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# Long-term outcomes of different rehabilitation programs in patients with long COVID syndrome: a cohort prospective study

Irina A. Grishechkina (1) Andrey A. Lobanov (1), Sergey V. Andronov (1), Andrey P. Rachin (1), Anatoliy D. Fesyun (1,2), Elena P. Ivanova (1), Stefano Masiero (3,4), Maria Chiara Maccarone (3)

*(1) National Medical Research Center, Moscow, Russia; (2) Moscow State University of Food Production, Moscow, Russia; (3) Physical Medicine and Rehabilitation School, Department of Neuroscience, University of Padova, Padua, Italy; (4) Department of Neuroscience, Rehabilitation Unit, University of Padova, Padua, Italy, Italy.*



***Abstract***

After the resolution of the acute SARS-COV-2 infection, an important percentage of patients do not fully recover and continue to present several symptoms. Nevertheless, there is a lack of data in the literature on the effects of rehabilitation programs on medium- and long-term long COVID symptoms. Therefore, the aim of this study was to evaluate the long-term outcomes after rehabilitation programs in long COVID syndrome patients. A prospective cohort study was conducted from August 2021 to March 2022, involving 113 patients with long COVID syndrome. The patients in the experimental group (EG, n=25) received a tailored and multidisciplinary rehabilitative program, involving aquatic exercises, respiratory and motor exercises, social integration training and neuropsychologic sessions, LASER therapy and magnetotherapy. Patients in the other three comparison groups received eastern medicine techniques (CG1), balneotherapy and physiotherapy (group CG2), self-training and home-based physical exercise (CG3). Once the several rehabilitation protocols had been performed, a structured telephone contact was made with the patients after 6 months ± 7 days from the end of the rehabilitation treatment, in order to record the frequency of hospital ad-missions due to exacerbation of post-exacerbation syndrome, death or disability, and the need for other types of care or drugs. The patients in the comparison groups were more likely to request therapeutic care for emerging long COVID symptoms ($\chi^2$=6.635, p=0.001; $\chi^2$=13.463, p=0.001; $\chi^2$=10.949, p=0.001, respectively), as well as more likely to be hospitalized ($\chi^2$=5.357, p=0.021; $\chi^2$=0.125, p=0.724; $\chi^2$=0.856, p=0.355, respectively) when compared to the patients of the EG. The relative risk (RR) of hospital admissions in the observed cohort was 0.143 ±1,031 (CI: 0.019; 1.078); 0.580±1,194 (CI: 0.056; 6.022); 0,340±1,087 (CI: 0.040; 2.860). The RR of hospital admissions for patients with long COVID syndrome was reduced by 85.7%; 42.0% and 66.0%, respectively, when the experimental rehabilitation technique was employed. In conclusion, a tailored and multidisciplinary rehabilitative program seems to have a better preventive effect not only in the short term, but also over the next 6 months, avoiding the new onset of disabilities and the use of medicines and specialist advice, than other rehabilitative programs. Future studies will need to further investigate these aspects to identify the best rehabilitation therapy, also in terms of cost-effectiveness, for these patients.

**Key Words**: Long COVID syndrome; rehabilitation; exercise therapy; relative risk; balneotherapy; health resort medicine.

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After resolution of the acute SARS-COV-2 infection, an important percentage of patients does not fully recover and continue to present several symptoms. This condition of persistence of signs and symptoms that continue or develop after acute SARS CoV-2 infection has been called long COVID syndrome.[1] The syndrome is characterized by the presence of symptoms for at least 2 months and the impossibility to e-plain them with an alternative diagnosis. Common symptoms include

fatigue, breath-lessness, cognitive dysfunction, as well as a number of other symptoms that can lead to the impairment in carrying out daily activities and self-care.[2-7] These symptoms can be intermittent or recurrent over time.[1] The pathogenetic mechanisms of long COVID syndrome are still debated, but long-term tissue damage and pathological inflammation (related to virus persistence, immune dysregulation and autoimmune reactions) seem to play a role in the medium- and long-term persistence of symptoms.[3,4,8] Additionally, patients in the early stages of rehabilitation after the acute COVID-19 infection can present impaired microcirculation and reduced capacity to maintain an upright posture, which are largely accountable for symptoms such as fatigue, shortness of breath and low tolerance to physical exertion.[9–14] Based on these findings, a rehabilitation program for patients with Long COVID syndrome was developed in the "National Medical Research Centre for Rehabilitation and Balneology" of the Ministry of Health of Russia (Patent Application # 2022113192 - 17 May 2022), incorporating the main components of respiratory rehabilitation for chronic lung diseases,[15,16] balance and motor training, and a tailored aquatic exercise intervention.[17] The results of this preliminary study seemed to confirm the effectiveness of physical exercise in ameliorating impaired upright posture and normalizing walking patterns. In addition, aquatic exercise carried out in mineral-rich water seemed to add a protective effect on the microcirculatory system, in the lymph flow and in tissue metabolism.[14] Nevertheless, the lack of data in the literature on the effects of rehabilitation programs on medium- and long-term long COVID symptoms,[18,19] and the heterogeneity in durations and contents of the few existing studies,[20-23] determined the need for further investigations. Therefore, with this further analysis we aim to increasing knowledge on rehabilitation programs in patients with long COVID syndrome, evaluating also clinical outcomes in the long-term.

## Materials and Methods

### *Study population*

This work was planned as part of an open, prospective, randomized, parallel-group study,[24] to evaluate the effect of a program of aquatic exercises conducted in a bromine sodium chloride water with salinity of 120 g/dm3, diluted to 40 g/m3. Patient recruitment and follow-up were performed from August 2021 to March 2022. The study was conducted in four medical centers: the experimental group (EG) of patients was recruited in the "National Medical Research Center for Rehabilitation and Balneology" of the Ministry of Health of Russia, comparison group 1 (CG1) in the regional polyclinics in Moscow and Omsk; comparison group 2 (CG2) in a regional rehabilitation centre (the Republic of Buryatia); comparison group 3 (CG3) in another regional rehabilitation centre (Krasnodar Territory). Patients in the EG and in the CG1, CG2 and CG3 consisted of patients with long COVID syndrome who had indications for rehabilitation treatment.[25]

*Inclusion criteria included:*

- age greater than 18 years old;
- infection from SARS-CoV-2 virus confirmed by a Polymerase Chain Reac-tion (PCR) analysis;
- diagnosis of long COVID syndrome, after the resolution of the COVID-19 acute infection (U 09.9).[25]

*Exclusion criteria included*:

- refusal to sign the informed consent form;
- re-infection with SARS-CoV-2 virus during the follow-up period;
- participation in other rehabilitation protocols during the study period due to comorbidities;
- pregnancy or lactation;
- participation in other clinical studies in the year before the inclusion in this study.

### *Study intervention*

The patients in the EG were recruited among the group of patients with long COVID syndrome who took part in the previous randomized clinical trial (n=25).[14] Their rehabilitation program included 7-8 sessions of multidisciplinary rehabilitative interventions, involving a tailored protocol of aquatic exercises, respiratory and motor exercises, social integration training and neuropsychologic sessions, LASERtherapy and magne-totherapy .[17] The CG1 (n=25) performed 7-8 sessions of a rehabilitation program that included climatotherapy, traditional oriental medicine methods (acupuncture, manual therapy, Qigong breathing), exercise therapy, LASERtherapy and magnetotherapy.[26,27] Patients in CG2 (n=29) received respiratory and motor exercise therapy physiother-apy combined with inhalation of mineral water, balneotherapy with dry carbon dioxide baths and magnetotherapy for 10-15 sessions, in addition to climatotherapy.[27] Pa-tients in CG3 (n=34) performed self-training and home-based physical exercise.

### *Outcomes evaluation*

Once the informed consent had been signed and the several rehabilitation protocols had been performed, a structured telephone contact was made with the patients in-volved in the study after 6 months ± 7 days from the end of the rehabilitation treatment. The telephone survey was conducted by the same interviewer, to avoid differences in the compilation of the questionnaires. The following data were collected from patients or their relatives (in the case of loss of contact with the patient): extent of lung damage according to the Computerized Tomography (CT) scan during the acute COVID-19 infection, comorbidies, drugs consumption, number of hospital admissions, number of ambulance calls due to exacerbation of long COVID symptoms, new onset of disability, need for specialist consultations and eventual death of the patient and its causes. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of National Medical Research Center (Project identification code # IW, protocol # 6, 26 July 2021).

***Table 1***. *Demographics characteristics and comorbidities divided by patient group*

| Data | Experimental group (n=25) | Comparison group 1 (n=25) | Comparison group 2 (n=29) | Comparison group 3 (n=34) |
|---|---|---|---|---|
| **Demographics** | | | | |
| Average age, years, Me, [Q1 ;Q3] | 60 [52.71] | 65 [57.73] | 62 [50; 73] | 52 [39; 64] |
| Under 50, abs. count (n=), % | 6 (24.00 %) | 4 (16.00 %) | 6 (20.70 %) | 16 (47.10%) |
| 50-60 years old, abs. n=) | 8 (32.00 %) | 6 (24.00 %) | 6 (20.70 %)) | 4 (11.80%) |
| 61-70 years old, abs. count (n=) | 4 (16.00 %) | 9 (36.00 %) | 6 (20.70 %) | 10 (29.40%) |
| Over 70, absentee count (n) | 7 (28.00 %) | 6 (24.00 %) | 11 (37.90 %) | 4 (11.70%) |
| Male sex, age, abs. quantity (n=) | 7 (28.00 %) | 5 (20.00 %) | 8 (27.60 %) | 10 (29.40 %) |
| **The extent of lung damage according to the CT scan in the acute phase of the disease** | | | | |
| Less than 50%, abs. quantity (n= ) | 18 (72.00 %) | 14 (56.00 %) | 17 (58.60 %) | 18 (72.00 %) |
| 50% and more, abs. quantity (n=) | 7 (28.00 %) | 11 (44.00 %) | 12 (41.4 %) | 7 (28,00 %) |
| **Comorbid pathology** | | | | |
| Chronic Obstructive Pulmonary Disease abs. quantity (n=) | 1 (4,00 %) | 1 (4.00 %) | 2 (6.90 %) | 1 (2.90 %) |
| Arterial hypertension, abs. quantity (n=) | 16 (64.00 %) | 9 (36.00 %) | 16 (55.20 %) | 1 (2.90 %) |
| Coronary heart disease, abs. quantity (n=) | 2 (8.00 %) | 3 (12.0 %) | 2 (69.0 %) | 1 (2.90 %) |
| Diabetes mellitus, abs. quantity (n=) | 3 (12.00 %) | 4 (16.0 %) | 6 (20.70 %) | 0 (0.00 %) |
| Obesity, abs. quantity (n=) | 12 (48.00 %) | 0 (0.00%) | 2 (6.90 %) | 0 (0.00 %) |

***Statistical analysis***

The results were processed using the Statistica for Windows, v. 8.0 software pack-age (Stat Soft Inc., США). The data were statistically processed using descriptive statis-tics and intergroup comparisons were made using the chi-square test ($\chi 2$). In addition, the relative risk of new hospital admissions in the patient cohorts was calculated. The significance of differences was considered to be established at $p<0.05$.[24,28]

## Results

A total of 120 patients were included in the study, 113 patients (aged between 21 and 85, mean age 58.4 years) completed the study, 7 patients (5.83%) dropped out. The majority of patients included in the study were female (30 male and 83 female patients, 26.55% and 73.45%, respectively). The four groups were comparable regarding gender ($\chi^2$=0.67, p=0.41) and age (U=4.0 Z=-0.21, p=-0.83). The demographics characteristics, the extent of lung damage according to the CT scan during the acute COVID-19 infection and the comorbidities divided by patient group are shown in Table 1. The mean time since the onset of the acute COVID-19 infection was 6.5±2.5 months. As can be seen in Table 2, the groups differed in the frequency of new hospital ad-missions, prevailing in the comparison groups. In particular, a significantly greater number of new hospital admissions was recorded in the CG1. Indeed, after 6 months ± 7 days from the end of the rehabilitation treatment, the patients in the comparison groups were statistically significantly more likely to request therapeutic care for emerging long COVID symptoms ($\chi^2$=6.635, p=0.001; $\chi^2$=13.463, p=0.001; $\chi^2$=10.949, p=0.001, respec-tively), as well as more likely to be hospitalized ($\chi^2$=5.357, p=0.021; $\chi^2$=0.125, p=0.724; $\chi^2$=0.856, p=0.355, respectively) when compared to the patients of the EG. The relative risk (RR) of hospital admissions in the cohort of patients treated in the EG compared with the other patient groups was 0.143±1.031 (CI: 0.019; 1.078) when compared to CG1, 0.580±1.194 (CI: 0.056; 6.022) when compared to CG2, 0.340±1.087 (CI: 0.040; 2.860) when compared to CG3. The RR of hospital admissions was reduced by 85.7%; 42.0% and 66.0%, respectively, when the experimental rehabilitation technique was used. Moreover, patients in the comparison groups tended to consult a Pulmonologist more frequently, to have more General Practioners consultations (with a statistically signifi-cant difference in the comparison between EG and CG1), and to ask for an ambulance service more often during the six months due to the exacerbation of long COVID symptoms. There were no patient death or new onset of disability in any of the analyzed groups.

## Discussion

At a time of increased morbidity due to the COVID-19 infection outcomes, it has been found that survivors of

***Table 2**. Outcomes in the patient cohort during the 6-month period and need for other types of care*

| Data | Experimental group (n=25) | Comparison group 1 (n=25) | Comparison group 2 (n=29), | Comparison group 3 (n=34) |
|---|---|---|---|---|
| **Outcomes of post-COVID 19 syndrome after 6 months** | | | | |
| Hospital admissions,abs. quantity., (n=), (%) | 1 (4.00%) | 7 (28.00%)** | 2 (6.90 %) | 4 (11.76 %) |
| Disabilities, abs.quantity, (n=), (%) | 0 (0.00%) | 0 (0.00%)* | 0 (0.00%)* | 0 (0.00%)* |
| Deaths, abs. quantity,(n=), (%) | 0 (0.00%) | 0 (0.00%)* | 0 (0.00%)* | 0 (0.00%)* |
| **Need for specialist consultations and ambulance calls** | | | | |
| General practitioner,abs. quantity, (n=), (%) | 4 (16.00%) | 17 (68.00%) ** | 19 (65.52%)** | 20 (58.82%)** |
| Pulmonologist, abs.quantity, (n=), (%) | 0 (0.00%) | 4 (16.00 %) * | 4 (13.79%)* | 3 (8.82%)* |
| Ambulance calls, abs.quantity, (n=), (%) | 0 (0.00%) | 0 (0.00 %) * | 3 (10.34%)* | 4 (11.76%)* |

** criterion not applicable; ** Differences are statistically significant p<0.05*

the infection of any severity can need for rehabilitative interven-tions due to the so-called long COVID syndrome .[2,3,5-8,29] This implies the development of tailored rehabilitation services, in order to target the different rehabilitative needs of these patients.[2,3,6,8,15,29] Due to the complexity of the long COVID syndrome, previous studies that evaluated the individual rehabilitation approaches have shown that they range from self-exercises aimed at increasing physical activity,[30,31] and traditional convalescent programs,[32,33] to the use of complex, high-tech rehabilitation strategies,[34] involving different organs and systems. Subsequently, worldwide many rehabilitation programs are being developed, taking into account the severity of patients' dominant symptoms, the resources available from local health systems and the need to comply with anti-epidemic measures.[20,23,35] However, so far there is a shortage of studies evaluating the medium- and long-term outcomes of different rehabilitation pro-grams.[36-40] Our study tries to bridge this gap, evaluating different kind of rehabilitative protocols at six months. In the future, these findings could be employed to develop further analysis to assess the clinical and economic effects of the specific rehabilitation programs.[15,20,27,41-45] Based on our results, a tailored and multidisciplinary rehabilitative program, in-volving aquatic exercises, respiratory and motor exercises, social integration training and neuropsychologic sessions, LASER therapy and magnetotherapy, seemed to reduce the request for long COVID symptoms care and the need for hospitalization. Moreover, the need for specialist consultations and ambulance calls seemed to be reduced after the multidisciplinary experimental protocol. Therefore, we can conclude from our preliminary data presented above that the use of this experimental program seemed to have a preventive effect lasting 6 months, reducing the relative risk of new hospital admissions and the need for therapy and other types of care due to a less frequent exacerbation of the symptoms. Since the economic cost of a treatment is evaluated by calculating not only the direct expenses, but also the indirect medical, as well as non-medical costs, our results suggest a reduction in overall expenses for patients treated with a multidisciplinary and personalized protocol. In addition, an interesting point addressed by this paper is the possibility of offering patients with long COVID syndrome different rehabilitation strategies, which go beyond the hospital setting. As already suggested, among the extra-hospital settings, the spa set-ting seems to be suitable for the multidisciplinary care of these patients, benefiting from a team composed of numerous professional figures and from several rehabilitation strategies.[46-48] For long COVID patients, a comprehensive rehabilitative approach comprising a multidisciplinary and multi-professional team, offering neuromuscular, cardiorespiratory, and psychological interventions, is strongly recommended.[49] In spa setting, neuromotor rehabilitation with aquatic muscle strength and balance exercises, respiratory exercises, and educative and psychologically supportive interventions, should be conveyed to COVID-19 survivors.[46,50-52] Implementing health resort medi-cine and balneotherapy strategies into the rehabilitation programs can reduce the COVID-19 financial burden on healthcare systems, particularly in countries where health resort medicine is commonly accessible and can help patients to ameliorate

their func-tional status after the acute infection, in order to return to their previous status. In conclusion, a tailored and multidisciplinary rehabilitative program, involving aquatic exercis-es, respiratory and motor exercises, social integration training and neuropsychologic sessions, LASER therapy and magnetotherapy, seemed to have a preventive effect not only in the short term, but also over the next 6 months, avoiding the new onset of disa-bilities and the use of care and specialist advice. The spa setting has also proved to be appropriate for the multidisciplinary management of this type of patient.
In future, similar studies will be essential to understand what kind of treatments should be employed to target long Covid patients rehabilitation needs, even from a cost-effective point of view.

## List of acronyms

SARS-COV-2 - Severe Acute Respiratory Syndrome COronaVirus 2
EG - experimental group
CG1 - control group 1
CG2 - control group 2
CG3 - control group 3

## Contributions of Authors

Conceptualization, AL and IG; methodology, AL; software, SA; validation, AP and EI.; formal analysis, SA, IG and AL; investigation, IG and SA; resources, AF and AR; data curation, IG and SA; writing—original draft preparation, IG, SA and AL; writing—review and editing, EI, IG, SM, AP and MCM; visualization, SA; supervision, AR; project administration, IG; fundraising, AR and AF. All the authors have read and approved the published version of the manuscript.

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## Conflict of Interest

The authors declare no conflicts of interest.

## Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## Corresponding Author

Maria Chiara Maccarone, Physical Medicine and Rehabilitation School, Department of Neuroscience, University of Padua, 35128 Padua, Italy
ORCID ID: 0000-0003-2793-1334
E-mail: mariachiara.maccarone@phd.unipd.it

*E-mails and ORCID iD of co-authors*

*Irina A. Grishechkina: GrishechkinaIA@nmicrk.ru*
*ORCID iD: 0000-0002-4384-2860*
*Andrey A. Lobanov: alobanov89@gmail.com*
*ORCID iD: 0000-0002-6615-733X*
*Sergei V. Andronov: sergius198010@mail.ru*
*ORCID iD: 0000-0002-5616-5897*
*Andrey P. Rachin: RachinAP@nmicrk.ru*
*ORCID iD: 0000-0003-4266-0050*
*Anatoliy D. Fesyun: fad68@yandex.ru*
*ORCID iD: 0000-0003-3097-8889*
*Elena P. Ivanova: IvanovaEP@nmicrk.ru*
*ORCID iD: 0000-0002-2781-4325*
*Stefano Masiero: stef,masiero@unipd.it*
*ORCID iD: 0000-0002-0361-4898*

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