefore, the specific objective of the MBSR course is to help participants reduce the level of subjective suffering and acquire and maintain greater well-being (8).

Detailed history-taking, including medical history, was provided to all participants, and written informed consent was obtained.

Participants included in the study received usual care with drug therapy, treatment, and evaluations during the study period.

In addition, patients received an 8-week MBSR program (2 hours per week) in a group format (focus groups of 4-9 persons each).

Patients were divided into a total of 6 focus groups (trying to respect the 12-month-period from discharge as much as possible). We managed to complete the 8 sessions in a total of two months (April-May 2023) (Figure 1).

In each of the 8 sessions carried out after ICU discharge, a different topic was addressed, in line with the MBSR program and our research protocol.

The themes of the individual sessions were:

1. Overview of mindfulness; 2. Facing difficulties; 3. Mindful breathing; 4. Staying present; 5. Allowing (letting it be); 6. Thoughts are not facts; 7. Taking care of yourself; 8. Dealing with future struggles.

The contents of each session concerned: psychoeducation, exercise and homework for each theme.

The original MBSR program was kept unchanged. However, we added a brief segment of psychoeducation to the first session to reflect on the distress of long consequences of ICU stay and of patients suffering from it, to show how Mindfulness-Based Interventions can be helpful for it. Finally, lectures and exercises on compassion were provided to the partecipants.

MBSR consisted of discussion and interaction among the participants in order to facilitate their learning, and of psychoeducation based on cognitive therapy and formal meditational exercises.

Homework was assigned to the participants at every session, which was supposed to take 20 - 45 minutes every day with a meditation-guide CD.

The therapists were clinical psychologists and nurses who had at least 5 years of Mindfulness experience and had undergone MBSR training provided by a Mindfulness Training Center, with an update course in the last three years.

The therapists followed the intervention protocol schedule at each session to ensure treatment integrity.

A research assistant directly observed the sessions and checked for treatment adherence.

There was no restriction on any co-interventions during the study period. However, patients were asked to refrain from participating in any type of Mindfulness-Based Interventions (MBIs) or from engaging in meditational exercises, yoga or other cognitive behavioral therapies during the study.

Measurements

General Characteristics

The study participants self-reported demographic characteristics (sex, age, education, marital status, caregiver, pain sites) using a structured instrument developed by the research team in a strictly individual interview, to protect each participant's privacy.

Outcomes and Instruments

We assessed pain with the Brief Pain Inventory-Short form (BPI-SF) (12). The BPI-SF is a brief, simple, self-administered questionnaire for evaluating pain, which addresses the relevant aspects of pain-history, intensity, timing, location and quality—and the pain's ability to interfere with the patient's activities. The short questionnaire we used is divided into two parts: Pain Intensity and Pain Interference. Pain intensity, with 4 domains, was rated on a NRS of 0 (no pain) to 10 (the worst pain imaginable) numeric rating scale (NRS). Pain interference with the 7 domains of functioning was rated on a NRS of 0 (does not interfere) to 10 (completely interferes).

In a previous validation study alpha coefficients for the pain severity and the pain interference scale were above 0.75 (12). The Italian version of the BPI-SF was carried out in 1996 (12).

We assessed anxiety and depression with the Hospital anxiety and depression scale (HADS). The HADS (13) is a 14-item scale designed to f1123assess anxiety and depression, with emphasis on reducing the impact of physical illness on the total score. The HADS includes 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. For each scale, the scores collected indicate: no problem score 0-7; mild problems score 8-10; moderate problems score 11-14; severe problems score 15-21. In a previous validation study the sensitivity and specificity for both HADS-A and HADS-D were approximately 0.80 (13).

The Italian version of the HADS was prepared in 2011 (14) and recently updated to 2020 (15).

We assessed the insomnia with the Insomnia Severity Index (ISI). The ISI (16) is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. The usual recall period is the "last month" and the dimensions evaluated are: severity of sleep onset, sleep maintenance, and early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item (e.g., 0 = no problem; 4 = very severe problem), yielding a total score ranging from 0 to 28. The total score is interpreted as follows: absence of insomnia (0–7); sub-threshold insomnia (8–14); moderate insomnia (15–21); and severe insomnia (22–28). In a previous validation study ISI internal consistency was excellent for both samples (Cronbach α of 0.90 and 0.91) and a cutoff score of 10 was optimal (86.1% sensitivity and 87.7% specificity) for detecting insomnia cases in the community sample (15). The ISI questionnaire maintains good psychometric properties in the Italian version, thus confirming that this instrument is reliable for detecting insomnia severity and identifying patients' symptoms (16).

We assessed the adherence to the intervention. The participants' adherence to the intervention was assessed using frequency of attendance at the MBI program. The patients who attended less than four (out of eight) sessions were considered dropouts, in line with the study protocol.

Quality control

Controls and quality standards were maintained throughout the study.

Researchers with unified training collected the relevant data, followed up, and stored the data in a dedicated electronic database. One researcher was assigned to check the data entries from each patient, and a third-party statistics agent rechecked all entries. In case of extreme or missing values, or in case of missing answers to the questionnaires the data were rechecked by the project coordinator.

Validity and Realibility

The research protocol was pilot tested prior to the beginning of the study among the research group.

Interventionists utilised a protocol manual to ensure intervention fidelity. Psychotherapeutic staff, physicians and nurses, were trained to ensure consistency. The participants of both groups did not participate in other studies during the intervention period and continued to participate in previously started activities.

None of the participants involved had carried out any previous mindfulness practices prior to our study.

Statistical analysis

Outcome data were analyzed and reported according to the CONSORT guidelines (17). We examined the differences at baseline (clinical-demographic data collected at enrollment), at 6 and 12 months between the intervention and control groups, and between participants who withdrew and those who remained in the study by means of chi-square and independent samples t tests.

Normally distributed measurement data were represented by means and standard deviations accordingly. Measurement data with non-normal distributions were represented by medians and interquartile ranges (IQR), and the number of cases or percentages represented the counting data.

All statistical analyses were performed using IBM SPSS software (version 25.0; IBM, Armonk, NY, USA), with the significance level set at 5% (two-tailed).

The independent t test or chi-square atests were applied to assess homogeneity between the intervention and control groups at 6 months and 12 months as appropriate.

Ethical approval and informed consent

The LONGCOVID trial was registred at ClinicalTrials.gov (ClinicalTrials.gov ID: NCT05815693) (ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt

Release Date: March 28, 2023; first patient enrolled 09/04/2023).

Ethical approval was obtained from the Institutional Ethics Committee (doc. 6534 of 16.03/23). The study questionnaires were introduced to each participant, and each participant was asked to answer the questions. The study protocol was in line with the Declaration of Helsinki, as revised in 2013, and 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).

Written informed consent was obtained from all participants and they were informed (a) that all information would be handled strictly confidential, and (b) that it was possibility to withdraw the consent at any time.

Patient contributions

During the drafting of the research protocol, ten patients suffering from problems related to Long-COVID were involved to evaluate understanding of the project and understand whether the questionnaires to be used were simple or too long and complex (18). Positive feedback regarding the simplicity and understanding of the project came from 10 out of 10 patients.

At the end of the study, all included patients were involved to jointly evaluate the results of the article. The article was sent in the original language, via email, to each included patient. A total of 33 patients responded and all approved the work.

Results

Sample

One hundred and fourty-one patients were considered eligible (admitted to the Intensive Care Unit for COVID-related pneumonia and discharged after at least 48 hours of ICU-stay). After inclusion criteria assessments, a total of 105 patients (52 allocated to the intervention group and 53 allocated to the control group) were included in our trial (Figure 2). Of these, a total of 93 patients took part in the follow-up interviews and included in the analyses (47 in the intervention arm and 46 in the control arm). The average age of the study population was 60 years, and 65.6% were male (Table 1). The average stay in Intensive Care was 28 days and the hospital stay (post-ICU) was 19 days. No significant differences emerged between the characteristics of patients allocated to the intervention group or the control group (Table 1).

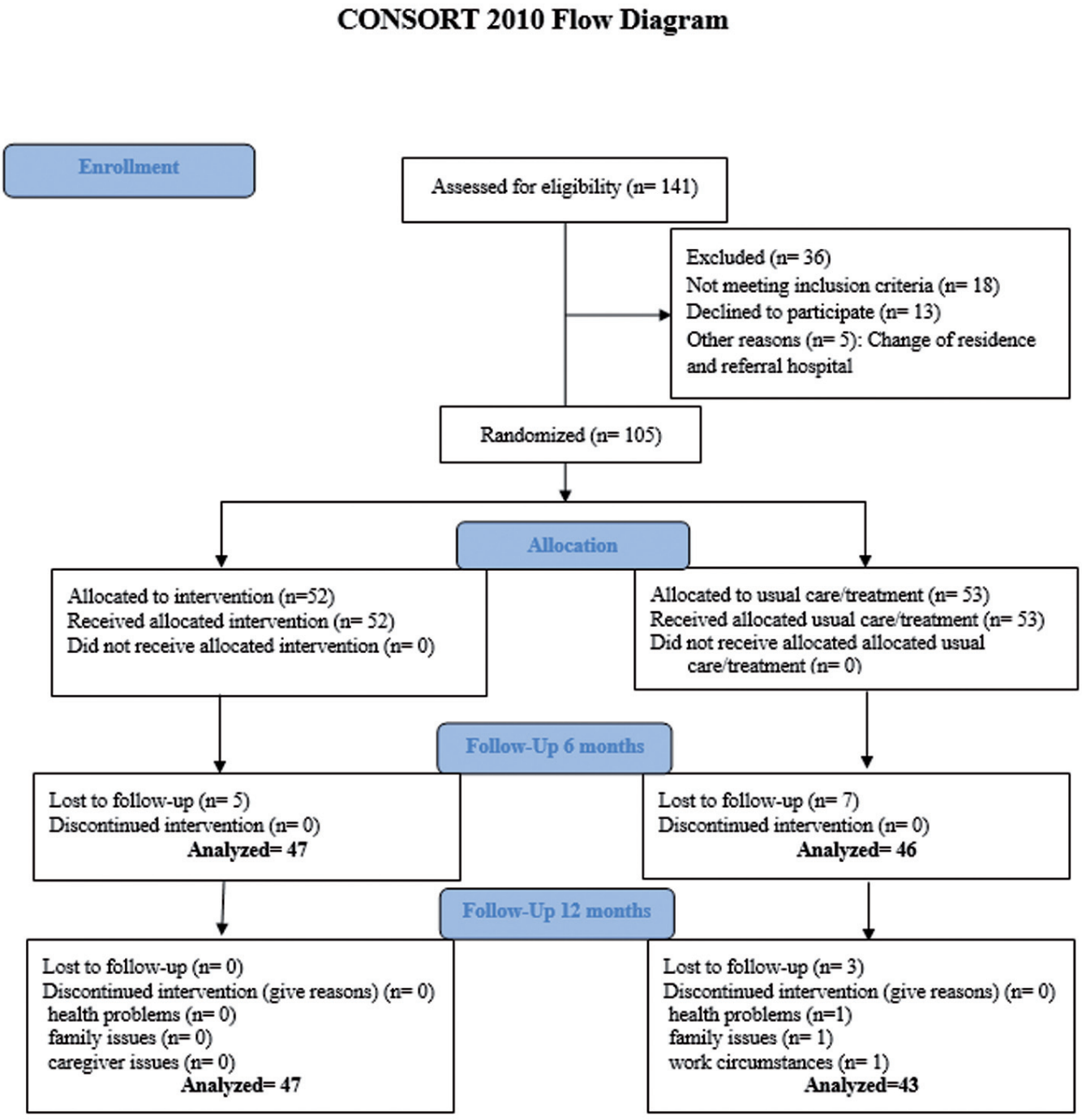

Figure 2 - Flowchart of four phases (recruitment, randomization, allocation, 6- and 12-month follow-up) modified from CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement.

Intervention Adherence

No patients attended less than four sessions and were thus considered dropouts (dropout rate = 0%). However, five patients in the intervention group did not participate in the 6-month follow-up interviews. The average number of MBSR program sessions was 7.1/8.

Pain

The assessment of pain, pain intensity and interference of pain in people's lives was assessed using the BPI-SF questionnaire.

We observed lower intensity among patients in the experimental group for the domain: least pain

Table 1 - Demographic and clinic characteristics of studied population.

	All patients (n=93)	IG (n=47)	CG (n=46)	p.
Gender, n (%)				
Male	61 (65.6)	28 (59.6)	33 (71.7)	.217
Female	32 (34.4)	19 (40.4)	13 (28.3)	
Age in years, mean (sd)	60.02 (9.93)	58.95 (10.64)	61.1 (915)	.324
Marital status, n (%)				
married/engaged	65 (69.9)	34 (72.3)	31 (67.4)	.602
unmarried	19 (20.4)	8 (17.1)	11 (23.9)	
widower	9 (9.7)	5 (10.6)	4 (8.7)	
Anthropometric data, mean (sd)				
Weight in kg	79.45 (±8.26)	80.76 (±7.96)	78.10 (±8.43)	.097
BMI	27.71 (±2.35)	27.95 (±2.15)	27.47 (±2.55)	.399
ICU days, mean (sd)	28.67 (±9.63)	29.57 (±9.51)	28.8 (±10.4)	.941
Hospital ICU days, mean (sd)[1]	19.66 (±11.91)	21.17 (±10.27)	17.67 (±13.03)	.100
Anamnesis, n (%)				
diabetes	48 (51.6)	22 (46.8)	26 (56.5)	.348
hypertension	28 (30.1)	16 (34)	12 (26.1)	.403
kidney failure	23 (24.7)	9 (19.1)	14 (30.4)	.207
heart attack	12 (12.9)	5 (10.6)	7 (15.2)	.510
NYHA (I, II, III)	12 (12.9)	5 (10.6)	7 (15.2)	.510
oncological pathologies	8 (8.6)	3 (6.4)	5 (10.9)	.440
neurological pathologies	3 (3.22)	2 (4.3)	1 (2.2)	.570
Year of admission to ICU, n (%)				
2020	51 (54.8)	26 (55.3)	25 (54.3)	.925
2021	42 (45.2)	21 (44.7)	21 (45.7)	
Clinical characteristics				
p/f entrance, median (IQR)	141 (126-156)	145 (130-165)	139.5 (120-155.2)	.253
ETT, n (%)	78 (83.9)	39 (82.9)	39 (84.8)	.813
ETT in hours, median (IQR)	336 (0-480)	336 (0-480)	330 (0-486)	.739
tracheostomy, n (%)	12 (12.9)	7 (14.9)	5 (10.9)	.562
tracheostomy in hours, median (IQR)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	.711
hemodialysis, n (%)	13 (14)	7 (14.9)	6 (13)	.797
hemodialysis in hours, median (IQR)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	.811
PiCCO, n (%)	10 (10.8)	4 (8.5)	6 (13)	.480
PiCCO in hours, median (IQR)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	.809
Swan-Ganz, n (%)	3 (3.2)	1 (2.1)	2 (4.3)	.557
Swan-Ganz in hours, median (IQR)	0.0 (0-0)	0.0 (0-0)	0.0 (0-0)	.809

Legend: BMI - body mass index; ICU - intensive care unit; p/f - partial pressur of oxygen/fraction of inspired oxygen; ETT - endo-tracheal tube; IQR= interquartile range 25-75; PiCCO - pulse contour cardiac output; NYHA -New York Heart Association; [1]Hospital Stay after ICU. Statistically significant difference (P<0.05).

in the last 24 h (0.91 vs 1.43, p= .035) six months after the intervention and the statistical significance remained stable even at 12 months (2.20 vs 2.83, p= .012) (Table 2).

An improvement in pain interference was observed in the experimental group, relating to the domains: interference with general activity (1.52 vs 2.21, p= .004), interference with mood (2.60 vs 4.13, p= .002), interference with sleep (3.06 vs 3.73, p= .015) and interference with enjoyment of life (2.67 vs 3.69, p= .007) six months after the intervention. An improvement in pain interference was observed

Table 2 - Results between **experimental** and control groups at 6 and 12 months from program MBSR.

	Scores at 6 months			Scores at 12 months		
	IG (n= 47)	CG (n= 46)	p.	IG (n= 47)	CG (n= 43)	p.
Pain						
Chronic Pain- case, n (%)	26 (55.3)	25 (54.3)	.925	26 (55.3)	24 (55.8)	.962
Worst pain in the last 24 h, M (SD)	4.93 (0.67)	4.89 (0.84)	.622	5.27 (1.48)	5.41 (0.85)	.587
Least pain in the last 24 h, M (SD)	0.91 (0.66)	1.43 (1.06)	**.035**	2.20 (0.70)	2.83 (1.23)	**.012**
Pain on average, M (SD)	1.87 (0.67)	2.02 (1.76)	.569	2.55 (0.90)	3.04 (1.29)	.051
Pain right now, M (SD)	0.91 (1.22)	1.15 (1.02)	.288	1.65 (1.36)	1.67 (1.04)	.919
Pain Interference with general activity, M (SD)	1.52 (1.06)	2.21 (1.28)	**.004**	1.81 (1.07)	2.04 (1.74)	.507
Pain Interference with mood, M (SD)	2.60 (1.84)	4.13 (2.62)	**.002**	2.48 (1.29)	3.32 (1.99)	**.031**
Pain Interference with general work, M (SD)	2.08 (1.60)	1.58 (2.24)	.127	1.97 (1.92)	1.69 (1.61)	.501
Pain Interference with walking ability, M (SD)	1.41 (1.96)	1.10 (1.80)	.479	2.46 (1.16)	2.04 (1.84)	.178
Pain Interference with relationship with other people, M (SD)	1.82 (1.08)	1.56 (1.69)	.452	2.41 (0.95)	2.48 (1.65)	.804
Pain Interference with sleep, M (SD)	3.06 (1.71)	3.73 (1,74)	**.015**	3.0 (1.66)	3.74 (1.80)	**.017**
Pain Interference with enjoyment of life, M (SD)	2.67 (2.25)	3.69 (1.28)	**.007**	3.23 (1.50)	3.76 (1.23)	.077
Anxiety						
Absence of anxiety 0-7, n (%)	9 (19.1)	8 (17.4)	.826	9 (19.1)	8 (18.6)	.947
Mild anxiety 8-10, n (%)	11 (23.4)	8 (17.4)	.472	9 (19.1)	9 (20.9)	.832
Moderate anxiety 11-14, n (%)	12 (25.5)	9 (19.6)	.491	11 (23.4)	7 (16.3)	.398
Severe anxiety 15-21, n (%)	15 (31.9)	21 (45.6)	.173	18 (38.3)	19 (44.2)	.570
Depression						
Absence of depression 0-7, n (%)	8 (17.4)	5 (10.6)	.392	10 (21.3)	7 (16.3)	.545
Mild depression 8-10, n (%)	18 (38.3)	17 (36.9)	.893	13 (27.6)	14 (32.6)	.612
Moderate depression 11-14, n (%)	13 (27.7)	12 (26.1)	.864	15 (31.9)	14 (32.6)	.877
Severe depression 15-21, n (%)	8 (17)	12 (25.5)	.287	9 (19.1)	8 (18.6)	.947
Insomnia						
Absence of insomnia- 0-7, n (%)	25 (53.2)	14 (30.4)	**.026**	21 (44.7)	18 (41.9)	.787
Sub-threshold insomnia- 8-14, n (%)	8 (17)	12 (26.1)	.287	13 (27.7)	11 (25.6)	.823
Moderate insomnia- 15-21, n (%)	6 (12.8)	9 (19.6)	.372	5 (10.6)	6 (13.9)	.631
Severe insomnia- 22-28, n (%)	8 (17)	11 (23.9)	.409	8 (17)	8 (18.6)	.844

Legend: *BPI-SF*-Brief Pain Inventory-Short Form; *HADS* - hospital anxiety and depression scale; *ISI* -Insomnia Severity Index. Statistically significant difference (P<0.05).

in the experimental group, relating to the domains: interference with mood (2.48 vs 3.32, p= .031) and interference with sleep (3.0 vs 3.74, p= .017) 12 months after the intervention (Table 2).

No gender differences emerged from statistical sub-analysis of data (male vs female participants) in the benefits of MBSR for pain intensity or pain interference.

No other significant findings emerged.

Anxiety and Depression

For the evaluation of cases of anxiety, no difference emerged in the reduction in the prevalence of non-cases, mild cases, moderate or severe cases between the intervention group and the control group. However, a statistically significant difference emerged in the mean score of the HADS-Anxiety scale in favor of the intervention group (11.28 vs 13.15, t= -3.636, p< .001) at 6 month and at 12 months (10.88 vs 13.41, t= -5.167, p< .001) (Figure 3).

For the evaluation of cases of depression, no difference emerged in the reduction in the prevalence of non-cases, mild cases, moderate or severe cases between the intervention group and the control group (Table 2). However a statistically significant difference emerged in the mean score of the HADS-Depression scale in favor of the intervention group (9.95 vs 11.23, t= -2.823, p= .007) at 6 month and at 12 months (9.67 vs 10.69, t= -2.458, p= .018) (Figure 3).

No gender differences emerged from statistical

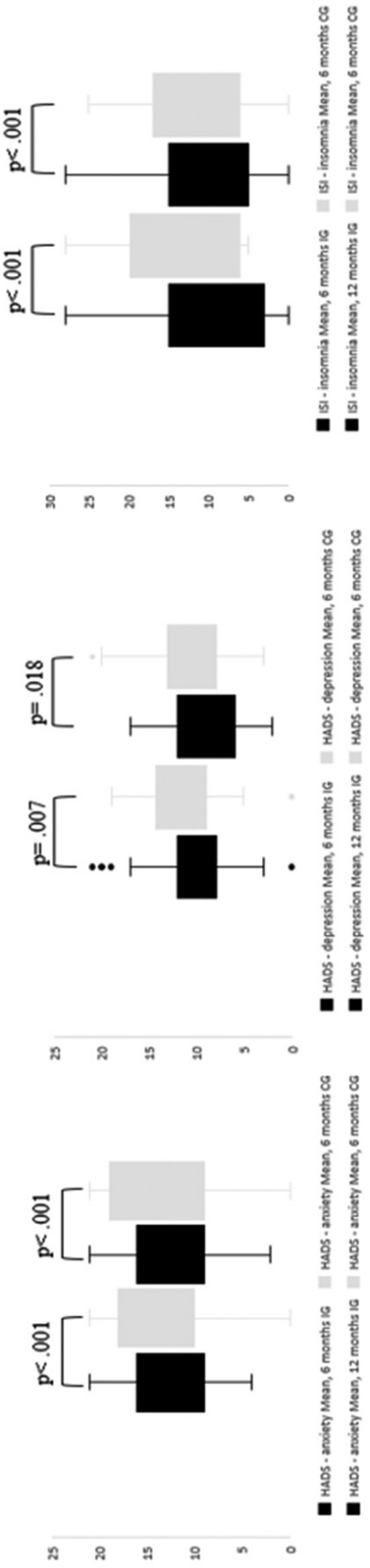

Figure 3 - Comparison between the intervention and control groups on the average anxiety and depression scores (assessed with the HADS scale) and average insomnia scores (assessed with the ISI scale) at 6 months and 12 months.

sub-analysis of data (male vs female participants) in the benefits of MBSR for anxiety or depression.

No other significant findings emerged.

Insomnia

No difference emerged in the reduction in the prevalence of non-cases, sub-threshold insomnia, moderate or severe between the intervention group and the control group at 12 months.

However a statistically significant difference emerged in the mean score of the Insomnia Severity Index in favor of the intervention group (9 vs 13.6, t= -8.801, p< .001) at 6 month and at 12 months (9.1 vs 11.1, t= -3.569, p< .001) (Figure 3).

No gender differences emerged from statistical sub-analysis of data (male vs female participants) in the benefits of MBSR for insomnia.

No other significant findings emerged.

Concurrent psychopathology

Table 3 show the concurrent caseness of chronic pain, anxiety, depression and insomnia in individual patients. The chi-square2 test was performed only if there was at least 1 prevalence associated with the comparison variable. No significant difference emerged between the prevalence of individual associations between the intervention group and the control group.

The four variables evaluated were simultaneously present in at least 12 (25.5%) patients at T0 and in 15 (31.9%) patients at T1 for the Intervention group, while they were simultaneously present in at least 16 (34.8%) patients at T0 and 14 (32.6%) patients at T1 for the control group (Figure 3).

No gender differences emerged from statistical sub-analysis of data (male vs female participants) in the benefits of MBSR for concurrent psychopathology.

No other significant findings emerged.

Discussion

The aim of this study was to evaluate the effectiveness of an MBSR program among patients suffering from anxiety, chronic pain, depression, insomnia who survived an intensive care unit admission for COVID-19. As per protocol, our evaluations were carried out 6 months and 12 months after the MBSR program which took place over a total of 2 months between April and May 2023. It is important to underline that of the 52 patients in the experimental group and therefore subjected to the

Table 3 - Concurrent caseness of chronic pain, anxiety, depression and insomnia in individual patients.

	Data at 6 months			Data at 12 months		
Caseness	IG (n=47)	CG (n=46)	p.	IG (n=47)	CG (n=43)	p.
Chronic Pain n, %	3 (6.4)	3 (6.5)	.978	5 (10.6)	3 (6.9)	.542
Chronic Pain and Anxiety n, %	0	0	-	1 (2.1)	0	-
Chronic Pain and Depression, n %	2 (4.2)	0	-	0	0	-
Chronic Pain, Anxiety and Depression, n %	9 (19.1)	6 (13)	.423	5 (10.6)	7 (16.3)	.431
Chronic Pain. Anxiety and Insomnia n, %	0	0	-	0	0	-
Chronic Pain, Depression and Insomnia n, %	0	0	-	0	0	-
Anxiety n, %	0	0	-	0	0	-
Anxiety and Depression n, %	7 (14.9)	0	-	6 (12.7)	3 (6.9)	.521
Anxiety and Insomnia, n, %	1 (2.1)	0	-	0	0	-
Anxiety, Depression and Insomnia n, %	9 (19.1)	16 (34.8)	.089	11 (23.4)	11 (25.6)	.810
Depression n, %	0	3 (6.5)	-	0	1 (2.3)	-
Depression and Insomnia n, %	0	0	-	0	0	-
Insomnia n, %	0	0	-	0	0	-
Chronic Pain, Anxiety, Depression and Insomnia n, %	12 (25.5)	16 (34.8)	.330	15 (31.9)	14 (32.6)	.948

The chi-square test was performed only if there was at least 1 prevalence associated with the comparison variable. Statistically significant difference (P<0.05).

MBSR program, 47 patients (90.4%) presented for follow-up evaluations at both 6 and 12 months. Our findings show a reduction in the perception of least pain in the last 24 hours, in the interference of pain with mood, general work, sleep and interference with enjoyment of life. At the same time, we observed lower scores on the scales for assessing anxiety, depression and insomnia. However, we would like to point out that, in our opinion, these reductions appear purely statistical and do not emerge as clinically relevant. However, it is important to underline that psychosocial factors play key roles in criticall illness and associated psychosocial and physical disability (19). Cognitive behavioral therapy (CBT), has demonstrated effectiveness for various chronic conditions and is widely recommended for patients with chronic illness (20,21).

A fact that makes us reflect is that in the intervention group, the four conditions analyzed (pain, anxiety, depression and insomnia) are less concomitant 6 months after the MBSR program (12 patients with all 4 conditions) and more concomitant at 1 year from the MBSR program (16 patients with all four conditions). This leads us to hypothesize that the MBSR program does not remain stable over time, at least not up to 1 year and further management of patients or a new treatment program is necessary (22,23). Rehabilitation involves the provision of nationally coordinated multidisciplinary programs to assess, test, diagnose and treat patients, including those who were not hospitalized during the acute phase of the infection; research requires coordinated and co-created multidisciplinary studies to understand the clinical consequences and develop treatment pathways for Long-COVID (1).

Although research generally points positive correlations between practice frequency and outcomes, the absence of correlations has also been reported (24), indicating that further investigation is needed regarding the influence of adherence to mindfulness practice on positive outcomes following interventions. The intervention group presented high levels of attendance to class. However, the type and amount of daily mindfulness practice are not always associated with relevant clinical outcomes. One possible explanation for this result is the use of self-report measures to assess both the health-related improvements and the adherence to practice. As self-report measures are subjective, it is possible that participant's expectation towards the practice played a role in their perception of improvements regardless of the amount of practice.

Mindfulness researchers have long advocated the potential of mindfulness for enhancing public health (8). And indeed, public health as pursued in many countries overlaps in promising ways with modernized "mindfulness" approaches, commonly traced to Kabat-Zinn's pioneering work in the early 1980s (8). Perhaps most prominently, modern approach to mindfulness

resonate with the public health field's emphasis on causally "upstream" approaches to foster salutary health behaviors and other protective factors that build resilience and prevent disease before it arises, helping engender communities that "can withstand known and novel threats that thrive every day" (8, 24). Moreover, reviews and meta-analyses suggest that in the USA and Europe, interventions oriented to mindfulness can foster well-being in general populations, and favorably affect conditions that include depression, anxiety, stress, insomnia, addiction, psychosis, pain, hypertension, bad weight control, and cancer-related symptoms (8, 25, 26). Reviews suggest that mindfulness approaches may be cost-effective and foster individual resilience (8, 24, 25). Emerging evidence suggests that mindfulness might also plausibly play a key role in building resilience at the level of populations and systems (25).

Limit

The main limitation of the study was that it did not reach the hypothesized sample size and that it lost 3 patients (6.5%) in the control group for the interviews carried out 12 months after the intervention. However, due to the unpredictable evolution of the COVID-19 pandemic, which saw various waves one after the other, this was a possibility that we had already considered. A further limitation of the study is its monocentric design influenced by the specificity of the case selection and the use of self-administered tools for the assessment of outcomes.

Implication for nursing practice

This short randomized trial provides evidence that physical, psychological, and cognitive symptom clusters exist among post-COVID-19 in ICU survivors. Our results indicate that the symptom clusters identified at baseline were sustained for 12 months, with an immediate benefit after the MBSR program. The patient's self-assessment constitutes the most reliable information on the experience of psychological and/or social disorders. It is currently known that post-COVID symptomatology is highly heterogeneous and more complex than expected, which may explain why a consensus on the definition of Long-COVID is not yet available. Several Authors have discussed aspects such as whether or not a previous positive diagnosis of COVID-19 is necessary. Patients with Long-COVID may not experience associated physiological changes and behaviors. Dealing with pain, anxiety, depression, or sleep-rest disorder can reduce the patient's energy for other activities and cause irritability, which in turn leads to worsening symptoms of insomnia and fatigue, causing greater irritability, depression and pain. Promoting the use of psychoeducation can have significant benefits in symptom management and acceptance. The main objective is to provide participants with the opportunity to develop self-care skills and improve their overall quality of life. The nurse may coach the patient, suggest self-directed meditation, or provide a recorded audio guide to help elicit the relaxation response. By trying and applying various cognitive and behavioral self-management techniques, participants learn how to set realistic goals and manage or accept some specific conditions in their life. In addition to improving outcomes for managing symptoms of pain, anxiety, depression, or insomnia, psychoeducation can also promote better communication between patient and healthcare provider and help reduce healthcare costs. Furthermore, nurses can encourage and support the patient's use of new methods to modify and manage specific symptoms, unless they are specifically contraindicated. Strategies may include seeking calm and solitude, knowing one's condition, pursuing interesting activities as a form of distraction, reciting prayers, or socializing.

Conclusions

Mortality rate during intensive care was high during the COVID-19 outbreak, often also associated with co-infections (27), but also severe long-term functional, physical and psychological problems emerged among COVID-survivors.

Long-COVID is an important public health problem and one of the approaches to address this problem is through MBSR. Understanding symptom clusters in COVID-survivors may result in greater therapeutic benefits by integrating treatments for concurrent symptoms, thus improving quality of life.

Despite the limitations of our study that used a randomized controlled design, had a small sample size, and employed different outcome measures, MBSR is a promising modality for Long-COVID among healthy individuals. The main results of this RCT demonstrate that the MBSR program reduced some chronic symptoms, improving the patients' insomnia and psychological disorders within one year.

In the light of what emerged from our study, we suggest a MBSR program in addition to pharmacological therapy to be carried out once a

year. Studies with larger sample sizes that attempt to test an MBSR program twice a year are needed.

Data availability: The datasets used during the study are avaible upon reasonable request from the corresponding Author.
Ethical Approval: The study was approved by the Institutional Ethical Committe and was registered on ClinicalTrials.gov Identifier: NCT05815693. All participants provided their informed written consent to participate during the enrollment. Consent was obtained by the nursing staff. The study protocol was in line with the Declaration of Helsinki, as revised in 2013, and the Oviedo Convention.
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Appendix:
BPI-SF = Brief Pain Inventory- Short form.
COVID-19 = COronaVIrus Disease 19.
SD = standard deviation.
HADS = Hospital anxiety and depression scale.
ICU = Intensive Care Unit.
ISI = Insomnia Severity Index.
MBSR = Mindfulness-based stress reduction.
N == number.
NRS §= Numerical Rating Scale.
RCT = randomized controlled trial.
vs = Versus.

Riassunto

L'impatto della "riduzione dello stress basata sulla consapevolezza" nei sopravvissuti al Covid-19. Uno studio randomizzato e controllato

Introduzione. Il Long-COVID rappresenta una condizione clinica caratterizzata dal mancato rientro del paziente affetto da COVID-19 nello stato di salute precedente all'infezione acuta. La riduzione dello stress basata sulla consapevolezza si concentra sull'aumento della consapevolezza e dell'accettazione delle esperienze momento per momento, comprese le emozioni difficili e il disagio fisico.

Obiettivo. Esaminare gli effetti di un intervento di riduzione dello stress basato sulla consapevolezza sugli esiti funzionali e psicosociali dei pazienti con Long-COVID.

Disegno. Studio randomizzato e controllato a due bracci con disegno a misure ripetute.

Metodi. I pazienti sono stati assegnati in modo casuale al percorso di psicoeducazione (gruppo di intervento) o alle cure abituali (gruppo di controllo) (53 vs 52 pazienti per gruppo). Nel gruppo di intervento è stato implementato un programma di Mindfulness di 8 settimane (2 ore settimanali) in formato di gruppo e il programma Mindfulness. I risultati dello studio includevano dolore cronico (intensità del dolore e interferenza del dolore) valutato con il Brief Pain Inventory (risultati primari), ansia e depressione valutate con la Hospital anxiety and depression scale ed insonnia valutata con l'Insomnia Severity Index. I dati sono stati raccolti a 6 mesi e 12 mesi dopo il programma Mindfulness.

Risultati. Una riduzione dell'intensità del dolore e dell'interferenza del dolore su alcune attività della vita quotidiana è stata osservata 6 e 12 mesi dopo l'intervento. Una differenza statisticamente significativa è emersa nel punteggio medio dei sintomi di ansia a favore del gruppo di intervento (11.28 vs 13.15, t= -3.636, p< .001) a 6 mesi e a 12 mesi (10.88 vs 13.41, t= -5.167, p< .001) e nel punteggio medio dei sintomi depressivi a favore del gruppo di intervento (9.95 vs 11.23, t= -2.823, p= .007) a 6 mesi e a 12 mesi (9.67 vs 10.69, t = -2.458, p= .018). I sintomi dell'insonnia sono stati statisticamente ridotti 6 mesi dopo il programma Mindfulness (punteggio: 53.2 vs 30.4, x= 4.944, p= .026).

Conclusioni. Alla luce di quanto emerso nel nostro studio, suggeriamo un programma di Mindfulness in aggiunta alla terapia farmacologica da effettuare una volta all'anno sui pazienti con consequenze di COVID-19. Sono necessari studi con campioni di dimensioni più ampie che tentano di testare un programma di consapevolezza due volte l'anno.

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