TESIS DE LA UNIVERSIDAD DE ZARAGOZA
2024
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Mario Samper Pardo

Caracterización de pacientes con COVID persistente y efectividad de un recurso comunitario en formato de APP para mejorar su calidad de vida. Metodologías mixtas

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http://zaguan.unizar.es/collection/Tesis

ISSN 2254-7606

Prensas de la Universidad
Universidad Zaragoza

Universidad de Zaragoza
Servicio de Publicaciones

ISSN 2254-7606

Universidad Zaragoza
1542

Tesis Doctoral

CARACTERIZACIÓN DE PACIENTES CON COVID PERSISTENTE Y EFECTIVIDAD DE UN RECURSO COMUNITARIO EN FORMATO DE APP PARA MEJORAR SU CALIDAD DE VIDA. METODOLOGÍAS MIXTAS

Autor

Mario Samper Pardo

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UNIVERSIDAD DE ZARAGOZA
Escuela de Doctorado

Ciencias de la Salud y del Deporte

2024

Repositorio de la Universidad de Zaragoza – Zaguan http://zaguan.unizar.es

TESIS DOCTORAL

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Programa de Doctorado en Ciencias de la Salud y del Deporte

Caracterización de pacientes con COVID persistente y efectividad de un recurso comunitario en formato de APP para mejorar su calidad de vida. Metodologías mixtas

MARIO SAMPER PARDO

Directoras: Bárbara Oliván Blázquez y Raquel Sánchez Recio

“Vivi come se dovessi morire domani.
Impara come se dovessi vivere per sempre.”

Mahatma Gandhi

“A Luna yo volveré, siempre está en mi pensamiento”

Bolero de Luna.

AGRADECIMIENTOS

Comenzar los agradecimientos a mis directoras. Por un lado, la doctora Bárbara Oliván Blázquez, por darme la oportunidad de participar en esta investigación, además de su trabajo, tesón y confianza. Por otro lado, la doctora Raquel Sánchez Recio, por su implicación, enseñanzas y consejos. Sin ellas esto no habría sido posible. Ambas han sido un modelo a seguir durante estos años y lo seguirán siendo. Les deseo lo mejor en su trayectoria académica y personal.

A la investigadora principal del Grupo Aragonés de Investigación en Atención Primaria (GAIAP), la doctora Rosa Magallón Botaya, por su disponibilidad e intención facilitadora en todo momento.

A mis compañeras y compañeros de GAIAP, de la Universidad de Zaragoza y a todos/as los/as que estuvieron trabajando a mi lado en algún momento durante estos años. Vuestro trabajo, apoyo y resolución de problemas han sido indispensables.

A mis profesoras y profesores del Grado de Trabajo Social, del Máster de Gerontología Social y del Máster de Trabajo Social en Salud Mental de la Universidad de Zaragoza, por inculcarme las bases y fundamentos de todo lo que hoy me ha llevado hasta aquí. Mención especial para mis tutoras de prácticas, Nati, Virginia y Eva, por su mentoría inicial en el trabajo social y la salud mental.

A toda mi familia, en especial, a mi madre y a mis hermanas, Bea y Yoli, por haberme guiado en el camino de la vida y enseñado cómo con esfuerzo y perseverancia se puede conseguir todo lo que uno se propone.

A mis amigas, amigos, compañeras de trabajo y a todas las personas que han formado parte de este proceso en algún momento, en especial a los que han sabido escucharme.

A todas y todos ellos, mi mayor reconocimiento y gratitud.

PROYECTO DE INVESTIGACIÓN

Esta tesis se enmarca en el Proyecto FIS (Fondos de Investigaciones Sanitarias), financiado por el Instituto de Salud Carlos III: "Proyecto COV-RACAP: Análisis de la sintomatología y la calidad de vida de personas con diagnóstico de COVID persistente, y efectividad de las recomendaciones de activos de salud desde Atención Primaria de Salud (PI21/01356)".

Además, su aprobación ética fue otorgada por el Comité Ético de Investigación Clínica de Aragón (PI21/139 y PI21/454). De este modo, los procedimientos llevados a cabo para la creación de esta obra cumplieron con los estándares éticos del comité mencionado anteriormente y con la Declaración de Helsinki de 1975. Todos los participantes firmaron un formulario de consentimiento informado, sus datos fueron anonimizados y solo se utilizarán para los fines del estudio.

LISTADO DE PUBLICACIONES DE LA TESIS

La presente tesis doctoral, de acuerdo con el informe correspondiente, autorizado por las directoras de tesis y el Órgano Responsable del Programa de Doctorado, se presenta como un compendio de cinco publicaciones. Las referencias completas de los artículos que constituyen esta tesis son los siguientes:

Manuscrito I

Samper-Pardo, M., León-Herrera, S., Oliván-Blázquez, B., Benedé-Azagra, B., Magallón-Botaya, R., Gómez-Soria, I., Calatayud, E., Aguilar-Latorre, A., Méndez-López, F., Pérez-Palomares, S., Cobos-Rincón, A., Valero-Errazu, D., Sagarra-Romero, L., & Sánchez-Recio, R. (2022). Development and Validation of a Mobile Application as an Adjuvant Treatment for People Diagnosed with Long COVID-19: Protocol for a Co-Creation Study of a Health Asset and an Analysis of Its Effectiveness and Cost-Effectiveness. International journal of environmental research and public health, 20(1), 462. https://www.mdpi.com/1660-4601/20/1/462

Factor de Impacto (JCR 2021): 4,614 (Q2)

Manuscrito II

Samper-Pardo, M., León-Herrera, S., Oliván-Blázquez, B., Méndez-López, F., Domínguez-García, M., & Sánchez-Recio, R. (2023). Effectiveness of a telerehabilitation intervention using ReCOVery APP of long COVID patients: a randomized, 3-month follow-up clinical trial. Scientific reports, 13(1), 7943. https://doi.org/10.1038/s41598-023-35058-y

Factor de Impacto (JCR 2022): 4,6 (Q2)

Manuscrito III

Samper-Pardo, M., León-Herrera, S., Oliván-Blázquez, B., Gascón-Santos, S., & Sánchez-Recio, R. (2023). Clinical characterization and factors associated with quality of life in Long COVID patients: Secondary data analysis from a randomized clinical trial. PLoS one, 18(5), e0278728. https://doi.org/10.1371/journal.pone.0278728

Factor de Impacto (JCR 2022): 3,7 (Q2)

Manuscrito IV

Samper-Pardo, M., Oliván-Blázquez, B., Magallón-Botaya, R., Méndez-López, F., Bartolomé-Moreno, C., & León-Herrera, S. (2023). The emotional well-being of Long COVID patients in relation to their symptoms, social support and stigmatization in social and health services: a qualitative study. BMC Psychiatry, 23(1), 68. https://doi.org/10.1186/s12888-022-04497-8

Factor de Impacto (JCR 2022): 4,4 (Q2)

Manuscrito V

Samper-Pardo, M., Formento-Marín, N., Oliván-Blázquez, B., León-Herrera, S., & Benedé-Azagra, B. (2023). Use of community resources as health assets for rehabilitation of people with Long COVID in northeastern Spain two years after the outbreak of the COVID-19 pandemic: qualitative study. Archives of public health, 81(1), 125. https://doi.org/10.1186/s13690-023-01139-7

Factor de Impacto (JCR 2022): 3,3 (Q2)

DIFUSIÓN DE RESULTADOS

El doctorando ha participado en diversos congresos y jornadas, nacionales e internacionales, presentando dieciocho comunicaciones con los resultados preliminares de esta tesis:

Título	Efectividad de recomendaciones de salud para personas con COVID persistente: diseño de una APP
Autoría	Mario Samper Pardo, Sandra León Herrera, Alejandra Aguilar Latorre, Fátima Méndez López, María Beltrán Ruiz, Bárbara Oliván Blázquez
Evento	I Jornada de Innovación en Atención Primaria de Madrid
Lugar y fecha	En Madrid, a 18 de mayo de 2022
Presentación	Comunicación oral

Título	Empleo de recursos comunitarios para la mejora de la sintomatología de COVID persistente
Autoría	Mario Samper Pardo y Sandra León Herrera
Evento	XXXI Congreso Internacional REFUTS 2022
Lugar y fecha	En Zaragoza, a 27 de junio de 2022
Presentación	Comunicación oral

Título	Deepening in the symptomatology of Long COVID patients and their fluctuation over time
Autoría	Mario Samper Pardo, Bárbara Oliván Blázquez, Alejandra Aguilar Latorre y Rosa Magallón Botaya
Evento	27th WONCA Europe Conference
Lugar y fecha	En Londres, a 30 de junio de 2022
Presentación	Comunicación oral

Título	Analysis of the impact on emotional well-being and quality of life of patients diagnosed with Long COVID
Autoría	Mario Samper Pardo, Bárbara Oliván Blázquez, Alejandra Aguilar Latorre y Rosa Magallón Botaya
Evento	27th WONCA Europe Conference
Lugar y fecha	En Londres, a 30 de junio de 2022
Presentación	Póster

Título	Long COVID sufferers' personal experiences with discrimination and social stigma
Autoría	Mario Samper Pardo, Bárbara Oliván Blázquez, Alejandra Aguilar Latorre y Rosa Magallón Botaya
Evento	27th WONCA Europe Conference
Lugar y fecha	En Londres, a 30 de junio de 2022
Presentación	Póster

Título	Análisis de la alfabetización en salud según el nivel de estudios en pacientes con diagnóstico de COVID persistente.
Autoría	Mario Samper Pardo y Sandra León Herrera
Evento	VII Congreso Internacional de Investigación en Salud
Lugar y fecha	En Murcia, a 20 de septiembre de 2022
Presentación	Comunicación oral

Título	Impacto del COVID persistente en la salud autopercepción según la edad real y percibida
Autoría	Sandra León Herrera y Mario Samper Pardo
Evento	VII Congreso Internacional de Investigación en Salud
Lugar y fecha	En Murcia, a 20 de septiembre de 2022
Presentación	Comunicación oral

Título	Need for prevention and intervention programs in mental Health disorder in people with Long Covid
Autoría	Mario Samper Pardo, Sandra León Herrera, Alejandra Aguilar Latorre, Bárbara Oliván Blázquez, y Rosa Magallón Botaya
Evento	13th EUSPR Conference and Members' Meeting
Lugar y fecha	En Estonia, a 28 de septiembre de 2022
Presentación	Póster

Título	Impact of social support from family and friends on the perceived general health of patients diagnosed with Long COVID
Autoría	Mario Samper Pardo, Sandra León Herrera, Bárbara Oliván Blázquez, Alejandra Aguilar Latorre, Fátima Menéndez López, David Lerma Irureta y Rosa Magallón Botaya
Evento	95th EGPRN Meeting
Lugar y fecha	En Amberes, a 20 de octubre de 2022
Presentación	Comunicación oral destacada

Título	Correlación entre la situación laboral y la salud física y mental de pacientes con diagnóstico de COVID persistente.
Autoría	Mario Samper Pardo, Sandra León Herrera, Alejandra Aguilar Latorre, Fátima Méndez López, Raquel Sánchez Recio y Bárbara Oliván Blázquez,
Evento	I Jornada científica sobre necesidades clínicas de la COVID persistente: abordaje multidisciplinar desde una perspectiva del sistema de salud
Lugar y fecha	En Zaragoza, a 27 de octubre de 2022
Presentación	Póster con defensa oral

Título	Caracterización de una cohorte de 100 pacientes con COVID persistente de la Comunidad Autónoma de Aragón
Autoría	Sandra León Herrera, Mario Samper Pardo, Fátima Méndez López, Estela Calatayud Sanz, Isabel Gómez Soria, Sara Pérez Palomares y Bárbara Oliván Blázquez
Evento	I Jornada científica sobre necesidades clínicas de la COVID persistente: abordaje multidisciplinar desde una perspectiva del sistema de salud
Lugar y fecha	En Zaragoza, a 27 de octubre de 2022
Presentación	Póster con defensa oral

Título	"Proyecto COV-RACAP: Análisis de la sintomatología y calidad de vida de personas con diagnóstico de COVID persistente y efectividad de las recomendaciones de activos de salud desde APS"
Autoría	Mario Samper Pardo
Evento	I Jornada científica sobre necesidades clínicas de la COVID persistente: abordaje multidisciplinar desde una perspectiva del sistema de salud
Lugar y fecha	En Zaragoza, a 27 de octubre de 2022
Presentación	Comunicación Oral

Título	Affective state of people suffering from Long COVID and associated factors. Cross-sectional descriptive study.
Autoría	Bárbara Oliván Blázquez, Mario Samper Pardo, Sandra León Herrera, Alejandra Aguilar Latorre, Fátima López Méndez y Rosa Magallón Botaya
Evento	31st European Congress of Psychiatry
Lugar y fecha	En París, a 25 de marzo de 2023
Presentación	Póster

Título	Evolution of the affective state of a cohort of people suffering from Long COVID and associated factors.
Autoría	Bárbara Oliván Blázquez, Sandra León Herrera, Mario Samper Pardo, Fátima López Méndez, Alejandra Aguilar Latorre, y Marimar Martínez Perrochan
Evento	31st European Congress of Psychiatry
Lugar y fecha	En París, a 25 de marzo de 2023
Presentación	Póster

Título	Recursos comunitarios e innovación para pacientes con COVID persistente
Autoría	Mario Samper Pardo
Evento	I ciclo de divulgación IIS Aragón, Jornadas de Salud y Ciencia
Lugar y fecha	En Zaragoza, a 26 de marzo de 2023
Presentación	Comunicación oral

Título	Interference of sleep problems in the self-perceived general health of Long COVID patients, and their need for treatment
Autoría	Sandra León Herrera, Mario Samper Pardo, Bárbara Oliván Blázquez, Alejandra Aguilar Latorre, Fátima Méndez López, Marimar Martínez Perrochan, Rosa Magallón Botaya
Evento	28th WONCA Europe Conference
Lugar y fecha	En Bruselas, a 7 de junio de 2023
Presentación	Póster

Título	Utilization of mental health services by people suffering from Long COVID and its relationship with the level of emotional wellbeing
Autoría	Sandra León Herrera, Mario Samper Pardo, Bárbara Oliván Blázquez, Alejandra Aguilar Latorre, Fátima Méndez López, Marimar Martínez Perrochan, Rosa Magallón Botaya
Evento	28th WONCA Europe Conference
Lugar y fecha	En Bruselas, a 7 de junio de 2023
Presentación	Comunicación oral

Título	Citizen Science perspective in addressing the symptoms and quality of life of people with Long COVID
Autoría	Sandra León Herrera, Alejandra Aguilar Latorre, Mario Samper Pardo, Juan Mérida Conde y Bárbara Oliván Blázquez
Evento	Implementation research scientific conference
Lugar y fecha	En Bilbao, el 14 de junio de 2023
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ÍNDICE GENERAL

Resumen

Introducción:

La COVID persistente engloba los síntomas de infección, probable o confirmada, por SARS-CoV-2 que se prolongan o desarrollan tres meses después de la infección inicial, y que no pueden ser explicados mediante un diagnóstico alternativo. Se estima que un porcentaje de entre el 10-20% del total de infectados por COVID-19 desarrollan COVID persistente. Su multivariada y fluctuante sintomatología afecta en el desempeño funcional de los pacientes y, consecuentemente, en su calidad de vida. Los tratamientos de rehabilitación han demostrado ser efectivos para mejorar estos síntomas persistentes. El objetivo principal de esta tesis fue analizar la efectividad clínica de una intervención de telerehabilitación a través de una APP, como tratamiento adyuvante en comparación con el tratamiento habitual (TAU), a corto y medio plazo, para mejorar la calidad de vida de pacientes con diagnóstico de COVID persistente. Se establecieron tres objetivos secundarios: 1) Caracterizar el perfil de pacientes con diagnóstico de COVID persistente en relación con aspectos sociodemográficos, clínicos, afectivos, cognitivos, variables funcionales y sociales; así como identificar factores asociados a la calidad de vida de estos pacientes; 2) Profundizar sobre el bienestar emocional de pacientes con diagnóstico de COVID persistente, así como su percepción sobre apoyo social y experiencias de discriminación y estigma social; y 3) Profundizar sobre el uso y adaptación de los recursos comunitarios disponibles como activos para la salud y su utilidad por parte de pacientes con diagnóstico de COVID persistente.

Métodos:

El diseño se basó en metodologías mixtas, mediante métodos cuantitativos y cualitativos.

En primer lugar, se implementó un ensayo clínico aleatorizado (ECA) con dos grupos paralelos. Las personas participantes fueron pacientes con COVID persistente reclutados desde varios centros de Atención Primaria de Salud (APS) de la provincia de Zaragoza. Un total de 100 participantes cumplieron criterios y fueron aleatorizados. El grupo control siguió su TAU. El grupo intervención, también mantuvo su TAU, acudió a tres sesiones motivacionales y utilizó ReCOVery APP durante toda la intervención. Para desarrollar dicha APP se partió de las cinco etapas del proceso de recomendación de activos para la salud, y se diseñaron seis módulos con contenido rehabilitador: ejercicios físicos, ejercicios respiratorios, ejercicios cognitivos, adherencia a la dieta mediterránea, higiene del sueño y empleo de recursos comunitarios. La calidad de vida medida con el cuestionario SF-36 fue la variable principal. Las variables sociodemográficas, número de síntomas persistente, tiempo desde la infección inicial, estado cognitivo, afectivo, funcional, calidad del sueño, actividad física realizada, soporte social (apoyo social percibido y apoyo social comunitario), constructos personales (autoeficacia, activación del paciente en su propia salud y alfabetización en salud) y tiempo de uso de la APP se consideraron variables secundarias. Las variables se midieron antes de la intervención (basal), después de la intervención (post 3 meses) y a medio plazo (post 6 meses). Se realizó un análisis descriptivo de todas las variables y se desarrolló una comparación entre grupos. Para analizar la efectividad de la APP se realizó un análisis por protocolo comparando los resultados de los cuestionarios administrados al inicio del estudio (antes de la intervención -pre-) e inmediatamente después de la intervención (posterior a la intervención -post-), a corto y medio plazo, para comprobar la existencia de diferencias

estadísticamente significativas entre ambos grupos. Además, para analizar las variables asociadas a una mejora de las variables analizadas se realizaron regresiones lineales.

En segundo lugar, se desarrolló un análisis de datos secundarios con los datos recopilados al comienzo del ECA, para caracterizar el perfil de pacientes con COVID persistente. Para ello, se realizaron análisis descriptivos, bivariados y multivariados.

Además, previo a la implementación del ECA y creación de la APP, se realizó un estudio cualitativo basado en entrevistas individuales semiestructuradas y grupos focales a 35 personas participantes con COVID persistente. La temática de las intervenciones recogía aspectos sobre su bienestar emocional y el empleo de recursos comunitarios. Se empleó el enfoque de la teoría fundamentada para el análisis de datos.

Resultados:

En la medición basal se observó que mayor número de síntomas persistentes (b = -0.900, IC 95% = [-1.523, -0.263], p = 0.008), peor funcionamiento físico (b = 1.587, IC 95 % = [0.679, 2.521], p = 0.002) y peor calidad del sueño (b = -0.538, IC 95 % = [-1.092, -0.022], p = 0.035) son predictores de una peor salud física. Por otro lado, mayor nivel educativo (b = 13.167, IC 95% = [-1.391, 23.535], p = 0.017), menor número de síntomas persistentes (b = -0.621, IC 95% = [-1.245, -0.052], p = 0.057) y menor afectación afectiva (b = -1.402, IC 95% = [-1.964, -0.958], p < 0.001) son predictores de peor salud mental.

En la medición post tres meses, no hubo diferencias significativas entre los grupos, a excepción de una disminución en el número de síntomas persistentes, a favor del grupo control (valor p: 0,09; IC 95% = [-0.44, 5.41]). El 25% de participantes realizaron un uso significativo de la APP, lo que sugiere una baja adherencia. Además, los modelos multivariados revelaron modelos significativos: menor número de síntomas persistentes fue predicho por una mayor alfabetización en salud (b = 0.226, IC 95% = [0.087, 0.365], p = 0.002); mejor funcionamiento cognitivo fue predicho por una mayor autoeficacia (b

= 0.346, IC 95% = [-0.538, -0.154], p = 0.001); mayor funcionamiento físico fue predicho por el sexo masculino y mayor tiempo de uso de la APP (b = -2.454, IC 95% = [0.928, 8.732], p = 0.016; b = 0.001, IC 95% = [0.000, 0.002], p = 0.005, respectivamente); y mayor apoyo social comunitario fue predicho por una mayor autoeficacia y mayor tiempo de uso de la APP (b = 0.634, IC 95% = [0.042, 1.226], p = 0.036; b = 0.004, IC 95% = [0.001, 0.008], p = 0.021, respectivamente).

Finalmente, en la medición a los seis meses no se identificaron diferencias significativas a favor del grupo intervención entre el inicio y el final de la intervención. Sin embargo, todas las personas participantes del estudio mejoraron significativamente su salud física ($p < 0.001$) y salud mental ($p < 0.001$). Además, los modelos multivariantes mostraron que existen modelos significativos relacionados con la mejora de la calidad de vida general y la salud mental, predichos por un mayor tiempo de uso de ReCoVery APP (b = 0.001, IC 95% = [0.000, 0.000], p = 0.009; b = 0.001, IC 95% = [0.000, 0.000], p =0.003, respectivamente), y mayor autoeficacia (b = 0.675, IC 95% = [0.088, 1.262], p =0.025; b = 0.860, IC 95% = [0.194, 1.527], p =0.012, respectivamente).

En lo que concierne al estudio cualitativo, por un lado, las personas participantes identificaron niveles bajos en su bienestar emocional y calidad de vida, principalmente derivado de sus propios síntomas persistentes y las limitaciones funcionales que les ocasionaban en su vida diaria. Varios pacientes refirieron angustia y ansiedad hacia el futuro, así como miedo a una reinfección, a la reincorporación laboral o a la atención sanitaria. La mayoría de las personas participantes identificaron situaciones discriminatorias desde APS. Por otro lado, se observó cómo las personas participantes que habían utilizado recursos comunitarios percibían mejoras en su salud física y mental. La principal barrera identificada para su utilización fue su propia sintomatología.

Discusión:

Todas las personas participantes mejoraron significativamente su salud física y mental durante el transcurso de la intervención y seguimiento, por lo que el paso del tiempo parece favorecer su recuperación. A corto y medio plazo, la telerehabilitación ofrecida mediante ReCOVery APP no fue efectiva para mejorar la calidad de vida de los pacientes con COVID persistente, en comparación con el grupo control. No obstante, se identificaron modelos significativos relacionados con la mejora de la calidad de vida y la salud mental, predichos por un mayor tiempo de uso de la APP. Estos hallazgos indican que la telerehabilitación puede ser una estrategia prometedora para la recuperación de los pacientes con COVID. Sin embargo, se necesitan más investigaciones para mejorar la adherencia de este grupo de pacientes.

En definitiva, la pérdida de calidad de vida, la necesidad de atención en salud, así como las incógnitas que giran en torno a esta patología, todavía hacen de esta enfermedad una temática digna de investigación para el sector de la salud.

Abstract

Introduction:

Persistent COVID includes symptoms of probable or confirmed SARS-CoV-2 infection that persist or develop three months after initial infection and cannot be explained by an alternative diagnosis. It is estimated that 10-20% of those infected with COVID-19 will develop persistent COVID. Its multivariate and fluctuating symptomatology affects patients' functional performance and consequently their quality of life. Rehabilitation treatments have been shown to be effective in improving these persistent symptoms. The main objective of this work was to analyse the clinical effectiveness of a telerehabilitation intervention through an APP, as an adjunctive treatment compared to treatment as usual (TAU), in the short and medium term, to improve the quality of life of patients diagnosed with persistent COVID. Three secondary objectives were defined: 1) To characterise the profile of patients diagnosed with persistent COVID in terms of socio-demographic, clinical, affective, cognitive, functional and social variables; and to identify factors associated with the quality of life of these patients; 2) To delve into the emotional well-being of patients with a diagnosis of persistent COVID, as well as their perception of social support and experiences of discrimination and social stigma; and 3) To delve into the use and adaptation of available community resources as health assets and their usefulness by patients with a diagnosis of persistent COVID.

Methods:

The design was based on mixed methodologies, using quantitative and qualitative methods.

First, a randomized clinical trial (RCT) with two parallel groups was implemented. Participants were patients with persistent COVID recruited from several Primary Health Care (PHC) centers in the province of Zaragoza. A total of 100 participants met criteria and were randomized. The control group maintained their TAU. The intervention group also maintained their TAU, attended three motivational sessions, and used the ReCOVery APP throughout the intervention. The APP was developed based on the five stages of the active health recommendation process, and six modules with rehabilitative content were designed: physical exercise, respiratory exercise, cognitive exercise, adherence to the Mediterranean diet, sleep hygiene and use of community resources. Quality of life measured with the SF-36 questionnaire was the main variable. Sociodemographic variables, number of persistent symptoms, time since initial infection, cognitive, affective, functional status, sleep quality, physical activity performed, social support (perceived social support and community social support), personal constructs (self-efficacy, patient activation in own health and health literacy) and time of APP use were considered secondary variables. Variables were measured before the intervention (baseline), after the intervention (post 3 months) and at mid-term (post 6 months). A descriptive analysis of all variables was performed and a between-group comparison was developed. To analyse the effectiveness of the APP, a per protocol analysis was performed comparing the results of the questionnaires administered at baseline (pre-intervention - pre) and immediately after the intervention (post), in the short and medium term, to check for statistically significant differences between the two groups. In addition, to analyse the variables associated with an improvement in the variables analysed, linear regressions were performed.

Secondly, a secondary data analysis was developed using the data collected at the start of the RCT to characterise the profile of patients with persistent COVID. For this, descriptive, bivariate and multivariate analyses were performed.

In addition, prior to the implementation of the RCT and creation of the APP, a qualitative study was conducted based on semi-structured individual interviews and focus groups with 35 participants with persistent COVID. The themes of the interventions covered aspects of their emotional wellbeing and the use of community resources. The grounded theory approach was used for data analysis.

Results:

At baseline measurement, higher number of persistent symptoms (b = -0.900, 95 % CI = [-1.523, -0.263], p = 0.008), worse physical functioning (b = 1.587, 95 % CI = [0.679, 2.521], p = 0.002) and worse sleep quality (b = -0.538, 95 % CI = [-1.092, -0.022], p = 0.035) were found to be predictors of poor physical health. On the other hand, higher educational level (b = 13.167, 95% CI = [-1.391, 23.535], p = 0.017), fewer persistent symptoms (b = -0.621, 95% CI = [-1.245, -0.052], p = 0.057) and less affective involvement (b = -1.402, 95% CI = [-1.964, -0.958], p < 0.001) are predictors of better mental health.

At the three-month post measurement, there were no significant differences between groups, except for a decrease in the number of persistent symptoms, in favor of the control group (p-value: 0.09, 95% CI = [-0.44, 5.41]). Significant use of the APP was made by 25% of participants, suggesting low adherence. In addition, multivariate models revealed significant patterns: fewer persistent symptoms was predicted by higher health literacy (b = 0.226, 95% CI = [0.087, 0.365], p = 0.002); better cognitive functioning was predicted by higher self-efficacy (b = 0.346, 95% CI = [-0.538, -0.154], p = 0.001); higher physical functioning was predicted by male gender and longer APP use time (b = -2.454,

95% CI = [0.928, 8.732], p = 0.016; b = 0.001, 95% CI = [0.000, 0.002], p = 0. 005, respectively); and greater community social support was predicted by greater self-efficacy and longer APP use (b = 0.634, 95% CI = [0.042, 1.226], p = 0.036; b = 0.004, 95% CI = [0.001, 0.008], p = 0.021, respectively).

Finally, at the six-month measurement, no significant differences in favor of the intervention group were identified between the beginning and the end of the intervention. However, all study participants significantly improved their physical health ($p < 0.001$) and mental health ($p < 0.001$). In addition, multivariate models showed that there are significant patterns associated with improved overall quality of life and mental health, predicted by longer ReCoVery APP use (b = 0.001, 95% CI = [0. 000, 0.000], p = 0.009; b = 0.001, 95% CI = [0.000, 0.000], p =0.003, respectively), and higher self-efficacy (b = 0.675, 95% CI = [0.088, 1.262], p =0.025; b = 0.860, 95% CI = [0.194, 1.527], p =0.012, respectively).

Regarding the qualitative study, on the one hand, participants identified low levels of emotional well-being and quality of life, mainly due to their own persistent symptoms and the functional limitations they caused in their daily lives. Several patients reported distress and anxiety about the future, as well as fear of reinfection, return to work or health care. Most of the participants identified discriminatory situations from PHC. On the other hand, it was observed that participants who had used community resources self-perceived improvements in their physical and mental health. The main barrier identified for their use was their own symptomatology.

Discussion:

All participants significantly improved their physical and mental health throughout the intervention and follow-up, so the passage of time seems to favor their recovery. In the short and medium term, the telerehabilitation offered by ReCOVery APP was not

effective in improving the quality of life of patients with persistent COVID compared to the control group. However, significant patterns were identified related to improved quality of life and mental health, predicted by longer APP use. These results indicate that telerehabilitation may be a promising strategy for the recovery of patients with COVID. However, further research is needed to improve adherence in this patient group.

Ultimately, the loss of quality of life, the need for healthcare, as well as the unknowns surrounding this pathology, continue to make this disease a topic worthy of research for the healthcare sector.

Listado de abreviaturas y acrónimos

APP	Aplicación móvil
APS	Atención Primaria de Salud
BMJ	British Medicine Journal
CAMFiC	Societat Catalana de Medicina Familiar i Comunitària
CDC	Centro para el Control y la Prevención de Enfermedades
CTFPHC	Canadian Task Force on Preventive Health Care
ECA	Ensayo clínico aleatorizado
GTM	Grupo de Trabajo Multidisciplinar
ICTV	Comité Internacional de Taxonomía de Virus
IHME	Instituto de Medición y Evaluación de la Salud
NHS	Servicio Nacional de Salud
NICE	Instituto Nacional para la Calidad de la Sanidad y de la Asistencia
OCEBM	Oxford Centre for Evidence-Based Medicine
OMS	Organización Mundial de la Salud
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Síndrome respiratorio agudo severo por coronavirus tipo dos
SEMG	Sociedad Española de Médicos Generales y de Familia
SNS	Sistema Nacional de Salud
TAU	Tratamiento habitual
TRA	Test rápido de detección de antígenos

1. INTRODUCCIÓN

1.1 Enfermedad por SARS-CoV-2

En diciembre de 2019, la Comisión Municipal de Salud y Sanidad de Wuhan (Hubei, China) informó a la Organización Mundial de la Salud (OMS) sobre la existencia de un grupo de 27 ciudadanos con diagnóstico de neumonía etiológicamente desconocida (1). El 7 de enero de 2020, el Centro para el Control y la Prevención de Enfermedades (CDC, por sus siglas inglés) de China, detectó a partir de una muestra faríngea un coronavirus ignorado hasta el momento. Seguidamente, el Comité Internacional de Taxonomía de Virus (ICTV, por sus siglas en inglés) identificó este nuevo coronavirus como el agente causal responsable de una epidemia por síndrome respiratorio agudo severo, abreviado SARS-CoV-2 (del inglés severe acute respiratory syndrome coronavirus 2), para distinguirlo del SARS-CoV de 2002 (2). Se trata de un coronavirus de tipo dos perteneciente a la familia de los Coronaviridae (3).

En consecuencia, a principios de 2020 se produjo una importante emergencia sanitaria, fundamentada en la veloz propagación del SARS-CoV-2 (4). A pesar de los esfuerzos para contener la infección en el país oriental, el virus se extendió rápidamente a las naciones adyacentes durante el primer mes. A esto le siguió una amplia difusión viral por los países europeos y del resto de continentes, lo que obligó a decretar estados de alarma y establecer estrictas medidas para la población global (5). El 11 de marzo de 2020, con 118.629 infecciones por SARS-CoV-2 contabilizadas en 114 países y, consecuentemente, 4.292 personas fallecidas, la OMS declaró este brote como una pandemia mundial (6). Tras casi un mes de este hecho, a día 9 de abril de 2020, el número mundial de población contagiada superó el millón y medio de personas y el de

fallecimientos se encontraba próximo a los cien mil (7). Desde marzo a mayo de 2020, Europa fue considerada el epicentro mundial de los casos de COVID-19 (4).

La principal vía de transmisión de esta infección es la vía aérea, al inhalar las gotas de Flügge emitidas por la persona infectada (8). De este modo, las personas contagiadas al hablar, estornudar o toser emiten estas microgotas y los virus contenidos en su interior presentan capacidad de desarrollar la infección en un nuevo organismo (8). Una vez producida la transmisión, se estima que los síntomas pueden aparecer tras un periodo de incubación de 2 a 10 días (9). Sin embargo, algunos sujetos infectados han superado la enfermedad sin llegar a desarrollar síntomas, es decir, de manera asintomática (10).

El SARS-CoV-2 ha causado diversas manifestaciones clínicas agrupadas bajo el nombre de COVID-19. Esta afectación se caracteriza por un amplio espectro de síntomas y gravedades. Su presentación clínica más frecuente se trata de una infección respiratoria aguda, que varía desde un cuadro de resfriado común hasta una neumonía grave, síndrome de distrés respiratorio, shock séptico y/o fallo multiorgánico (11,12). El diagnóstico de COVID-19, a nivel microbiológico, puede realizarse mediante diferentes pruebas de laboratorio: 1) Prueba de amplificación del ácido nucleico viral, como la Reverse Transcription Polymerase Chain Reaction (RT-PCR); 2) Test rápido de detección de antígenos (TRA); y 3) Diagnóstico serológico formal; siendo esta última la que mayor fiabilidad presentaría (13).

La gran mayoría de los individuos infectados por SARS-CoV-2 se recuperan por completo en un periodo medio de dos semanas, cuando la fase aguda de la enfermedad ha sido leve, y la recuperación podría prolongarse de tres a seis semanas cuando haya sido grave (10). Sin embargo, datos empíricos indican que entre el 10-20% de contagiados desarrolla y/o mantiene una variedad de síntomas prolongados a medio y largo plazo

(14,15). Esta condición posterior a la COVID-19 ha sido mayoritariamente denominada por la comunidad científica como COVID persistente.

1.2 COVID persistente. Fisiopatología y epidemiología

El desconocimiento sobre por qué algunos individuos infectados por COVID-19 no lograban recuperarse, provocó que algunos organismos científicos de salud se pusieran tras la pista de la COVID persistente. En agosto de 2020, la British Medicine Journal (BMJ) publicó evidencia, a modo de indicaciones, sobre el manejo de los síntomas Post-COVID-19 (14). La OMS reconoció la existencia de diversos síntomas persistentes tras la recuperación de COVID-19 en su actualización N.º 36 del 9 de septiembre de 2020 (16). En noviembre del mismo año, el CDC de Estados Unidos indicó que algunas personas pueden presentar síntomas durante semanas o incluso meses después de recuperarse de la enfermedad aguda, reconociendo sus intereses por profundizar en los efectos a medio y largo plazo de la COVID-19 (17). En diciembre de 2020, el Instituto Nacional para la Calidad de la Sanidad y de la Asistencia del Reino Unido (NICE, por sus siglas en inglés) publicó una guía para el manejo de los efectos a largo plazo de la COVID-19, a petición del Servicio Nacional de Salud (NHS, por sus siglas en inglés) de dicha nación (18). Este documento estableció una distinción entre los síntomas que continúan de cuatro a doce semanas tras la infección, como sintomatología en curso posterior a la COVID-19 (Post-COVID-19), y aquellos síntomas que persisten por más de doce semanas, como COVID persistente, excluyendo la anosmia y ageusia (18). De este modo, el periodo de doce semanas permite a profesionales de la salud descartar el proceso habitual de recuperación de un cuadro de COVID-19.

En España, el Ministerio de Sanidad, en su actualización del 15 de enero de 2021 del documento "*Información científica-técnica. Enfermedad por coronavirus, COVID-*

19" incorporó un nuevo apartado en el que verifica la existencia de la COVID persistente, asegurando que, pese a no existir una clara definición de la patología, se trata de una realidad que afecta a un gran número de personas y, por tanto, genera un impacto en la sanidad y la sociedad del momento (19).

Finalmente, fue en octubre de 2021 cuando la OMS definió esta nueva patología como los síntomas de infección, probable o confirmada, por SARS-CoV-2 que se prolongan o desarrollan tres meses después de la infección inicial, y que no pueden explicarse por un diagnóstico alternativo (20).

El mecanismo que desencadena la COVID persistente todavía es una incógnita. Se barajan algunas hipótesis como: 1) La persistencia del virus en el organismo, que podría causar una infección latente o crónica, como ocurre en la hepatitis C o el ébola; 2) Una respuesta inflamatoria tardía y una tormenta de citoquinas; y 3) La existencia de autoanticuerpos que alteran la función inmunológica. Otros grupos también investigan posibles alteraciones metabólicas o de la microbiota (21).

Los síntomas y efectos de la COVID persistente sólo pueden explicarse cuando se han descartado otras afectaciones etiológicamente similares, mediante un cribado médico (16). Los síntomas de la COVID persistente pueden persistir desde la fase aguda tras la infección inicial, o comenzar después de la recuperación. Además, esta sintomatología se ha clasificado como fluctuante, es decir, su grado de intensidad puede variar a lo largo de la enfermedad sin seguir un progresivo aumento-descenso, pudiéndose producir crisis de mayor afección; también, pueden desaparecer durante indeterminados períodos y resurgir, incluso con mayor intensidad que en ocasiones anteriores (22). La cohorte internacional realizada por Davis et al. (2021) llegó a contabilizar 203 posibles síntomas propios de esta enfermedad (23). De acuerdo con el metaanálisis de López-León et al. (2021) (24), que cuenta con una muestra total de más de cincuenta mil participantes Post-

COVID-19, entre los síntomas más predominantes se encuentran: fatiga (58 %), cefalea (44 %), trastorno de atención (27 %), caída del cabello (25 %), disnea (24 %), ageusia (23 %), anosmia (21 %), disnea post-actividad (21 %). %), dolor en las articulaciones (19 %), tos (19 %), sudoraciones (17 %), náuseas o vómitos (16 %), dolor/presión torácica (16 %), pérdida de audición o tinnitus (15 %), ansiedad (13 %), depresión (12 %), trastornos digestivos (12 %), pérdida de peso (12 %), signos cutáneos (12 %), aumento de la frecuencia cardiaca restrictiva (11 %), palpitaciones (11 %), dolor (11 %), fiebre intermitente (11 %), capacidad pulmonar reducida (10 %), apnea del sueño (8 %), escalofríos (7 %), problemas de salud mental (7 %), enfermedad psiquiátrica (6 %), ojos rojos (6%), fibrosis pulmonar (5%), rubefacción discontinua (5%) y diabetes mellitus, esputo, edema de extremidades, mareos, accidente cerebrovascular, dolor de garganta, trastornos del estado de ánimo, disforia, trastorno obsesivo compulsivo, hipertensión nueva, miocarditis, insuficiencia renal, trastorno de estrés postraumático, arritmia y paranoia (<5%). El desarrollo y evolución de estos síntomas persistentes puede suponer una alteración total del organismo, así como un malestar general, principalmente caracterizado por fatiga crónica y dolor musculoesquelético (23). Existe un gran impacto en el funcionamiento del sistema respiratorio, además de aumentar el potencial para desarrollar trastornos metabólicos, cardiovasculares, gastrointestinales, neurológicos y mentales, entre otros (25). Hoy en día, todavía no es posible predecir cómo será el desarrollo natural de la afectación en una determinada persona, ni cuánto tiempo persistirán sus síntomas. No obstante, se estableció que la prevalencia de diversos síntomas disminuía gradualmente, en torno a los 6-12 meses (26,27).

1.2.1 Epidemiología de la COVID persistente

Según la OMS (28), durante los dos primeros años de pandemia aproximadamente 145 millones de personas en todo el mundo se han visto afectadas por los síntomas prolongados de la COVID-19. En Europa, en el mismo periodo de tiempo, 17 millones de personas se han visto afectadas por esta patología, lo que representa un 16% de los 102,4 millones de personas infectadas por COVID-19. De este modo, la OMS estima que entorno al 10-20% de infectados por COVID-19 desarrollan COVID persistente.

En concordancia con estos datos, en marzo de 2022 el Grupo de Trabajo Multidisciplinar (GTM) que asesora el Ministerio de Ciencia del Gobierno de España, elaboró un informe sobre la situación del COVID persistente. Este documento valora que, en esos momentos, la COVID persistente es una realidad que afecta a más de un millón de individuos en dicho país (29). En España, a julio de 2023, el total de casos contabilizados por COVID-19 es de alrededor de 14 millones (7). Sin embargo, no existe un registro oficial con el número de afectados por COVID persistente.

Con respecto a los afectados, tanto las personas que sufrieron los síntomas de la COVID-19 de manera leve, moderada o grave, pueden desarrollar COVID persistente. Más en concreto, el Instituto de Medición y Evaluación de la Salud (IHME, por sus siglas en inglés) indicó que el 6,8% de casos COVID-19 asintomáticos y el 15,2% sintomáticos, llegaron a desarrollar COVID persistente (30). El recientemente citado informe del GTM recoge que el perfil de personas afectadas por la COVID persistente está representado por mujeres adultas de entre 30 y 50 años (29). Este dato resulta concordante con evidencias científicas que sugieren una mayor prevalencia de esta enfermedad en mujeres (80%) de mediana edad (48-58 años) (31). No resulta frecuente en personas menores de 18 años y muy improbable en menores de 12 años (32).

1.2.2 Tratamiento de la COVID persistente

La OMS solicitó a los países que intensifiquen el desarrollo de investigaciones con el objetivo de encontrar soluciones eficaces ante el nuevo desafío que supone la COVID persistente (28). Los enigmas que rodean a esta enfermedad dificultan la existencia de un tratamiento farmacológico específico. En función del cuadro y analíticas de cada paciente, los tratamientos prescritos pueden incluir fármacos antivirales, antiinflamatorios (ante la presencia de tormenta de citoquinas), inmunomoduladores (ante la detección de autoanticuerpos), sustitución de déficits nutricionales (ante alteraciones nutricionales y/o de microbiota) y tratamiento para síntomas específicos (33).

Los tratamientos de rehabilitación han demostrado ser efectivos para mejorar los síntomas persistentes Post-COVID-19 (34). Las investigaciones de Stam et al. (2020) y Ali et al. (2021) afirman que la rehabilitación temprana Post-COVID-19 es vital para obtener una mejoría general y una mejor funcionalidad a medio y largo plazo (35,36). No obstante, Kiekens et al. (2020) afirman que estos tratamientos deben establecerse con cautela y de manera personalizada, en concordancia con las capacidades y necesidades de cada paciente (37).

La rehabilitación basada en ejercicios físicos se trata de un elemento fundamental en la recuperación de las personas con COVID persistente (22). Resulta efectiva especialmente para reducir los síntomas de fatiga, disnea, dolor musculoesquelético, capacidad funcional, e incluso el deterioro cognitivo y los problemas de salud mental (22). Estas actividades físicas suelen basarse en ejercicio aeróbico, entrenamiento de resistencia y de los músculos respiratorios (38–40). El estudio de cohorte observacional prospectivo de Nopp et al. (2022), logró mejoras significativas en presencia de disnea, fatiga y calidad de vida, mediante una intervención basada en un programa individualizado de rehabilitación pulmonar durante 6 semanas (38). La

investigación de Compagno et al. (2022), mediante un programa de rehabilitación extrahospitalaria multidisciplinar (reacondicionamiento físico y psicológico), logró mejoras significativas en la salud física y mental percibida, entre otras (39). El ensayo controlado aleatorio de Jimeno-Almazán et al. (2022) ofreció al grupo intervención un programa supervisado de ejercicios aeróbicos y de fuerza de 8 semanas, mientras que el grupo control realizó actividad física general, sin sesiones supervisadas. Tras la intervención existieron diferencias significativas a favor del grupo intervención en fatiga, estado funcional, fuerza muscular y depresión (40).

Con respecto a la rehabilitación para abordar los déficits cognitivos, se recomiendan ejercicios cognitivos de tipo restaurador, así como estrategias compensatorias basadas en estimulación, modificación ambiental y herramientas de asistencia (41). Además, puede resultar beneficioso en su recuperación la atención de profesionales de la salud mental, debido al efecto negativo que la propia enfermedad ha tenido sobre el organismo, en relación con su proceso de adaptación (42,43).

1.2.3 Calidad de vida en pacientes con COVID persistente

Tradicionalmente, los resultados puramente biomédicos han sido los principales hallazgos de valoración para las investigaciones de salud. Sin embargo, durante las últimas décadas el estudio y evaluación de la calidad de vida de diversos colectivos de pacientes han conseguido ponerse en el pódium de las investigaciones sanitarias (44). La calidad de vida es considerada un concepto importante y objeto de estudio, aplicable a cualquier grupo poblacional (45).

En 1994, la OMS publicó su definición del concepto calidad de vida, como: "*La percepción de un individuo de su posición en la vida en el contexto de la cultura en la que vive y en relación con sus objetivos, expectativas, normas y preocupaciones*" (46).

De este modo, la calidad de vida es un concepto multidimensional, que incluye evaluaciones subjetivas sobre aspectos positivos y negativos de la vida. Aunque la salud es uno de sus principales dominios, también existen otros, como el trabajo, la vivienda, la educación, las relaciones sociales o los valores culturales (47).

La dificultad de evaluar la calidad de vida está en que todos los individuos, grupos y disciplinas académicas pueden interpretar este término de diferentes maneras (45). No obstante, las investigaciones han desarrollado herramientas y técnicas para realizar evaluaciones rigurosas. De hecho, se ha verificado que la evaluación de este concepto es imprescindible para la elección de estrategias terapéuticas y la implementación de intervenciones educativas desde Atención Primaria de Salud (APS) ante cualquier problema de salud (48), como puede ser la COVID persistente.

La sintomatología persistente Post-COVID-19 produce una afectación en la salud física y psíquica del paciente. En consecuencia, sus esferas laboral, familiar y social pueden estar viéndose afectadas y, en definitiva, su calidad de vida (49). Las capacidades físicas de los afectados para realizar acciones cotidianas se encuentran mermadas. Incluso, las limitaciones pueden llegar a afectar en su funcionalidad para algunas actividades básicas de la vida diaria (p.ej. bañarse, vestirse o caminar) (50). Alrededor del 50% de las personas con COVID persistente continúan viendo efectos negativos en sus actividades diarias después de 3 a 5 meses, y el 15 % después de 8 meses desde la infección inicial (51–53). Una encuesta realizada por la Sociedad Española de Médicos Generales y de Familia (SEMG) a 1.834 participantes que presentaban síntomas compatibles con la COVID persistente durante 2020, concluye que el estado de salud de los encuestados ha empeorado 4,82/10 puntos de media, mientras que el grado de discapacidad ha aumentado en casi 6,32/10 puntos, en comparación con su situación previa a la infección por COVID-19 (54).

Por otro lado, las personas con COVID persistente presentan signos y síntomas compatibles con patologías mentales, como: depresión, ansiedad y alteraciones del sueño (55). Burton et al. (2022) afirman que la falta de opciones de tratamientos, junto a la incertidumbre que rodea la evolución de su enfermedad, generan preocupaciones y miedos que derivan en los citados síntomas (55). El estudio de Ireson et al. (2022) concluye que estos pacientes expresan sentirse en un constante desafío mental, debido al impacto de la enfermedad en casi todas sus acciones cotidianas (56). Además, muchos de ellos expresaron la búsqueda autónoma de alternativas de tratamiento como su única opción de esperanza para continuar viviendo con la enfermedad. De hecho, muchos manifiestan no reconocerse a sí mismos, debido a los cambios significativos que han experimentado en cuanto a sus capacidades (57). De igual manera, el estudio Kingstone et al. (2020) afirma que los pacientes con COVID persistente parecen estar insatisfechos y decepcionados con la atención que reciben desde el Sistema Nacional de Salud (SNS), solicitando "comprensión, empatía y apoyo", por parte de profesionales de APS (58). La investigación de Taylor et al. (2021), que incluye el discurso de profesionales de la salud con diagnóstico de COVID persistente, destaca que sus participantes han generado mayor empatía por las personas con enfermedades crónicas, en particular cuando los síntomas no tienen explicación (59).

Para las personas con COVID persistente, otros ámbitos que se ven afectadas son el laboral y el social. En el ámbito laboral, se estima que la capacidad de trabajo, la productividad personal, e incluso las interacciones interpersonales, son inferiores a los niveles previos a la enfermedad (23). Así mismo, la SEMG concluye que el 46% de afectados por la COVID persistente está de baja temporal o trabaja con mucha dificultad, el 15,6% trabaja en condiciones de normalidad, un 9,5% abandonó su trabajo y a un 2,9% se le ha reconocido una incapacidad permanente por COVID persistente (54). Por lo tanto,

esta afectación debe reconocerse como una condición con potencial incapacitante, al menos temporalmente (49). Con respecto al ámbito social, Macpherson et al. (2022) explican que el desconocimiento sobre la enfermedad por parte de la población general, acompañado en muchos casos de la incomprensión, hace que las personas con COVID persistente hayan reducido sus círculos sociales, incluso llegando a optar por el aislamiento domiciliario (57).

1.3 La importancia de la Atención Primaria de Salud en el manejo de la COVID persistente y la recomendación de activos comunitarios

El devastador inicio de la pandemia por COVID-19, asociado al desconocimiento y la incertidumbre, generaron un colapso temporal del SNS fundamentalmente caracterizado por la falta de recursos personales y materiales (60–62). Más de cien países sufrieron interrupciones en sus servicios de salud esenciales durante los primeros meses de dicha pandemia (63). La COVID-19 ha provocado numerosos cambios en el SNS, y por supuesto en la APS. Esta pandemia supone un antes y un después, tanto a nivel organizativo de los servicios de salud como en la manera de abordar las necesidades y demandas de la población (64,65).

Este escenario, sumado a las incógnitas que giran en torno a la COVID persistente, han dificultado la atención a este colectivo de pacientes. Se ha sugerido que su atención y seguimiento debe ser realizado y dirigido por médicos generales de APS (66). En octubre de 2020, el director general de la OMS afirmó: *"los gobiernos deben reconocer los efectos a largo plazo de la COVID-19 y asegurar el acceso a los servicios de salud a estos pacientes. Esto incluye atención primaria y, cuando sea necesario, cuidados especiales y rehabilitación"* (67). Sin embargo, las recomendaciones para la atención médica ambulatoria para las personas con COVID persistente siguen siendo imprecisas

y, por tanto, los profesionales de la salud tienden a realizar comparaciones con condiciones similares a la hora prescribir tratamientos (68), así como a basarse en guías de manejo fundamentadas en opiniones de expertos (18,20,69,70).

En España, las primeras guías nacionales sobre esta afectación fueron *la "Guía Clínica para la Atención al paciente COVID persistente / Long COVID"* (69) *y la "Guía de Práctica Clínica de Manifestaciones Persistentes de la Covid-19"* (70). El primer documento fue coordinado por la SEMG y los colectivos de pacientes LONG COVID ACTS. El segundo por la Societat Catalana de Medicina Familiar i Comunitària (CAMFiC). En ambas publicaciones se recomienda, entre otras, la inclusión de estos pacientes en la comunidad, como un punto a destacar. No obstante, la valoración de las necesidades y recursos comunitarios disponibles para los afectados por la COVID persistente todavía resulta una tarea pendiente.

Este enfoque supone un cambio en los modelos de atención tradicionales de profesionales de APS, colocando al paciente en el centro de su atención mediante un enfoque biopsicosocial (71). Las actividades comunitarias son aquellas actividades que están dirigidas a promover la salud, incrementar la calidad de vida y el bienestar de la población, potenciando las capacidades personales para el abordaje de sus propios problemas, demandas y necesidades (72). Dentro de los recursos comunitarios, encontramos lo que se ha denominado como un "activo para la salud". Se trata de cualquier factor o recurso que mejora las capacidades personales para sostener la salud y el bienestar, y que les ayuda a reducir las desigualdades en salud. Es decir, fortalece las habilidades personales para mantener o mejorar la salud física, psíquica y social, contrarrestando situaciones de estrés (73). La principal diferencia entre un recurso comunitario y un activo para la salud está en que un recurso comunitario puede no estar siendo utilizado para generar salud. Sin embargo, un activo para la salud siempre será

definido por la propia comunidad como un elemento que mejora la salud y el bienestar a nivel individual, grupal o comunitario (74).

De este modo, los activos para la salud pueden servir para reorientar la práctica profesional en todos los niveles de actuación de APS: consultas individuales, grupos de educación para la salud o proyectos de salud comunitaria. La manera de implementarlos se ha denominado como "recomendación de activos para la salud" (75), término derivado del inglés "social-prescribing", que se refiere al proceso por el cual determinado personal sanitario recomienda un activo de la comunidad al paciente para mejorar su bienestar, salud percibida o resolución de un problema, en el contexto de la consulta (76). En otras palabras, la recomendación de activos para la salud aboga por la creación de diferentes mecanismos formales para prescribir alternativas no farmacológicas, que tengan un impacto positivo en su salud. Esta técnica ha demostrado efectividad en la promoción de comportamientos saludables para problemas de salud prevalentes en APS, como: educación diabetológica (77), reducción de factores de riesgo cardiovascular (78), prevención de caídas en población geronte (79) y aumento de la actividad física realizada (80,81). De hecho, uno de los objetivos del "Plan de Acción de Atención Primaria y Comunitaria 2022-23", publicado por el Ministerio de Sanidad del Gobierno de España, es que sea accesible en todas las regiones (82). Su nombre está presente en diversos planes autonómicos del país (en Aragón, Andalucía, Asturias, etc) (83). De acuerdo con la estrategia de Atención Comunitaria del Sistema de Salud de Aragón (83), la recomendación de activos para la salud debe realizarse mediante una metodología concreta que consta de cinco etapas:

Etapa 1. Preparación y contextualización: establecer el objetivo y finalidad del trabajo, población diana destinataria, ámbito, así como tema de trabajo (p.ej., bienestar mental, actividad física, etc).

Etapa 2. Identificación y caracterización de las actividades comunitarias utilizables:

- Fase 1. Listado de actividades que se realizan en la comunidad: Realizar una reunión con profesionales del centro de salud para hacer un listado de actividades que conozcan que se están llevando a cabo en la comunidad relacionadas con los temas elegidos.

- Fase 2. Caracterización de las posibles actividades: Esta fase implica contactar con interlocutores de cada actividad identificada en la lista anterior para caracterizarla.

- Fase 3. Selección de actividades comunitarias y visibilización: De entre las actividades comunitarias identificadas en el listado anterior se escogerán las pertinentes.

Etapa 3. Formalización de la conexión actividad comunitaria – centro de salud: el grupo de trabajo establecerá la organización interna de APS y formalizará el compromiso y la metodología con el interlocutor de la actividad comunitaria.

Etapa 4. Recomendación de activos: puede empezar a llevarse a cabo el proceso de recomendación en: 1) Consultas individuales en el contexto de la entrevista motivacional desde medicina, enfermería, trabajo social, o fisioterapia, entre otros; 2) Actividades grupales del equipo de APS, como en sesiones de rehabilitación; o 3) Donde el equipo coordinador del proyecto haya previsto.

Etapa 5. Evaluación y dinamización: evaluación de todo el proceso y de las actuaciones generadas en la dinamización y recomendación de activos que se hayan llevado a cabo.

La metodología de activos también puede servir para desarrollar procesos en los que la ciudadanía descubra factores positivos de su comunidad y se favorezcan las redes de relaciones y apoyos mutuos que mejoren el empoderamiento, la participación y el abordaje de las cuestiones de salud de la zona.

1.4 Telerehabilitación destinada a pacientes con COVID persistente

En la última década, la telemedicina se ha implantado gradualmente a nivel global debido al impacto del mundo digital en las sociedades más desarrolladas (84). Sin embargo, la irrupción de la pandemia por COVID-19 supuso un gran impulso y aceleración de este proceso, debido a las dificultades de acceso y las medidas restrictivas necesarias para frenar su propagación (85). En consecuencia, esta herramienta se ha consolidado como imprescindible para afrontar las necesidades derivadas de dicha emergencia sanitaria (86). Este sistema de atención se implantó mayoritariamente en los países desarrollados, donde la brecha tecnológica entre los servicios urbanos y rurales es menor que en los territorios en vías de desarrollo (87). Varios estudios han demostrado que las visitas virtuales mejoran el acceso a los profesionales de la salud, reduciendo así los tiempos de espera (88,89). Las principales limitaciones para la implementación de la telemedicina han recaído en las regulaciones administrativas y la falta de marcos legales sólidos (90), además de la inversión económica necesaria en recursos tecnológicos y la reticencia de algunos profesionales y pacientes (85).

Dentro de los recursos y opciones que ofrece la telemedicina se encuentra la telerehabilitación. Durante los primeros meses de pandemia por COVID-19, las ya citadas deficiencias del SNS, junto con las medidas gubernamentales restrictivas, imposibilitaron ofrecer atención rehabilitadora clásica (en modalidad presencial-supervisada) (61). Este hecho ha contribuido a una mayor implementación de estrategias de telerehabilitación para diversas patologías (91).

En esta misma línea, en 2021 comenzaron a surgir los primeros estudios a pequeña escala sobre la efectividad de la telerehabilitación en pacientes Post-COVID-19 y COVID persistente (92–95). Estas investigaciones obtuvieron resultados beneficiosos para el funcionamiento físico y respiratorio o la calidad de vida, entre otros (92–95). En 2022

comenzaron a surgir los primeros ensayos clínicos aleatorizados (ECAs) sobre esta área (96–98). El estudio de Pehlivan et al. (2022), con treinta y cuatro pacientes posthospitalizados por COVID-19, logró mejoras significativas en la disnea y el funcionamiento físico a través de la telerehabilitación (96). El estudio de Li et al. (2022), con dos grupos paralelos de pacientes con disnea persistente Post-COVID-19, diseñó una aplicación móvil (APP, por sus siglas en inglés) con la que obtuvo mejoras en el rendimiento físico a favor del grupo intervención (97). La revisión sistemática de Vieira et al. (2022) confirma que la telerehabilitación contribuye positivamente en la recuperación de las secuelas Post-COVID-19 (98). Más recientemente, el programa de telerehabilitación de Rodríguez-Blanco et al. (2023) ha demostrado su efectividad para mejorar la función física y respiratoria Post-COVID-19 (99). El estudio de Hajibashi et al. (2023) ofreció telerehabilitación pulmonar combinada con relajación muscular durante seis semanas en pacientes posthospitalizados por COVID-19. Sus resultados mostraron mejoras significativas en la calidad del sueño o la ansiedad, pero no en la disnea, ni en el funcionamiento físico (100).

Las conclusiones de estas investigaciones sugieren que la telerehabilitación puede ser una buena opción para la recuperación de las personas con COVID persistente (96,97,99,100). Sin embargo, en algunos de estos estudios se han incluido pacientes infectados por COVID-19 hace menos de 3 meses, por lo que no serían considerados pacientes con COVID persistentes, según la definición de la OMS mencionada anteriormente (20). Además, se desconocen los efectos a medio plazo de este tipo de intervenciones. Por ello, todavía es preciso comprender mejor los tratamientos de telerehabilitación y los procesos de rehabilitación que contribuyen a la recuperación de las personas con COVID persistente.

Por todo lo anterior, dado el uso y efectividad significativa de la telemedicina, la falta de tratamiento para pacientes con COVID persistente y los estudios experimentales realizados hasta la fecha, se podría considerar oportuno implementar una estrategia de telerehabilitación para abordar esta afectación.

2. OBJETIVOS

Los objetivos que se plantearon en la presente tesis fueron los siguientes:

2.1 Objetivo principal

Analizar la efectividad clínica de una intervención de telerehabilitación a través de una APP, como tratamiento adyuvante en comparación con el tratamiento habitual (TAU), a corto y medio plazo, para mejorar la calidad de vida de pacientes con diagnóstico de COVID persistente. Además de identificar variables relacionadas con su calidad de vida.

2.2 Objetivos secundarios

2.2.1 Caracterizar el perfil de pacientes con diagnóstico de COVID persistente en relación con aspectos sociodemográficos, clínicos, afectivos, cognitivos, variables funcionales y sociales; así como identificar factores asociados a la calidad de vida de estos pacientes.

2.2.2 Profundizar sobre el bienestar emocional de pacientes con diagnóstico de COVID persistente, así como su percepción sobre apoyo social y experiencias de discriminación y estigma social.

2.2.3 Profundizar sobre el uso y adaptación de los recursos comunitarios disponibles como activos para la salud y su utilidad por parte de pacientes con diagnóstico de COVID persistente.

3. METODOLOGÍA

La línea de investigación de la presente tesis doctoral ha sido abordada a través de metodologías mixtas: metodología cuantitativa, mediante un ECA y un análisis de datos secundarios del ECA, y metodología cualitativa, a partir de entrevistas individuales semiestructuradas y grupos focales.

Todas las metodologías empleadas implantaron los mismos criterios de inclusión, así como el mismo procedimiento de reclutamiento. De este modo, la población de estudio está compuesta por pacientes con COVID persistente, mayores de edad (18 años o más) y atendidos desde APS. Para su reclutamiento, se llevó a cabo una estrategia de muestreo intencional [34] entre pacientes diagnosticados de COVID persistente atendidos en siete centros de APS de la provincia de Zaragoza, y también mediante la colaboración de la asociación de afectados "Long COVID Aragón". El reclutamiento fue realizado por médicos de familia de APS que se ofrecieron voluntarios tras una reunión informativa del proyecto.

A continuación, este apartado presenta los aspectos metodológicos más destacados, de acuerdo con el propósito de responder al objetivo principal y objetivos secundarios.

3.1 Metodología para dar respuesta al objetivo principal

Ensayo clínico aleatorizado

Con la finalidad de dar respuesta al objetivo principal de la presente tesis se llevó a cabo un ECA, para analizar la efectividad clínica a corto y medio plazo de ReCOVery, una APP diseñada ad hoc para esta intervención. Los resultados de esta investigación se encuentran en:

- **Manuscrito I**: Protocolo de co-creación de ReCOVery y diseño del ECA (101).
- **Manuscrito II**: Efectividad de ReCOVery a corto plazo (102).
- **Manuscrito VI** (ubicado en el Anexo I): Efectividad de ReCOVery a medio plazo. Este manuscrito todavía se encuentra en vías de publicación.

A continuación, se muestran los aspectos metodológicos más destacables del ECA y, finalmente el proceso de creación y desarrollo de la APP.

Diseño del estudio

Se desarrolló un ECA con dos grupos paralelos de pacientes con COVID persistente. El primer grupo mantiene su TAU, establecido por su médico de APS (grupo control), y el segundo también mantiene su TAU, y además utiliza ReCOVery APP, como tratamiento adyuvante en su recuperación (grupo intervención). También, el grupo intervención asiste a tres sesiones presenciales basadas en metodología motivacional y manejo de dicha APP, con el objetivo de promover su adherencia.

Muestreo y tamaño de la muestra

La metodología del ECA estableció un tamaño muestral necesario de 78 sujetos, según su principal variable, "calidad de vida", a través del cuestionario Short Form-36 Health Survey Questionnaire (SF-36). Finalmente, se superó el tamaño de muestra necesario.

Participantes

Un total de 100 sujetos han participado en este estudio. Los criterios de exclusión planteados han sido: no tener una prueba diagnóstica de COVID-19 positiva, previa a los 3 meses anteriores; tener un diagnóstico de enfermedad grave no controlada; riesgo significativo de suicidio; embarazo y lactancia; participación en un ensayo clínico en los últimos seis meses; tratamiento rehabilitador o psicoterapéutico estructurado existente

por profesionales de la salud y la presencia de cualquier problema médico, psicológico o social que pueda interferir significativamente con la participación del paciente en el estudio.

Recopilación de datos

Se realizó una evaluación basal (previa al inicio de la intervención), una evaluación de efectividad a corto plazo (3 meses después del inicio de la intervención) y una evaluación de efectividad a medio plazo (6 meses después del inicio de la intervención). Todas las evaluaciones se realizaron durante un período de dos semanas consecutivas. Las evaluaciones fueron realizadas por dos investigadores independientes con experiencia previa en proyectos y acciones similares. Estas evaluaciones se realizaron de forma presencial en un Centro de APS de la ciudad de Zaragoza.

Variables de estudio

A continuación, en la Tabla 1 se recogen las variables de estudio y cuestionarios implementados. En el caso de los cuestionarios, se utilizaron adaptaciones españolas validadas de la escala original. Para las variables sociodemográficas, clínicas y de tiempo de uso de la APP, se diseñó un cuestionario ad hoc, basado en evidencias previas (23,24,103,104).

Tabla 1. Variables de estudio y cuestionarios

Áreas	**Variables de estudio / Cuestionarios**
Variables sociodemográficas	Sexo; edad; estado civil; nivel educativo; situación laboral
Variables clínicas	Tiempo desde la infección (meses); número de síntomas persistentes autoinformados al momento de cada evaluación
Empleo de ReCOVery	Tiempo de uso de la APP (minutos)
Calidad de vida	-Short Form-36 Health Survey Questionnaire (SF-36) (105)
Estado cognitivo	-Montreal Cognitive Assessment (MoCA) (106)
Estado afectivo	-Hospital Anxiety and Depression Scale questionnaire (HADS) (107)
Estado funcional y actividad física	-Thirty-second Sit-to-Stand Test (SST-30) (108) -International Physical Activity Questionnaire-Short Form (IPAQ-SF) (109)
Calidad del sueño	-Insomnia Severity Index questionnaire (ISI) (110)
Soporte social	-Medical Outcomes Study Social Support Survey questionnaire (MOS-SS) (111) -Perceived Community Support Questionnaire (PCSQ) (112)
Constructos personales	-Self-Efficacy Scale-12 (GSES-12) (113) -Patient Activation Measure questionnaire (PAM) (114) -Health Literacy Europe Questionnaire (HLS-EUQ16) (115)

Co-creación de ReCOVery APP

Para el diseño, desarrollo, recomendación y evaluación de ReCOVery APP, se implementó una adaptación del proceso de recomendación de activos para la salud de la estrategia de Atención Comunitaria del Sistema de Salud de Aragón (83), mediante las cinco etapas descritas a continuación:

Etapa 1. Inicio y contextualización

En primer lugar, se estableció como objetivo principal ofrecer rehabilitación a través de recursos comunitarios a los pacientes de APS diagnosticados de COVID persistente, con el fin de paliar sus síntomas y, consecuentemente, mejorar su calidad de vida. Para ello se creó un equipo multidisciplinar, que incorporaba las áreas de medicina, enfermería, psicología, trabajo social, fisioterapia y terapia ocupacional. Para profundizar sobre el colectivo de futuros participantes, se diseñó un estudio cualitativo con entrevistas semiestructuradas y grupos focales (posteriormente detallado), con el fin de identificar sus necesidades, así como los recursos comunitarios útiles para favorecer su recuperación.

Etapa 2. Identificación y caracterización de posibles actividades comunitarias

En segundo lugar, se realizó el estudio cualitativo en el que la mayoría de las personas participantes expresaban emplear recursos comunitarios. Sin embargo, desde su autopercepción la mejoría era escasa. Tras ello, el equipo multidisciplinar pudo identificar y caracterizar algunas actividades comunitarias potenciales y se elaboró un listado de actividades (p. ej., actividad de ejercicio aeróbico realizado al aire libre, club de lectura en centro cívico, grupo de marcha nórdica promocionado por una asociación vecinal, actividades de estimulación cognitiva destinadas a personas mayores, grupo de teatro, grupos matutinos de andarines, etc). Tras contactar con los interlocutores de cada actividad, se concluyó por consenso del grupo multidisciplinar que no existían suficientes recursos comunitarios adaptados y viables para este colectivo de pacientes, en parte, por la variabilidad de perfiles que se esperaba reclutar. Además, coincidente con el desarrollo de esta fase, durante los meses de diciembre de 2021 a marzo de 2022 se produjo un considerable aumento del número de casos por COVID-19 contabilizados en la Comunidad Autónoma de Aragón (116). En consecuencia, la APS se encontraba sobrecargada. Por todo ello, se planteó la necesidad de crear un recurso comunitario ad hoc para este colectivo de pacientes, acorde a sus necesidades y demandas identificadas en el estudio cualitativo. Como resultado, se propuso la creación una APP con contenido rehabilitador que poder implementar en un futuro desde APS.

Etapa 3. Construyendo conexión comunitaria

En tercer lugar, se realizó el proceso de creación y desarrollo de la APP, posteriormente denominada “ReCOVery”. El método iterativo seleccionado para el desarrollo de ReCOVery fue el diseño centrado en el ser humano (117). Esta técnica busca resolver problemas específicos a partir de la comprensión de las necesidades y las

diferentes perspectivas de los propios usuarios como posibles destinatarios de la intervención (118). De esta forma, resulta posible promover un tratamiento adaptado y personalizado. Por ello, el diseño inicial de ReCOVery se guio por los síntomas, necesidades y otra información que se obtuvo a través del estudio cualitativo. Posteriormente, se recopiló la evidencia científica disponible (18,69,70) sobre recomendaciones sanitarias y ejercicios de recuperación para pacientes con COVID persistente. El mismo equipo multidisciplinar se encargó del diseño y creación de contenidos para cada área de rehabilitación. De este modo, se diseñaron seis módulos que incluir en la APP:

- 1. Recomendaciones para la adherencia a la dieta mediterránea
- 2. Recomendaciones para mejorar la calidad del sueño y el descanso
- 3. Ejercicios físicos, mediante representaciones gráficas
- 4. Ejercicios de fisioterapia respiratoria, con apoyo de videotutoriales
- 5. Ejercicios de estimulación cognitiva, con diferentes niveles de dificultad
- 6. Recomendaciones de participación en recursos de la comunidad

Cada uno incluye un área de rehabilitación, disponiendo de varias opciones y niveles de adaptación para satisfacer las necesidades específicas de los pacientes.

En cuanto a la arquitectura de la APP, se creó una APP móvil nativa con lenguaje Java a través de Android Studio, haciéndola compatible con Android, una de las principales plataformas. Por lo tanto, la APP se puede ejecutar en todos los dispositivos inteligentes Android con una versión de software superior a 5.0. Se optó por el diseño de una APP nativa, en lugar de híbrida, con el fin de obtener un mejor rendimiento a largo plazo, así como poder hacer uso de herramientas propias del dispositivo, como las notificaciones, permitiendo así que la APP se mantenga actualizada. Así, la APP envía notificaciones periódicas de recordatorio, con opciones de configuración. Cada módulo

consta de autoevaluaciones diarias donde se informa la autopercepción de los usuarios. Estos datos crean gráficos estadísticos sobre la evolución en las diferentes áreas, lo que permite al usuario ver su progreso con una perspectiva temporal. Las respuestas a estas autoevaluaciones se almacenan en una base de datos del servidor SQL en la nube alojada en Azure y también se guardan localmente en el propio dispositivo del paciente en una base de datos SQLite. ReCOVery garantiza la privacidad y seguridad de los datos del usuario.

Previo al inicio de la intervención, el contenido de la APP fue evaluado periódicamente tanto por pacientes con COVID persistente (futuros usuarios) como por profesionales de la salud, para asegurar su idoneidad y facilitar su adaptación y transferencia, siguiendo la combinación entre la metodología SCRUM (119) y la metodología ágil, siendo esta última óptima para el desarrollo de software (120). En este caso, la creación de la APP se distribuyó en varios ciclos de desarrollo incrementales e interactivos (sprints). Al final de cada sprint, los pacientes seleccionados y el equipo multidisciplinar proporcionaban su visto bueno o sugerían posibles modificaciones que se acordaron de forma consensuada. Con respecto a las pruebas de campo, se solicitó a los usuarios que informasen sobre cualquier error o fallo en la APP, así como sugerir posibles modificaciones para futuras mejoras. También se realizaron breves entrevistas cualitativas individuales para detallar más la experiencia ideal que los pacientes preferirían tener en relación con el funcionamiento de ReCOVery.

Etapa 4. Recomendación de activos (ReCOVery a pacientes COVID persistente)

En cuarto lugar, se solicitó a médicos de APS de la provincia de Zaragoza que identificaran a pacientes potenciales que cumplieran con los criterios de inclusión, anteriormente citados. Una vez realizada la captación, verificación y aleatorización de las personas participantes, se realizó la recomendación de uso de la APP. De este modo, se

aleatorizaron en dos grupos paralelos. Aquellos asignados al grupo intervención tuvieron acceso a la APP con contenido rehabilitador y asistieron a tres sesiones basadas en metodología motivacional, manejo del APP y fortalecimiento de sus constructos personales (alfabetización en salud, autoeficacia y activación personal), así como empleo de recursos comunitarios potenciales. Se realizaron dos sesiones individuales y una sesión grupal durante tres semanas consecutivas. Las sesiones se basaron en la guía motivacional de Miller W. y Rollnick S. (2013) (121), que pretendía promover la adherencia al APP. Las sesiones fueron dirigidas por un trabajador social y una terapeuta ocupacional, previamente entrenados para dichas acciones. Las sesiones individuales tuvieron una duración de 20-30 min, durante las cuales se instaló la APP y se resolvieron dudas sobre su manejo. Las sesiones grupales se realizaron con un mínimo de ocho y un máximo de doce participantes y no excedieron de una hora por sesión. Todas las personas participantes completaron las sesiones durante las mismas semanas.

Es importante considerar que durante la intervención ReCOVery APP fue privada, por lo que únicamente las personas participantes asignadas al grupo intervención tenían acceso a ella desde sus teléfonos personales, evitando así posibles filtraciones al grupo control.

Etapa 5. Evaluación y Revitalización

Finalmente, para evaluar la efectividad de ReCOVery APP y del proceso de recomendación, se diseñó un ECA que evaluó los resultados a corto y medio plazo. La mejora de la calidad de vida de las personas participantes supondría considerar esta APP como un activo para la salud, pudiendo ser ofertado a toda la comunidad.

3.2 Metodología para dar respuesta a los objetivos secundarios

Análisis de datos secundarios

Se llevó a cabo un análisis de datos secundarios (122), mediante los datos basales recopilados al inicio del ECA. La finalidad de este estudio era dar respuesta al objetivo secundario:

"**2.2.1** Caracterizar el perfil de pacientes con diagnóstico de COVID persistente en relación con aspectos sociodemográficos, clínicos, afectivos, cognitivos, variables funcionales y sociales; así como identificar factores asociados a la calidad de vida de estos pacientes".

Los resultados de esta intervención se encuentran en el **Manuscrito III** de la presente tesis (123).

Se incluyeron el total de cien participantes reclutados en el ECA. Las variables de estudio también fueron las mismas que en el ECA, a excepción del cuestionario PCSQ, por tratarse de un área poco estudiada y que necesita de mayor soporte y evidencia.

Metodología cualitativa

Se diseñó y ejecutó un estudio cualitativo basado en entrevistas individuales semiestructuradas y grupos focales, a través del análisis temático basado en la teoría fundamentada, de carácter inductivo (124). La finalidad de este estudio era dar respuesta a los objetivos secundarios:

"2.2.2 Profundizar sobre el bienestar emocional de pacientes con diagnóstico de COVID persistente, así como su percepción sobre apoyo social y experiencias de discriminación y estigma social".

"**2.2.3** Profundizar sobre el uso y adaptación de los recursos comunitarios disponibles como activos para la salud y su utilidad por parte de pacientes con diagnóstico de COVID persistente".

Los resultados de esta metodología se encuentran en el **Manuscrito IV** (125) y **Manuscrito V** (126) de la presente tesis.

Muestreo y tamaño de la muestra

Se estableció que el tamaño de la muestra final dependería de la saturación de información, entendida como el punto en el que no surgieran nuevas categorías después del análisis de datos de los grupos focales (127). Inicialmente, un total de 39 sujetos estaban interesados en participar en el estudio. Finalmente, el tamaño de la muestra fue de 35 participantes, ya que cuatro pacientes se negaron a participar por incompatibilidad de horarios para asistir a las entrevistas. En este caso, el segundo grupo focal no aportó nuevas categorías, por lo que se concluyó que se había logrado la saturación de información. De esta forma, no fue necesario iniciar nuevos procesos de captación.

Participantes

La población de estudio estuvo formada por un total de 35 sujetos, 17 de ellos fueron entrevistados individualmente y 18 participaron en dos grupos focales, nueve en cada grupo.

Los criterios de exclusión fueron los siguientes: no poder responder al entrevistador por cualquier motivo, presentar alto deterioro cognitivo por cualquier motivo y/o recibir cuidados paliativos.

Recopilación de datos

Todas las entrevistas y grupos focales fueron realizados por un moderador y un asistente. El moderador y el asistente se presentaron a todas las personas participantes como investigadores del proyecto. Todas las sesiones se realizaron durante los meses de noviembre y diciembre de 2021, tanto en horario de mañana como de tarde, con el fin de facilitar la disponibilidad. Se realizaron en una sala anexa al centro un centro de APS de la ciudad de Zaragoza, con entrada independiente, con el objetivo de crear un ambiente de discusión alejado del contexto clínico de los servicios de APS.

Se planeó un protocolo estandarizado para guiar las entrevistas individuales y grupales. Se elaboró una lista de temas a abordar durante las entrevistas y grupos focales. Las entrevistas individuales duraron entre 20 y 60 min, y los grupos focales duraron entre 50 y 75 min. No fue necesario repetir ninguna entrevista, ni hubo interrupción durante las grabaciones. Todas las sesiones se grabaron en audio digitalmente y se obtuvieron transcripciones de estos registros para componer un conjunto final de datos cualitativos para el análisis de los datos.

Las transcripciones de las entrevistas y grupos focales fueron realizadas textualmente por dos investigadores externos, con experiencia previa en la realización de esta acción. Los nombres de las personas participantes fueron anonimizados con un código numérico asignado. Algunas de las personas participantes revisaron las transcripciones, aprobándolas y, finalmente, se agregaron las notas de campo realizadas durante las entrevistas.

4. RESULTADOS PUBLICADOS

Los resultados de esta tesis se encuentran publicados en los siguientes cinco manuscritos:

Manuscrito I

Samper-Pardo, M., León-Herrera, S., Oliván-Blázquez, B., Benedé-Azagra, B., Magallón-Botaya, R., Gómez-Soria, I., Calatayud, E., Aguilar-Latorre, A., Méndez-López, F., Pérez-Palomares, S., Cobos-Rincón, A., Valero-Errazu, D., Sagarra-Romero, L., & Sánchez-Recio, R. (2022). Development and Validation of a Mobile Application as an Adjuvant Treatment for People Diagnosed with Long COVID-19: Protocol for a Co-Creation Study of a Health Asset and an Analysis of Its Effectiveness and Cost-Effectiveness. International journal of environmental research and public health, 20(1), 462. https://www.mdpi.com/1660-4601/20/1/462

Manuscrito II

Samper-Pardo, M., León-Herrera, S., Oliván-Blázquez, B., Méndez-López, F., Domínguez-García, M., & Sánchez-Recio, R. (2023). Effectiveness of a telerehabilitation intervention using ReCOVery APP of long COVID patients: a randomized, 3-month follow-up clinical trial. Scientific reports, 13(1), 7943. https://doi.org/10.1038/s41598-023-35058-y

Manuscrito III

Samper-Pardo, M., León-Herrera, S., Oliván-Blázquez, B., Gascón-Santos, S., & Sánchez-Recio, R. (2023). Clinical characterization and factors associated with quality of life in Long COVID patients: Secondary data analysis from a randomized clinical trial. PLoS ONE, 18(5), e0278728. https://doi.org/10.1371/journal.pone.0278728

Manuscrito IV

Samper-Pardo, M., Oliván-Blázquez, B., Magallón-Botaya, R., Méndez-López, F., Bartolomé-Moreno, C., & León-Herrera, S. (2023). The emotional well-being of Long COVID patients in relation to their symptoms, social support and stigmatization in social and health services: a qualitative study. BMC Psychiatry, 23(1), 68. https://doi.org/10.1186/s12888-022-04497-8

Manuscrito V

Samper-Pardo, M., Formento-Marín, N., Oliván-Blázquez, B., León-Herrera, S., & Benedé-Azagra, B. (2023). Use of community resources as health assets for rehabilitation of people with Long COVID in northeastern Spain two years after the outbreak of the COVID-19 pandemic: qualitative study. Archives of public health, 81(1), 125. https://doi.org/10.1186/s13690-023-01139-7

Manuscrito I. Development and Validation of a Mobile Application as an Adjuvant Treatment for People Diagnosed with Long COVID-19: Protocol for a Co-Creation Study of a Health Asset and an Analysis of Its Effectiveness and Cost-Effectiveness.

International Journal of
Environmental Research and Public Health

MDPI

Protocol

Development and Validation of a Mobile Application as an Adjuvant Treatment for People Diagnosed with Long COVID-19: Protocol for a Co-Creation Study of a Health Asset and an Analysis of Its Effectiveness and Cost-Effectiveness

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Citation: Samper-Pardo, M.; León-Herrera, S.; Oliván-Blázquez, B.; Benedé-Azagra, B.; Magallón-Botaya, R.; Gómez-Soria, I.; Calatayud, E.; Aguilar-Latorre, A.; Méndez-López, F.; Pérez-Palomares, S.; et al. Development and Validation of a Mobile Application as an Adjuvant Treatment for People Diagnosed with Long COVID-19: Protocol for a Co-Creation Study of a Health Asset and an Analysis of Its Effectiveness and Cost-Effectiveness. *Int. J. Environ. Res. Public Health* **2023**, *20*, 462. https://doi.org/10.3390/ijerph20010462

Academic Editor: George Crooks

Received: 21 October 2022
Revised: 20 December 2022
Accepted: 21 December 2022
Published: 27 December 2022

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Abstract: Objective: To analyse the overall effectiveness and cost-efficiency of a mobile application (APP) as a community health asset (HA) with recommendations and recovery exercises created bearing in mind the main symptoms presented by patients in order to improve their quality of life, as well as other secondary variables, such as the number and severity of ongoing symptoms, physical and cognitive functions, affective state, and sleep quality. Methods: The first step was to design and develop the technologic community resource, the APP, following the steps involved in the process of recommending health assets (RHA). After this, a protocol of a randomised clinical trial for analysing its effectiveness and cost-efficiency as a HA was developed. The participants will be assigned to: (1st) usual treatment by the primary care practitioner (TAU), as a control group; and (2nd) TAU + use of the APP as a HA and adjuvant treatment in their recovery + three motivational interviews (MI), as an interventional group. An evaluation will be carried out at baseline with further assessments three and six months following the end of the intervention. Discussion: Although research and care for these patients are still in their initial stages, it is necessary to equip patients and health care practitioners with tools to assist in their recovery. Furthermore, enhanced motivation can be achieved through telerehabilitation (TR).

Keywords: long COVID-19; APP; health asset; co-creation; effectiveness; cost-efficiency; primary health care

1. Introduction

Coronavirus (COVID-19), caused by the severe acute respiratory syndrome SARS-CoV-2, has had a serious impact on the whole world and has triggered unprecedented health, social, and economic crises [1]. Most patients infected by SARS-CoV-2 recover in no more than a month depending on the severity of their symptoms [2,3] However, it is believed that irrespective of the severity of symptoms, around 20% of people continue to show or develop multisystemic symptoms after five weeks or more following the acute infection, while 10% continue to display symptoms after twelve weeks, despite receiving negative PCR test results and developing antibodies [4].

In the absence of a clear definition, this new symptomology had been referred to interchangeably as "Long COVID" or "Post-COVID" [5–7]. It is in this context that the National Institute for Health and Care Excellence (NICE) states that COVID-19 symptoms can last for 4–12 weeks and that those whose symptoms continue beyond this period and with no alternative diagnosis will be considered to have "Post-COVID syndrome" [8]. In October 2021, the World Health Organisation (WHO) released an official definition of the condition, referring to it as "Post-COVID condition" [9], a condition that occurs in individuals who were previously likely to have been infected (without diagnostic test confirmation) or confirmed to have been infected with SARS-CoV-2.

The characteristic symptoms of this new condition are confusing, unspecific, and can be ongoing or fluctuate over time [10,11]. The most prevalent symptoms include chronic fatigue, breathlessness, fever, coughing, headaches, chest pain and/or a sore throat, muscle pain, general aches and pains, palpitations, tingling, diarrhoea, rashes, myalgia, brain fog and neurological symptoms, as well as symptoms of depression and anxiety stemming from extreme fatigue and other physical symptoms, among other causes [12–14]. There is a higher prevalence among women than men, with the latter making up 20% of diagnoses [15].

There are still many unknown factors (diagnosis, etiology, and disease phenotypes) that are grouped under the umbrella of long COVID-19, and the response to this illness is in its initial stages [13,16]. Therefore, it is necessary to promote research, especially in the field of primary health care (PHC) [17], as it is these health care practitioners who routinely treat long COVID-19 patients. To generate this evidence, a broader outlook should be adopted that does not focus on deficit care models, and patients themselves should be involved through co-production in health and the opportunities presented by citizen science [18]. In this way, citizens can actively contribute to the research by employing their own intellectual effort, knowledge, tools, and resources.

In the case of health issues, it will allow for the analysis and implementation of more viable interventions based on patients' experiences, utilising the knowledge of their strengths and challenges they face. They should be included and involved in care planning with a view to co-production in health with contextualised and salutogenic biopsychosocial care models. Consequently, the recognition of patients' individual, family, and community health assets (HAs) would be valuable. Understanding how these general resilience resources operate and enable greater consistency, would, in turn, allow them to understand, manage, and find purpose in their condition [19]. This project, based on a qualitative study, has taken the insights (practical wisdom) of those who are suffering from ongoing symptoms having contracted COVID-19 into account. Therefore, the needs of this group in their stages of recovery and the possible responses from the health system and especially from PHC have been jointly considered.

The recommendation of health assets (RHA) or social prescribing (SP) is a tool that can be used in PHC. It complements the biopsychosocial model and allows for the contextualisation of care through a multidisciplinary and intersectoral approach based on health determinants while granting individuals and communities the necessary means to improve and exercise greater control over their wellbeing [20–23]. HAs can be defined as any factor or resource which enhances the ability of individuals, communities, and populations to maintain and sustain health and wellbeing. Whether at an individual, family, or community level, the common denominator granted by these assets is the strengthening of individuals or groups' ability to maintain or improve physical, mental, or social health and to deal with stressful situations. HAs could be seen as general resources to overcome inequality and as essential to strengthen knowledge and skills with regard to maintaining good health, boosting morale, and empowering individuals and communities. As a consequence, there would be less vulnerability and dependence on the healthcare system [24,25]. RHA creates formal mechanisms through HAs to provide certain individuals with non-clinical healthcare alternatives. Thus, within the framework of therapy, we can recommend pre-existing non-clinical community resources.

To implement RHA, it is important to understand the current state of affairs. Following the COVID-19 pandemic, there have been changes made to the use of many clinical and non-clinical resources. Within this context and as an alternative solution to varying requirements, the pandemic has led to increased use of new technologies in diverse settings, including HAs, to ensure efficient communication between practitioners and patients [26,27]. However, this change has been in the works for around a decade, with the promotion of new technology and its increased use among the general population [28]. A clear example of this is the introduction of telerehabilitation (TR): the provision of rehabilitation services through electronic systems using information and communication technology. TR goes beyond hospital settings, helping to evaluate the effectiveness of rehabilitation in everyday activities [29]. Numerous recent studies looking at different diseases have demonstrated the efficiency of using a mobile application (APP) in the treatment of symptoms [30–32]. In addition, using TR for post-COVID patients has been proven to be effective, leading to improvements in dyspnoea, fatigue, and ability [33,34]. To sum up, RHA is a technique used to treat a wide variety of patients, including those diagnosed with long COVID-19.

Medical rehabilitative treatment options for these patients are still proving to be limited, imprecise, and not entirely effective. However, there are no large-scale studies demonstrating the efficacy of pharmacological treatment and, as such, it is essential to continue working on the rehabilitation options offered to these patients [35]. In addition, scientific evidence suggests that early rehabilitation is essential to regain normal functionality [36,37]. Rehabilitation options similar to those offered to patients with chronic fatigue syndrome have always been indicated, that is, gradual and personalised physical and respiratory exercise therapies led by professionals [38,39]. In addition, as the development of the symptoms has been confirmed, it has become necessary to offer cognitive–behavioural therapy and attention from mental health professionals, given the negative impact of the disease itself on the patient's quality of life [40,41]. Based on this evidence, it seems necessary to consider all these types of therapies in addition to ensuring healthy lifestyle habits, such as diet or sleep quality, to develop a comprehensive rehabilitation plan for long COVID-19 patients.

In light of this challenge, while co-creating the treatment and rehabilitation process, the need to create a community RHA for this patient group to be implemented at the earliest convenience was identified. This was due to the urgency stemming from the number and variety of symptoms presented by patients, as well as the uncertainty that still exists concerning certain pathophysiological aspects of Long COVID. Given the lack of existing resources for the group concerned, the need to design and develop an APP was raised, called ReCoVery. As far as we know, there are only two projects with a design and with purposes such as the ones presented in this study. However, these other two projects have not yet published their results since they are in the development phase of the clinical trial [42,43]. One of the projects is based on therapies such as those used for patients with fibromyalgia given the shared inability to objectify some symptoms. The two studies will serve as precedents for this project. However, it is considered necessary to design and implement a specific rehabilitation plan for this group of patients, which considers all the effects on their vital areas.

For the reasons outlined above, it would be a community resource, designed through a process of identification and co-creating content with Long COVID patients, who could later use the APP to support their recovery by means of TR. Hence, the objective of this study is to analyse the overall effectiveness and cost-efficiency of an APP as a community HA with recommendations and recovery exercises created bearing in mind the main symptoms presented by patients in order to improve their quality of life, as well as other secondary variables, such as the number and severity of ongoing symptoms, physical and cognitive functions, affective state, and sleep quality. A secondary objective is the analysis of personal factors, such as activation, self-efficacy, or health literacy as mediators of the effectiveness of the treatment.

2. Materials and Methods

2.1. Methodology to Design and Develop the Community Resource (ReCoVery APP)

This methodology is based on the steps involved in the RHA process.

2.1.1. Start and Contextualisation

Firstly, the project was prepared and contextualised. The main objective was then established as offering rehabilitation through community resources to PHC patients diagnosed with long COVID-19 in the Spanish region of Aragón in order to improve their quality of life, as well as to alleviate their symptoms. To this end, a multidisciplinary team of general practitioners, nurses, psychologists, social workers, physiotherapists, and occupational therapists was created. To contextualise the environment and patient group, a qualitative study was carried out with semi-structured interviews and focus groups in order to identify their needs as well as the resources to be used during the treatment and, particularly, to delve deeper into the identification of community HAs during their recovery.

2.1.2. Identification and Characterisation of Possible Community Activities

Secondly, after detecting the patients' lack of knowledge and difficulties due to their specific symptoms in the use or suitability of community resources, the multidisciplinary team was able to identify and characterise usable community activities. A list of activities carried out in the community was created, establishing certain criteria for the selection of activities in order to create a "map of HA for Long COVID patients". After contacting interlocutors from each resource/activity, it was concluded by consensus that there were no sufficient rehabilitation community resources for this patient group according to the criteria established by the multidisciplinary team. Therefore, the need to create an ad hoc developed resource for this group that was also in line with the needs and demands established in the qualitative study, was considered. As a result, an APP with recovery content was designed and was treated as an HA in itself that, as requested by its users, needed to suit their needs.

2.1.3. Building Community Connection

Thirdly, this phase was dedicated to the process of creation and development of the APP ReCoVery. The iterative method selected for the development of ReCoVery was human-centred design [44,45]. This technique looks to resolve specific problems based on the understanding of the needs and different perspectives of the users themselves as possible recipients of the intervention. In this way, it is possible to promote an adapted and personalised treatment, as well as to ensure adherence to it. For this reason, the initial design of ReCoVery was guided by symptoms, detected needs, and other information that was obtained through individual qualitative interviews and focus group discussions with patients diagnosed with long COVID-19. Subsequently, available scientific evidence was collected on health recommendations and recovery exercises for patients with Long COVID. Within the multidisciplinary team, different work subgroups were created to work on the design and creation of content for each rehabilitation area.

Prior to the start of the intervention, the content of the APP was periodically evaluated both by patients with Long COVID (future users) and by general practitioners, nurses, physiotherapists, occupational therapists, social workers, and psychologists to ensure its suitability and facilitate its adaptation and transfer following the combination between the SCRUM methodology [46] and the agile methodology, with the latter being optimal for software development [47]. In this case, the creation of the APP was distributed in various incremental and interactive development cycles (sprints). At the end of each sprint, the selected patients and the multidisciplinary team had to give their approval or suggest possible modifications that were consensually implemented.

Regarding the architecture of the APP, a native mobile APP with Java language was created through Android Studio, making it compatible with Android, one of the main platforms. Therefore, the APP can be run on all Android smart devices with a software

version higher than 5.0. The design of a native APP was chosen, instead of a hybrid one, in order to obtain improved performance in the long term, as well as to be able to make use of the device's own tools, such as notifications, thus allowing the APP to be kept up to date.

ReCoVery consists of six main modules, as detailed below, each one including a rehabilitation area for long COVID-19 patients, with various options and levels of adaptation being available to meet the specific needs of the patients, as well as self-report registration. In addition, the APP sends periodic reminder notifications, with configuration options.

Regarding the download and use, for new users this APP will not be publicly available, thus guaranteeing that it will only be downloaded onto the intended devices. The APP will be installed on the mobile devices of the participants during the first intervention session, where they will be provided with a username and the personal access password necessary to log in. In the event of having to reinstall the APP, due to a change in device or any other situation, it will be necessary to contact the research staff to make an appointment and carry out the installation process again.

ReCoVery will automatically record usage data, including logins, visits to each module and specific content, time of use, and any other interaction with the APP. In addition, each module consists of daily self-assessments where the self-perception of the users is reported. These data create statistical graphs regarding evolution in the different areas, allowing the user to see their evolution with a time perspective. The answers to these self-assessments will be stored in a SQL server database in the cloud hosted in Azure and will also be locally saved on the patient's own device in a SQLite database. ReCoVery ensures the privacy and security of user data. In addition to carrying out the download process on-site, an authentication process must be completed for the installation by providing an identification code and a personal password. This information is only requested the first time the patient logs in, meaning that access to the APP will be remotely revoked in the event of loss, theft, or any reported improper use after contacting the research staff.

With regard to field tests, users will be asked to report any bugs or crashes in the APP, as well as suggest possible modifications for future improvement. Brief individual qualitative interviews will also be conducted to further detail the ideal experience that the patients would prefer to have in relation to the functioning of ReCoVery. The research team will carry out new bibliographic research in order to obtain and incorporate new scientific evidence on the subject. These results were used to identify potential areas for improvement, and an updated version of ReCoVery (V.2.0) will be created.

2.1.4. Recommendation of the APP to Patients

Fourthly, the established protocol for the recommendation of the APP was implemented. To this end, PHC general practitioners in Aragón were asked to identify potential patients who could then be offered the possibility to participate. Following this referral, the evaluating researcher contacted the patients to confirm or decline their participation. They were then invited to the research group's headquarters for baseline tests, and the APP was recommended to them. This process continued until there was a sufficient sample size, as detailed below. Moreover, means of communication between practitioners and patients were established to monitor the intervention and resolve any arising problems.

2.1.5. Evaluation and Revitalisation

Finally, evaluations could be carried out, in accordance with the previously established parameters, through the users' contributions and following the quality of health promotion interventions, with the ultimate goal of offering this HA to the whole community.

Figure 1 shows the flowchart of the APP's design and development process.

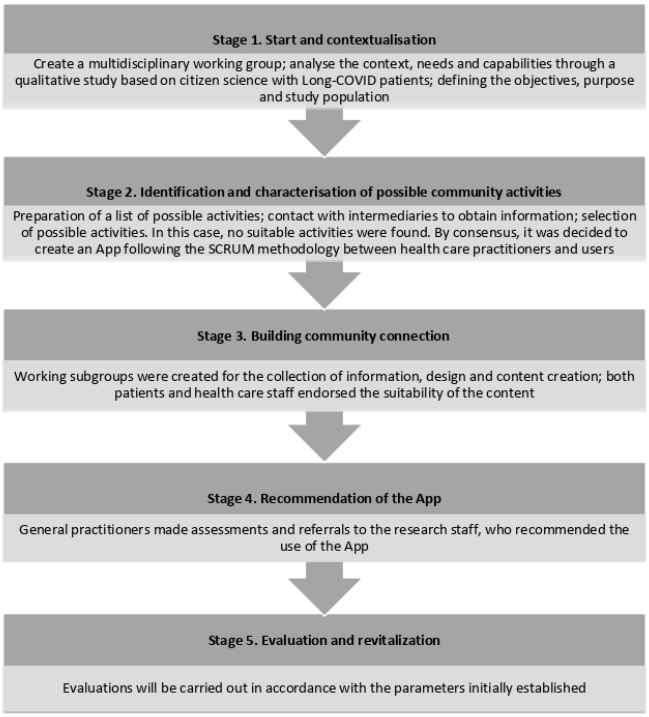

Figure 1. Design process and recommendation of a rehabilitation community resource (APP).

2.2. APP's Validation, Effectiveness and Cost-Efficiency as a HA

2.2.1. Study Design

Randomised ecological clinical trial was represented in two parallel groups. The two interventions to which the patients will be assigned will be: (1st) usual treatment by the primary care practitioner (TAU—control group); and (2nd) TAU + use of the APP as a HA and adjuvant treatment in their recovery, plus three face-to-face motivational interview sessions to enhance adherence (intervention group).

2.2.2. Study Population

The study population will be people with ongoing COVID symptoms who are aged 18 years or over and being treated by PHC. Exclusionary criteria are: diagnosis of a serious uncontrolled illness, which may interfere with the APP recommendations; significant risk of suicide; pregnancy and breastfeeding; participation in another clinical trial within the last six months; existing structured rehabilitative or psychotherapeutic treatment by health professionals and the presence of any medical, psychological or social problem that may significantly interfere with the patient's participation in the study.

Patients will be recruited by PHC professionals. They will explain the nature of the study and invite patients to participate. Patients from the Association of Long COVID Patients in Aragón will also participate. Recruitment will happen consecutively until the sample size will be reached.

2.2.3. Sample Size

To calculate the sample size, we will use the data obtained in the study of Dalbosco-Salas et al. [34] because the intervention is similar to ours, and it is developed in PHC, despite being a clinical trial. To the best of our knowledge, to date there are no studies

carried out with post-COVID-19 patients that evaluate a similar intervention with a clinical trial methodology. We will use the difference pre-post score of the short-form 36-item questionnaire (SF-36), the value of the possible highest standard deviation (SD), and a minimum expected difference of 19.3 points in the pre-post rating, which were all taken into account. Accepting a risk alpha of 0.05 and a power of 95% in a bilateral contrast, 70 subjects would be required. A maximum loss-to-follow-up rate of 10% has been estimated. The total sample required is 78 subjects, distributed between the two groups (control–intervention).

2.2.4. Patient Inclusion

When the PHC practitioner identifies a potential participant, they will fill out a referral form indicating that the patient meets the criteria and then provide the patient with an information leaflet. The health care professional will inform the researcher once the patient has confirmed their consent. The evaluating researcher will then contact the participant and confirm whether or not they will be included in the study based on the inclusion and exclusion criteria.

2.2.5. Randomisation, Allocation and Masking of Study Groups

Once baseline data have been collected, the participants will be randomised. An independent statistician will perform the individual randomisation using a computer-generated random number sequence (blinded sequence). The randomisation will be carried out using a list of patients (Figure 2). Given the nature of the interventions, participants will not be blind to their allocation. A researcher will call them to explain their assigned intervention and will request that participants do not inform other researchers of their allocation.

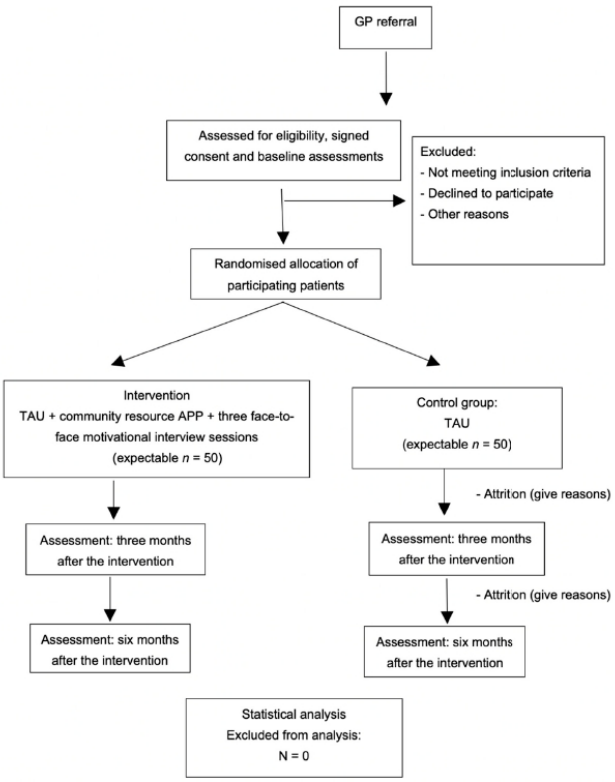

Figure 2. Flowchart of the study: randomisation, sampling, and monitoring of patients.

2.2.6. Intervention

1st Recommended treatment (TAU) prescribed by health care professionals in accordance with NICE Guidelines and CAMFiC's Manifestaciones persistentes de la COVID-19: Guía de práctica clínica [Ongoing manifestations of COVID-19: Clinical Practice Guidelines] and its subsequent updates.

2nd TAU plus the use of the APP as a community resource + three face-to-face motivational interviewing sessions to increase adherence.

The content of the APP is based on scientific evidence that aims to alleviate the symptoms of patients diagnosed with long COVID-19 [48–52]. Depending on their health status, the participants will find all the advises useful, or only those that respond to their health needs based on the persistent symptoms they present will be helpful. However, it is emphasized that, if they cannot carry out any of the recommendations or exercises, or it causes them any type of discomfort, they should stop doing them immediately. The information provided in the APP has been divided into six work areas: (1) recommendations for following the Mediterranean diet; (2) recommendations for improving the sleep quality; (3) physical exercise recommendations with visual aids (i.e., charts); (4) respiratory physiotherapy exercises supported by video tutorials; (5) cognitive stimulation exercises with different levels of difficulty and (6) use of community resources. There is an additional section on behavioral activation and evidence-based documentation on managing long COVID-19. In all these sections, self-assessments and records are provided to record their activity so that patients can graphically observe their evolution over time as they continue to use the APP.

The content and operation of each of each section is detailed below:

1. Diet

According to the Clinical Guide for Long COVID patient care of the Spanish Society of General and Family Physicians (SEMG) [49], eating habits should be taken into account to supply possible nutritional deficiencies. This APP aims to provide healthy eating pattern recommendations based mainly on the adherence to the classic Mediterranean diet. Specifically, the intake of vitamin D, vitamin B12, B complex, folic acid, and omega-3 fatty acids is recommended, according to some previous studies [53,54]. These nutrients are involved in the proper functioning of the metabolism, as well as in the immune system, so they could be beneficial for long COVID-19 patients. For the monitoring and evaluation of patients, this APP will offer a weekly evaluation based on 8 questions that will measure the patient's adherence to the Mediterranean diet, showing an evolutionary chart of it.

2. Sleep hygiene

The quality of sleep and rest are fundamental components to feel physically and psychologically well. The amount of sleep needed varies by person and age, but most adults need between 7 and 8 h of sleep each night [55–57]. Given the great negative impact that has been found in various studies regarding the quality of sleep of long COVID-19 patients, it has been considered necessary to offer sleep guidelines to sleep well and improve rest [58,59]. However, in case of serious sleep problems, it is recommended to consult with a medical professional. This APP performs a daily evaluation of the self-perception that people have about their rest through 3 questions, presenting a history chart of it.

3. Physical exercise

It has been shown that physical exercise can have benefits in multiple pathologies with which the long COVID-19 syndrome shares similarities both in its symptoms and possible pathogenic mechanisms. In this specific syndrome, the data are still insufficient, but the latest recommendations emphasize the need for personalized and symptom-adjusted physical activity to reduce long COVID-19 symptoms and promote recovery in these people [52]. Within this APP basic physical, exercises will be offered. This content was developed by a physiotherapist, and both the physical exercised and the instructions provided to the APP's user patients were based on the recommendations proposed by

different guides about the management of this disease or other pathologies with similar symptoms available in the current scientific evidence [50,51].

4. Respiratory physiotherapy

For the treatment of persistent respiratory symptoms, such as dyspnea, the different existing guidelines about the management of this disease recommend breathing exercises, that is, respiratory physiotherapy [49,51,60]. That is why a physiotherapist developed the respiratory exercises proposed in the content of this APP, based on the guidelines mentioned above. Similar to physical activity, this type of exercise must be graded and personalized to the characteristics of each patient, something that is stated in the instructions prior to carrying out these exercises.

5. Cognitive exercises

The most common cognitive impairment profile in long COVID-19 involves impaired executive function or planning, difficulty sustaining attention, decreased processing speed, deficits in short-term memory, abstraction and orientation, and even language impairment and anomie [61]. That is why an occupational therapist specialized in neurology developed three levels (i.e., easy, medium difficulty, difficult) of cognitive stimulation exercises aimed at working on all the cognitive skills that may be affected in the adult population with long COVID-19. In addition, a series of complementary voluntary activities were developed so that patients can stimulate all of the aforementioned within their activities of daily living (e.g., remembering a shopping list to stimulate memory).

6. Community resources: socialization and emotional well-being

This section, based on the effectiveness of RHA [20–23], mentioned in the introduction section, aims to improve the physical and emotional wellbeing of the participants through integration in the community, as well as socialization with peers. To achieve a good quality of life, it is not only essential to take care of our body through good habits, but also necessary to know how to live in the community (i.e., that our relationships with others are healthy). Therefore, the purpose of this section is to promote the participation in the process of local development through the use of different services, associations, or cultural activities, as well as groups affected by the same pathology.

In addition to the use of the APP, the intervention group will attend three face-to-face sessions held over three consecutive weeks with the aim of encouraging adherence to the APP, based on a motivational interview (MI). The first and second sessions will be individual, and the third will be a group session. All of them will be conducted by two study researchers with training to standardise the intervention, as well as with specific training, to carry out these sessions in accordance with Miller and Rollnick's guidelines [62]. MIs will be conducted for 20–30 min, in alignment with the health belief model, which identifies the link between treatment adherence and health behavior [63–65].

This way of working follows Miller and Rollnick's [62] definition of MI, which is "A collaborative, goal-oriented style of communication with particular attention to the language of change. It is designed to strengthen personal motivation for and commitment to a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion". Thus, MI is an interviewing method centred around the patient, which aims to evoke behavioural change by helping patients to understand and solve their problems [66]. Additionally, in the first session, the APP will be installed, and the participant will be taught how to manage and use it. The second session will be focused on sharing experiences of the first week of using the APP, addressing technological and content concerns, and setting goals they want to achieve through its use. The third session will be in groups (around 10–15 participants in each group) and will last for approximately one hour. In this last session, the benefits of using the APP and other community HAs as an adjuvant treatment will be discussed.

2.2.7. Variables and Instruments

An evaluation will be carried out at baseline with further assessments three and six months following the end of the intervention. The assessors administering the instruments will be blind to the type of treatment given to the patients. Patients will be contacted by phone at six weeks to monitor their adherence to APP recommendations and exercises in the intervention group and important changes in their health (e.g., reinfection) or treatment in both the control and intervention groups.

The main variable will be quality of life, assessed by the SF-36 Questionnaire [67], which measures eight dimensions of health: physical function, physical role, aches and pains, general health, vitality, social function, emotional role, and mental health. In addition, it incorporates a declared health progress item. The eight dimensions define two main components of health: physical summary component and mental summary component, where scores above or below 50 indicate better or worse health status, respectively, than the mean of the reference population. The items are scored on Likert-type scales ranging from 1 to 3.5 or 6 depending on the type of item. The eight scales are scored from 0 to 100, with higher scores indicating better health status. The official Spanish version of the questionnaire [68] will be used.

Secondary results: The following variables will be collected

- Socio-demographic variables: gender, age, civil status, education, household, and occupation. Roles will also be collected using the Spanish version of the Role Checklist, whose test–retest reliability, measured by weighted Kappa, is 0.74 [69,70], an inventory divided into two parts. The first part evaluates the presence of the ten main roles of people's life over time. Individuals should indicate whether they have performed each of the roles in the past (any time up to the week immediately preceding the assessment), whether they are currently being performed (on the day the checklist is completed and during the seven days prior), and if they plan to perform them in the future (any time from the following day). It is possible to mark more than one time for each role. The second part measures the value that the individual attributes to each role ("Not at all valuable", "Somewhat valuable", or "Very valuable"). People should mark the value they consider for each of ten roles, even if they have never played them or do not plan to do so in the future [71].
- Clinical variables: clinical history, contraction of COVID-19, timeline of developing Long COVID, number of residual symptoms, and their severity measured via an analogue visual scale [72], days taken on sick-leave. Residual symptoms include: gastrointestinal symptoms, loss of smell, loss of taste, blurred vision, eye problems (increased dioptre, dry eyes, conjunctivitis), tiredness or fatigue, cough, fever (over 38 °C), low-grade fever (37–38 °C), chills or shivering without fever, bruising, myalgia, headaches, sore throat, dyspnoea, chronic fatigue, dizziness, tachycardia, orthostatic hypotension, joint pain, chest pain, back pain (cervical, dorsal or lumbar), neurological symptoms (tingling, spasms, etc.), memory loss, confusion or brain fog, short attention and concentration span, loss of libido or erectile dysfunction, altered menstrual cycle, urinary symptoms (infections, overactive bladder), hair loss, and other symptoms that can be considered residual [73,74].
- Cognitive variables:
  - (a) To assess the presence of cognitive impairment, the official Spanish version of the Montreal Cognitive Assessment (MoCA) [75–77] will be used, which is a test with adequate internal consistency (Cronbach' alpha of 0.76) that assesses six cognitive domains (memory; visuospatial ability; executive function; attention, concentration or working memory; language; and temporo-spatial orientation). It is out of a total score of 30 points, and a correction of one point can be made in the case of subjects with fewer than 12 years of schooling. The cut-off point for the detection of mild cognitive impairment in its original version is 26. This test has been used to assess cognitive impairment of people with long COVID-19 [78,79].

(b) The Symbol Digit Modalities Test (SMDT) will also be used to detect dysfunction related to divided attention, visual tracking, perceptual, and motor speed and memory, both in children and adults, and with a test-retest reliability of between 0.84 and 0.93 in a sample of healthy adults. It consists of converting a series of 120 symbols of different shapes into the numbers that correspond to each one following the key provided. This must be conducted consecutively and as quickly as possible within 90 s after completing a 10-digit practical test. The total score is obtained by counting the number of correct substitutions completed out of a maximum score of 110. A score below 33 is considered a clear indicator of some type of cognitive disorder [80,81].

(c) To measure short-term memory impairment, the Spanish version of the Memory Impairment Screen (MIS) will be used. This brief test assesses the existence of memory disorders using free recall (without clues) or selective recall (with semantic clues) of four words. In dementia screening, it presents adequate interobserver (0.85) and test–retest (0.81) reliability. Two points are awarded per word obtained by free recall and one point per word recalled with the help of semantic clues. The total scores range from zero to eight, with a score of four or less indicating possible cognitive impairment [82,83].

(d) To assess whether verbal fluency is affected, the Semantic Verbal Fluency Test (Animals) (test-retest reliability of 0.68) will be used, which consists of counting the number of correct words reproduced in 1 min within the category 'Animals'. Normally, a person without impairment will be able to reproduce about 16 words in 1 min [84,85].

- Functional physical variables:

(a) Cardiorespiratory capacity will be measured by a 6 min walk test (6MWT) [86]. It is a functional cardiorespiratory test that measures the maximum distance a subject can walk for 6 min. The test measures and records baseline and post-test heart rate, oxygen saturation (SpO2), and dyspnea according to the Borg scale [87]. The 6MWT walk had good test-retest reliability ($88 < R < 94$). We will use the most recent official Spanish version [88].

(b) Leg strength and endurance will be measured by Sit to Stand Test [89]. We will use 30-s Sit to Stand Tests, which are used specifically to test for respiratory diseases [90]. The test evaluates endurance at a high power, speed, or velocity in terms of muscular or strength endurance by recording the number of times a person can stand up and sit down completely in the space of 30 s. The 30-s chair stand has good test-retest reliability ($84 < R < 92$). We will use the 30 s Sit to Stand Test that has been translated in Spanish and used for COVID-19 patients [91].

- Affective state through the Hospital Anxiety and Depression Scale (HADS) questionnaire [92]. The HADS is a scale based on self-report that was developed to detect depression and anxiety disorders in medical patients in primary care settings. The HADS includes 14 items that assess symptoms of anxiety and depression (HADS-A and HADS-D, respectively), with each item corresponding to a 4-point (zero to three) scale, with scores ranging from 0 to 21 for symptoms of both anxiety and depression, with higher scores indicating more severe symptoms. The HADS has been translated into a number of languages, including Spanish [93], to facilitate its use in international trials [94].
- Sleep quality through the Insomnia Severity Index (ISI). The ISI [95] works through self-reporting and measures a patient's perception of nocturnal and diurnal symptoms of insomnia: difficulties initiating sleep, staying asleep, early morning awakening, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to sleep deprivation, and degree of distress or concern caused by sleep deprivation. This scale has seven items, with each answer ranging from zero to four, and an overall score ranging from 0 to 28, with a higher score

indicating a higher severity of insomnia. The Spanish version of the ISI [96] shows an adequate internal consistency (Cronbach alpha = 0.82). It has also been used in other studies of people with long COVID-19 [97].

Social support will be measured by the Medical Outcomes Study Social Support Survey (MOS-SS) [98]. It is a self-report instrument consisting of four subscales (emotional/informational, tangible, affectionate, and positive social interaction) and an overall functional social support index. It has good reliability (Cronbach's alpha $\geq$ 0.91) and is quite stable over time. It has 19 items, as well as a 5-point Likert Scale. Higher scores indicate more support. We will use the official Spanish version [99]. Community social support will also be assessed using the Perceived Community Support Questionnaire (PCSQ) [100], which provides information on social resources as perceived by the members of the community. It consists of 25 questions assessing four aspects: community integration, community participation, social support from informal systems, and social support from formal systems. It is a Likert-type questionnaire with a scale of one to five. The authors have identified the reliability of the different scales to range between 0.75 and 0.88, which was assessed using the Cronbach's alpha coefficient [100,101]. In previous research, it has been found to provide an adequate assessment of community experiences of both adults and young people [102].

- Physical activity will be measured using the International Physical Activity Questionnaire-Short Form (IPAQ-SF) [103]. It assesses the levels of habitual physical activity over the preceding seven days. It has seven items and records activity at four levels of intensity: vigorous-intensity activity and moderate-intensity activity (walking and sitting). We will use the official Spanish version [104]. IPAQ-SF has sufficient validity for the measurement of total and vigorous physical activity and poor validity for moderate activity and good reliability [105].
- Adherence to a Mediterranean diet will be measured using the 14-item Mediterranean Diet Adherence Screener (MEDAS), encouraging compliance to a Mediterranean diet [106]. It includes items on food consumption and intake habits. The total score ranges from 0 to 14, with a higher score indicating greater adherence to the Mediterranean diet [107].
- Personal constructs. The personal factors relating to behaviour that will be collected are the following:
  - (a) Self-efficacy will be measured using the Self-Efficacy Scale-12 [108]. The original scale consisted of 17 items that are scored on a 5-point Likert scale. Woodruff and Cashman [109] obtained a factor structure, based on the original 17-item scale, that represented the three aspects underlying the scale, i.e., willingness to initiate behavior, 'Initiative', willingness to expend effort in completing the behavior, 'Effort', and persistence in the face of adversity, 'Persistence'. Five items were excluded because of low item-rest correlations and ambiguous wording, resulting in a 12-item version of the scale (GSES-12). This scale has 3 factors: Initiative (willingness to initiate behavior), Effort (willingness to make an effort to complete the behavior), and Persistence (persevering to complete the task in the face of adversity). Internal consistency of the original scale was 0.64 for initiative, 0.63 for effort, and 0.64 for persistence. The total scale obtained a Cronbach's Alpha coefficient of 0.69 [110].
  - (b) Patient activation in their own health will be measured using the Patient Activation Measure (PAM) questionnaire with regard to the management of their health [111]. It evaluates the patient's perceived knowledge, skills, and confidence to engage in self-management activities through 13 items with a Likert Scale from one (strongly disagree) to four (strongly agree). The resulting score ranges between 13 and 52. Higher scores indicate higher levels of activation. There is only an official Spanish version for chronically ill patients. It has an item separation index for the parameters of 6.64 and a reliability of 0.98 [112].

(c) Health literacy will be measured using the Health Literacy Europe Questionnaire (HLS-EUQ16) [113]. Health literacy is defined as the knowledge of the population, their motivation, and their individual ability to understand and make decisions related to the promotion and maintenance of their health. The questionnaire consists of 16 items, scored between 1 (very easy) and 4 (very difficult). The score of each subject was obtained as the sum of the scores of the 16 items. The final score can be transformed into a dichotomous response: very difficult and difficult = 0, as well as easy and very easy = 1. Higher scores indicate worse health literacy. It presents a high consistency (Cronbach's alpha of 0.982) in the official Spanish version [114].

- For the analysis of the cost-efficiency, the Client Service Receipt Inventory will be used [115], collecting information on the entire range of services and support used by study participants. It retrospectively collects data on the use of services over the preceding six months (e.g., rates of use of individual services, mean intensity of service use, rates of accommodation use over time). We will use the official Spanish version [116].

2.2.8. Statistical Analysis

Analysis of the outcomes at baseline consist of the following measures. First, descriptive analysis of all of the variables (frequencies for categorical variables; means and standard deviation for continuous variables) will be carried out. A univariate analysis (one-way ANOVA and chi-square) will be used to examine the data and test whether there are baseline differences between groups after randomisation.

Statistical analyses will be chosen based on the sub-sample size (parametric or non-parametric tests). Data collection and statistical analyses will be performed using Excel software, SPSS software (version 25.0) [117], and the R statistical software environment (version 3.6.2) [118].

Clinical effectiveness analysis: The report of the results will follow a pre-specified plan based on CONSORT guidelines [119] in order to compare the two groups. Initially, a descriptive comparison (proportions, means, or medians) will be carried out between groups for prognostic variables in order to establish their baseline comparability after randomisation. To analyse the clinical effectiveness, a repeated-measure linear regression will be conducted, including all evaluations over time. For this purpose, the main variable, SF-36 score, will be used as a continuous variable. The models will include adjustments for the baseline value of the SF-36 and for any other variable that would show differences in the baseline measurement. Possible group per time interactions will be examined using linear regression. Similar analyses will be carried out using the secondary outcomes (number and severity of persistent symptoms, Montreal Cognitive Assessment, Sit-to-Stand Test, and HAD test). To counteract the problem of multiple comparisons we will use Bonferroni correction.

Cost-efficiency and cost-utility analysis are as follows. The effectiveness of the interventions will be estimated using the difference between the SF-36 score at the baseline and at the three and six-month follow-up, and the utility will be estimated using QALYs at the three and six-month follow-up. QALYs will be calculated based on these scores using the Spanish EQ-5D tariffs [120]. Along with the number and severity of the ongoing symptoms, scores will also be used as an outcome for the analysis. Cost-efficiency will be explored through the calculation of incremental cost-efficiency ratios (ICERs) for the intervention group using the TAU group as the control. ICER is defined as the ratio between incremental costs and incremental effectiveness. In the same way, cost utility will be explored through the calculation of incremental cost-utility ratios (ICURs), which are defined as the ratio between incremental costs and incremental utilities measured on QALYs. QALYs gained in each evaluation are approximated by using the area under-the-curve technique [121]. Total costs will be calculated by adding direct and indirect costs. Direct costs will be calculated by adding the costs derived from the medication and the use of health services

and clinical tests. The medication costs will be calculated by determining the price per milligram during the study period according to the Vademecum during the last year of the study, including value-added tax (VAT). The total cost of drug treatment will be calculated by multiplying the price per milligram by the daily dose in milligrams and the number of days the treatment is received. Costs derived from the use of health services will be calculated considering the data from the Oblikue database [122]. Indirect costs will be calculated based on the number of days taken on sick-leave and multiplying them by the Spanish minimum daily wage during the study period 2019–2020. We assume that data will be missing at random (MAR). Only patients with both cost and relevant outcome data at three and six-month follow-up will be included in the cost-efficiency and cost-utility analyses. Notwithstanding, sensitivity analysis imputing missing three and six-month data will test the robustness of the cost-efficiency and cost-utility results. The imputations will be performed using the package "mice" [123], freely available in cran-R [118].

Variables collected, instruments, and measures are shown in Table 1.

Table 1. Study variables.

Instruments	Assessment Areas
Gender, ages, civil status, education, household, occupation. Role Checklist [71]	Socio-demographic variables
Clinical history, contraction of COVID-19, timeline of developing Long COVID, number of residual symptoms and their severity (EVA), days taken on sick-leave [73,74]	Clinical variables
SF-36 [68,124]	Quality of life
Montreal Cognitive Assessment [75–77] The Symbol Digit Modalities Test (SMDT) [80,81] Memory Impairment Screen (MIS) [82,83] Semantic Verbal Fluency Test (Animals) [84,85]	Cognitive variables
6 min walk test (6MWT) [86] Sit to Stand Test 30 sg [89]	Functional physical variables
HADS [92]	Affective state
Insomnia Severity Index (ISI) [95]	Sleep Quality
Medical Outcomes Study Social Support Survey (MOS-SS) [98] Perceived Community Support Questionnaire [125]	Social Support
International Physical Activity Questionnaire-Short Form (IPAQ-SF) [103]	Physical Activity
14-item Mediterranean Diet Adherence Screener (MEDAS) [106]	Adherence to a Mediterranean diet
Self-Efficacy Scale [108] Patient Activation Measure Questionnaire (PAM) [111] Health Literacy Europe Questionnaire (HLS-EUQ16) [113]	Personal constructs
Client Service Receipt Inventory [115]	Social and health services used

2.2.9. Ethical Considerations

Ethical approval was granted by the Clinical Research Ethics Committee of Aragón (PI21/139 and PI21/454). The procedures carried out for the creation of this work complied with the ethical standards of the previously mentioned committee and with the 1975 Declaration of Helsinki. All of the subjects will sign a comprehensive consent form, their data will be anonymised, and will only be used for the purposes of the study. Participants and health care professionals will be informed of the results. Patients of the TAU

group will be invited to use the APP at the end of the study. The ethics committee will be notified of any protocol modifications.

3. Results

The initial development of the ReCoVery APP has been completed at the design and architecture level. The therapeutic content (videos, information, and other types of media) has been uploaded to the APP, allowing for a fully functional version. Regarding the APP's validation, effectiveness, and cost-efficiency study, we are now completing the recruitment phase. To date, 60 patients have participated in the study, being assessed and randomized.

4. Discussion

COVID-19 has severely impacted the global population, especially long COVID-19 patients. It is estimated that the worldwide prevalence of this syndrome approaches 10% [126]. The treatment and care of these patients have become a social responsibility, which should be addressed by future research. Additionally, given the health and symptoms experienced by those suffering from long COVID-19, TR is considered a potentially useful tool for the rehabilitation of these patients [127]. This is a global health issue and, therefore, a shared global response is necessary.

To the best of our knowledge, no randomized clinical trials have been performed using TR on Long COVID patients. However, effective studies based on respiratory, physical, or cognitive TR with other groups of patients support the potential viability of this study. As for respiratory TR, two bibliographic reviews of controlled trials of TR for the provision of pulmonary rehabilitation have concluded that TR may be as effective as face-to-face pulmonary/respiratory rehabilitation in individuals suffering from chronic respiratory diseases [128,129]. However, a randomized controlled trial by Cox et al. (2022) concluded that respiratory TR may not be as effective as pulmonary rehabilitation, but it is safe for patients and would have clinically significant benefits [130]. More similar to long COVID-19 patients, a pilot study by González-Gerez et al. (2021) verified that respiratory TR is effective, safe, and feasible for COVID-19 patients having mild-moderate symptoms in the initial stage [131]. Furthermore, the study by Liu et al. (2020) associated respiratory rehabilitation with an improved quality of life in patients infected with COVID-19 [132]. Similarly, the benefits of TR based on physical activity may become comparable with conventional face-to-face rehabilitation approaches while also producing less interference in the patient's daily life [133]. In this line, the study by Nambi et al. (2021) identified significant improvements in the physical component of the low-intensity aerobic activity group in COVID-19 patients [134]. Additionally, a pilot study by Abodonya et al. (2021) verified a significant improvement in the quality of life of COVID-19 patients who underwent a TR intervention based on physical activity [135]. In addition, prior evidence verifies that TR based on physical exercises may improve the quality of life of groups of patients, such as those suffering from multiple sclerosis [136,137]. Finally, a systematic review has verified that cognitive TR produces benefits in various cognitive domains, such as verbal fluency and executive functions [138].

Various studies, however, have revealed that early rehabilitation interventions are essential for post-COVID patients to avoid progressive deterioration before the symptoms become chronic [139]. Therefore, in addition to physical, respiratory, and cognitive interventions, this study has also included healthy lifestyle habits (adherence to the Mediterranean diet, sleep hygiene, and RHA), following the existing clinical guidelines for long COVID-19 patients in order to improve the quality of life of these patients.

This project has strengths and limitations. The strengths of this study include the design of a qualitative needs assessment and the co-creation of a community-based TR resource that can be widely used. It will provide a wealth of information on the interplay between the quality of life of people with long COVID, ongoing symptoms, and personal factors on health behaviour. Study limitations include the possible attrition of participants due to reinfections leading to health deterioration or seeking other health care resources

during the course of the study. However, possible reasons for attrition and other issues will be recorded.

5. Conclusions

Although the research and care of these patients is still in its early stages, there is a need to equip patients and healthcare professionals with tools to help them in their recovery. In this line, it is worth highlighting the role of PHC and community nursing, turning out to be professional mediators between general practitioners and the community. Through this complementary work, it is intended to access comprehensive health care, obtain the acquisition of habits, capacities, and behaviors that promote self-care.

Funding: This work is supported by Carlos III Health Institute, grant number PI21/01356, FEDER Funds 'Another way to make Europe'. The funding body will conduct an audit trial once a year.

Institutional Review Board Statement: Ethical approval was granted by the Clinical Research Ethics Committee of Aragón (PI21/139 and PI21/454). The procedures carried out for the creation of this work complied with the ethical standards of the previously mentioned committee and with the 1975 Declaration of Helsinki. Clinical Trial Registration: ISRCTN registry ISRCTN91104012.

Informed Consent Statement: Informed consent will be obtained from all subjects involved in the study.

Acknowledgments: This is a short text to acknowledge the contributions of specific colleagues, institutions, or agencies that aided the efforts of the authors. The authors thank the Network for Research on Chronicity, Primary Care, and Health Promotion (RICAPPS, code RD21/0016/0001-Health Institute Carlos III, Spain), the Primary Health Care Research Group of Aragon (GAIAP-B21-17R) of the Department of Science, the University and Knowledge Society of the Aragon (Spain) government, and FEDER Funds 'Another way to make Europe'.

Conflicts of Interest: The authors declare no conflict of interest.

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Manuscrito II. Effectiveness of telerehabilitation intervention using ReCOVery APP of long COVID patients: a randomized, 3-month follow-up clinical trial.

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Effectiveness of a telerehabilitation intervention using ReCOVery APP of long COVID patients: a randomized, 3-month follow-up clinical trial

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The main objective of this study is to analyze the clinical efficacy of telerehabilitation in the recovery of Long COVID patients through ReCOVery APP for 3 months, administered in the Primary Health Care context. The second objective is to identify significant models associated with an improvement in the study variables. An open-label randomized clinical trial was conducted using two parallel groups of a total of 100 Long COVID patients. The first group follows the treatment as usual methods established by their general practitioner (control group) and the second follows the same methods and also uses ReCOVery APP (intervention group). After the intervention, no significant differences were found in favour of the group intervention. Regarding adherence, 25% of the participants made significant use of the APP. Linear regression model establishes that the time of use of ReCOVery APP predicts an improvement in physical function (b = 0.001; *p* = 0.005) and community social support (b = 0.004; *p* = 0.021). In addition, an increase in self-efficacy and health literacy also contribute to improving cognitive function (b = 0.346; *p* = 0.001) and reducing the number of symptoms (b = 0.226; *p* = 0.002), respectively. In conclusion, the significant use of ReCOVery APP can contribute to the recovery of Long COVID patients.
Trial Registration No.: ISRCTN91104012.

According to the World Health Organization (WHO)[1], approximately 145 million people across the globe have been affected by Long COVID symptoms during the first 2 years of the pandemic. In the WHO's European region, approximately 17 million people have been affected by this pathology, representing some 16% of the 102.4 million people infected by COVID-19 in this region and time period.

Given these data, the National Institute of Statistics has estimated that approximately 10–20% of infected people developed persistent symptoms more than twelve weeks following infection[2]. In 2020, and as a basis for future research, the UK's National Institute for Health and Care Excellence (NICE) distinguished between symptoms that continue four to twelve weeks after infection (ongoing symptomatic post-COVID-19, except for the loss of smell and taste) and those that persist for longer than twelve weeks (scientifically referred to as Long COVID)[3]. In October 2021, the WHO defined this new pathology as symptoms of a probable or confirmed SARS-CoV-2 infection that extend or develop 3 months after the initial infection, and that cannot be explained by an alternative diagnosis[4]. In this manuscript, this pathology is referred to as "Long COVID", a term that has been coined by the existing scientific evidence.

The underlying etiology of Long COVID, as well as its duration and degree of severity, remain limited. The study by Taquet et al.[5] showed that, although persistent symptoms tend to be common with other viral infections, they appear to be more frequent with this particular infection. Previous research had suggested a higher prevalence of this disease in women (80%) as compared to men, mainly middle-aged women (between 48 and 58 years)[6]. More than two hundred symptoms of this pathology have been recorded, which may be persistent

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or cyclical over time[7]. According to systematic reviews, some of the most prevalent symptoms are fatigue or extreme tiredness, dyspnoea, myalgia, arthralgia, headache, cough, alteration to smell and taste, brain fog, lack of attention and concentration, as well as there being effects on mental health, among others[7–9]. These prolonged symptoms are disabling and affect the patient's physical and mental health, altering their social, work, and family environment and their quality of life[10].

It has been suggested that the management of Long COVID patients should be carried out and directed by general practitioners (GP)[11]. However, recommendations for outpatient medical care for these patients remain imprecise, and as such, GPs tend to rely on comparisons with similar conditions[12]. The great variability and fluctuation of symptoms make it difficult to provide suitable treatment[11]. A previous qualitative study verified the despair felt by Long COVID patients in Spain given the lack of improvement after different rehabilitation therapies[13]. Individualized rehabilitation and a global treatment plans are required, in a holistic sense of the disease, including, among others, local treatments, such as healthy lifestyles, physical rehabilitation, respiratory physiotherapy, cognitive rehabilitation, or psychological intervention[14]. However, the lack of knowledge to address this disease, in addition to the collapse of the health system, caused by the COVID-19 pandemic, has made it difficult to offer face-to-face supervised rehabilitative care, leading to the increased use of telerehabilitation (TR) strategies[15].

A recent systematic review has verified that TR can improve dyspnea, functionality, and physical components of quality of life in COVID-19 and Long COVID patients[16]. Nevertheless, the meta-analysis by Seid et al.[17] concludes that more studies are still required to investigate the effects of TR on the quality of life of these patients. The initial studies on the effectiveness of TR for Long COVID patients began to emerge in 2021, obtaining results that were beneficial for physical and respiratory functioning or quality of life, among others[18–21], but they were observational, pilot studies or without a control group. These studies would serve as support for future large-scale investigations. It was in 2022 when the first clinical trials on TR for LONG COVID patients began to be published. The study by Li et al.[22], with two parallel groups of one hundred and twenty previously hospitalized for COVID-19 with persistent dyspnea, designed a TR mobile application (APP), and improvements in physical performance were obtained in favor of the intervention group. Similarly, the study by Pehlivan et al.[23] with thirty-four post-hospitalized COVID-19 patients, achieved significant improvements in dyspnea and physical functioning through TR. More recently, the study by Hajibashi et al.[24] offered pulmonary TR combined with muscle relaxation for six weeks in post-hospitalized patients with COVID-19. Their results showed significant improvements for sleep quality or anxiety, but not for dyspnea or other variables related to physical functioning[24]. Finally, a 14-day TR program (strength and breathing exercises) carried out in Spain has proven effective in improving post-COVID-19 physical and respiratory function[25] . All these studies suggest that TR may be a good option for the recovery of Long COVID patients. However, there seems to be controversy, given that some of them have included patients infected with COVID-19 less than 3 months ago, and cannot be considered Long COVID patients according to the previously mentioned WHO definition. In addition, the long-term effects of these types of interventions are unknown. For these reasons, it is still necessary to gain a better understanding of the TR treatments and rehabilitative processes that contribute to an individual's recovery from Long COVID.

Due to all of the above, due to the increasing use of TR programs, the lack of treatment for these patients and the experimental studies carried out in other territories, it has been considered opportune to design and create a mobile APP called ReCOVery that serves as a TR for Long COVID patients. This APP is based on clinical guidelines for the management of patients with Long COVID and the needs identified by affected patients. ReCOVery has content that rehabilitates in order to improve the quality of life and strengthen the personal constructs (health literacy, activation and self-efficacy) of these patients, through their own rehabilitation and empowerment.

Hence, the main objective is to analyze the clinical efficacy of a TR through the ReCOVery APP, as compared to Treatment as Usual (TAU) for 3 months, administered in the Primary Health Care (PHC) context, as adjuvant treatment for individuals diagnosed with Long COVID. The second objective is to identify significant models associated with an improvement in the study variables.

Methodology

Study design. This study is an open-label randomized clinical trial (RCT) using two parallel groups of Long COVID patients. The first group follows the TAU methods established by the primary health care GP (control group) and the second follows the TAU methods and also uses the APP ReCOVery, as a coadjutant treatment in their recovery (intervention group). In addition, the intervention group attend three face-to-face sessions based on motivational methodology and APP management, with the aim of promoting adherence to the APP. Table 1 below shows the checklist for the description and replication of interventions (TIDieR).

This RCT was registered in the ISRCTN Registry platform (Registry No.: ISRCTN91104012) on 10/02/2022. The original study protocol specifies multiple methodological aspects and has recently been published[26].

Recruitment of participants. The purposive sampling method was used to invite individuals to participate in the study. Potential study participants were PHC patients from the territory of Aragón (Spain), as well as interested parties from the "Long COVID Aragón" association for those affected, who were redirected to their GPs. When the GPs identified potential participants, they were provided with an information document and a form to verify that they met the criteria. Once the informed consent of the patient was obtained, the GPs notified the investigator so that he could contact the interested participants, subsequently reconfirming their inclusion or not according to the established criteria. Therefore, the settings in which the recruitment of potential participants was carried out were PHC offices.

The study population consisted of Long COVID patients (with a positive COVID-19 diagnostic test for longer than the previous twelve weeks and persistent symptoms) and adults (18 years or older). The exclusion

1. Brief name
Effectiveness of a telerehabilitation intervention using ReCOVery APP of Long COVID patients: A randomized, 3-month follow-up clinical trial
2. Why
Long COVID patients are suffering a great impact on their quality of life. However, the etiology of this pathology is still unknown. Different telerehabilitation strategies are being implemented to combat the varied and fluctuating symptoms. Hence, the main objective of this study is to analyze the efficacy of the ReCOVery mobile application over a period of 3 months. A second objective is to identify significant patterns associated with improvement
3. What (materials)
ReCOVery is a mobile application designed for this study and intended to offer rehabilitation treatment that improves the quality of life of Long COVID patients. Thus, the application was installed only on the personal devices of the participants in the intervention group
4. What (procedures)
First, the baseline assessments were performed face-to-face. Secondly, after randomization, the participants of the intervention group were summoned to three face-to-face sessions, the first two individual and the third group. From the first session until the next evaluation, the participants of the intervention group will have access to ReCOVery. Finally, after twelve weeks, all the participants are summoned again for a second evaluation
5. Who provided
A multidisciplinary approach was used, involving GPs, psychologists, physiotherapists, nurses, occupational therapists and social workers. All of them presented similar previous experiences in research, presented scientific knowledge about the pathology and, the corresponding ones, were taught to complete the selected scales and carry out the necessary interventions
6. How
The vast majority of the intervention was performed electronically, using ReCOVery. However, two individual sessions and one group session were held face-to-face at the beginning of the intervention. In addition, the evaluations were also carried out face-to-face. During the intervention, a contact telephone number was offered to all participants to notify any adverse event
7. Where
This project was developed in various primary care health centers in the territory of Aragon (Spain), both the recruitment and the evaluations
8. When and How Much
The intervention and, therefore, access to the APP began in March 2022 (baseline evaluation) and was available to participants in the intervention group until June 2022 (12-week evaluation). In that period of time they had access twenty-four hours a day, so they could use it freely
9. Tailoring
From the beginning it was planned that it should be the participants themselves who self-regulate. In this way, the contents were the same for everyone, but their intensity had to be controlled by themselves
10. Modifications
No modifications occurred to the planned intervention during the course of the study
11. How well (planned)
Adherence to the intervention protocol was good, given the number of dropouts was within the estimate. The reasons for abandonment were not going to the appointment or being reinfected with COVID-19 during the intervention
12. How well (actual)
The complete scheduled intervention program was delivered to both study groups (once the intervention was completed it was offered to the control group), without any deviation from the planned protocol

Table 1. Template for intervention description and replication (TIDieR) checklist.

criteria were: not having a positive COVID-19 diagnostic test for more than the previous twelve weeks; having a diagnosis of severe uncontrolled illness; significant risk of suicide; pregnancy and lactation; participation in a clinical trial over the past 6 months; existing structured rehabilitative or psychotherapeutic treatment by health professionals and the presence of any medical, psychological or social problems that may significantly interfere with the patient's participation in the study.

Recruitment was carried out consecutively until the estimated sample size was attained. The recruitment time was 3 months, from January to March 2022. A total of 100 PHC patients from the region of Aragon (Spain) were recruited.

Sample size. To perform the estimated calculation of the necessary sample, the Spanish study by Dalbosco-Salas et al.[19] was considered. Although the study is longitudinal, it presents a similar intervention that was also carried out in the PHC setting. To the best of our knowledge, no studies have been identified that consider Long COVID patients evaluating a similar intervention using a clinical trial methodology. Therefore, the pre-post score difference of the SF-36 instrument was used, considering the value of the highest possible standard deviation (SD) and a minimum expected difference of 19.3 points for the pre-post rating. A risk of 0.05 was accepted as well as a power of 95% in a two-sided contrast, and a maximum dropout rate of 10%. The minimum required sample size was 78 subjects.

Given the demand of the potentially interested participants, the researchers agreed to accept approximately 28% more participants, in accordance with the personal and material means available at that time. Therefore, the final sample size included 100 participants, 22 more than the required sample size.

Randomization, assignment, and blinding of study groups. An independent researcher performed the individual randomization process using a computer-generated blind sequence with an alphabetically organized list of participants. Assignment to the intervention or control group was not blind, given the nature of the study. This researcher called each participant to confirm the assigned intervention and requested that they did not inform third parties of their assignment.

Participants in the control group were asked to continue with their current routines (complementary with exclusion criteria) and refrain from beginning any rehabilitation or similar activities that could affect this process. The intervention group was summoned in person and individually, and were asked to bring their personal mobile device with a charger to proceed with the installation of the APP and the start of the intervention.

Development and evaluation of the APP and interventions. All participants continued with their TAU and were overseen by their PHC professionals and other medical specialists.

Participants assigned to the intervention group had access to the APP with rehabilitative content and attended three sessions on motivational methodology, APP management, and strengthening of their personal constructs (health literacy, self-efficacy, and personal activation). Two individual sessions and one group session were held over three consecutive weeks, after completing the baseline assessments and randomization process. The sessions were based on the motivational guide by Miller and Rollnick[27], which intended to promote adherence to the APP. The individual sessions were guided by a clinical psychologist and lasted 20–30 min, during which the APP was installed and doubts regarding its use and management were resolved. It is important to consider that during the intervention ReCOVery APP was private, so that only the participants assigned to the intervention group had access to it from their personal phones, thus preventing possible leaks to the control group. The group sessions were held with a minimum of eight and a maximum of twelve participants and did not exceed one hour per session. These sessions were led by two clinical psychologists. All participants completed the sessions during the same weeks, with individual sessions being a prerequisite for group session attendance in the third week.

As for the ReCOVery APP architecture, a native APP was created with Java language, using the Android Studio platform. The design of a native APP was chosen, as opposed to a hybrid one, in order to make use of the device's own tools, such as notifications. This allowed the APP to remain updated. A human-centered design was selected. This technique aims to solve problems and needs by understanding the users themselves. Thus, the initial ReCOVery design was guided by symptoms, identified needs, and other information obtained through individual qualitative interviews and focus group discussions with patients diagnosed with long-term COVID-19[13]. Subsequently, the available scientific evidence was compiled using health recommendations and recovery exercises for patients with Long COVID. Different work subgroups were created in the multidisciplinary team to design and create content for each rehabilitation area. ReCOVery consists of six main modules, which need to be graduated and customized according to the specific needs and characteristics of each patient, as indicated in the previous instructions, thereby avoiding irreversible damage.

All of the details on the creation process, contents, and bibliographical references for the ReCOVery APP are detailed in the protocol article of this study[26].

The main modules of the APP are:

1. Recommendations for adherence to the Mediterranean diet. Among others, it is recommended that potential nutritional deficiencies in vitamin D, vitamin B12, complex B, folic acid, and omega-3 fatty acids be supplied.
2. Recommendations to improve the quality of sleep and rest. The need to attain an average of 7 to 8 h of sleep each night is encouraged to ensure sufficient rest.
3. Physical exercise recommendations with graphic representations. The contents and instructions in this section were based on guidelines for the management of this disease or other pathologies with similar symptoms.
4. Respiratory physiotherapy exercises with video tutorial support.
5. Cognitive stimulation exercises with different difficulty levels. Three levels of cognitive stimulation exercises are provided, which are aimed at working on cognitive skills focused on executive function, difficulty maintaining attention, decreased processing speed, verbal fluency, and short-term memory deficits.
6. Participation in community resources. The aim is to promote participation in the local development process through different services, associations, or cultural activities, as well as groups affected by the same pathology.

Follow-up of the intervention and adverse events. This was a remote and uncontrolled intervention. However, a follow-up call was made six weeks after the start of the intervention, that is, halfway through the process.

Prior to the start of the intervention, the researchers established the following adverse events: reinfection with COVID-19, use of emergency medical services, hospitalization or surgical interventions, or any other circumstance that could disrupt the intervention. In addition, all participants were provided with a telephone number to report any adverse events occurring throughout the study, either by phone call or text message. Participants were also asked about the occurrence of adverse events during the follow-up call and the second assessment. During the intervention, it was not necessary to assess adverse events other than those mentioned above. Two independent researchers, blind to the group assignment, assessed all reported adverse events (re-infections). Any disagreements were resolved through the participation of a third researcher.

Main variable and measure. A total of two measurements were taken 3 months apart. These evaluations were carried out in person at a PHC Center in the participant's city in order for them to be evaluated individually. The evaluations were carried out by two independent researchers with past experience in similar projects and actions. However, both researchers were instructed to evaluate using theoretical and practical sessions, avoiding

biases in the process. A baseline evaluation (T0) was carried out prior to the start of the intervention, and a second effectiveness evaluation (T1) was carried out 3 months after the end of the first evaluation. Both evaluations were conducted over a period of two consecutive weeks. In addition, in the future, a new evaluation, which is not included in this article, will be made 6 months from the start of the intervention (T2).

The main variable is quality of life, which was assessed using the Short Form-36 Health Survey Questionnaire (SF-36)[28]. This questionnaire measures eight dimensions of health (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and emotional wellbeing), which are grouped into two main components: physical health and mental health. Items are scored on five or six Likert scales ranging from one to three points, depending on the item type. The eight scales are scored from zero to one hundred, with scores above or below fifty indicating a better or worse health status, respectively. The Cronbach's alpha obtained in this study was 0.84.

Secondary variables. As for the secondary study variables, an ad hoc questionnaire was designed for the sociodemographic, clinical, and use of ReCOVery APP variables. In addition, a total of 10 validated scales were selected to further examine the Long COVID patient profiles. In all cases, validated Spanish adaptations of the original scale were used.

- The following sociodemographic variables were studied: gender (man, woman, other), age, civil status (married or in a couple/single, separated, divorced, or widowed), education (no studies or primary studies/secondary or university studies), and occupation (employee, unemployed, employee with temporary work disability (TWD), retired, others).
- The clinical variables related to post-COVID-19 that were studied were time since infection (months) and the number of self-reported persistent symptoms at the time of each evaluation, using a list of thirty persistent symptoms typical of Long COVID patients according to past literature[7–9,29].
- The use of ReCOVery APP variables were: time of APP use during the 3 months, expressed in minutes. As for adherence to the APP, significant use was estimated as being fifteen minutes a day, for five days a week, for twelve weeks (one thousand two hundred minutes or more).
- Cognitive domains, such as memory, attention, language, or working memory, were assessed using the Montreal Cognitive Assessment (MoCA) questionnaire[30]. This has a total score of thirty points with the cut-off point for the detection of mild cognitive impairment being less than twenty-six points. The Cronbach's alpha obtained in this study was 0.457.
- The physical functioning variable was measured using the thirty-second Sit-to-Stand Test[31]. This test assesses endurance at high power as well as speed in terms of muscular endurance or strength and records the number of times an individual can stand up and sit down completely. It has good test–retest reliability ($0.84 < R < 0.92$).
- Affective status, in relation to depression and anxiety disorders, was measured with the Hospital Anxiety and Depression Scale (HADS) questionnaire[32]. The HADS contains fourteen items, each of which corresponds to a four-point Likert-type scale (zero to three), with scores ranging from zero to forty-one for its total score. Higher scores indicate more severe symptoms. The Cronbach's alpha obtained in this study was 0.91.
- Sleep quality was measured using the Insomnia Severity Index (ISI) questionnaire[33]. This self-report scale has seven items, with each response ranging from zero to four, and an overall score ranging from zero to twenty-eight, with a higher score indicating a greater severity of insomnia. The Cronbach's alpha obtained in this study was 0.86.
- Social Support was measured using the Medical Outcomes Study Social Support Survey (MOS-SS) questionnaire[34]. This is a self-report instrument consisting of four subscales (emotional/informational, tangible, affectionate, and positive social interaction) and an overall functional social support index. It has nineteen items and uses a five-point Likert scale. Higher scores indicate more support. The Cronbach's alpha obtained in this study was 0.94.
- Community social support was measured using the Perceived Community Support Questionnaire (PCSQ)[35]. This consists of twenty-five Likert-type items with a scale from one to five evaluating: community integration, community participation, social support of informal systems, and social support of formal systems. Higher scores suggest more community social support. The Cronbach's alpha obtained in this study was 0.49.
- Regular physical activity levels were measured using the International Physical Activity Questionnaire-Short Form (IPAQ-SF)[36]. This has seven items and records activity at four intensity levels. The number of minutes walked score was used in the analysis of this study.
- The following personal factors related to behavior were collected:

  (a) Self-efficacy, measured with the Self-Efficacy Scale-12 (GSES-12)[37]. This scale contains twelve items with a Likert scale from one to five. The resulting score ranges between twelve and sixty. Higher scores indicate greater self-efficacy. The Cronbach's alpha obtained in this study was 0.76.
  (b) Patient activation in their own health was measured using the Patient Activation Measure (PAM) questionnaire regarding the management of their health[38]. This questionnaire contains thirteen items with a Likert scale from one (strongly disagree) to four (strongly agree). The resulting score ranges between thirteen and fifty-two. Higher scores indicate better activation. The Cronbach's alpha obtained in this study was 0.87.
  (c) Health literacy was measured using the Health Literacy Europe Questionnaire (HLS-EUQ16)[39]. This questionnaire contains sixteen items, ranging from 1 to 4. The resulting score ranges between sixteen and sixty-four. Higher scores indicate poorer health literacy. The Cronbach's alpha obtained in this study was 0.87.

Statistical analysis. Firstly, a descriptive analysis of all of the variables was carried out, using frequencies and percentages for categorical variables and means and standard deviation for continuous variables. A between-groups comparison was developed after randomization according to the study variables, with chi-square being used for categorical variables and Student T for continuous variables.

To analyze the APP's effectiveness, a per-protocol analysis was performed, comparing baseline, 3 months, and the 3-month-baseline differences between both groups using Student T. To analyze the variables associated with effectiveness, a linear regression was performed considering the difference in the score at 3 months and at baseline for each of the variables as the dependent variable. The independent variables of age, gender, minutes of APP use, increase in self-efficacy, health literacy, and patient activation were introduced into the model.

Ethical questions. Ethical approval was granted by the Clinical Research Ethics Committee of Aragon (PI21/454). The procedures followed during the creation of this work complied with the ethical standards of the previously mentioned committee and with the Declaration of Helsinki of 1975. All of the subjects signed an informed consent form. Their data were anonymized and will only be used for study purposes. The ethics committee will be notified of any relevant modifications.

Ethical approval and consent to participate. This study received the approval of the Ethics Committee for Clinical Research of Aragon, Spain. All procedures were carried out in accordance with the ethical standards of this Committee. Written informed consent was obtained from all study participants.

Results

Initially, a total of 182 participants were evaluated for eligibility, of which 82 (45.05%) did not participate. As reflected in Fig. 1, 72 participants did not meet the inclusion criteria and 10 did not participate due to a lack of interest. Ultimately, 100 participants were included and randomized, 52 in the intervention group and 48 in the control group. The 3-month evaluation was completed by 87 participants, 45 of which belonged to the intervention group and 42 to the control group. A total of 13 participants were excluded from the 3-month analyses, 4 due to reinfection and 9 for their failure to attend a face-to-face session or the evaluation session.

Firstly, as seen in Table 1, the descriptive analysis revealed that of the 100 participants, 80 were female and 20 were male. The participants had a mean of 16.47 (SD: 5.99) persistent symptoms, low quality of life (both physical and mental health) and low physical and mental functioning (reflected in the scores from the MoCa and Sit-to-Stand Test), and high scores on depression and anxiety, social support, and self-efficacy perception. In Table 2, a comparison between the intervention and control groups is also shown. This analysis subsequently revealed no significant differences between groups.

As seen in Table 3, the analysis comparing the pre-intervention and 3-month post-intervention data, and considering the raw scores of both groups, a significant decrease was found in the number of persistent symptoms, with there being less in the control group (p-value: 0.09; CI: −0.44–5.41). There were no differences between groups for the other variables.

Upon analyzing the APP use in the intervention group, the range of use during the 3 months oscillated between 10.95 min and 5,764.81 min. The mean amount of use was 835.52 min (SD: 1090.57) during the 3 months. Only 17 participants (25%) from the intervention group engaged in significant use of the APP (with significant use being considered as being at least 15 min per day, for 5 days per week, for 12 weeks). This data suggests a poor adherence to the mobile APP.

As for the variables associated with an improvement in the analyzed variables, the multivariate models revealed that there were no significant models related to the effectiveness in the quality of life (SF-36 physical and mental health), affective state, sleep quality, and social support. However, significant models did show a decrease in the number of persistent symptoms, and an improvement in cognitive functioning (MoCA), physical functioning (Sit-to-Stand Test), and Community social support (PCSQ). As Table 4 shows, the decrease in persistent symptoms was predicted by an increase in health literacy, explaining 19.2% of the variance. The improvement in cognitive functioning was predicted by an increase in the self-efficacy construct, which explains 36.5% of the variance. The improvement in physical functioning was predicted by the minutes of APP use and being a man. This model explains 28.7% of the variance. Finally, improvement in community social support was predicted by the minutes of APP use and an increase in health literacy. This model explains 19.8% of the variance.

Discussion

The findings of this study indicate that the use of ReCOVery APP for 3 months was not significantly more effective in producing an improvement in the quality of life of Long COVID patients. Mostly, the participants did not significantly use the APP nor allowed it to be an effective tool. However, linear regressions model identified significant models of improvement predicted by time of ReCOVery APP use, increased self-efficacy, increased health literacy, and male gender. These evidences with adequate adherence could achieve significant improvements and encourage new management guidelines based on this evidence.

Our effectiveness analyses revealed more improvement in the intervention group in terms of mental health (SF-36), cognitive state (MoCA), physical state (Sit-to-Stand), community social support (PCSQ), and patient activation (PAM), although without attaining significant improvement as compared to the control group. The great impact suffered by these patients suggests that different RCTs have already been implemented and have evaluated the effectiveness of a rehabilitative intervention on the quality of life of post-COVID-19 patients[40–42]. Contrary to our study, some studies did achieve significant improvements in the quality of life of COVID-19 patients. The RCT by Nambi et al.[41] identified significant improvements in the physical component of the SF-12 scale for the low-intensity versus high-intensity aerobic activity group[40]; like Liu et al.[40], finding improvements

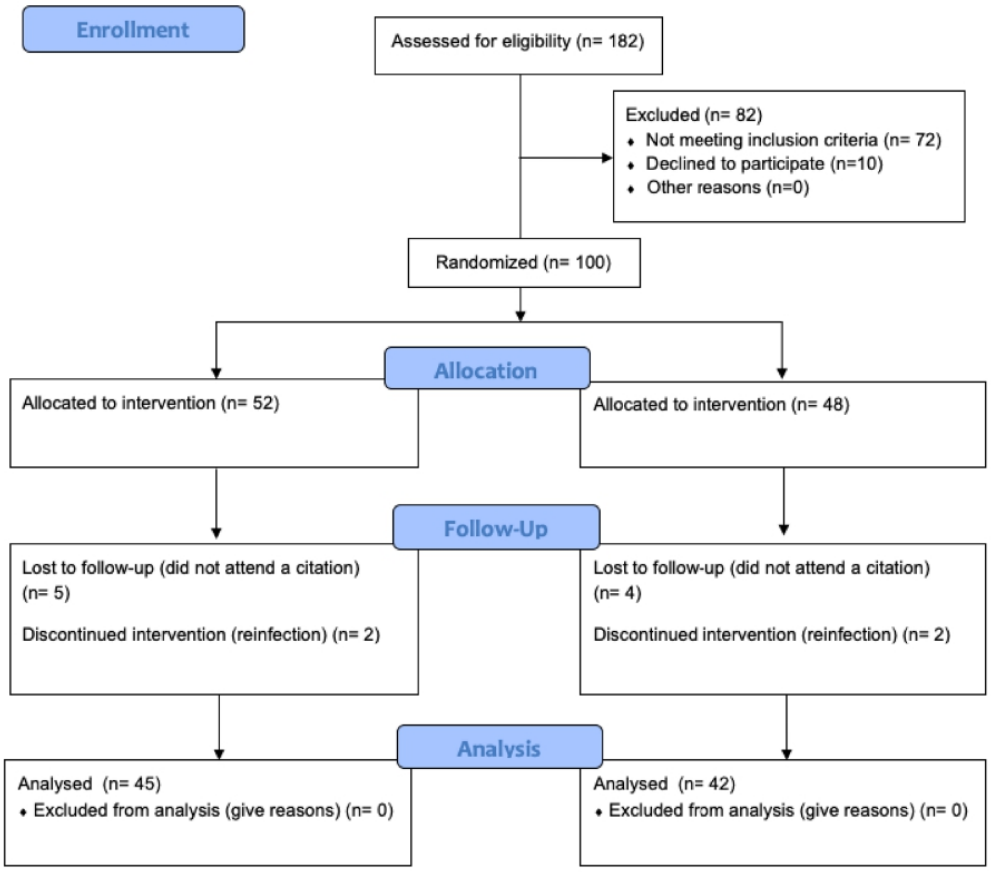

Figure 1. CONSORT Flowchart.

in all vital dimensions of the SF-36 after six weeks of respiratory rehabilitation training[41]. Moreover, the pilot study by Abodonya et al.[43], based on the effects of inspiratory muscle training for 2 weeks, verified a significant improvement in quality of life in favor of the intervention group according to the EQ-5D-3L questionnaire[42]. These studies, however, have relied upon a small number of participants[40,42] or have certain potential limitations with regard to internal validity[41]. Moreover, it is crucial to highlight that many of these RCTs, according to their inclusion criteria, were carried out with post-COVID-19 patients, but without persistent symptomatology for 3 months or more. In this way, it is necessary to differentiate and emphasize that they would not be Long COVID patients, as in our study. In this sense, Long COVID patients may present greater deterioration, given that the initial period of rehabilitation is essential[43]. In fact, depending on the patient's condition, some interventions can cause important damage[43], as seen in the RCT by Mohamed and Alawna[45], in which an intervention based on aerobic activity led to a decrease the quality of life of post-COVID-19 patients[44]. Therefore, it should be considered that the chronic symptoms of Long COVID patients may require a longer rehabilitation period, greater than twelve weeks.

Thus, TR in post-COVID-19 patients (possibly in the first weeks after infection) is feasible to improve their quality of life[45]. However, large-scale studies are still needed with patients with persistent symptoms for at least least twelve weeks after infection. In fact, a case report by Mayer et al.[47] a Long COVID patient participated in biweekly physiotherapy sessions for eight weeks, achieving improvements in some physical variables studied, but not their quality of life[46]. Regarding TR, A systematic review states that TR appears to be useful for Long COVID patients. However, this study warns that a subgroup of patients presents adverse effects (episodes of dizziness)[45]. In this same line, the study by Vieira et al.[16] suggests investigating mixed models of classic rehabilitation and TR, with face-to-face and remote elements, so that trained professionals can adjust and/or stop the activity at the most precise moments. As background to this reality, it is worth noting the study of Lau et al.[48], in which a physical training intervention was used for the recovery of patients infected by SARS-CoV in 2002. The intervention did not offer a significant improvement in the quality of life of the participants[47].

However, the non-significant improvements in this study make it necessary to consider adherence to ReCOVery APP. The adherence to the APP was low, with only 25% of the participants in the intervention group engaging in significant APP use during the twelve weeks. It is not known if APP adherence decreased over the weeks,

Variables	Total sample N = 100	Intervention group N = 52	Control group N = 48	*p*-value
*Gender (%)				
Men	20 (20%)	8 (15.4%)	12	0.230
Women	80 (80%)	44 (84.5%)	33	
Age	48.28 (9.26)	48.25 (10.36)	48.31 (8.01)	0.963
Perceived age	58.10 (14.69)	59.69 (15.02)	56.38 (14.27)	0.260
*Marital status (%)				
Married or in a couple	70 (70%)	35 (67.3%)	35 (72.9%)	0.541
Single, separated, widowed	30 (30%)	17 (32.7%)	13 (27.1%)	
*Educational level (%)				
Without studies or primary studies	9 (9%)	5 (9.6%)	4 (8.3%)	0.823
Secondary or university studies	91 (91%)	47 (94.4%)	44 (91.7%)	
*Employment (%)				
Employee	46 (46%)	20 (38.5%)	26 (54.2%)	0.350
Unemployed	5 (5%)	4 (7.7%)	1 (2.1%)	
TWD	37 (37%)	21 (40.4%)	16 (33.3%)	
Retired	9 (9%)	6 (11.5%)	3 (6.3%)	
Others	3 (3%)	1 (1.9%)	2 (4.2%)	
Time since the contagious	16.12 (6.34)	15.75 (6,56)	16.52 (6.14)	0.545
Number of persistent symptoms	16.47 (5.99)	17.50 (5.29)	15.35 (6.55)	0.074
SF-36				
SF-36 Physical health	32.19 (16.61)	29.06 (13.67)	35.58 (18.86)	0.053
SF-36 Mental health	34.77(19.31)	32.64 (17.98)	37.09 (20.59)	0.254
Montreal cognitive assessment	23.64 (3.85)	23.48 (4.20)	23.81 (3.46)	0.667
Sit-to-Stand test	10.37 (3.49)	9.87 (3.77)	10.92 (3.10)	0.131
Affective state (HADS)	17.61 (8.31)	17.86 (7.98)	17.33 (8.74)	0.752
Insomnia severity index	11.34 (6.58)	11.13 (7.21)	11.56 (5.89)	0.745
Social support (MOS-SS)	83.84 (16.33)	83.42 (16.22)	84.29 (16.61)	0.792
Community social support	82.06 (14.29)	82.33 (15.51)	81.7 (12.99)	0.846
Self-efficacy	44.66 (7.51)	44.57 (6.49)	44.75 (8.55)	0.910
Patient activation	39.82 (6.16)	38.92 (7.24)	40.79 (4.61)	0.210
Health literacy	32.10 (7.03)	32.94 (7.84)	31.18 (5.98)	0.125

Table 2. Description of sociodemographic and clinical variables and comparations of intervention-control groups. Statistics used: Mean and standard deviation except for variables with *, for which frequencies and percentages have been used. For comparation, T student except form variables with *, for which chi-squared has been used. *TWD* Temporary work disability, *HADS* Hospital anxiety and depression scale, *MOS-SS* Medical outcomes study social support survey (MOS-SS).

potentially leading to an improvement over the short term, but not over the medium term, as identified by some recently mentioned studies. Furthermore, a recent study by Deng et al.[49] verifies that treatment adherence is a common problem for people with mental disorders, such as depression or anxiety, which may occur with Long COVID patients, given the negative impact on their emotional well-being, as verified by our analyses (mental Health SF-36) and previous evidence[48]. Rather, a systematic review of post-COVID-19 TR states that TR can increase patient adherence as compared to face-to-face rehabilitation, given its convenience and accessibility[16]. In addition, it is mentioned that daily communication via a software platform or reminders would increase participant adherence. These statements are inconsistent with the results of this study. The low adherence of our results remains a mystery that could possibly be resolved by future qualitative research on our participants.

Moreover, our linear regressions model identified significant models that explained the improvement in cognitive functioning (Mocha), physical functioning (Sit-to-Stand Test), and community social support (PCSQ), as well as the decreased number of symptoms, in relation to the time of APP use and the improvement of other secondary study variables. After reviewing the scientific evidence, these results are analyzed below in relation to evidence on COVID-19 and evidence with other pathologies.

An increase in health literacy predicts a decrease in the number of persistent symptoms. As noted by Liu et al.[42], health literacy refers not only to the knowledge of health and care of the health system, it is defined as an individual's ability to obtain and process knowledge and information to maintain and improve health through self-management in collaboration with health providers[49]. A European survey has verified that health literacy has a positive impact on patients with chronic diseases, especially those having a lower level of education or health knowledge[39]. In this way, the participants who have increased their health literacy may have self-managed their persistent symptoms better, possibly making better use of health services and thus reducing said symptoms. In turn, the increase in health literacy and greater use of the ReCOVery APP are predictors of greater community

Variables	Intervention group N = 52 mean (SD)	Control group N = 48 mean (SD)	Significance *p*-value (CI)
Primary outcomes			
SF-36 Physical Health			
Baseline (T0)	29.06 (13.67)	35.58 (18.86)	0.053 (−13.12; 0.07)
3 months (T1)	33.80 (12.19	42.30 (20.31)	0.021 (−16.30; 1.40)
T1–T0	4.56 (12.14)	8.02 (14.38)	0.234 (−9.20; 2.28)
SF-36 Mental health			
Baseline (T0)	32.64 (17.98)	37.09 (20.59)	0.252 (−12.16; 3.24)
3 months (T1)	37.35 (20.01)	40.29 (19.59)	0.491 (−11.38; 5.50)
T1–T0	5.07 (16.10)	3.20 (18.27)	0.615 (−5.49; 9.23)
Secondary outcomes			
Number of persistent symptoms	17.50 (5.29)	15.35 (6.55)	0.074 (−0.23; 4.52)
Baseline (T0)	16.48 (4.65)	14.00 (6.64)	
3 months (T1)	−0.27 (3.03)	−1.43 (3.79)	0.09 (−0.44; 5.41)
T1–T0			0.188 (−0.58; 2.90)
Montreal cognitive assessment			
Baseline (T0)	23.48 (4.20)	23.81 (3.46)	0.667 (−1.85; 1.19)
3 months (T1)	24.13 (4.45)	24.14 (3.84)	0.991 (−1.78; 1.76)
T1–T0	0.91 (4.24)	0.30 (2.87)	0.439 (−0.93; 2.14)
Si-to-Stand Test			
Baseline (T0)	9.87 (3.77)	10.92 (3.10)	0.131 (−2.42; 0.31)
3 months (T1)	10.65 (3.66)	11.28 (3.89)	0.462 (−2.30; 1.05)
T1–T0	0.32 (2.24)	−0.28 (4.84)	0.806 (−1.36; 1.06)
Affective state			
Baseline (T0)	17.86 (7.98)	17.33 (8.74)	0.752 (−2.80; 3.86)
3 months (T1)	17.20 (8.72)	16.00 (9.95)	0.553 (−2.80; 5.20)
T1–T0	−0.28 (4.84)	−1.21 (6.17)	0.441 (−1.45; 3.30)
Insomnia severity index			
Baseline (T0)	11.13 (7.21)	11,56 (5,89)	0.745 (−3.03; 2.17)
3 months (T1)	10.50 (5.53)	10,33 (5,94)	0.893 (−2.30; 2.63)
T1–T0	−0.54 (5.35)	−1,47 (5,94)	0.449 (−1.50; 3.36)
Social support			
Baseline (T0)	83.42 (16,22)	84.29 (16.61)	0.792 (−7.39; 5.65)
3 months (T1)	82.82 (17,32)	82.26 (16.59)	0.878 (−6.67; 7.79)
T1–T0	−0.15 (12.03)	−1.09 (8.60)	0.675 (−3.50; 5.38)
Community social support			
Baseline (T0)	82.33 (15.51)	81.7 (12.99)	0.846 (−5.10; 6.22)
3 months (T1)	84.53 (20.53)	79.92 (12.87)	0.211 (−2.66; 11.87)
T1–T0	2.42 (18.5)	−2.45 (12.22)	0.153 (−1.84; 11.59)
Self-efficacy			
Baseline (T0)	44.57 (6.49)	44.75 (8.55)	0.910 (−3.21; 2.86)
3 months (T1)	43.31 (9.10)	44.92 (8.69)	0.399 (−5.41; 2.17)
T1–T0	−1.00 (6.59)	0.28 (5.80)	0.336 (−3.92; 1.35)
Patient activation			
Baseline (T0)	38.92 (7.24)	40,79 (4.61)	0.210 (−4.26; 0.52)
3 months (T1)	40.24 (6.90)	39,92 (5.72)	0.816 (−2.39; 3.02)
T1–T0	0.91 (8.44)	−1.36 (5.32)	0.136 (−0.72; 5.28)
Health literacy			
Baseline (T0)	32.94 (7.84)	31.18 (5.98)	0.125 (−1.00; 4.51)
3 months (T1)	32.00 (7.35)	30.32 (7.16)	0.291 (−1.46; 4.81)
T1–T0	−0.53 (6.89)	−0.05 (7.54)	0.760 (−3.61; 2.65)

Table 3. Outcome data at baseline and 3-month follow-up.

social support. A recent systematic review states that associations between self-reported health literacy and medication adherence are quite consistent[50], so in this intervention, better health literacy and increased APP

Decrease in the number of persistent symptoms	Coefficient	*p* value	CI below 95%	CI above 95%
Increase in health literacy	0.226	0.002	0.087	0.365
R^2	0.192			
R^2_{adj}	0.102			
Cognitive functioning (MoCA)	**Coefficient**	***p* value**	**CI below 95%**	**CI above 95%**
Increase in self-efficacy	0.346	0.001	− 0.538	− 0.154
R^2	0.365			
R^2_{adj}	0.265			
Physical functioning (Sit-to-Stand Test)	**Coefficient**	***p* value**	**CI below 95%**	**CI above 95%**
Gender	− 2.454	0.016	0.928	8.732
Minutes of APP use	0.001	0.005	0.000	0.002
R2	0.287			
R2adj	0.226			
Community social support (PCSQ)	**Coefficient**	***p* value**	**CI below 95%**	**CI above 95%**
Increase in self-efficacy	0.634	0.036	0.042	1.226
Minutes of APP use	0.004	0.021	0.001	0.008
R2	0.198			
R2adj	0.135			

Table 4. Linear regression model with regard to improvements in the number of persistent symptoms, cognitive functioning (MoCA), physical functioning (Sit-to-Stand Test), and Community social support (PCSQ).

use would make people follow the recommendations to begin rehabilitation processes in the community, in addition to attending associations for affected people. According to this idea and with regard to the COVID-19 pandemic, low levels of health literacy are related to the ability to assess and trust online health information[51], so an increase in knowledge of the management of Long COVID in terms of risks, contagion, as well as positive psychological repercussions, could have encouraged the integration of these patients in community services. In fact, a meta-analysis relating literacy on the measures resulting from the COVID-19 pandemic indicates that people with low health literacy revealed a greater tendency to accept misinformation about COVID-19 circulating over social media platforms and social networks, as well as decision-making related to health[52].

Furthermore, improved cognitive functioning is predicted by an increase in the self-efficacy construct (GSES-12). As with our results, a prospective multicenter observational study by Jongen et al.[54] concluded that self-efficacy can positively affect the cognitive performance of patients with multiple sclerosis[53]. In fact, self-efficacy has the potential to reduce cognitive stressors[54]. A cross-sectional study of patients with cerebral palsy related to increased self-efficacy with improved quality of life, both mental and physical, through the use of the GESES-12 and SF-36 questionnaires[55].

Finally, improved physical functioning (Sit-to-Stand) is predicted by the minutes of APP use and by being a man. The intervention group's baseline score on the Sit-to-Stand Test improved, whereas that of the control group worsened. A systematic review including RCTs with patients having post-COVID-19 sequelae based on physical rehabilitators also verified the improvement of these patients on the 30-s Sit-to-Stand scale[56]. More specifically, the study by De Souza et al.[58], based on low-intensity pulmonary rehabilitation for COVID-19 survivors, saw improvements in this test, in addition to their daily physical activity and fatigue[57]. For this reason, rehabilitation exercises, both physical and respiratory, as well as the daily APP recommendations have led to improvements in this area. Moreover, previous evidence supports the idea that men with chronic diseases have a greater genetic predisposition than women to improve their physical functioning[58], given the greater bone and muscle wear and tear suffered by women with aging[59]. Therefore, improvements in physical functioning would be expected to be greater in the participating men.

In terms of study limitations, first, the development of the intervention overlapped with periods in which COVID-19 infections were on the rise, affecting PHC care in the region. Second, the variables collected are based on the self-perceptions of the participants; therefore, we must trust their statements, even if it is not possible to objectively verify them. Third, the symptoms themselves cause not only physical but also mental limitations, to starting and following rehabilitative interventions. Finally, due to the nature of the intervention, all participants were informed of the assigned intervention during the RCT. There are also various strengths to the study. To the best of our knowledge, it is the first RCT conducted exclusively on Long COVID patients, challenging the chronological order of symptoms and obtaining scientific evidence to support future research with this group of patients. In addition, a specific APP has been designed and used for this study.

Future RCTs are required to assess the efficacy of TR-based interventions on Long COVID patients. As for APP use, mixed-method studies should be carried out to investigate the specific causes of poor adherence to the APP and to determine how to improve adherence and compliance rates. These studies are necessary to identify new significant models that contribute to improving the quality of life and symptoms of these patients, while also promoting evidence on their clinical management to support PHC professionals.

Data availability

The datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

Received: 27 January 2023; Accepted: 11 May 2023
Published online: 16 May 2023

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Acknowledgements
The authors would like to thank the Network for Research on Chronicity, Primary Care, and Health Promotion (RICAPPS, code RD21/0016/0005-Health Institute Carlos III, Spain), the Primary Health Care Research Group of Aragon (GAIAP-B21-20R) of the Department of Science, the University and Knowledge Society of the Aragon (Spain) government, and FEDER Funds 'Another way to make Europe'.

Author contributions
M.S.-P., B.O.-B. and S.L.-H. drew up the research design. M.S.-P., B.O.-B. and S.L.-H. developed the study and coordinated the fieldwork. B.O.-B. made the analysis. F.M.-L., M.D.-G., and R.S.-R. have helped with project coordination. M.S.-P. and B.O.-B. wrote the manuscript. B.O.-B. is the principal researcher for the project. All authors reviewed the manuscript content and approved the final version for submission. Not applicable given that the data are anonymous and no individual images are presented.

Funding
This work is supported by the Carlos III Health Institute grant number PI21/01356, FEDER Funds 'Another way to make Europe'. The financing entity will conduct an audit trial once a year.

Competing interests
The authors declare no competing interests.

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Manuscrito III. Clinical characterization and factors associated with quality of life in Long COVID patients: Secondary data analysis from a randomized clinical trial.

PLOS ONE

RESEARCH ARTICLE

Clinical characterization and factors associated with quality of life in Long COVID patients: Secondary data analysis from a randomized clinical trial

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Citation: Samper-Pardo M, León-Herrera S, Oliván-Blázquez B, Gascón-Santos S, Sánchez-Recio R (2023) Clinical characterization and factors associated with quality of life in Long COVID patients: Secondary data analysis from a randomized clinical trial. PLoS ONE 18(5): e0278728. https://doi.org/10.1371/journal.pone.0278728

Editor: Gustavo Plaza-Manzano, Complutense University of Madrid: Universidad Complutense de Madrid, SPAIN

Received: November 21, 2022

Accepted: April 29, 2023

Published: May 16, 2023

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Data Availability Statement: The data sets used and/or analyzed during this study are available on the ZENODO platform. They were registered and published on 02/20/2023 with DOI: 10.5281/zenodo.7656949.

Funding: Financial support for the conduct of the research was obtained from the Health Institute Carlos III (ISCIII) (grant number PI21/01356).

Abstract

Background

Long COVID patients suffer a negative impact on their quality of life, as well as their functioning, productivity or socialization. There is a need to better understand the individual experience and circumstances surrounding these patients.

Objective

To characterize clinical picture of Long COVID patients and to identify factors associated with quality of life.

Methods

A secondary data analysis from a randomized clinical trial (RCT) was carried out with 100 Long COVID patients treated by Primary Health Care and residents in the territory of Aragon (northeast of Spain). The main variable of the study was quality of life, evaluated using the SF-36 Questionnaire, in relation to socio-demographic and clinical variables. In addition, ten validated scales were used that contemplated their cognitive, affective, functional and social status, as well as personal constructs. Correlation statistics and linear regression model were calculated.

Results

Long COVID patients suffer a decrease in their levels of physical and mental health. On the one hand, the higher number of persistent symptoms (b = -0.900, p = 0.008), worse physical functioning (b = 1.587, p = 0.002) and sleep quality (b = -0.538, p = 0.035) are predictors of worse quality of life, physical subscale. On the other hand, higher educational level (b = 13.167, p = 0.017), lower number of persistent symptoms (b = -0.621, p = 0.057) and higher

However, ISCIII were not involved in collection, analysis or interpretation of data, in the writing of the report, and in the decision to submit the paper for publication. Bárbara Oliván-Blázquez is the main researcher of this project. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

affective affectation (b = -1.402, p<0.001) are predictors of worse quality of life, mental subscale.

Conclusion

It is necessary to design rehabilitation programs that consider both the physical and mental health of these patients, thus obtaining an improvement in their quality of life.

Introduction

Since the World Health Organization (WHO) declared COVID-19 a highly contagious and harmful pandemic for the human species on March 11, 2020 [1–4], the main health organizations around the world, together with government agencies and scientific health corporations, are under the arduous task of expanding scientific knowledge about the pathophysiology of this new coronavirus, thus trying to minimize its spread and consequent impact on quality of life of the world population [5].

Even though most people infected with COVID-19 turn out to be asymptomatic or develop mild-moderate symptoms, it is estimated that around 15% of those affected have progressed to greater severity, requiring hospital care in some cases [6, 7]. Initially, a mean recovery time was established after COVID-19 infection of 2 to 3 weeks until the disappearance of symptoms (except for the recovery of smell and taste, in the case of partial or total alteration) [8–11]. Subsequently, scientific evidence has estimated that a large percentage of those affected could maintain symptoms for 5 weeks or more after the acute infection, and that around 10–20% would see symptoms persist after 12 weeks or more [12]. Given this confusing panorama, the National Institute for Health and Care Excellence (NICE) established that the symptoms of COVID-19 can last 4–12 weeks and people who maintain or develop symptoms for a longer period and that cannot be explained by an alternative diagnosis are considered to be "Post-COVID Syndrome" [13]. In the scientific field, this new disease has been defined in a pragmatic way, "such that after the COVID-19 infection it does not recover after several months", identifying it as "Long COVID" [14, 15]. Given the need to establish the limits of the disease, in October 2021, the WHO registered the definition of this condition as the condition that occurs in adult individuals with a history of probable or confirmed infection by SARS-CoV-2, with symptoms typical of the disease usually 3 months after onset, without explanation by alternative diagnosis, referring to it as "Post COVID Condition" [16].

Despite rapid characterization of the acute phase of COVID-19, the underlying etiology of prolonged symptoms is still limited. The prevalence of Long COVID illness is higher in women (80%) than in men (20%) [17]. The type of symptoms, duration and degree of severity, as well as associated risk factors, are still being studied. It is worth mentioning the international cohort carried out by Davis et al. (2021) has come to count 203 symptoms of this disease [18], coming to involve at least 10 organ systems, as verified by other studies [19]. Among the most predominant symptoms are profound fatigue, myalgia, dyspnea, cough, fever, low-grade fever, dysthermia, palpitations, headache, arthralgia, odynophagia, dizziness, hypotension, bruising and skin rashes, neurological symptoms such as tingling, cognitive deficits, sleep disorders and mental health problems, of the anxious-depressive type [20–27].

The development and evolution of these persistent symptoms supposes a total alteration of the organism, as well as a general malaise characterized mainly by chronic fatigue and musculoskeletal pain [18]. Consequently, there is a great impact on the functioning of the respiratory

system, in addition to increasing the potential to develop metabolic, cardiovascular, gastrointestinal, and neurological disorders, among others, and alter the emotional well-being of these patients [28].

The physical and mental repercussions are affecting different areas of life such as family, work or social and consequently, their quality of life [29]. Therefore, Long COVID must be recognized as a condition with disabling potential, at least temporarily [30]. Several investigations report that at least 50% of Long Covid patients continue to see negative effects on their daily activities, which were previously carried out regularly, after 2–5 months and 15% after 8 months of infection [23, 31, 32]. These limitations may occur in activities of daily life such as bathing, dressing, or walking [33]. Additionally, because of cognitive dysfunction and other symptoms, it is estimated that work capacity and personal productivity are lower than pre-disease levels [18].

On the other hand, the persistent symptoms and sequelae add to the psychosocial impact of interrupted access to health care (such as arranging for regular medication), basic personal routines (such as walking to local stores), social interactions (such as meeting with friends) and support networks [34–37]. Therefore, support should be personalized with input from a multi-professional team (e.g., primary care physician, social worker, rehabilitation teams) [38].

This global impact of prolonged COVID should not be ignored. The quality of life of these patients has suffered a great impact. There is an urgent need to offer rehabilitation treatments to long-term COVID patients, as well as help healthcare workers understand what is required for recovery. The health system, research institutes, and public policies should be involved in their response. To do this, it is necessary to better understand the clinical characterization and individual experiences of patients. In summary, the loss of quality of life, the need for health care, as well as the clinical characterization and diagnostic recognition, make this disease an idea worthy of investigation for the health sector [39].

Hence, the objective of this study is to characterize clinical picture of patients diagnosed with Post COVID-19 Syndrome, in relation to sociodemographic, clinical, affective, cognitive, functional and social variables; as well as to identify factors associated with quality of life of these patients from PHC.

Methodology

Study design

This research study is a secondary data analysis [40] of data collected at the start of a randomized clinical trial (RCT) [41] called: "Analysis of symptoms and quality of life of people with prolonged diagnosis of COVID-19, and the efficacy of an intervention in primary health care using ICT", registered on 10/02/2022, with reference number ISRCTN91104012.

Sample size

The sample size was established in the RCT study, as can be seen in its protocol article [41]. The methodology of the RCT established a necessary sample size of 78 subjects, according to its main variable, "quality of life", through the SF-36 questionnaire. Finally, a total of 100 Long COVID participants were included in this study Therefore, the necessary sample size was exceeded. Of these participants, 20 were men and 80 women.

Recruitment and participants

The study population has been Post COVID-19 Syndrome patients, of legal age (18 years or older) and treated by Primary Health Care. The exclusion criteria put forward for its collection

have been: not having a positive diagnostic test for COVID-19 for more than the previous 3 months; have a diagnosis of severe uncontrolled disease; significant risk of suicide; pregnancy and lactation; participation in a clinical trial in the last six months; existing structured rehabilitative or psychotherapeutic treatment by health professionals and the presence of any medical, psychological or social problem that may significantly interfere with the patient's participation in the study.

Patients were recruited by PHC professionals, who participated in the clinical trial within a PHC setting, as detailed in the RCT protocol article [41]. The Long COVID Association of Aragon (Spain) also participated in the recruitment.

This process was carried out consecutively until reaching the sample size.

Variables and instruments

This study contemplated multiple variables that allow us to know about the Long COVID patient from a broad perspective. For this, in addition to sociodemographic and clinical variables, a total of 10 scales were selected.

- Socio-demographic variables: gender (man, woman, other), age, civil status (married or in couple/single, separated, divorced or widowed), education (no studies or primary studies/ secondary or university studies) and occupation (employee, unemployed, employee with temporary work disability (TWD), retired, others).
- Clinical variables related to post-COVID-19: time since infection (months), number of residual symptoms and their severity measured through a Visual Analogue Scale. Persistent symptoms included were: Gastrointestinal symptoms, total or partial loss of smell or taste, eye problems (blurred vision, increased dioptres, dry eyes, conjunctivitis), tiredness or fatigue, cough, sore throat, dyspnea, fever (over 38˚C), low-grade fever (37˚C—38˚C), chills or chills without fever, headaches, drowsiness, dizziness, tachycardia, orthostatic hypotension, bruising, myalgia, joint pain, chest pain, back pain (cervical, dorsal or lumbar), neurological symptoms (tingling, spasms, etc.), cognitive (memory loss, brain fog or confusion or poor attention and concentration capacity), loss of libido or erectile dysfunction, alteration of the menstrual cycle, urinary symptoms (infections, overactive bladder), hair loss and other symptoms that can be considered residual [20–27].
- Quality of life was evaluated by the SF-36 Questionnaire [42], which measures eight dimensions of health: physical function, physical role, aches and pains, general health, vitality, social function, emotional role, and mental health. The eight dimensions define two main components of health: physical summary component and mental summary component. The eight scales are scored from 0 to 100, with higher scores indicating better health status. The official Spanish version of the questionnaire was used [43]. The Cronbach's alpha obtained was 0,841.
- Cognitive status was assessed by the official Spanish version of the Montreal Cognitive Assessment (MoCA) [44], which assesses six cognitive domains (memory, visuospatial ability, executive function, attention, concentration or working memory, language and temporal-spatial orientation). It is about a total score of 30 points and the cut-off point for the detection of mild cognitive impairment is 26 points. Cronbach's alpha obtained in this study is 0.457.
- Physical functioning was evaluated using the 30-second Sit to Stand Test [45], specifically used to detect respiratory diseases [46]. The test assesses endurance at high power, speed in

terms of muscular endurance or strength, by recording the number of times a person can stand up and sit down completely. It has good test-retest reliability (0.84 <R< 0.92).

- Physical activity was assessed using the International Physical Activity Questionnaire-Short Form (IPAQ-SF) [47]. It assesses the levels of habitual physical activity over the preceding seven days. It has seven items and records activity at four levels of intensity: vigorous-intensity activity and moderate-intensity activity (walking and sitting). The official Spanish version was used [48]. The minute walking score was used for the analysis.
- Affective status was assessed through the Hospital Anxiety and Depression Scale (HADS) questionnaire [49]. The HADS is a self-report-based scale that was developed to screen for depression and anxiety disorders in medical patients in primary care settings. The HADS includes 14 items that assess symptoms of anxiety and depression, each item corresponding to a 4-point Likert-type scale (zero to three), with scores ranging from 0 to 42 for its total score. Higher scores indicate more severe symptoms. The HADS has been translated into several languages, including Spanish [50]. Cronbach's alpha obtained in this study is 0.91.
- Sleep quality was assessed using the Insomnia Severity Index questionnaire (ISI). The ISI [51] measures the patient's perception of nocturnal and daytime symptoms of insomnia. This self-report scale has seven items, with each response ranging from zero to four, and an overall score ranging from 0 to 28, with a higher score indicating greater severity of insomnia. The Spanish version was used (Cronbach's alpha = 0.82) [52]. In this study, the Cronbach's alpha obtained was 0.86.
- Social Support was evaluated using the Medical Outcomes Study Social Support Survey (MOS-SS) [53]. It is a self-report instrument consisting of four subscales (emotional/informational, tangible, affectionate and positive social interaction) and an overall functional social support index. It has 19 items and uses a 5-point Likert Scale. Higher scores indicate more support. The official Spanish version was used (Cronbach's alpha ≥0.91) [54]. Cronbach's alpha obtained in this study was 0.94.
- Personal constructs. The personal factors relating to behaviour that were collected are the following:

  a. Self-efficacy was evaluated using the Self-Efficacy Scale-12 (GSES-12). This scale has 3 factors: Initiative (willingness to initiate the behavior), Effort (willingness to try to complete the behavior), and Persistence (persevering to complete the task in the face of adversity). The official scale obtained a Cronbach's alpha of 0.69 [55]. Cronbach's alpha obtained in this study was 0.76.

  b. Patient activation in their own health was evaluated using the Patient Activation Measure (PAM) questionnaire regarding the management of their health [56]. It evaluates the patient's perceived knowledge, skills and confidence to engage in self-management activities through 13 items with a Likert Scale from one (strongly disagree) to four (strongly agree). The resulting score ranges between 13 and 52. Higher scores indicate higher levels of activation. The official Spanish version for chronically ill patients was used (Cronbach's alpha = 0.98) [57]. The Cronbach's alpha obtained in this study was 0.87.

  c. Health literacy was evaluated using the Health Literacy Europe Questionnaire (HLS-EUQ16) [58]. Health literacy is defined as the population's knowledge, motivation, and individual capacity to understand and make decisions related to promoting and maintaining their health. It contains 16 items, ranging from 1 to 4. Higher scores indicate

worse health literacy. The official Spanish version for chronically ill patients was used (Cronbach's alpha = 0.98) [59]. The Cronbach's alpha obtained in this study was 0.87.

Statistical analysis

Statistical analyses were carried out using the IBM SPSS Statistics version 22.0.0.0 and Microsoft Excel computer programs. First, the sample distribution was analyzed, obtaining Shapiro–Wilk statistic values that were lower than 0.05 for all of the variables except for the number of symptoms, SF-36 general health and SF-36 mental health. However, non-parametric statistics were used. Subsequently, a descriptive analysis was performed: in cases of quantitative variables, median, mean, standard deviation and interquartile range were used; frequency and percentages were used for qualitative variables. In addition, a descriptive analysis was carried out according to sex. To verify if there were significant differences, the chi-square test was performed for quantitative variables and for qualitative variables it was performed using the Mann-Whitney U and the Kruskal-Wallis test. A bivariate analysis was performed; SF-36 physical health and SF-36 mental health were analyzed as a continuous scale with a minimum of 0 and a maximum of 100. Spearman correlations between SF-36 physical health or SF-36 mental health and the rest of the continuous variables were calculated. This bivariate analysis for qualitative variables was also performed using Mann-Whitney U and Kruskal-Wallis test, and the chi-square test was performed for quantitative variables. A linear multivariate model was developed for SF-36 physical health and SF-36 mental health as dependent variables. The independent variables (sociodemographic variables, number of persistent symptoms, MoCA, sit to stand, HADS, IPAQ, ISI, MOS, GSES-12, PAM and HLS-EUQ16) were added into the regression model [60], and a final model was obtained. Confounder variables were not adjusted in the linear regression analysis. In the model, occupation was introduced as having or not an active skilled occupation. In addition, a multicollinearity test was performed. Linear regression was used since the residuals of the model had a finite mean, constant variance, and normal distribution. However, bootstrapping analysis with 2000 samples was also conducted. All levels of significance were established at 0.05.

Ethics considerations

Ethics approval was granted by the Clinical Research Ethics Committee of Aragon (PI21/139 and PI21/454). The procedures carried out for the creation of this work complied with the ethical standards of the previously mentioned committee and with the 1975 Declaration of Helsinki. All of the subjects signed an informed consent form, their data were anonymised and will only be used for the purposes of the study. Participants and healthcare professionals will be informed about the results. The ethics committee will be notified of any protocol modifications.

Results

A total of 100 people participated, of which 80 were women and 20 men. The median age was 47 years (IQR 11 years, range: 29–72). Table 1 presents the description of the total sample, as well as the comparison by gender, based on the variables collected. The profile of the participant was a woman, whose age was around 48 years old, married, with secondary or university studies, employed or temporarily unable to work, with low quality of life, but high social support and perception of self-efficacy. There are no significant differences by sex in sociodemographic and clinical variables, except for general health assessed by the SF-36, in which women have a significantly higher score than men. The 8 dimensions of quality of life of the SF-36

Table 1. Description of sociodemographic and clinical variables of the total sample and comparing by gender.

Variables	Total sample N (%) mean (SD)/median (IQR)	Male N(%) mean (SD)/median (IQR)	Female N(%) mean (SD)/median (IQR)	p-value
Gender				
Male	20 (20%)			
Female	80 (80%)			
Age	48,28 (9.27)/47 (11)	48 (8.3) / 49.5 (8.75)	48.35 (9.54) / 47 (14)	0.918
Marital status				
Married or in couple	70 (70%)	15 (75%)	55 (68.8%)	0.585
Single, separated, divorced or widowed	30 (30%)	5 (25%)	25 (31.2%)	
Educational level				
Primary studies	9 (9%)	4 (20%)	5 (6.3%)	0.055
Secondary or university studies	91 (91%)	16 (80%)	75 (93.7%)	
Occupation				
Employee	46 (46.9%)	5 (25%)	41 (52.6%)	
Unemployed	5 (5.1%)	0	5 (6.4%)	
TWD	37 (37.8%)	13 (65%)	24 (30.8%)	0.059
Retired	9 (9.2%)	2 (10%)	7 (9%)	
Others	1 (1%)	0	1 (1.2%)	
SF-36				
Physical function	51,05 (25,11) / 50 (40)	58.5 (26.26) / 57.5 (26.26)	49.18 (24.64) / 47,5(24.64)	0.163
Physical role	6.75 (21.86) / 0 (0)	10 (27.38) / (0 (0)	5.93 (20.37) / 0 (0)	0.510
Bodily pain	32.61 (26.03) / 22 (30)	29.6 (23.7) / 22 (22.70)	33.36 (26.67) / 22 (26.67)	0.599
General health	38.35 (17.74) / 40 (25)	30.95 (17.4) /27.5 (17.40)	40.2 (17.44) / 40 (17.44)	0.022
Vitality	27.5 (13.86) / 25 (25)	31 (13.43) / 32.5 (13.43)	26.62 (13.91) / 25 (13.91)	0.172
Social function	39(29.85) / 31.25(46.87)	33.12 (28.75) / 25 (28.75)	40.46 (30.11) / 37.5 (30.11)	0.317
Emotional role	21 (39.54) / 0 (0)	25 (44.42) / 0 (0)	20 (38.46) / 0 (0)	0.795
Mental health	51,6 (15.96) / 52 (24)	49 (17.16) / 44 (36)	52.25 (15.69) / 52 (15.69)	0.294
SF-36 Physical Health	32.19(16.61) /28.5 (20.06)	32.26 (17.77) / 24.88 (19.5)	32.17 (16.43) /29.13 (16.43)	0.701
SF-36 Mental Health	34.77 (19.3) / 29.06(26.16)	34.53 (19.83) / 25.75 (18.59)	34.84 (19.3) / 30.06 (19.3)	0.766
N° persist. symptoms	16.47 (5.99) / 16.5 (8)	13.85 (6.54) /14 (13.25)	17.12 (5.71) / 17 (8.75)	0.058
MoCA	23.64 (3.85) / 25 (4.75)	22.1 (4.67) / 22 (6.25)	24.02 (3.54) / 25 (3)	0.068
Sit to Stand Test	10.37 (3.49) / 10.5 (4)	10 (3.56) / 10 (4)	10.46 (3.49) / 11 (4)	0.621
HADS	17.61 (8.31) / 16 (12)	18.45 (9.98) / 20 (16)	17.4 (7.9) / 16 (11.5)	0.685
ISI	11.34 (6.58) / 11.5 (11)	13.1 (7.13) / 12 (10.5)	10.9 (6.41) / 10 (11.5)	0.229
MOS-SS	83.84 (16.33) / 91 (29)	83.65 (18.42) / 92,5 (18.25)	88.88 (15.89) / 91 (29)	0.692
IPAQ-SF	338.9 (349.24) / 257,5 (288.75)	394.7 (280.7) /297,5 (446,25)	324.93 (364.56) / 240 (315)	0,168
GSES-12	44.66 (7.51) / 46 (10)	43.9 (9.26) / 47,50 (11)	44.85 (7.07) / 46 (8.75)	0,846
PAM	39.82 (6.16) / 40 (8.75)	39.3 (5.57) / 40 (7.5)	39.95 (6.44) / 40 (4.75)	0,710
HLS-EUQ16	32.1 (7.03) / 32.5 (8.75)	32.4 (5.57) / 33 (9.75)	32.02 (7.38) / 32 (9)	0.714

https://doi.org/10.1371/journal.pone.0278728.t001

have been regrouped into 2 variables, the SF-36. 36 Physical Health and SF-36 Mental Health, to obtain a broader view, in which there are no significant differences by gender. Likewise, for both men and women, the median scores on the cognitive assessment (MoCA) and physical functioning (Sit to Stand Find), indicate a deterioration in physical and cognitive functioning. The self-efficacy scales (PAM and HLS-EUQ16) also collect negative scores in Long COVID patients.

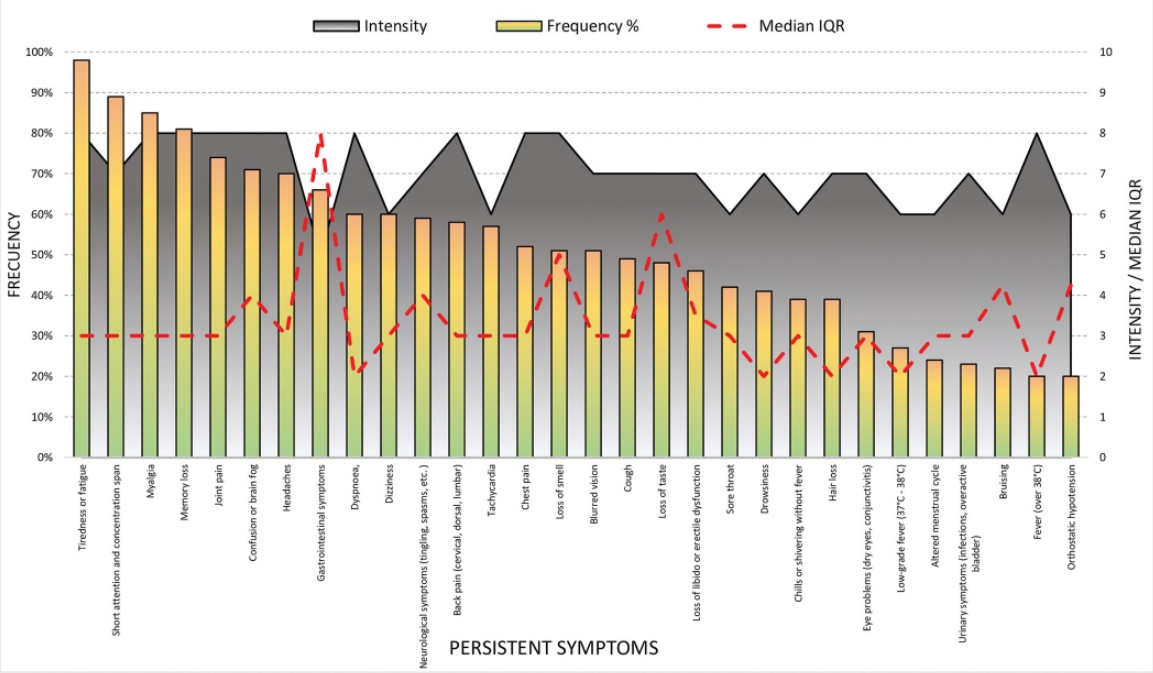

Fig 1. Description of persistent symptomatology, frequency and intensity.

https://doi.org/10.1371/journal.pone.0278728.g001

Delving into the persistent symptoms, as can be observed on Fig 1, the median the time since the contagious is 18 months and the number of persistent symptoms is 16.5 (IQR 8). The most frequent symptoms are tiredness or fatigue (98%), myalgia (85%), joint pain (74%), memory loss (81%), confusion or brain fog (71%) and short attention and concentration span (89%), and having an intensity of 7 or 8 points above 10.

Tables 2 and 3 show the bivariant analysis related the quality of life (SF-36 physical health and SF-36 mental health) and the collected variables. There is a relationship between the SF-36 physical health and occupation, the number of persistent symptoms, physical and cognitive functioning, affective state, patient´s activation and health literacy. Higher number of persistent symptoms, cognitive and affective affectation, higher activation and lower health literacy, lower SF-36 physical health score; while higher physical functioning and patient´s activation are associated to a higher SF-36 physical health score. Employees and retired patients have a higher SF-36 physical health score compared to unemployed patients and patients with sick leave. Regarding SF-36 mental health score, there is a relationship between SF-36 mental health score and the number of persistent symptoms, physical and cognitive functioning, affective state, sleep quality, physical activity and self-efficacy. Higher number of persistent symptoms, cognitive and affective affectation, and sleep quality affectation, lower SF-36 mental health score; on the other hand, higher physical functioning, physical activity and self-efficacy are associated to a higher SF-36 mental health score.

Regarding the linear regression model, the results are shown in Table 4, where it can be observed that the number of persistent symptoms (b = -0.900, 95% CI = [-1.523,-0.263], p = 0.008), physical functioning (b = 1.587, 95% CI = [0.679,2.521], p = 0.002) and sleep quality

Table 2. Comparation SF-36 physical health score and SF-36 mental health score, according to the gender, marital status, educational level, and employment status.

Variables	SF-36 Physical health				SF-36 mental health			
	Median (IQR)	P-value	Confidence interval 95%		Median (IQR)	P-value	Confidence interval 95%	
			Inferior	Superior			Inferior	Superior
Gender								
Men	24.87 (20.81)	0.701	-8,500	6,250	25.75 (35.72)	0.776	-9,500	7,500
Women	29.12 (20.56)				30.06 (23.69)			
Marital status								
Married or in couple	27.75 (17.06)	0.746	-5.000	7.500	33,25 (28.25)	0.724	-9.625	6.875
Single, separated, widowed	29 (23.63)				28 (23.47)			
Educational level								
Without studies or primary studies	26.50 (13.88)	0.796	-11,250	7,250	27.37 (26.19)	0.890	-14,250	11,375
Secondary or university studies	29 (21.75)				29.62 (26.79)			
Employment status								
Employee	38.75 (22.69)				35.5 (26.38)			
Unemployed	27.20 (18.75)	<0.001	-20,056	50,806	31.25 (20.45)	0.240	-20,056	50,806
TWD	23 (13.12)				25.25 (18.31)			
Retired	34.50 (31.62)				43.75 (28.93)			

TWD: temporary work disability.

https://doi.org/10.1371/journal.pone.0278728.t002

(b = -0.538, 95% CI = [-1.092,-0.022], p = 0.035) are predictors of SF-36 physical health score. Higher number of persistent symptoms, worse physical functioning and quality of sleep are predictors of worse quality of life, physical subscale. Whereas educational level (b = 13.167, 95% CI = [-1.391,23.535], p = 0.017), number of persistent symptoms (b = -0.621, 95% CI = [-1.245,-0.052], p = 0.057) and affective state (b = -1.402, 95% CI = [-1.964,-0.958], p<0.001)

Table 3. Correlation between SF-36 physical health score and SF-36 mental health score and age, number of persistent symptoms, cognitive and physical functioning, affective state, sleep quality, social support, number of steps walked, and personal construct (self-efficacy, patient´s activation and health literacy).

Variables		SF-36 Physical health			SF-36 mental health			
	Spearman Rho coefficient	P-value	Confidence interval 95%		Spearman Rho coefficient	P-value	Confidence interval 95%	
			Inferior	Superior			Inferior	Superior
Age	-0.072	0.477	-0.255	0.128	-0.064	0.525	-0.240	0.161
Number of persistent symptoms	-0.378	<0.001	-0.644	-0.297	-0.486	<0.001	-0.557	-0.130
Montreal Cognitive Assessment	0.304	0.002	0.152	0.477	0.229	0.022	0.66	0.441
Sit to Stand Test	0.524	<0.001	0.372	0.648	0.447	<0.001	0.289	0.590
Affective state (HADS)	-0.472	<0.001	-0.797	-0.563	-0.723	<0.001	-0.797	-0.615
Insomnia Severity Index	-0.430	0.097	-0.577	-0.262	-0.375	<0.001	-0.557	-0.227
Social support (MOS-SS)	0.124	0.221	-0.065	0.362	0.068	0.504	-0.133	0–334
IPAQ-SF	0.139	0.168	-0.046	0.322	0.203	0.042	-0.11	0.377
Self-efficacy	0.182	0.070	0.012	0.405	0.262	0.008	0.67	0.440
Patient´s activation	0.202	0.044	0.044	0.403	0.183	0.068	0.000	0.389
Health literacy	-0.208	0.038	-0.360	-0.003	0.182	0.182	0.065	0.190

HADS: Hospital Anxiety and Depression Scale, MOS-SS: Medical Outcomes Study Social Support Survey (MOS-SS), IPAQ-SF: International Physical Activity Questionnaire-Short Form

https://doi.org/10.1371/journal.pone.0278728.t003

Table 4. Linear regression models in relation to the SF-36 physical and mental health score.

SF-36 Physical health score	Coefficient	P-value	Confidence interval 95%		Collinearity statistics	
			Inferior	Superior	Tolerance	VIF
Constant	20.713	0.449	-38.564	74.170		
Number of persistent symptoms	-0.900	0,008	-1.523	-0.263	0.640	1.562
Sit to Stand Test	1.587	0,002	0.679	2.521	0.615	1.627
Insomnia Severity Index (ISI)	-0.538	0,035	-1.092	-0.022	0.554	1.807
R2	0.519					
R2adj	0.437					
SF-36 mental health score	**Coefficient**	**P-value**	**Confidence interval 95%**		**Collinearity statistics**	
			Inferior	**Superior**	**Tolerance**	**VIF**
constant	23.952	0,462	-31.904	102.756		
Educational level	13.167	0.017	1.391	23.535	0.777	1.286
Number of persistent symptoms	-0.621	0.057	-1.245	-0.052	0.689	1.451
Affective state (HADS)	-1.402	<0.001	-1.964	-0.958	0.473	2.116
R2	0.545					
R2adj	0.468					

https://doi.org/10.1371/journal.pone.0278728.t004

are predictors of SF-36 mental health score. Higher educational level, higher affective affectation and lower number of persistent symptoms are predictor of worse quality of life, mental subscale. The models explain 51.9% of the SF-36 physical health variance, and 54.50% of the SF-36 mental health variance.

Discussion

This is an analysis of secondary data from an RCT conducted in Spain with 100 Long COVID patients with a diagnostic test for COVID-19 performed 12 weeks or more ago and regularly attended by primary helth care. In this way, it has been tried to obtain scientific evidence that helps to characterize clinical picture of Long COVID patients, as well as to identify factors associated with quality of life.

After becoming infected and the subsequent development of the disease, it has been determined that Long COVID patients have low levels of quality of life. Our study has identified low levels in all the dimensions evaluated in the SF-36 questionnaire, although with great variability, as expressed by the wide interquartile ranges (IQR), especially in the dimensions of physical and social function. In other words, even though the median of the eight subscales is low, there are large differences between the baseline status of patients with lower and higher scores. This could express variability of profiles, making it difficult to identify the effects of the disease. Greater variability is observed in mental health than in physical health of Long COVID patients. Along the same lines as our results, there are several studies that have determined a reduction in all vital areas after COVID-19 infection as for the most part, the participants presented persistent symptoms [36, 61, 62]. Two of these studies also used the SF-36 scale. However, other studies have been identified in which this questionnaire is used months after COVID-19 infection, which show a reduction in some areas, but not in all, since not all patients had persistent symptoms [28, 63–65]. The bibliographic review carried out with Ceban et al. (2022) verified that Long COVID patients have suffered significant functional deterioration or reduction in at least one dimension of their quality of life, compared to uninfected controls or their own state prior to infection [66]. In addition, our study verifies that women have significantly higher general health, according to the SF-36 subscale, than men. These results would be contradictory to previous evidence that has shown that women have a

greater potential to develop persistent symptoms with greater intensity and repercussion than men, so their general health becomes more affected [67, 68]. However, after regrouping the eight dimensions in physical health and mental health, it is found that there are no significant differences between men and women for these two general dimensions. Therefore, it is essential to treat this data with caution and continue investigating whether there are differences by gender.

The results of this study have been able to describe a representative profile of the Long COVID patient. Our sample is made up mostly of women. This is due because the impact of this disease on women is considerably greater [69, 70]. The answer to this reality could revolve around existing immunological differences based on sex, influenced by genetic or hormonal levels among others, which contribute to women developing stronger immune responses than men, such as a greater initial inflammatory reaction and increased production of antibodies [71, 72]. Furthermore, various studies affirm that this has also happened with COVID-19, which may favor persistent symptoms [73–75]. Therefore, from a genetic perspective, sex could be playing a determining role in the development of persistent symptoms after COVID-19 infection [8, 27]. On the other hand, the average age of the participants was 48, like other studies with Long COVID patients [28, 76–78]. However, there seems to be variability in this aspect, as there are other studies in which the average age is around 10 years older [79–82]. The explanation of these results of sex and age could be justified by a greater number of women workers in social and health services in the PHC, thus considering the workers of these services as people at high risk of infection. Consequently, a notable percentage of health workers were infected during the first months of the pandemic, and they could be the future Long COVID patients [83, 84].

Regarding some socio-demographic variables that make up the Long COVID patient profile, our linear regression model has identified that a higher educational level is a predictor of worse mental health in the SF-36. Possibly, Long COVID patients with a higher educational level know about the lack of available treatments and the ignorance of health professionals. This uncertainty causes frustration among Long COVID patients, thus reducing their mental health, as a previous qualitative study indicated [29]. On the other hand, our correlation analyzes reveals that people who are actively employed or retired have a significantly higher physical health score compared to those who are unemployed or in a situation of TWD. Employment habits have a positive impact on the physical health of the population, being the day being regulated activity at work [85], recently verified by studies carried out in times of COVID-19 [86, 87]. As for retired people, it is possible that they relate some health problems to their age or inability to work. This can reduce attributing certain symptoms, such as muscle or joint pain or memory loss, to the direct effects of their illness, in addition to feeling well physically because of their long-term progressive deterioration and life trajectory.

Also, our bivariant analysis conclude that the number of persistent symptoms has a negative impact on their health i.e. the higher the number, the worse physical and mental health data. The patients in this study present 16.5 symptoms on average, with an intensity of 7-8/10. The most frequent persistent symptoms are tiredness and fatigue (98%), short attention span and concentration (89%) and myalgia (85%). These results seem to be common among those affected, being in the same line as previous evidence [70, 88]. Existing literature reinforces that patients with a greater number of persistent symptoms suffer greater repercussions on physical function and a psychological burden that generates greater emotional discomfort [89–91]. Our linear regression results also conclude that a However, our linear regression results also conclude that a higher number of symptoms would be a predictor or poor physical health, but a lower number of symptoms would be a predictor of poor mental health. This fact could be reinforced by the frequent fluctuation and scarce disappearance of the symptoms themselves.

There are periods of time in which these patients may present fewer symptoms, but without recovering, which supposes an inexhaustible mental battle [92]. This reality was also reflected in another previous study, that is, it may be independent of the number of persistent symptoms of emotional well-being of the Long COVID patient [29]. In short, these results should be interpreted with caution, since the emotional well-being of these patients can be determined by other factors, such as a mental background prior to infection.

Furthermore, the results of the MoCA questionnaire verify the cognitive impairment suffered by these patients. Among the most persistent self-reported symptoms are: Short attention and concentration span (89%), Memory loss (81%) and Confusion or brain fog (71%), accompanied by neurological symptoms. These symptoms make it difficult or impossible to carry out routine activities of life, from cooking to driving, and therefore diminishing their quality of life [18, 76, 93, 94]. The study by Rass et al. (2021) used this same questionnaire 3 months after infection, finding frequent cognitive deficits, regardless of the severity of the disease, even in patients with mild disease [64]. The prevalence of this deterioration is higher after a follow-up period of 6 months, compared to other similar infections [95], which is why it is explained that in a longer time since the contagion these types of deficits persist. Thus, this cognitive impairment has the potential to affect routine actions, self-care and activities in society, which affects their quality of life [92]. Similarly, it occurs with the score obtained in the HADS questionnaire, which suggests the existence of moderate-severe anxiety-depressive disorders. This result is related to worse mental health, according to the linear regression results. Symptoms of anxiety, depression or sleep disorders would be very frequent among Long COVID patients [96, 97]. These symptoms are negative for the quality of life of people with persistent symptoms [64], as has been said.

Our results have also established a significant correlation between worse health literacy (HLS-EUQ16) and worse physical health in the SF-36. The low level of health literacy in this sample would be contradictory to the possibility of having health professionals, given their high rates of infection [98]. Research on this scale already predicts that the motivation and ability to access, understand and use information to maintain good health, which is associated with a state of good health [99, 100], so Long COVID patients would not be an exception. Also, the correlation between poor sleep quality and poor mental health should be highlighted, according to the results obtained in the ISI questionnaire and in mental health on the SF-36. Recent studies carried out with the general population affirm that sleep is causally related to the development of mental health problems [101, 102]. Reinforcing our results, several narrative reviews have verified how patients infected with COVID-19 frequently develop sleep problems accompanied by symptoms of anxiety and depression, among others [103, 104]. In addition, poor sleep quality is a predictor of impaired physical health of the SF-36, as would occur in the general population, and especially for females [105, 106].

On the other hand, correlation analyzes have concluded that physical functioning (Sit to Stand Test), self-efficacy (GSES-12) and patient activation (PAM) have the potential to promote good physical and mental health among Long COVID patients. A sedentary lifestyle contributes to the mortality of the world population, while regular and moderate physical exercise produces beneficial effects on people's health, such as the prevention of chronic diseases and increased life expectancy [107]. Physical exercise would be a non-pharmacological strategy for the treatment of musculoskeletal-type diseases, in addition to being a stimulant of the immune system, as has been shown with pathologies similar to Post COVID-19 Syndrome [108]. For these reasons, worse physical functioning in Long COVID patients is a predictor of worse physical health in the SF-36. These results are consistent with linear regression analysis. On the other hand, the high self-efficacy of the sample would refer to self-confidence to achieve a goal. In relation to health, a health behavior such as physical exercise, persistent over time, will

improve health [109–111]. In addition, the activation of patients (PAM) with chronic diseases refers to their skills, knowledge and abilities to manage their own health, as well as the health care of their environment [112, 113]. Recent studies of chronic patients relate low levels of activation with a higher degree of dependence for ADLs, worse management of their chronic conditions and progressive worsening of their symptoms [114, 115]. For this reason, despite not having identified studies that contemplate these personal constructs with Long COVID patients, they seem to be of great interest for Long COVID disease and its rehabilitation process towards a better quality of life.

Limitations and strengths

Our study has some limitations. First, although the secondary data analysis of RCTs are a good starting point to know the baseline situations of some investigations [116], they have some limitations. For example, causal interference is not possible, and the associations can be difficult to interpret. As this was an exploratory study, no calculation of the sample size or adjustment of the p value was performed. Therefore, the findings should be interpreted with caution and should only be considered. Secondly, a convenience sampling [117] was carried out, since some people were informed through an association of those affected. However, they were asked to contact their APS physician for referral and to confirm that they met the inclusion and exclusion criteria. Thirdly, some study variables have not been included, such as reinfections/need for hospital admission or vaccination doses administered. However, it has been considered that these variables do not answer the research question of this study.

Regarding the strengths, research on the Long COVID disease is scaled up and, particularly, the impact on the quality of life of those affected. For this reason, this study adds to the existing studies that show the great affectation that these patients suffer in their quality of life, as well as the associated factors. In addition, all the participants are usually attended in PHC consultations, so our results are representative of a PHC clinical population with this pathology.

Conclusion

In conclusion, patients diagnosed with Long COVID suffer a decline in their physical and mental health, which are proportionally and significantly correlated with the number of symptoms they present, cognitive impairment, a low affective-emotional state, related problems with their quality sleep and an acceptable level of health literacy. However, good physical functioning, as well as the patient's personal constructs of self-efficacy and activation, can help maintain a good self-perception of physical and mental health in Long COVID patients. In addition, our linear regression analysis has identified that a greater number of symptoms, poorer physical functioning, and poorer quality of sleep are predictors of poorer physical health. Similarly, a higher educational level, a greater affective impact and a lower number of symptoms are predictors of poorer mental health. Based on the evidence generated in this study, the need to design extensive rehabilitation programs that consider both the physical and mental health of patients diagnosed with Long COVID is verified, thus obtaining an improvement in their quality of life.

Supporting information

S1 Table. Frequency and intensity of persistent symptomatology.
(DOCX)

Acknowledgments

The authors would like to thank the Network for Research on Chronicity, Primary Care, and Health Promotion (RICAPPS, code RD21/0016/0001-Health Institute Carlos III, Spain), the Primary Health Care Research Group of Aragon (GAIAP-B21-20R) of the Department of Science, the University and Knowledge Society of the Aragon (Spain) government, and FEDER Funds 'Another way to make Europe'.

Declarations

Consent for publication. Not applicable given that the data are anonymous and no individual images are presented.

Registration. This RCT was registered in the ISRCTN Registry platform (registry number: ISRCTN91104012) on 10/02/2022.

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Manuscrito IV. The emotional well-being of Long COVID patients in relation to their symptoms, social support and stigmatization in social and health services: a qualitative study.

Samper-Pardo *et al. BMC Psychiatry* (2023) 23:68
https://doi.org/10.1186/s12888-022-04497-8

BMC Psychiatry

RESEARCH

Open Access

The emotional well-being of Long COVID patients in relation to their symptoms, social support and stigmatization in social and health services: a qualitative study

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Abstract

Background Long COVID patients have experienced a decline in their quality of life due to, in part but not wholly, its negative emotional impact. Some of the most prevalent mental health symptoms presented by long COVID patients are anxiety, depression, and sleep disorders. As such, the need has arisen to analyze the personal experiences of these patients to understand how they are managing their daily lives while dealing with the condition. The objective of this study is to increase understanding about the emotional well-being of people diagnosed with long COVID.

Methods A qualitative design was created and carried out using 35 patients, with 17 participants being interviewed individually and 18 of them taking part in two focus groups. The participating patients were recruited in November and December 2021 from Primary Health Care (PHC) centers in the city of Zaragoza (Northern Spain) and from the Association of Long COVID Patients in Aragon. The study topics were emotional well-being, social support networks, and experience of discrimination. All an inductive thematic content analyses were performed iteratively using NVivo software.

Results The Long COVID patients identified low levels of self-perceived well-being due to their persistent symptoms, as well as limitations in their daily lives that had been persistent for many months. Suicidal thoughts were also mentioned by several patients. They referred to anguish and anxiety about the future as well as a fear of reinfection or relapse and returning to work. Many of the participants reported that they have sought the help of a mental health professional. Most participants identified discriminatory situations in health care.

Conclusions It is necessary to continue researching the impact that Long COVID has had on mental health, as well as to provide Primary Health Care professionals with evidence that can guide the emotional treatment of these patients

Keywords Long COVID, Emotional well-being, Social support, Stigmatization, Qualitative study

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Background

The highly contagious coronavirus disease (COVID-19) that broke out at the end of 2019 led to a global pandemic [1, 2], posing a serious threat to health and well-being worldwide [3, 4]. The virulence of COVID-19 in the human body can vary greatly, with some patients

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displaying no symptoms and others dying from the disease [5]. It is estimated that around 10 to 20% of people affected by COVID-19 display ongoing symptoms for the months following the acute phase of the disease [6, 7]. In October 2021, the World Health Organization (WHO) released an official definition of the condition in the adult population, referring to it as a Post-COVID Condition [8]. This text will refer to it as Long COVID given its frequent use and wide acceptance in the scientific community.

Long COVID

Long COVID is a multisystemic syndrome that is characterized by a variety of physical and neuropsychiatric symptoms that are persistent or cyclical and last for weeks after having contracted the acute Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection [9–11]. Various studies indicate that Long COVID is more prevalent in adult women who have had severe COVID-19 symptoms and a history of psychiatric problems [5, 12, 13].

It is estimated that the average recovery period following an infection of COVID-19 varies between two to 3 weeks depending on the severity of symptoms [14–16]. The United Kingdom's Office for National Statistics states that, irrespective of their severity, one in five people may experience symptoms after the first 5 weeks or more following the initial infection, while one in 10 people may experience symptoms after 12 weeks or more [17]. Due to this unprecedented scenario, at the end of 2020, the National Institute for Health and Care Excellence (NICE) announced that COVID-19 symptoms may last for four to 12 weeks, and thus diagnosing people who maintain or continue to develop symptoms that cannot be explained by an alternative diagnosis as having Long COVID [18]. In addition, proof of having COVID through the use of a diagnostic test was not set out as a criterion as many people did not take one, especially during the first months of the pandemic or in the case of asymptomatic patients [18].

Regarding the characteristic symptomatology of this new pathology, it is confusing, not very specific [19], and may be persistent or fluctuating over time [18]. Patients with Long COVID may present a combination of symptoms that have an effect at the respiratory, dermatological, cardiovascular, gastrointestinal, and/or neuropsychiatric levels [20–24]. The most predominant symptoms include extreme fatigue, shortness of breath, low-grade fever, cough, headache, chest and/or throat pain, muscle and joint pain, palpitations, diarrhea, loss of smell and/or taste, skin rashes, cognitive deficits such as mental fog, myalgias, and tingling in the upper and lower extremities [25–29]. Moreover, while less common, low oxygen saturations [30], as well as cardiovascular abnormalities such as arrhythmias, a high heart rate, myocarditis, or acute heart failure [31], have also been observed. It is important to note that similar symptoms, such as chronic fatigue, illness, or depression, were reported in patients during the SARS-CoV outbreak in 2002 [32].

The UK National Health Service (NHS) added depression and anxiety to the list of the most frequent COVID-19 symptoms, associating them as potential effects of experiencing extreme fatigue and other prolonged physical symptoms [33]. However, several studies point to the existence of neurological aspects that would contribute to this mental discomfort [12, 16].

Long COVID and mental health

An increasing number of studies are researching the negative emotional impact on people who have had COVID-19 and have persistent symptoms; among the most prevalent mental pathologies are anxiety, depression, sleep disorders, post-traumatic stress disorder (PTSD), and mood fluctuations [34–39]. A recent report has detected similar symptoms in affected children [40]. The existing evidence suggests that patients with Long COVID have experienced reductions in their quality of life [41, 42]. A study carried out with hospitalized COVID-19 patients concluded that after eight to 12 weeks following the contraction of the infection, patients with persistent symptoms suffer a deterioration in all domains of their lives, including their mental health, when compared to the infected population without persistent symptoms [26]. In this respect, it has not yet been concluded whether these mental symptoms are triggered by the disease itself and its duration, or whether it is a neurological impact that causes them, such as a cognitive impairment caused by moving megakaryocytes from the bone marrow to the brain, thereby blocking blood flow [43]. In the case of psychiatric symptoms, COVID-19 could affect the brain indirectly by increasing cytokines [13], and some patients may even experience the appearance of white brain spots or microbleeds after the infection [44, 45]. Therefore, it is estimated that there may be a neurological cause that affects mental health after COVID-19 infection [12].

However, even setting aside the possible organic causes, genetic agents are not the only moderators of health, since there are various interactions between environmental and social factors on the health of the population. To our knowledge, the scientific evidence on the self-perceived mental health of Long COVID patients is still limited. Some qualitative studies have been identified where patients refer to their emotional well-being, in relation to their Long COVID pathology, highlighting the complexity and emotional challenges of living

with the disease [46–51]. These patients are fearful about becoming reinfected with COVID-19 and experiencing the consequent deterioration and have anxiety due to the uncertainty regarding the evolution and scientific ignorance of society in general and, particularly, of health professionals [46, 48, 49]. Patients with Long COVID seem to be dissatisfied and disappointed with the treatment they receive from the health care system [50]. Likewise, some patients present depressive symptoms related to their own symptomatology and the physical state in which they find themselves compared to what is usual for them [49]. They state that they cannot recognize themselves, due to the significant changes they have experienced in terms of their capacities [51]. In addition, the change in sleep patterns, the inability to perform physical exercise, and a worse economic situation have been related to the emotional discomfort of these patients [52, 53].

Moreover, there are few studies on other social aspects, such as social support or society's stigma and discrimination toward this group of patients. In general, people with adequate social support have a lower mortality risk compared to those without it [54]. Therefore, social isolation is considered a mortality risk factor for any cause of death [55]. This highlights the impact that poor social networks have on mental illnesses [56]. In general terms, social support can be a moderator for mental illnesses through other psychosocial factors [57, 58]. Various studies have examined social support through different lenses such as social integration and participation as well as both the real and perceived instrumental and emotional support received [59–61]. In relation to social isolation, there are other social variables such as stigma and discrimination. Consequently, some studies have delved into the stigma generated during the pandemic. Specifically, the study by Bhanot et al., (2021) indicates that the most stigmatized people have been those infected by COVID-19, the direct contacts of those affected, front-line health personnel, and people belonging to the lowest social classes. Among these groups would be Long COVID patients, as infected people and also with persistent symptoms, especially due to the fear of contagion generated at the beginning of the pandemic [62]. This stigmatization is in relation to the difficulty experienced in accessing different health services in the context of health care system deficits [63]. Consequently, this social rejection leads to the social isolation of these patients and negatively affects their physical and psychological health and general well-being. Furthermore, this discrimination may reduce their likelihood of seeking medical care and treatment, for fear of being shamed and stigmatized by society [62, 64].

Therefore, the objective of this study is to deepen our understanding of the emotional well-being of people diagnosed with Long COVID, as well as their social support and experiences of discrimination and social stigma.

Methods

A qualitative design was created and carried out in order to collect information from patients suffering from Long COVID using an intentional sampling method. This research represents the first part of a study funded by the Carlos III Health Institute (PI21/01356), with the objective of establishing community interventions to improve the quality of life of patients with Long COVID using a citizen science approach.

Participants agreed to participate in the study and signed a consent form. Ethical approval was granted by the Ethics Committee for Clinical Research of Aragon (PI21/139 and PI21/454). All the procedures required for the development of this work complied with the ethical standards of this Committee and with the Declaration of Helsinki of 1975. All participants signed an informed consent form and their data were anonymized and only used for the purposes of the study.

In-depth interviews and focus groups were used to collect subjective data and gain an understanding of the processes involved in the generation of the discourse [65]. Highlighting the suitability of this type of methodology should be highlighted, since it allows us to delve into the subjectivity of the patient and generates significant evidence that brings us closer to understanding the emotional impact on various groups of people [66–68]. The research team used both individual interviews and focus groups to encourage more content to be shared in the discourse through social interactions. The study used two interviewers who were external researchers with scientific knowledge about Long COVID and who had previous experience in conducting qualitative research with Primary Health Care patients. Neither interviewer had had previous contact with any of the interviewees, nor were they aware of their identities. Before carrying out the interviews, they were both provided with the interview guides so that they could rehearse the individual interviews and focus groups through role-playing.

The participating patients were recruited from PHC centers in the city of Zaragoza (Northern Spain) and from the Association of Long COVID Patients in Aragon. When health professionals identified a potential patient, they informed them about the possibility of participating in the study and verified whether they met the inclusion criteria. Prior informed consent, as well as the individual's data and contact details were provided to the research group so they could contact the patient and verify that they did not meet the exclusion criteria. Through this procedure, the members of the Association interested in participating were identified as potential candidates.

The inclusion criteria for participating patients were outlined as the following: 1) being over 18 years old; 2) having been diagnosed with Long COVID by a general practitioner (GP) or specialized doctor; and 3) having tested positive for COVID-19 (PCR, antigens test, or serology). The exclusion criteria were the following: 1) not being able to respond to the interviewer; 2) presenting a high cognitive impairment from any cause; 3) and be receiving palliative care.

Finally, 35 patients were included in the sample. An independent researcher carried out the individual randomization process using a computer-generated blind sequence with a list of participants. In total, 17 participants were interviewed individually and 18 participated in two focus groups. The allocation was not blind due to the nature of the study. A researcher called each participant to confirm the assigned intervention and their participation. The interviews and focus groups were carried out in November and December 2021. The data obtained in the study are considered representative of the population that met the inclusion criteria given that they are similar to other studies in terms of gender, age, number, and intensity of persistent symptoms [69–71].

All participants met the study criteria and agreed to participate in their assigned intervention. Table 1 shows the main demographic data of the 35 participants in terms of the variables: age, gender (men/women/other), marital status (single/married or in a relationship/separated or divorced/widowed), educational level (no formal studies but can read and write/primary education/secondary education/university education), employment status (employee/employee with temporary work disability/ unemployed, receiving unemployment benefits/ unemployed, not receiving unemployment benefits/ retired).

The sample included patients with various profiles in terms of their gender, age, time elapsed since infection, educational level, and marital status. Of the 35 patients, 71.4% were women, with a mean age of 49 years (SD: 10.81), with secondary education (54.3%) or university education (34.3%), married or in a relationship (54.3%), and in a situation of temporary work disability (62.9%). In addition, the average time elapsed since infection was 15 months (SD 4.0).

A standardized protocol was designed to guide the individual interviews and focus groups and was based on a list of topics and informal interviews with patients with Long COVID in the PHC setting that had been developed by other researchers who were developing other research studies with patients suffering from this condition. The research design was guided by the researchers of this study and PHC professionals. The list of topics was based on previously published studies [12, 17, 24, 41, 48, 51, 72]. Table 2 shows the list of topics and final questions that were used by the interviewers to guide the interventions. Firstly, the individual interventions were carried out and, secondly, the focus groups were carried out, to note the interactions between the participants, the differences in opinion, the debates, and the dynamics that arose.

Table 1 Characteristics of participating patients

Variables	Patients ($n = 35$) N (%)
Age	
20–40 years	8 (22.9%)
41–60 years	20 (57.1%)
> 60 years	7 (20%)
Gender	
Male	10 (28.6%)
Female	25 (71.4%)
Marital Status	
Single	4 (11.4%)
Married or in a relationship	19 (54.3%)
Separated or divorced	10 (28.6%)
Widowed	2 (5.7%)
Educational level (%)	
No formal studies but can read and write	1 (2.9%)
Primary education	3 (8.6%)
Secondary education	19 (54.3%)
University education	12 (34.3%)
Employment status (%)	
Employee	6 (17.1%)
Employee with TWD[a]	22 (62.9%)
Unemployed, receiving benefits	1 (2.9%)
Unemployed, not receiving benefits	1 (2.9%)
Retired	5 (14.3%)

[a] TWD: temporary work disability

The objectives of the study were indirectly addressed and the questions asked about the topics were answered in an open manner. The interviewers and/or moderators were introduced to the participants as health professionals and researchers. Specifically, they were two psychologists who were members of the research group and they assumed a minimal role of merely orientating the interviews and focus groups and limited their interventions to addressing the topics in the script. The environment for data collection where the interviews and focus groups took place was a meeting room in a health center. Only those participating in the interviews were present in order to ensure the confidentiality of the responses. The in-depth interviews lasted between 20 and 60 minutes and the discussion groups lasted between 40 and 75 minutes. All

Table 2 Topic list and questions for patients

Topic list	Questions for patients
Before the interview	1. Greetings, words of thanks, and introduction of the interviewer and observer 2. General information about the topic to be discussed and the objective of the session 3. Explanation of ethical aspects (confidentiality, informed consent, and permission to record) 4. Explanation of the interview dynamics (We will ask some questions to find out about your experiences. We are interested in your opinions. Before we continue, do you have any questions or any doubts? Do you agree to participate?)
Emotional well-being	How do you believe your ongoing symptoms have affected you on an emotional level?
Social support networks	Do you consider yourself to have a social network, such as family and friends, to support you through your ongoing symptoms? How do you consider your social network to be?
Experiences of discrimination and perceived social stigma	Do you believe you have faced discrimination due to having Long COVID? Is there a certain stigma surrounding it?

the sessions were digitally audio-recorded and transcriptions were made in order to obtain the final set of qualitative data for analysis. None of the interviews were repeated. In this way, as the same interviewers were used throughout the study, they were the ones who perceived that information saturation had already been reached in the focus groups as well as individual interviews.

In order to assess the scope of the discourse, an inductive thematic content analysis was carried out in pairs so as to explore, develop, and define the emergent categories of analysis that derived from the individual interview and group data [73]. This analysis was carried out by two researchers independently, although both used the topic list from which the categories emerged as a guide. There were no discrepancies, except for the idea of abrupt-appearing depression, which was consensual, as shown in the results. Subsequently, the categories that emerged were coded from the list of topics, based on previously published studies [12, 17, 24, 41, 48, 51, 72]. The analysis as a whole was carried out iteratively using the NVivo software, as agreed between the two researchers, and the interpretations of the data were discussed with the interviewers and participants to obtain their consent [74]. In this way, a methodological triangulation was carried out among participants, interviewers, and researchers who participated in the analysis of the results, resulting in greater consistency and rigor and ensuring a correct interpretation of the discourse.

Results

As shown in Fig. 1, a total of 10 categories were obtained, which after being analyzed, were unified and grouped into 3 main themes: 1) Emotional well-being; 2) Social support networks; and 3) Experiences of discrimination and perceived social stigma.

Emotional well-being

Very low moods are common among participants with Long COVID due to their symptoms and the limitations they face in their day-to-day lives that appear fairly suddenly and have been ongoing for many months. Patients report that they suffer from sudden episodes of sadness. In the interviews and focus groups, patients mentioned that they feel that having Long COVID is a battle for their bodies and they find it difficult to regain their previous life: they feel that they have suddenly aged and have to mourn the life they have lost. In addition, they are aware that depression and their state of mind make it difficult for them to do rehabilitation exercises and try to resume their previous social life. Suicidal ideas were also mentioned by several participants.

Well, I've been through a battle, this is like going through a battle. 1 day you have your life, and the next day it has been taken from you. (Female, 50 years old, 10 months with Long COVID).

I am at my best at home and locked up because I am not the same person I was, and I myself see that I am being consumed. (Male, 62 years old, 20 months with Long COVID).

I've been very down for a month and I don't even feel like doing the respiratory rehabilitation exercises. I [have become] the woman in pajamas. I don't feel like doing anything. (Female, 39 years old, 12 months with Long COVID).

I also thought about dying... you start to think that you do not want to live like this… (Female, 43 years old, 20 months with Long COVID).

Exactly, I asked myself why I should want to live like this... (Male, 49 years old, 9 months with Long COVID).

They report anguish and anxiety about the future, not only due to how their persistent symptoms could evolve but also due to the fear of possible reinfections and relapses. A fear of reinfection is apparent in the interviews and focus groups. Reinfection could lead to a

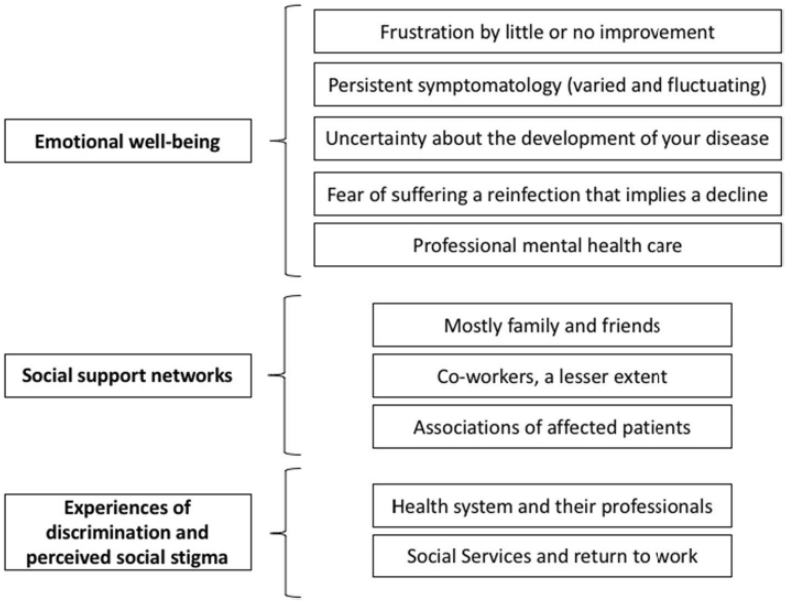

Fig. 1 Graphic representation of the central aspects of the results

relapse, and further impact their lives as well as the lives of their relatives and cohabitants.

Then there's the whole psychological issue, the [fear of] crowds… (Male, 43 years old, 8 months with Long COVID).

For us, catching it is no longer the problem. It's the fear of what comes after that…. for me catching it again is unthinkable, I don't know how I would deal with it. So, socially things are very difficult for me… and I also control my environment… (Female, 59 years old, 14 months with Long COVID).

Anguish and anxiety are also reflected in the interviews and focus groups in relation to the fear of having to return to work as they hold the belief that their state of health will not allow them to do their job correctly.

I am very concerned about the future… we should have support for readjusting to work when we return because I struggle to take my briefcase and run to a patient's emergency room because I am drowning [in work] and cannot do my job at the same pace as before… Now I have somewhat improved my concentration but I have a lot of responsibility. A lot. So, of course, if I make a mistake or commit negligence… (Female, 59 years old, 14 months with Long COVID).

I feel more depressed, and I try to be cheerful, but I wake up at four o'clock in the morning and it's hard for me to fall asleep. I'm worried, thinking about how this is going to end... Also, I have the issue of work, I am self-employed and have to work… (Male, 56 years old, 16 months with Long COVID).

Additionally, anger and frustration are also mentioned by the participants in response to their health status not having improved for months or still not having medical answers, etc.

At home, we spend the day arguing. Now we argue starting first thing in the morning and really, the most notable thing is that you don't see a way out. (Male, 40 years old, 11 months with Long COVID).

Many of the participants report that they have sought help from a mental health professional such as a psychiatrist, psychologist, or therapist. All those who have been to a mental health professional consider it to have been a very useful service that has helped them to cope with their situation. There is also a participant who talks about using her faith as a method to cope with the situation. Moreover, many participants have confirmed that the search for information has also been a means of trying to minimize fear, but they recognize that thinking about the uncertain evolution of the illness generates more anxiety. In addition, due to their desperation, some participants have tried to find a solution based on unreliable information. For example, using homeopathy or methods lacking scientific evidence. Therefore, it seems that refraining from seeking information leads to patients coping better.

What worked very well for me was going to a psychiatrist that the medical association gave us. I started to feel better. (Female, 59 years old, 14 months with Long COVID).

Psychologically, it has not affected me much. Perhaps it is due to my faith. I can say that it is thanks to God that I am here to tell the tale. (Female, 51 years old, 19 months with Long COVID).

I used to look for information online but, in the end, I decided that I am not going to look at anything apart from what the doctors tell me to. And now I'm happier. (Male, 60 years, 11 months with Long COVID).

Social support networks

Most participants report that they have received social support from family and close friends but also think that in social circles that are not as close, such as co-workers, there is less support. They also believe that ignorance about the disease has influenced the support they have received. Besides, many of the patients think that despite the willingness to help, it is not possible for others to understand the symptoms of the disease if they have not experienced it firsthand. Obviously, there is less support if there are COVID-19 deniers in the social network. Finally, the social support they have received from members of the Association of Long COVID Patients, which was created by the patients themselves, has been considered to be very relevant and useful.

Yes, yes, I do. My friends, well, the truth is that, yes, they are my lifelong friends... as well as my daughter, my siblings, all of them, yes. (Female, 63 years old, 20 months with Long COVID).

Yes, I think they try, but no one really understands you unless they have had it. Then, it takes a long time. It is long for me, for all of us. But I do have their support... (Female, 44 years old, 12 months with Long COVID).

I am a nurse, and there was no acknowledgment from my colleagues. Everyone thought I had anxiety when I had tachycardia... I asked for help and did not receive it. It was very hard. I don't know if it was the physical pain caused by the symptoms that was more difficult, or if it was the lack of understanding from my colleagues... (Female, 50 years old, 18 months with Long COVID).

> *When news about this began to appear, it was comforting because people then called you and said: "Hey, I've heard on the radio that there are more people like you." And it turns out I wasn't making this up. For me, that was wonderful. (Female, 64 years old, 20 months with Long COVID).*

My daughter, for example, does not believe in COVID and my friends are not vaccinated and do not believe in it. I tell them that I have long COVID but they tell me that I'm making things up in my head, and that makes you feel alone. (Female, 47 years old, 12 months with Long COVID).

Experiences of discrimination and perceived social stigma

In general, the participants affirm that they have not suffered discrimination from their social circle, including family, friends, and, to a less extent, from co-workers. It does appear in the discourse that most of the participants have suffered experiences of discrimination by health care workers and the social and health system prior to the long COVID disease being recognized. Participants attributed this to the initial lack of knowledge of what it meant to suffer from long COVID and the fear of becoming infected, which worsened throughout the first months and years of the pandemic.

Specifically, it happened to me at the hospital 1 day when I had an appointment with the pulmonologist. I was in the waiting room; I was wearing my mask and I started coughing. Well... I felt like I was a leper... (Female, 51 years old, 19 months with Long COVID).

> *Yes, there is or was some rejection. In the beginning, when I said that I had long COVID, which was not yet very well known, I was told "Get out of here, you are going to infect us", and that was from a doctor! They told me that I couldn't be there and that I should have stayed at home. Stigma doesn't come directly from people, but rather from fear and a lack of knowledge. More than telling these people you have to... no, it's the lack of knowledge like what I said at the beginning about doctors, that I had to go. They tell you that this is all psychological, you are somatizing, go to a mental health clinic... but well, fortunately, I think people are getting to know about it more and more. (Male, 44 years old, 12 months with Long COVID).*

Long COVID patients acknowledge that PHC professionals have taken an interest in them and have carried out regular follow-ups. However, they have identified greater discrimination on the part of specialist doctors, but they also recognize that there is not enough knowledge, nor action and treatment guidelines for their adequate health care. In general, participants claim that the blame for not knowing how to manage their persistent symptoms belongs to the health care system and not its professionals. Participants who are also health professionals are more critical of their fellow professionals. While they recognize that they are stressed and have limited knowledge and means, they should show more empathy.

The professionals do not believe you and come up with another problem [to explain symptoms], or tell

you directly that they do not know what is really best [for you]. Normally, what they do is treat it as a mental condition and it is not... (Male, 43 years old, 8 months with Long COVID).

But I know that I can't blame the doctors, I'm not going to blame the only ones who can fix it, but those above. What I would like to note is that we must fight for the medical establishment to take us seriously and that my GP goes out of her way for me. (Female, 59 years old, 14 months with Long COVID).

> *Well, yes, I am angry, not only with the health care system but also with professionals because I have told them: "the situation is stressing you out but we are sick and isolated at home, and you are not paying any damn attention." The way they are acting is an embarrassment. (Female, 50 years old, 18 months with Long COVID).*

Regarding the social security system, they are also very critical and feel discriminated against and misunderstood since most of them are being discharged a year after their sick leave began, and are not well enough to carry out their previous profession. They also criticize the review process and medical tribunals, etc., in which they feel that they are questioned regardless of the medical evidence they present. The participants who are health professionals also criticize the lack of recognition of COVID as an occupational disease when the infection was spread in the workplace.

There is no understanding at an institutional level. They do not help you, quite the contrary. That is what has seemed the hardest to me lately because they discharged me completely without even looking at me and without knowing how you really are, even though you have provided a thousand detailed reports, then that overwhelms you because if you can't cope with normal daily life, how are you going to consider going back to work? ... They think you're fine and that you can lead the life that you're used to, and therefore they don't help you. (Female, 44 years old, 13 months with Long COVID).

It's a very unpleasant feeling when you go for the INSS (Spanish National Institute of Social Services) review because you're treated like an animal. They put me on a chair, glued to a closet, and I had to leave everything on the floor. I was at the exit door next to the closet, in a cubicle as if I was - I don't know what... it's outrageous, outrageous. And you're always trying to show... You feel bad when you go in and worse when you come out. (Female, 59 years old, 14 months with Long COVID).

Discussion

This qualitative study has collected the self-perceived mental impact of patients with a Long COVID diagnosis. All participants have identified a reduction in their emotional well-being as well as an impairment in their general mental health due to the disease and its exhausting impact on many vital aspects. Elements with the potential to worsen their emotional state have been identified, such as the symptoms themselves, uncertainty about their evolution, and fear of suffering reinfection or discrimination from the health system, among others. In addition, it has been identified how they perceive social support from family and friends, and the positive impact of contact with mental health professionals. These data could serve as support for future research as well as indications for PHC professionals.

The qualitative methodology is an adequate method to obtain novel information of high value, as is the case of the experiences and subsequent sequelae of people infected with COVID-19, as well as the interactions of these patients with their community, health care system, and society [75, 76]. Research using qualitative methodology with Long COVID patients is still scarce, although it is possibly the most common in the study of this group of patients. Some existing articles, based on qualitative methodology, have delved into the emotional well-being of patients with Long COVID [46–51]. It is worth mentioning the study by Burton et al., (2021), which was able to identify factors such as persistent symptoms, lack of treatment, and uncertainty of evolution, which affect the mental health of patients. These results are in line with our findings, as will be detailed later [49]. Unlike other studies, the participants in this research have an average evolution time of 15 months from their initial COVID-19 infection, so their contributions may reflect a broader view of the evolution of the disease, as well as different experiences from a perspective of assimilation and great effort.

The approach and results obtained in this study are in line with the PERMA well-being theory, which states that adapting to living with a disabling or chronic illness has the potential to affect multiple components of well-being. It is also related to a reduced function of the individual regarding less social participation, which can lead to greater social isolation and negatively influence mental health and, in turn, be associated with a higher risk of developing mental pathologies [77, 78].

> *This study has delved into the emotional impact experienced by patients with Long COVID. Our participants emphasize a before and after in their lives and an irreparable change, referring to the adaptation process they have needed and continue*

to need to undergo for their new lives. It is not new that chronic diseases can be disruptive events in the lives of those affected [79]. Several studies describe this reality in relation to COVID-19, through ideas such as losing their sense of self, a significant impact on identity, and the separation between a pre-COVID life and a post-COVID life [51, 80–82]. Similar experiences have already been described by Charmaz (1983), who delved into the suffering of patients with chronic diseases caused by physical symptoms and psychological distress, in addition to daily limitations or social isolation [18, 83]. Ladds et al. (2020) describe the disease as "terrifying, confusing, and debilitating", based on the severity of its symptoms and several aspects reported by affected patients, such as the lack of medical knowledge, uncertain prognosis, and a stagnant evolution with no clear prospects for recovery [18]. In this sense, the participants in this study have established a direct relationship between persistent symptomatology and an anxious-deprived state, in addition to other aspects such as uncertainty. Reinforcing this idea, the previous bibliography affirms that fewer persistent symptoms are related to greater life satisfaction [72]. The Burton et al.'s study (2022) also states that post-COVID patients with ongoing symptoms have experienced mental health effects due to the symptoms themselves, the impact on their quality of life, the lack of care and health services, and the uncertainty of the trajectories of their disease, among other examples [49]. The negative mental effects can be related to physical symptoms, considering that a bidirectional relationship can be established between these variables: physical symptoms lead to poor mental health and a greater mental load can aggravate the perception of the physical symptomatology [35]. In addition, one of the keys to understanding the negative impact on the emotional well-being of these patients would not only be in the symptomatology itself (biological character) but also in the changes to patients' quality of life and routines (social character) [48]. Delving deeper into this idea, our results have related different negative sensations to their direct causes, according to the subjectivity of the patients, such as uncertainty due to the unknown development of their disease and frustration due to their lack of improvement and the lack of treatment and medical care. Coinciding with these findings, various studies have identified multiple causes that can generate concern, frustration, confusion, and anxiety in this group of patients, including: the lack of information and knowledge about the disease and its causes; ignorance of its evolution and the lack of treatment; the health care received; and the functioning of the health care system during the COVID-19 pandemic [18, 50, 80].

Regarding social support, most of the participants in this study have recognized family and friends as one of their main forms of support. Some studies confirm that this group of patients seek acceptance and understanding from those close to them, including family and friends, and also from health professionals [51]. In addition, other studies show how a multitude of family and friends were not only a source of emotional support but also offered their help with household chores or basic activities, although sometimes these actions turned out to be accompanied by misunderstanding and ignorance about the disease [48]. This last idea was reflected in our results, given that many participants say they feel understood only by other patients who experience the disease firsthand. In this sense, Macpherson et al. (2022) add that the closest relatives of the patients also require support, based on the need to understand the disease, which was recently cited by Ireson et al. (2022) [48, 51]. In short, family and friends are important companions who positively influenced the emotional well-being of patients, generating peace of mind in the face of various adversities, although some of them require professional action guidelines [81]. This study has also identified other sources of support, such as patients seeking alternative therapy or treatments, and professional help and mutual help groups, such as the Association of Long COVID Patients of Aragon, which has played a fundamental role in patients' attitudes, as reported by some of our participants [19]. As far as we know, no research has yet identified those elements with the potential to improve the emotional well-being of patients with Long COVID, and, as such, there should be an incentive to continue with this research.

Regarding the stigma generated, our study has identified two main sources of discrimination: the health care system and social services in relation to the workplace. Like in other studies [18, 80], a stigma generated by the general population, based on mistaken beliefs and ignorance of the disease, has been identified. In relation to the health system, patients with Long COVID claim to have encountered many difficulties in being treated by the relevant medical services, including mental health services [18]. This study has not been the only one to identify that, when patients try to receive optimal care, they are met with barriers, such as a lack of scientific knowledge about the disease, which has led some health professionals to question the veracity of the patient's symptoms or has resulted

in them associating the symptoms with psychiatric origins without carrying out previous tests [48]. Both a lack of knowledge and discriminatory treatment in health care settings have contributed to the emotional distress of many patients [50, 51, 82, 84]. As pointed out by Hadler (1996), "If you have to prove that you are sick, you cannot get better" [85]. Very similar experiences have been reported by fibromyalgia patients, who, at the beginning of the disease, had to fight for its diagnostic recognition, due to the refusal of health professionals to accept it [86]. Moreover, in relation to the workplace and, specifically, the process of returning to work is one of the issues that has caused the most anxiety and concern [81]. Our participants verify that there is a relationship between the inability to return to work and poor mental health, which is one of the biggest concerns for patients. This concern is not only due to their poor physical condition but also due to their cognitive and mental impact [18]. Regarding the process of being assessed by a medical committee to return to work, there are no other studies that have further explored the experiences of patients when describing this step and the misunderstanding generated when discharged from work. For many of our participants, the treatment they have received has been inhumane. Several of them have requested protection measures and investigations to carry out an adaptation of this process. These discriminatory experiences must be taken into account because they may have a negative impact on the health of those affected, thus generating health inequalities in stigmatized patients with Long COVID [87].

The results of this study suggest the need to address the mental symptoms that Long COVID patients have developed from a clinical perspective. Our patients have perceived improvements in their well-being after being treated by mental health professionals. In fact, some health care centers have implemented low-threshold therapies or counseling for the general population affected by COVID-19 to promote emotional support in the early stages of the disease [88]. Thus, the implementation of brief questionnaires aimed at identifying the psychological needs of patients with Long COVID is proposed to encourage referrals to specialized health professionals who support these patients in their mental recovery process alongside their physical rehabilitation [36]. As an alternative to the lack of specialized or complementary mental health services, Gómez-Conesa (2021) proposes approaching the different mental problems of patients with Long COVID using rehabilitation physiotherapy [89]. Nonetheless, there is still a lack of attention with regard to Long COVID and the prevalent mental health problems experienced by the patients [90]. Indeed, the multidisciplinary approach required in the management of this disease may become one of the greatest challenges for the health and social security system in the coming years [91]. It is necessary to not only implement purely clinical approach strategies, since this group of patients also narrates how their relationships with their community and society at the time have been affected by their illness, developing a tendency toward social isolation. For this reason, community reintegration must also be considered from a clinical point of view. Some studies refer to the effectiveness of the social prescription methodology in the context of the COVID-19 pandemic. This method allows GPs and other PHC professionals to suggest social and non-clinical activities to do in the community to their patients, thus caring for their physical health, as well as helping create a feeling of belonging within the community [92]. Social prescription was an important source of support for many people, especially for vulnerable groups, in the face of the interruption of various services due to the pandemic [93–95]. In addition, social prescription has the potential to improve the emotional well-being of the population [96], as shown in this study with community participation in the previously-mentioned Association. Therefore, given the results obtained and the lack of available treatments, this technique could be a useful tool for PHC professionals and improve the emotional well-being of the patients.

Regarding the strengths of this study, we believe that our data are representative of our patient population as it includes a wide range of sociodemographic profiles. Additionally, a large part of the sample was diagnosed over a year ago, and consequently, they have shared stories and experiences that are very rich in content from an evolutionary perspective, along with examples of the unawareness of those diagnosed most recently. In addition, the choice of a qualitative methodology has made it possible to actively evaluate Long COVID, its different areas of involvement, and the emotional impact in relation to important aspects of the participants' lives. A limitation of this study was that we did not assess poor psychiatric health prior to the COVID-19 infection and, as such, the results cannot express the prevalence of psychiatric illness before and after infection. In addition, by not collecting the experiences of mental health professionals, the subjective discourse of the participants makes it impossible to explain the complex relationship between pre-existing psychiatric illness and the burden of Long COVID on their current mental health.

Conclusions

Patients with Long COVID experience various factors that negatively affect their mental health and emotional well-being. Their personal testimonies are essential to understand and treat the disease with a comprehensive approach, since the biomedical model based on objective indicators is not consistent, which generates a stigma within health care. For this reason, health and social services must implement and strengthen access routes, care, guidance, and new programs for professionals addressing both the physical and mental health of patients with Long COVID.

Acknowledgments
The authors would like to thank the Network for Research on Chronicity, Primary Care, and Health Promotion (RICAPPS, code RD21/0016/0001-Health Institute Carlos III, Spain), the Primary Health Care Research Group of Aragon (GAIAP-B21-20R) of the Department of Science, the University and Knowledge Society of the Aragon (Spain) government, and FEDER Funds 'Another way to make Europe'.

Authors' contributions
BO-B, MS-P, and SL-H drew up the research design. BO-B, MS-P, and SL-H developed the study and coordinated the fieldwork. BO-B made the qualitative analysis. FM-L, RM-B, and CB-M have helped with project coordination. BO-B and MS-P wrote the manuscript. BO-B is the principal researcher for the project. All authors reviewed the manuscript content and approved the final version for submission.

Funding
This work is supported by the Carlos III Health Institute grant number PI21/01356, FEDER Funds 'Another way to make Europe'. The funding body will conduct an audit trial once a year.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study received the approval of the Ethics Committee for Clinical Research of Aragon, Spain. All procedures performed were in accordance with the ethical standards of this Committee. Written informed consent was obtained from all participants who were included in the study.

Consent for publication
Not applicable because the data are anonymous and there are no individual images.

Competing interests
The authors declare that they have no competing interests

Received: 3 August 2022 Accepted: 26 December 2022
Published online: 25 January 2023

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Manuscrito V. Use of community resources as health assets for rehabilitation of people with Long COVID in northeastern Spain two years after the outbreak of the COVID-19 pandemic: qualitative study.

Samper-Pardo *et al. Archives of Public Health* (2023) 81:125
https://doi.org/10.1186/s13690-023-01139-7

Archives of Public Health

RESEARCH Open Access

Use of community resources as health assets for rehabilitation of people with Long COVID in northeastern Spain two years after the outbreak of the COVID-19 pandemic: qualitative study

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Abstract

Introduction The epidemiology of Post COVID Condition is not yet known. There are different treatment options, but they are not recommended or suitable for all those affected. For this reason and due to the lack of health treatment, many of these patients have tried to carry out their own rehabilitation through the use of community resources.

Objective The objective of this study is to deepen into the understanding about the use of community resources as assets for health and rehabilitation by people with Long COVID and their utility.

Methodology A qualitative design was carried out with the participation of 35 Long COVID patients, of which 17 subjects were interviewed individually and 18 of them were part of two focus groups. The participating patients were recruited in November and December 2021 from the Primary Health Care centers and through the Association of Long COVID patients of Aragon. The research topics were the use of community resources, before and after their infection by COVID-19, rehabilitation through their use, as well as barriers and strengths for their employment. All analyses were performed iteratively using NVivo software.

Results Long COVID patients who have used community resources for rehabilitation have seen an improvement in their physical and mental health. Most of them, specifically those affected, have used green spaces, public facilities, physical or cultural activities and associations. The main barriers identified have been the symptoms themselves and the fear of reinfection, with the main advantage of these activities being the perceived health benefits.

Conclusion The use of community resources seems to be beneficial in the recovery process of Long COVID patients, so it is necessary to continue delving into this topic and promote the formal use of the Recommendation of Health Assets from Primary healthcare.

Keywords Community resources, Health assets, Rehabilitation, Long COVID, Qualitative study

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Text box 1. Contributions to the literature

- The formal social prescribing by Primary Health Care in Spain has been little studied, so these results are useful for professionals to implement it.
- As far as we know, there are no studies that have delved into the use of community resources as a rehabilitation method for Long COVID patients.
- The findings of this study contribute to the validation of social prescribing as a rehabilitation tool, specifically for Long COVID patients.

Introduction

In October 2021, the World Health Organization (WHO) established the official definition of "Post COVID-19 condition" [1], more commonly known as "Long COVID". It is regarded as a novel syndrome with multisystem involvement, characterized by a varied range of both physical as well as neuropsychiatric symptoms. These can be persistent or cyclical, lasting weeks after being infected with COVID-19 [2–4]. The epidemiology and pathophysiology of the disease, as well as the resulting complications, are not known in great depth [5]. As a result, the multidisciplinary approach required for the comprehensive care of patients will likely become one of the biggest challenges for health and welfare services in the coming years [6]. In this regard, the Long COVID forum group has declared that its present and future lines of investigation into Long COVID will focus on its clinical characteristics, through researching and developing treatments [7].

At present, the treatment options available for patients are limited. Only rehabilitative treatments have been shown to be effective in improving the symptoms of Long COVID since no large-scale experimental studies have been conducted on the effectiveness of pharmaceutical drugs to alleviate symptoms [8]. With regard to the rehabilitation offered to patients, various studies suggest that early rehabilitation is vital for overall improvement and better long-term functionality [9, 10]. By contrast, state that the starting point of rehabilitation should be established with caution since in some cases it may cause irreversible harm, thus meaning it is not appropriate for all patients [11]. The types of rehabilitation for Long COVID patients are judged to be similar to those for chronic fatigue syndrome, i.e., those physical and respiratory in nature. Although cognitive behavioral and graded exercise therapies have also been considered necessary, these have caused relapses in some patients [12–15]. Furthermore, this group of patients has required professional care for their mental health, due to the negative effect the disease itself has had on the body and vital aspects of their lives [16, 17].

The need to rehabilitate and treat Long COVID patients leads us to consider the current state of the Spanish National Health Service (SNS) in the wake of the pandemic since the beginning of 2020. Specifically, during the first months of the pandemic, the SNS collapsed and was immersed in a major crisis characterized by a lack of resources in both material and personnel. This made it necessary to develop ethical guidelines for action [18–20]. Over two years later, different services provided by SNS such as recovery and rehabilitation and monitoring and waiting times have been adversely affected and have failed to meet demand [21, 22]. In the context of care for Long COVID patients, in addition the above scenario, there is a lack of knowledge regarding the disease and a scarcity of management guidelines for patients. Taking this all into account, we must consider other courses of action.

With the aim of widening the search for alternative rehabilitation treatments for patients, a seldom studied trend first identified in the UK appears to be gaining momentum. The technique, known as "Social Prescribing", is being used by primary health care (PHC) centers as a method of rehabilitation for Long COVID patients. However, only one qualitative study conducted in the UK has assessed the effectiveness of the tool, which promotes the use of social prescribers, as well as the involvement and strengthening of community support services [23].

In Spain, the social prescribing technique has been rolled out in a number of regions for some years, even though it is still under development. In fact, one of the objectives of the "Action Plan for Primary and Community Healthcare 2022-23", published by the Ministry of Health in Spain, is for it to be accessible in every region. The tool was established in the country under the adapted name, "Recomendación de Activos para la Salud" (Recommendation of assets for health) or RAS. Its name is present in regional plans around the country (In Aragon, Andalusia, Asturias etc.) RAS calls for the creation of different formal mechanisms to prescribe non-clinical alternatives to patients under the PHC umbrella, which have a positive impact on their health. It is a multidisciplinary technique, with health as the underlying focus, which allows individuals and companies to have the necessary means to improve their health [24–27] .

In this regard, a health asset can be defined as being "any factor or resource that enhances the ability of individuals, communities and people to look after their health and wellbeing." They have the ability to improve the circumstances of individuals or groups, improve or look after their physical, mental and social health and deal with stressful situations [28]. For this reason, health assets are general resources used to deal with difficulties and inequalities, as well as enhance capacities and skills towards what enables individual and collective health and empowerment to overcome difficulties in the face of inequality. It is essential to focus on skills and abilities

that enhance health, improve self-esteem and individual and collective empowerment [29, 30].

For all of these reasons, given the challenge of providing a response to Long COVID patients and the lack of evidence on RAS as a rehabilitation strategy for these patients, this article aims to generate scientific evidence in this field, in order to avoid the process of excessive medicalization as well as relieving the pressure on the rehabilitation services of the SNS.

Hence, the objective of this study is to deepen our understanding of the use of community resources as assets for health and rehabilitation by people with Long COVID and their usefulness.

Methods

Study design

A qualitative study based on interviews in deep and focus groups was carried out, through the thematic analysis based on the grounded theory, of an inductive nature [31]. Qualitative methods are optimal for delving into human experiences such as emotions, attitudes and expectations [32]. For this reason, this methodology was chosen in order to collect subjective information and access the perceptions and experiences of Long COVID patients, in relation to the use of community resources as health assets. The intention of conducting in-depth interviews was to be able to argue from calm. However, focus groups were conducted as interpersonal interactions can generate answers and insights that did not emerge during in-depth interviews [32]. The authors followed the consolidated criteria for reporting qualitative research (COREQ) checklist.

The results obtained in this study contributed to the design of a randomized clinical trial called: "Analysis of symptoms and quality of life of people with a prolonged diagnosis of COVID-19, and the efficacy of an intervention in primary health care using ICT" (ISRCTN91104012), registered on 10/02/2022 [33].

Sampling and sample size

The inclusion criteria of the participants were the following: being over 18 years of age and having been diagnosed with Long COVID by a general practitioner (GP) or PHC specialist. The exclusion criteria were the following: not being able to respond to the interviewer for any reason, presenting high cognitive impairment for any reason and/or receiving palliative care.

An intentional sampling strategy [34] was carried out among patients diagnosed with Long COVID treated in seven PHC centers in the province of Zaragoza (Northern Spain), and also from the "Long COVID Aragón" Patients Association. A recruitment time of twenty days was established, during the month of November 2021. Recruitment was carried out by the GPs themselves, who volunteered after a meeting with a member of the research team, in which the objectives of the project were explained. Each GP made a list of potential patients, using purposive sampling to obtain a heterogeneous sample and to be able to explore the topics of interest with breadth and depth [35]. Subsequently, each GP made face-to-face contact with each of the possible participants to verify which met the selection criteria. The GPs were provided with information documents about the study, which they could offer to interested patients, in which a telephone number appeared where they could obtain more information and confirm their wish to participate. When a potential patient contacted the research group, a researcher (SL-H) is in charge of resolving possible existing issues and making an appointment in person at the research group's headquarters, located in a PHC center in Zaragoza. Once the face-to-face meeting took place, the same researcher (SL-H) re-verified that the potential participant met the selection criteria and proceeded to sign the informed consent.

The research team established that the final sample size would depend on information saturation, established as the point at which no new information was extracted. Initially, a total of 39 subjects were interested in participating in the study. Finally, the sample size consisted of 35 participants, since 4 patients refused to participate due to the incompatibility of schedules to attend the interviews. Information saturation occurs when no new categories emerged after analysis of focus group data [35]. In this case, the second focus group did not provide new categories, so it was concluded that information saturation had been achieved. In this way, it was not necessary to start new recruitment processes.

Participant's characteristics

A total of 35 subjects participated in this study, 17 of them were interviewed individually and 18 took part in two focus groups, nine in each group.

Regarding their sociodemographic characteristics, 71.4% were women, the mean age of the participants was 49 (SD: 10.81) and the mean number of months elapsed since COVID-19 infection was 14.80 (SD: 3.90). Table 1 shows the main characteristics of the participants in terms of age, sex, marital status, educational level and employment status. This sampling was used to analyze differences between different patient profiles.

Data collection

All interviews and focus groups were conducted by a moderator (MS-P) and an assistant (NF-M); both PhDs, graduates in social work and nursing, with previous experience and specific training in qualitative methodology. The moderator and the assistant introduced themselves to all the participants as project researchers in charge

Table 1 Sociodemographic characteristics of participating patients; Zaragoza, 2021

Variables	Patients (n = 35)
Age	
20–40	8 (22.9%)
41–60	20 (57.1%)
> 60	7 (20%)
Sex	
Male	10 (28.6%)
Female	25 (71.4%)
Marital Status	
Single	4 (11.4%)
Married or in a couple	19 (54.3%)
Separated or divorced	10 (28.6%)
Widowed	2 (5.7%)
Education level (%)	
No formal education but can read and write	1 (2.9%)
Primary education	3 (8.6%)
Secondary education	19 (54.3%)
University education	12 (34.3%)
Employment status (%)	
Employee	6 (17.1%)
Employee with TWD	22 (62.9%)
Unemployed with benefits	1 (2.9%)
Unemployed without benefits	1 (2.9%)
Retired	5 (14.3%)

TWD: temporary work disability

Table 2 Topic list and questions for patients. Zaragoza, 2021

Topic list	Questions for patients
Before the interview	1. Welcome, acknowledgements, and introduction of the interviewer and observer. 2. General information about the topic to be discussed and the purpose of the session. 3. Explanation of the dynamics of the interviews regarding ethical issues (confidentiality and informed consent and permission to record), and the functioning (the interest is about the participants´ opinions, there are no right or wrong answers).
Assets for health in people with Long COVID	Rehabilitation activities or resources you use that help you improve your state of health. Was it on your own initiative?
Patients´ awareness of community resources	Knowledge of community resources is health assets and rehabilitation assets. Benefits (if any) of using community resources Availability of community resources
Barriers and strengths regarding the use of community resources	Barriers Strengths
Adequacy of community resources to meet the needs of people with Long COVID	Are there community resources that satisfy the needs of people with Long COVID?

of conducting the interviews and focus groups. None of the members of the research team were related to the participants.

All sessions were held during the months of November and December 2021, both in the morning and in the afternoon, in order to facilitate availability. They were held in a room attached to the PHC center, with an independent entrance, with the aim of creating an environment for discussion, away from the clinical context of the PHC services. It was a neutral room so that the participants did not feel conditioned or uncomfortable. During the interventions there was no person not interviewed, in addition to the two researchers mentioned.

A standardized protocol was planned to guide individual and group interviews. A topic list to be addressed during the interviews and focus groups was prepared, as shown in Table 2. The topic list was based on the previous bibliography [36–39] and the clinical experience of the research team. The objectives of the study were addressed indirectly and the questions asked about the topics were answered openly and progressively. The interviewer and the moderator assumed a minimal role in the orientation and limited their interventions to address the themes of the script. First, individual interviews with patients were conducted, followed by two group interviews until information saturation was obtained. No prior pilot interviews were conducted. In-depth interviews lasted between 20 and 60 min and group discussions lasted between 50 and 75 min. It was not necessary to repeat any interview, nor was there any interruption during the recordings. All sessions were digitally audio-recorded and transcripts of these records were obtained to compose a final set of qualitative data for analysis.

Data analysis

The transcription of the interviews and focus groups were carried out verbatim by two external researchers, with previous experience in carrying out this action. The names of the participants were anonymized with an assigned numerical code. Some participants reviewed the transcripts, approving them and, finally, the field notes made during the interviews were added.

Thus, the grounded theory approach was employed for data analysis [31]. Data collection, analysis, and axial theoretical coding were performed using a constant comparison process [40].

All analyses were performed iteratively using Nvivo software. Two authors (BO-B and BB-A) reviewed the transcripts independently, coding the sentences that contained significant units of analysis. These were grouped into categories, through a combination of emerging codes. The same two researchers reviewed and compared their findings, reaching an agreement on codes and categories. Two rounds of coding and discussion were

carried out to achieve clearer categories and improve the reliability of the process. This process was iterative with subsequent transcripts. No new categories emerged at the end of the second focus group, implying that information saturation had been achieved. Subsequently, a grouping of categories was carried out and these, in turn, into subcategories based on the uniformity of themes and subthemes of a higher conceptual level.

To check for consistency, the moderator (MS-P) and the assistant (NF-M) in all interventions checked their agreements by blind review [40]. Any disagreements between the two investigators were resolved by discussion.

At each step, an independent author (RM-B), acting as a reviewer, verified that the data consistently supported the analyses, in order to improve reliability and transferability [34].

Finally, axial coding was performed. The categories that emerged in the previous step were reorganized creating new relationships between the concepts. Among all the categories that emerged in the first phase of open coding, those that seem most interesting are selected to delve into their explanation [41]. This action was carried out by three researchers (MS-P, BO-B and BB-A) until a final agreement was reached.

Results

As shown in Fig. 1, a total of four main themes were obtained: (1) Activities considered as assets for health by Long COVID patients; (2) Patients' awareness of community resources as heath assets; (3) Barriers and strengths of the use of community resources; and (4) The suitability of community resources to the needs of Long COVID patients. In addition, a total of seven subcategories were identified.

Activities considered as assets for health by long COVID patients

The majority of the patients undertook activities that are considered beneficial for their health if their physical condition allowed them to. These activities, which count as health assets, mainly comprise physical exercise, walking and also cognitive stimulation activities via Internet apps. Many of these activities done during rehabilitation make use of community resources, such as green spaces and swimming pools. A smaller number of patients consider participating in group community activities as a health asset, but the main activities identified were memory workshops, Nordic walking groups, Pilates and yoga. It should be noted that most of these activities were carried out on the patient's own initiative, without the involvement of the health system. This is especially true of PHC, which is the closest to the community with regard to the social prescribing of community resources.

> *I walk a lot now in the park or I go out cycling. (Male, 56)*

> *I am enrolled in an organization that offers memory workshops. The problem is that they are designed for older people. (Male, 40)*

> *Here in my neighborhood for example, they do yoga in the civic center and I did look into it but I thought*

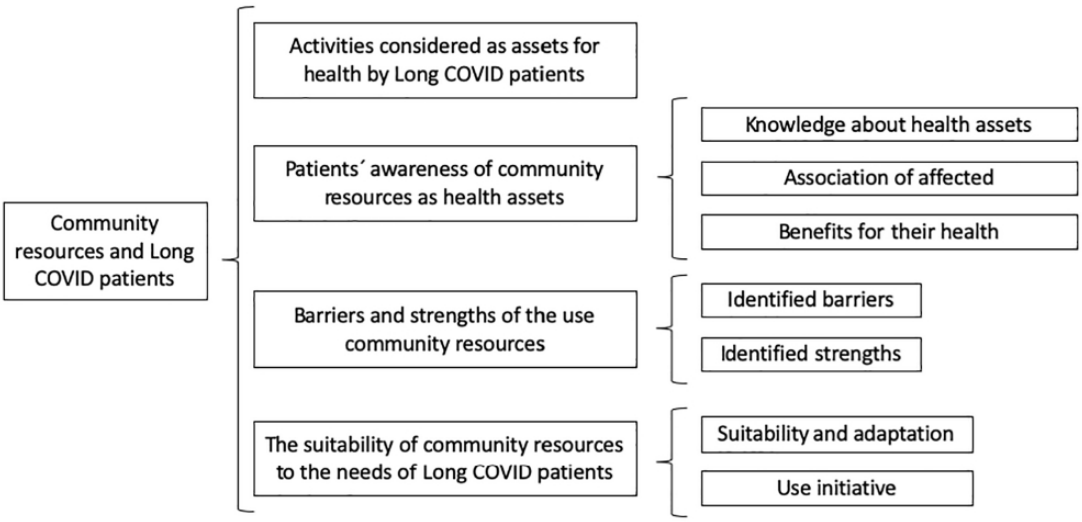

Fig. 1 Graphic representation of the central aspects of the results; Zaragoza, 2022

I wouldn't be able to keep up. (Female, 44)

I have been going to yoga sessions at the cultural center in my town for two months. It is going very well because I was not very good at the breathing techniques, and the truth is that it is noticeable. Also the stretching, the positions, etc.
(Male, 60)

Patients´ awareness of community resources as health assets

The majority of the participants identified parks, public transport, sports facilities and cultural activities organized by city councils etc. to be community resources. There are people who have a better knowledge of community resources, and who are overall more involved in the community and community activities. Furthermore, those that participate the most in community activities are retired or semi-retired people, who began to use community resources after finishing their careers.

When talking about community resources which are health assets, the majority of the participants said that they use parks and green spaces for Nordic walking or regular walking. People who had been involved the most in the community before their bout with Covid-19, say that they participate in other activities offered by local governments or neighborhood associations. This group considered these activities to be health assets to improve their symptoms. An example of these activities includes theatre, as they are working on their memory by memorizing scripts, an aspect which affects a large percentage of Long COVID patients. Other types of activities which stand out are yoga and Pilates. There are also patients who have enrolled on these types of community activities to improve their health, who did not do so previously. They report that they have found them to be very beneficial not only for the physical benefits but also in a psychological sense.

Some resources yes, maybe the bus sometimes, the parks for walks, sports facilities no. But I have been to the library sometimes. I've never been to local government activities.
(Male, 56)

I sometimes go to cultural centers, public parks because I walk (…) I am in two organizations in which I am very active. I belong to the 8 M assembly (Feminist society) where we have meetings and activities (…) I am also a member of COESPE (Pro-public pension pressure group) and we are very active… I am also retired, I live alone and do not work… it is not that I feel alone, but it is interesting to participate and do things with other people. It is productive and beneficial for both my physical and mental health.
(Female, 71)

I sought out yoga. I was a bit nervous as I hadn't done these sorts of activities before and the truth is it is going very well. I am more aware of my breathing and it helps me to relax.
(Male, 60)

There are patients who are members of their regional Long COVID Association and see it as a very valuable community resource and health asset. The association stepped up to respond to the needs of its members. As they say, there are people who have been involved since it was founded and it has helped them be active, and participate in activities. It also provides mental and social support and gives them hope in fighting the disease.

Yes, I am part of the Long COVID group in Aragon, this has also helped me a lot. Apart from the fact that they understand you, you don't have to explain things, we support each other. It is making me very active because I am quite involved. I am following all the topics, and reading everything that the scientists are sending me, news press releases, I am taking advantage of it a lot.
(Female, 44)

For me, there were some turning points. One of those was becoming aware of the 'Covid Persistence Collective.'
(Female, 64)

There is a general perception that the community resources they are using are helping them in their rehabilitation and state of mind.

Regarding the availability of community resources, in the urban environment, there is a perceived large availability of community resources. However, in the discourse, there is a lack of knowledge regarding them. Patients who live in rural areas, depending on the size of the town, say that they do not have the community resources, such as indoor swimming pools, that could be health assets. Therefore, they depend on having a car or public transport. Additionally, if they do have a car, they are not in a fit state to drive.

Everything can be improved. If we could have a heated swimming pool, it would be great for me. For example, if I want to go to a swimming pool to do exercises in the water, I would have to drive 30 km. Another thing is that driving is difficult because you

lack reflexes.
(Female, 70)

Barriers and strengths of the use community resources

As with barriers to the use of community resources as health assets, a declining state of health is mainly apparent in the discourse and fatigue is repeated as a main barrier.

At first, I was thinking of signing up for Yoga, but I get tired as soon as I do anything.
(Female, 44)

Another barrier that appears in the discourse is the fear that a new disease could cause a relapse in their health. Some people have improved their health status and they are scared of going back to the start and losing all of their improvement. On the other hand, aside from their physical and mental health, they have isolated themselves from society and are finding it difficult to rejoin. Lastly, it is apparent that feeling like a burden on others is also a barrier.

I notice that I feel I am very far away from 'normal' society
(Female, 42)

We have a fear of being infected again, know how it is… with a relapse, getting infected again I think it would ruin us… apart from being emotionally devastating, it could also be very dangerous physically.
(Male, 48)

I have realized that it has to be done step by step at my own pace because if I start doing things with a group of people, I will not be able to follow them. This would affect me mentally.
(Female, 70)

As a strength, they highlight their closeness and the fact that they are aware that they will be useful for their physical, mental and/or social condition.

When the local government organizes activities, I try to go in order to get out of the house and socialize a bit.
(Female, 50)

The suitability of community resources to the needs of people with long COVID

With regards to suitability, they are community resources that are generally viewed as useful in the recovery process. Notable examples are walking in parks and green spaces and yoga, which helps some people to be aware of their breathing. Other examples include memory workshops offered by local governments and elderly peoples' associations, however, the perception is that they need to be more adapted to their own specific needs (e.g. there is a marked deficiency in terms of verbal fluency).

However, it is the patients themselves who think about what community activities on offer can be useful to them during their rehabilitation. Only a few patients have had a health asset recommended to them by either PHC or mental health professionals. Normally it is the patient who looks for activities according to their needs or they are advised by friends and family. They try to participate in community activities as an additional treatment during their rehabilitation.

We are in a neighborhood association and memory workshops but they are not designed for us, they are designed for elderly people with differing needs.
(Female, 38)

Everything could be improved, and for patients with Covid, that goes without question. (Male, 62)

Discussion

This study is the first source of evidence in Spain on how the use of community resources, as a rehabilitation method, can improve physical and emotional well-being in patients diagnosed with Long COVID.

Scientific literature has demonstrated the benefits of health assets to improve physical and mental health [27, 37]. Some authors conclude that patients with general health problems and regularly in PHC consultations could benefit from social prescribing, thus decreasing the use of the SNS, making it a cost-effective alternative for the management of long-term conditions [42–44].

Among the main results of this study, it is noteworthy that most of the patients used a community resource, many rehabilitative in nature, to improve their physical and/or cognitive capabilities. The main motivation reported by the participants was to seek an improvement of the negative health effects arising from being infected with COVID-19 and its progression. Those who have used community resources reported improved physical ability and emotional management. Similarly, it has been shown that patients perceived that social prescribing increased their self-esteem and self-efficiency because they were able to access the help they needed and develop support networks [42]. This highlights how Long COVID patients were able to manage their health using community resources in their surroundings to meet their new needs which were not covered by the healthcare system.

Social prescribing, therefore, appears to be a useful tool in addressing persistent symptoms for these patients.

Another finding of the study, which is already present in the literature [27, 45], is that people with great ties and participation in their community before being infected with COVID-19, have greater knowledge of the resources at their disposal and make greater use of them. Therefore, strengthening these two aspects among the general population would have a positive impact on how people manage their own health. The factors influencing the effectiveness of social prescribing depend on the person's experiences with their referents, the type of activities on offer, the needs of the patients and the benefits for their health and well-being after the use of the resources [44].

The types of resources identified were mainly green spaces, local facilities, physical and cultural activities and societies. These types of resources are among the main types mentioned in the literature [46]. With respect to the availability of community resources, people living in urban environments report a greater availability of resources than those in rural areas. As established by the Spanish Ministry of Health's guidelines on community health [47], as well as inequalities in health, geographical inequality also exists. Those living in urban areas are advantaged over rural populations, with the latter being forced to travel to nearby localities.

Most of the health assets were suited to the patient's needs. Cognitive stimulation activities were an exception, as these cater for elderly patients with differing needs. In order to increase community engagement, it is essential to promote participation and collaboration between different entities in the community [48]. Collaborative work between social and health professionals and patients and community resources will enable the development of resources appropriate to the emerging needs of the population.

For social prescribing to be effective, patients have to be appropriately transferred from PHC to a relevant resource [44]. Regarding how they became aware of resources, the participants indicated that they mostly used their own initiative and, in some cases, they were referred to as a health asset by PHC professionals. In a qualitative study conducted in the United Kingdom, patients with Long COVID demanded greater awareness of available resources. After this need was identified, social prescribing was recommended to these patients through online platforms and by healthcare professionals [23].

On the subject of the knowledge of participants' barriers to using health assets, a number of factors stand out. These include a detreating health condition, fatigue, difficulties in resuming social contact, fear of reinfection and not being able to perform as they did before. Knowledge of these barriers would allow professionals and resources to approach patients to promote social prescribing or RAS. The use of social prescribing had a positive impact on increasing independence in the use of services, participation in community activities, control over their health and an improvement in the management of their health condition [37].

By contextualizing the results obtained, various factors that occurred during the pandemic should be considered. A number of community activities during the months with greater restrictions on gatherings were reduced compared to the pre-pandemic situation, which may have impacted the availability of resources. On the one hand, the lack of referral to community resources by PHC professionals may have been due to the fact that during the pandemic, this area of the health system was responsible for tracking COVID-19 cases and identifying COVID-19 contacts. In Aragon (Spain) specifically, the Community Care Strategy [49] has been in place since 2018. Despite this, however, its development was sidelined by other activities during the early years of the pandemic. On the other hand, regarding the identification of health assets, it should be noted that the participants had not received prior training on the asset model, making it difficult to identify resources.

The experiences of this group of patients show that much remains to be done, but that there is hope. Obtaining these results opens the doors to new lines of action. Health care must respond to the health problems of the population, among which are chronic diseases. The SNS could implement different prevention and health promotion strategies centered on a community approach. This requires adequate community infrastructures, in such a way that the involvement and collaboration of government agencies is needed. However, it would be a cost-effective strategy that could alleviate SNS waiting lists, especially after the COVID-19 pandemic [50]. In short, the need to care for Long COVID patients could contribute to the promotion of RAS and social prescribing, understanding it as a formal healthcare service for these patients, and those with similar symptoms.

Regarding the limitations of this study, due to the characteristics of community interventions and social prescribing, most of the studies that present evidence are qualitative in nature. It is, therefore, necessary to increase the number of quantitative studies [51]. Additionally, the symptoms which limit the patients do not come from the electronic medical records of the patient, but from personal accounts provided by the patient, meaning that self-perception bias may be present. With regards to the strengths of this study, it allows us to understand the characteristics of the use of health assets by Long COVID patients in order to promote social prescribing to this group, as there are no previous studies on this group of patients.

Conclusion

In conclusion, most patients that made use of community resources identified as active. This allowed them to improve their ability and emotional wellbeing and it can therefore be considered a useful tool for addressing the main persistent symptom reported by Long COVID patients. Formal social prescribing or RAS of resources by PHC professionals in Aragon (Spain) has been infrequent, so taking this into account will allow for the development of formal training programs at the institutional level to involve health professionals and encourage them to make use of the tool. Furthermore, exploring the motivations and barriers to using these resources will be useful for professionals to address them and favor the use of community resources for patients.

Abbreviations

WHO	World Health Organization
SNS	Spanish National Health Service
PHC	Primary Health Care
RAS	Recommendation of Assets for Health

Acknowledgements

The authors would like to thank the Aragonese Primary Care Research Group (GAIAP, B21_20R) that is part of the Department of Innovation, Research and University at the Government of Aragón (Spain) and the Institute for Health Research Aragón (IIS Aragón); the Research Network on Chronicity, Primary Care and Health Promotion (RICAPPS, RD21/0016/0005) that is part of the Results-Oriented Cooperative Research Networks in Health (RICORS) (Carlos III Health Institute); Feder Funds "Another way to make Europe", NextGenerationEU funds and the University of Zaragoza.

Authors' contributions

BO-B, MS-P, SL-H drew up the research design. BO-B, MS-P and SL-H developed the study and coordinated the fieldwork. BO-B made the qualitative analysis. NF-M and BB-A have helped with project coordination. MS-P, NF-M, BB-A and BO-B wrote the manuscript. BO-B is the principal investigator of the project. All authors reviewed the manuscript content and approved the final version for submission.

Funding

This study has been funded by Health Institute Carlos III (ISCIII) through the project grant number PI21/01356, Feder Funds "Another way to make Europe". The funders had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation. The trial will be audited once a year by the funding organization.

Data Availability

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

Declarations

Competing interests

The authors declare no conflict of interest.

Ethics approval and consent to participate

Ethics approval was granted by the Clinical Research Ethics Committee of Aragón (PI21/139). The procedures carried out for the creation of this work complied with the ethical standards of the previously mentioned committee and with the 1975 Declaration of Helsinki. Informed consent was obtained from all subjects involved in the study.

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Received: 28 September 2022 / Accepted: 22 June 2023
Published online: 06 July 2023

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5. DISCUSIÓN

Las principales organizaciones de salud y corporaciones científicas de todo el mundo, junto a los agentes gubernamentales, se encuentran bajo la ardua tarea de ampliar el conocimiento científico sobre la fisiopatología de la COVID persistente. La calidad de vida de estos pacientes ha sufrido un gran impacto que no debe ignorarse. Existe una urgente necesidad de ofrecer tratamientos de rehabilitación a este colectivo de pacientes, así como de ayudar a los profesionales de la salud a guiar sus intervenciones (128). Para ello, es necesario comprender mejor la caracterización clínica y las experiencias individuales de los pacientes. En resumen, la pérdida de calidad de vida, la necesidad de atención en salud, así como las incógnitas que giran en torno a esta patología, hacen de esta enfermedad una temática digna de investigación para el sector de la salud.

5.1 Diseño del proyecto de investigación

El diseño de metodologías mixtas se trata de una investigación que involucra datos cuantitativos y cualitativos, ya sea en uno o varios estudios dentro de una investigación (129). La investigación con metodologías mixtas puede generar evidencias más sólidas que las investigaciones con una única metodología, dado que los resultados se obtienen desde múltiples perspectivas (130). Además, la combinación de metodologías cuantitativas y cualitativas puede contribuir a los puntos fuertes y neutralizar las limitaciones que puede mostrar cada metodología cuando es utilizada de forma independiente (131). Una de las ventajas de implementar metodologías mixtas es que permite responder simultáneamente preguntas explicativas y confirmativas (132), por ejemplo, se puede utilizar metodología cualitativa para generar una teoría y métodos

cuantitativos para verificarla (130). Es decir, uno de los métodos puede proveer mayor profundidad, y juntos confirmarse o complementarse (129).

Con respecto a la metodología cuantitativa implementada, se considera que los ECAs se encuentran en la cima de la pirámide de la evidencia (133). El grado de evidencia clínica de un estudio ayuda a valorar la solidez de los resultados obtenidos. Además, los ensayos clínicos que cuentan con proceso de aleatorización suponen la mejor estrategia para minimizar el riesgo de sesgos (134). Por ello, las investigaciones sobre las prácticas clínicas deben respaldarse mediante este tipo de estudios (135). El Canadian Task Force on Preventive Health Care (CTFPHC), fueron los primeros en generar y organizar los niveles de evidencia, estableciendo que las evidencias generadas a partir de un ECA suponen el máximo nivel de evidencia (136). Más reciente resulta la clasificación propuesta por el Oxford Centre for Evidence-Based Medicine (OCEBM), en la que los ECAs se encuentran en el nivel 1b de evidencia (136). Además, este ECA siguió las directrices de la declaración CONSORT, asegurando un rigor metodológico y, consecuentemente, evitando sesgos (137). También, se realizó un análisis de datos secundarios del ECA. Estos análisis, cada día se encuentran más arraigados en las investigaciones de salud, dado que posibilita abordar nuevas preguntas de investigación mediante un conjunto de datos previamente recopilados (122).

En cuanto a los métodos cualitativos, se trata de una estrategia óptima para profundizar en experiencias humanas y percepciones subjetivas, como: emociones, sentimientos, actitudes y expectativas (138). En este caso, se realizaron entrevistas individuales semiestructuradas y grupos focales. La intención de realizar entrevistas individuales era poder argumentar desde la calma, sin existir interferencias o influencias externas (127). Sin embargo, también se consideró oportuno realizar grupos focales, dado que las interacciones interpersonales pueden generar respuestas e ideas que no surgieron

durante las entrevistas individuales (139). Esta investigación siguió la lista de verificación de criterios consolidados para informar investigaciones cualitativas (COREQ) (140).

5.2 Caracterización del paciente con COVID persistente

Perfil sociodemográfico

Mediante el análisis de datos secundarios del ECA, se ha concluido que el perfil sociodemográfico de las personas con COVID persistente está mayoritariamente representado por mujeres (80%) con una media de edad de 47 años, casadas o en pareja (70%), con estudios secundarios o universitarios (91%) y en situación laboral activa (46.9%) o en situación de incapacidad laboral temporal (37.8%). En concordancia, aunque con un tamaño muestral menor, el estudio cualitativo coincide en estas afirmaciones, excepto en la situación laboral, donde más de la mitad de las personas participantes se encontraban en estado de inactividad temporal (62.9%).

De este modo, existe un mayor número de mujeres afectadas por la COVID persistente que de hombres. El ECA de Del Corral et al. (2023), realizado en España, también contó mayoritariamente con mujeres (71,75%) (141), al igual que el estudio longitudinal de Del Corral et al. (2022), aunque en menor porcentaje (62,75%) (142). El estudio longitudinal realizado en Italia por De Luca et al. (2022), también estaba formado por más mujeres (62,32%) que hombres (143). Incluso, en el estudio de cohorte de Gonzalez-Reumatell et al. (2022), formado por niños y jóvenes españoles con COVID persistente, el 66% de las personas participantes pertenecían al sexo femenino (144). Dichas investigaciones han presentado un menor porcentaje de mujeres participantes que este ECA. Sin embargo, a escala internacional es posible identificar estudios con mayor prevalencia de mujeres, como el ECA desarrollado en Suecia por Kjellberg et al. (2023), que contaba con una pequeña muestra fundamentalmente compuesta por mujeres (90%)

(145), o el ECA de McNarry et al. (2022), dirigido desde EE. UU y realizado de forma totalmente remota, que estaba principalmente formado por mujeres (88%) (146).

La respuesta a una mayor prevalencia de la COVID persistente en el sexo femenino podría estar en torno a las diferencias inmunológicas existentes en función del sexo (147). Los niveles genéticos y hormonales femeninos contribuyen a que las mujeres desarrollen respuestas inmunitarias más fuertes que los hombres, como por ejemplo una mayor reacción inflamatoria inicial o una mayor producción de anticuerpos (148), lo que podría promover el desarrollo de la COVID persistente (149). Por tanto, desde una perspectiva genética, el sexo podría estar jugando un papel determinante en el desarrollo de síntomas persistentes tras la infección por COVID-19 (150,151). Otro aspecto destacable sería la existencia de un mayor número de mujeres trabajadoras en los servicios de salud, considerando así a los trabajadores de estos servicios como personas de alto riesgo de infección por COVID-19 (66). Un notable porcentaje de trabajadores de la salud se infectaron durante los primeros meses de la pandemia, y podrían ser los futuros pacientes con COVID persistente (152). Sin embargo, la existencia de estudios nacionales e internacionales con mayor porcentaje de hombres podría cuestionar las anteriores hipótesis citadas. El estudio de cohorte prospectivo de Pérez-González et al. (2022), realizado en el noroeste de España, cuenta con más hombres (59,7%) que mujeres (153). También, la cohorte de Huang et al. (2021) presentó un porcentaje similar de hombres (52%) que de mujeres (48%) (154). No obstante, ambos estudios presentan porcentajes con diferencias por sexo no significativas (153,154). Por lo tanto, se requieren más estudios para verificar si el sexo femenino puede tener mayor riesgo de desarrollar algunos síntomas prolongados tras la COVID-19.

El promedio de edad de los afectados fue de 48 años, al igual que otros estudios con población con COVID persistente (155–157). Sin embargo, parece haber variabilidad en

este aspecto, ya que existen otros estudios en los que la media de edad resulta ser alrededor de 10 años más (154,158,159), por lo que el rango de edad estaría en torno a los 48-58 años. Reforzando estos hallazgos y con respecto a la edad y sexo, el estudio de Poyraz et al. (2021), concluyó que el sexo femenino es un factor de riesgo asociados a desarrollar síntomas persistentes Post-COVID-19 (160). El estudio prospectivo y multicéntrico de Signfried et al. (2021), con más de trescientos pacientes COVID-19 hospitalizados, identificó el sexo femenino y la edad menor de 50 años como factores de riesgo para desarrollar COVID persistente (159). En relación, evidencias previas han demostrado que las mujeres tienen un mayor potencial para desarrollar síntomas persistentes con mayor intensidad y repercusión que los hombres, por lo que su salud general se vería más afectada (149,161). El análisis de datos secundarios del ECA, en un principio, verificaron que las mujeres tienen una salud general (subescala SF-36) significativamente superior que los hombres, lo que resultaría contradictorio con la evidencia previa señalada. Sin embargo, tras reagrupar las ocho subdimensiones de dicho cuestionario, en salud física y salud mental, se encuentra que no existen diferencias significativas entre hombres y mujeres para estas dos dimensiones generales. Por tanto, es fundamental tratar estos datos con cautela y seguir investigando si existen diferencias por sexo.

Respecto al nivel educativo, el modelo de regresión lineal ha identificado que un mayor nivel educativo es un predictor de peor salud mental (SF-36). No se han identificado evidencias previas sobre el nivel educativo y la COVID persistente, por lo que esta información puede resultar novedosa. El estudio de Montez y Friedman (2015) valoraba la correlación entre el nivel de estudios y la salud autopercibida, estableciendo que los adultos con enfermedades crónicas y niveles educativos altos son más conscientes de cómo será la evolución de su enfermedad y riesgos derivados (162). Posiblemente, los

pacientes con COVID persistente que presentan mayor nivel educativo conocen la falta de tratamientos disponibles y el desconocimiento existente entre los profesionales de la salud. Esta incertidumbre causa frustración entre este colectivo de afectados, lo que afecta a su salud mental, como indicó el estudio cualitativo.

Por otro lado, se identificó una correlación entre las personas participantes en situación laboral activa o jubilados y una mejor salud física (SF-36), en comparación con aquellos desempleados o en situación de incapacidad temporal. El estudio cualitativo verificó que existe una relación entre la imposibilidad de reincorporarse al trabajo y la mala salud, siendo esta realidad una de sus principales preocupaciones. El estudio cualitativo de Humphreys et al. (2021) afirma que es uno de los temas que más ansiedad y malestar les está generando a este colectivo de pacientes (163). No obstante, los hábitos laborales tienen un impacto positivo en la salud física de la población general (164). Esta información ha sido recientemente comprobada, en tiempos de pandemia por COVID-19 (165). En cuanto a los jubilados, es posible que relacionen algunos problemas de salud con su edad. Esto podría reducir atribuir ciertos síntomas, como dolor muscular o articular o pérdida de memoria, a los efectos directos de la COVID persistente. Además, en relación con el ámbito laboral, el estudio cualitativo ha profundizado en las experiencias de estos pacientes al describir el proceso de ser evaluado por un comité médico para reincorporarse al trabajo y la incomprensión que se muestra al ser dados de alta. Para las personas participantes en el estudio cualitativo, el trato que han recibido ha sido "inhumano". Estas experiencias discriminatorias deben tenerse en cuenta, dado que suponen un impacto negativo en la salud mental de las personas afectadas y agudizan las desigualdades en salud y estigmas en pacientes con COVID persistente.

Sintomatología persistente

Desde un punto de vista más patológico, resulta preciso contemplar los síntomas persistentes que presentan las personas participantes del ECA. En concreto, informaron que presentaban una media de 16,5 síntomas persistentes en el momento de la evaluación basal. El tiempo medio desde la infección inicial reportado en la medición basal fue de aproximadamente 16 meses. Los resultados del análisis de datos secundarios identifican que los síntomas más frecuentes entre las personas participantes han sido: cansancio o fatiga (98%), afectación en la capacidad de atención y concentración (89%), mialgia (85%), pérdida de memoria (81%), dolor articular (74%) y confusión o niebla mental (71%), con una intensidad media de 7-8/10. Otros estudios también han identificado entre sus síntomas persistentes la fatiga, disnea, déficits cognitivos, tos crónica y dolores musculares, además del impacto emocional (22,23).

De este modo, la mitad de los síntomas más reportados por las personas participantes tendría una repercusión directa en su deterioro cognitivo. Estos datos se han visto respaldados por las puntuaciones obtenidas mediante el cuestionario MoCA, los cuales sugieren deterioro cognitivo leve-moderado entre las personas participantes. El estudio de Rass et al. (2021) empleó este mismo cuestionario tres meses después de la infección por COVID-19, identificando déficits cognitivos frecuentes, independientemente de la gravedad de enfermedad inicial [64]. Además, el estudio de Taquet el al. (2021) explica que la prevalencia de este deterioro tras un seguimiento de 6 meses en pacientes Post-COVID-19 es mayor que en otras infecciones similares (166). Esta afectación cognitiva tiene el potencial de afectar las acciones rutinarias, desde cocinar hasta conducir, e incluso en el autocuidado y las actividades en sociedad de las personas con COVID persistente, tal y como recogen diversas publicaciones

(157,167,168). Los resultados del estudio cualitativo añaden que este deterioro cognitivo cobra un importante papel a la hora de plantearse retomar su vida laboral, coincidiendo en este aspecto con el estudio de Ladds et al (2020) (152).

El estudio de Naidu et al. (2021) afirma que los efectos mentales negativos en las personas con COVID persistente pueden estar relacionados con la propia sintomatología persistente (42). En consecuencia, se establece una relación bidireccional entre estas variables: los síntomas físicos conducen a una mala salud mental y una mayor carga mental puede agravar la percepción de la sintomatología física (42). Sin embargo, la regresión lineal del análisis de datos secundarios también concluye que un mayor número de síntomas sería predictor de una mala salud física, pero que un menor número de síntomas persistentes sería predictor de una mala salud mental. Este hecho, resultaría contradictorio, entre otros, con la cohorte de Ocsovszky et al. (2022), que correlaciona un menor número de síntomas persistentes Post-COVID-19 con una mayor satisfacción vital (169). Tal y como concluye el estudio cualitativo de Tabacof et al. (2022), hay periodos de tiempo en los que estos pacientes han presentado menos síntomas, pero sin recuperarse, lo que supone una batalla mental (167). Este hecho podría verse reforzado por la frecuente fluctuación y escasa desaparición de los propios síntomas. De hecho, los análisis cualitativos establecen que la afectación emocional puede ser independiente del número de síntomas persistentes de los pacientes con COVID persistente. Estos resultados deben interpretarse con cautela, ya que el bienestar emocional de estos pacientes puede estar determinado por otros factores. El estudio cualitativo de Burton et al. (2022) también afirma que los pacientes Post-COVID-19 con síntomas persistentes han experimentado efectos en la salud mental debido a los propios síntomas. No obstante, concluyen que el impacto en su calidad de vida, la incertidumbre evolución de su enfermedad y la falta de atención desde los servicios de salud, también contribuyen considerablemente en dicho

malestar emocional (55). Ireson et al. (2022) también refieren que una de las claves para entender el impacto negativo en el bienestar emocional de estos pacientes estaría no solo en la propia sintomatología (carácter biológico), sino también en los cambios en la calidad de vida y rutinas de los pacientes (carácter social) (56). Ladds et al. (2020), expresan que el pronóstico incierto y una evolución estancada, sin claras perspectivas de recuperación, merman la salud mental de los afectados (152). El estudio cualitativo ha relacionado diferentes efectos negativos con sus principales causas, más allá de la propia sintomatología, como: la incertidumbre desencadenada por el desconocimiento sobre el desarrollo de su enfermedad, la frustración determinada por su escasa o lenta mejoría y el miedo ocasionado por una posible reinfección. Diversos estudios manifiestan que los pacientes con COVID persistente presentan síntomas de preocupación, frustración, confusión, ansiedad, miedo y depresión (42,55,58,152). Estos resultados van en la misma línea que los obtenidos mediante los análisis cualitativos. Del mismo modo ocurre con la puntuación obtenida en el cuestionario HADS, que sugiere la existencia de trastornos ansioso-depresivos moderados-graves. Este resultado (HADS) está correlacionado con una peor salud mental (SF-36), según los resultados de la regresión lineal del análisis de datos secundarios.

Calidad de vida y variables relacionadas

Las personas participantes en el estudio cualitativo también han identificado un deterioro en su calidad de vida, debido a las consecuencias que les ha supuesto la enfermedad. Multitud de ellos identifican “un antes y un después tras el contagio”, siendo interpretado en muchas ocasiones como un daño irreparable en sus vidas. Esta reflexión ha resultado común con la de otros estudios cualitativos, en los que se refleja la idea de una vida pre-COVID y una vida post-COVID, en relación con la pérdida del sentido de

sí mismo y de la propia identidad personal (57,163,170). Bury M. (1992), en un artículo *"Chronic illness as biographical disruption",* ya expresaba la existencia de un proceso de adaptación necesario para someterse a sus nuevas vidas tras el diagnóstico de una enfermedad crónica, pudiendo tratarse de situaciones "irreversibles" (171). Experiencias similares también fueron descritas por Charmaz K. (1983), quien ahondaba en el sufrimiento de pacientes con enfermedades crónicas provocadas por los síntomas físicos, además de las limitaciones diarias o el aislamiento social (172). De hecho, el estudio cualitativo de Humphreys et al (2022), verifica que sus participantes con COVID persistente no han podido reanudar algunas actividades fundamentales para su identidad central, como su rol de padre/madre o de trabajador/a (163).

El análisis de datos secundarios del ECA ha identificado bajos niveles en todas las dimensiones evaluadas mediante el cuestionario SF-36, aunque con gran variabilidad (expresada por los amplios rangos intercuartílicos, RIC), especialmente en las dimensiones de función social y rol emocional. En otras palabras, aunque la mediana de las ocho subescalas es baja, existen grandes diferencias entre el estado basal de las personas participantes. Este dato podría suponer una amplia variabilidad de perfiles, dificultando así la identificación de los efectos de la enfermedad. En esta línea, se observa mayor variabilidad en la salud mental que en la salud física de los pacientes con COVID persistente. Diversos estudios han determinado una reducción en todas las áreas vitales tras la infección por COVID-19, y en su mayoría las personas participantes presentaban síntomas persistentes (173–175). El estudio de González et al. (2021), que realizó un seguimiento a 3 meses tras el alta de pacientes COVID-19 que fueron ingresados en UCI, afirma que sus participantes presentaban bajas puntuaciones en su dominio físico (45,9; IQR, 36,1-54,4) y mental (55,8; IQR, 40,6-58) de su calidad de vida, según el cuestionario SF-12 (175). Además, concluyó que el síntoma más común fue la disnea, el cual mostró

una fuerte correlación con el componente físico del SF-12 (175). La cohorte de Arnold et al. (2021), realizada en pacientes que requirieron de hospitalización por COVID-19, identificó que el 74% de participantes presentaban síntomas persistentes y que las puntuaciones del SF-36 mostraron una reducción del estado de salud en todos sus dominios, en comparación con las normas de población de la misma edad (174). El estudio de Bort et al (2021), también estableció una reducción en todos los dominios del SF-36, especialmente en los dominios de energía y salud general, en pacientes que requirieron de ingreso por COVID-19 (173). La revisión bibliográfica realizada con Ceban et al. (2022) verifica que los pacientes con COVID persistente han sufrido un deterioro funcional significativo o reducción en al menos una dimensión de su calidad de vida, en comparación con los controles no infectados o su propio estado previo a la infección (176).

Por otro lado, los análisis multivariantes de este estudio han revelado una correlación entre la mala calidad del sueño (ISI) y la mala salud mental (SF-36). Estudios recientes realizados con población general afirman que el sueño está causalmente relacionado con el desarrollo de problemas de salud mental (177,178). Reforzando estos resultados, varias revisiones bibliográficas han verificado cómo los pacientes infectados por COVID-19 desarrollan con frecuencia problemas de sueño, acompañados de síntomas de ansiedad y depresión, entre otros (179,180). Además, la mala calidad del sueño (ISI) también se correlacionó con una mala salud física (SF-36), como ocurriría en la población general, y especialmente en el sexo femenino (181,182).

Asimismo, cabe destacar una correlación significativa entre peor alfabetización en salud (HLS-EUQ16) y peor salud física (SF-36). El bajo nivel de alfabetización en salud de esta muestra sería contradictorio con la posibilidad de contar con profesionales de la salud, dadas sus altas tasas de infección (183). Algunas investigaciones ya predijeron que

una alta capacidad de acceder, comprender y utilizar la información para mantener una buena salud se asocia con un buen estado de salud general (184,185), por lo que los pacientes con COVID persistente no serían una excepción.

Por otro lado, los análisis de correlación han concluido que el funcionamiento físico (SST-30), la autoeficacia (GSES-12) y la activación del paciente (PAM) tienen el potencial de promover una buena salud física y mental (SF-36) entre los pacientes con COVID persistente. El sedentarismo contribuye a la mortalidad de la población mundial, mientras que el ejercicio físico regular y moderado produce efectos beneficiosos sobre la salud de las personas, como la prevención de enfermedades crónicas y el aumento de la esperanza de vida (186). El ejercicio físico sería una estrategia no farmacológica para el tratamiento de enfermedades de tipo musculoesquelético, además de ser un estimulante del sistema inmunológico, como se ha demostrado con patologías similares (187). Por estas razones, un peor funcionamiento físico en pacientes con COVID persistente es un predictor de peor salud física en el SF-36. Por otro lado, la alta autoeficacia (GSES-12) en relación con la salud, promueve el mantenimiento de conductas saludables, como el ejercicio físico. De este modo, la autoeficacia favorece que persista la acción favorable en el tiempo y, por tanto, mejora la salud de la persona (188,189). También, la activación de los pacientes (PAM) con enfermedades crónicas hace referencia a sus propias habilidades y conocimientos para gestionar su salud, así como el cuidado de la salud de su entorno (190,191). Estudios recientes de pacientes crónicos relacionan bajos niveles de activación con mayor grado de dependencia, peor manejo de sus condiciones crónicas y empeoramiento progresivo de sus síntomas (192,193). Por ello, a pesar de no haber identificado estudios que contemplen la autoeficacia y la activación del paciente en personas con COVID persistente, parecen ser de gran interés para la enfermedad y su proceso de rehabilitación hacia una mejor calidad de vida.

Barreras y fortalezas autopercibidas en relación con su interacción social

Tal y como se ha comentado, la propia sintomatología sería el elemento que mayor malestar físico y mental genera a los pacientes con COVID persistente. Sin embargo, a partir de los análisis cualitativos, se ha identificado una gran disforia fruto del trato recibido desde el SNS. Estos hallazgos se han basado en experiencias personales en relación con la atención médica ante un problema de salud derivado de su enfermedad y al proceso de valoración para posible incorporación laboral. Este estudio no ha sido el único en identificar que, cuando los pacientes intentan recibir una atención se encuentran con barreras, como la falta de conocimientos de los profesionales sanitarios sobre su enfermedad. Diversas investigaciones cualitativas han coincidido en que, tanto la falta de conocimiento como el trato discriminatorio en los entornos de APS, han contribuido a la angustia emocional de muchos pacientes (57–59). El estudio de Ireson et al. (2022) recoge cómo algunos profesionales de la salud han llegado a cuestionar la veracidad de los síntomas o a atribuir un origen psiquiátrico, de somatización, sin realización de pruebas previas (56). Como señaló Hadler (1996), “Si tienes que demostrar que estás enfermo, no puedes mejorar” (194). Experiencias muy similares fueron reportadas por pacientes con diagnóstico de fibromialgia, quienes, al inicio de la enfermedad tuvieron que luchar por su reconocimiento diagnóstico (195). El estudio de Bhanot et al. (2021) indica que entre las personas más estigmatizadas durante la pandemia han estado los infectados por COVID-19 y el personal sanitario (196). De este modo, los pacientes con COVID persistente estarían dentro del grupo de infectados. Los resultados cualitativos recogen cómo al presentar síntomas persistentes generaban miedo a poder contagiar a terceros, especialmente al inicio de la pandemia. Esta estigmatización está relacionada con la dificultad experimentada para acceder a los diferentes servicios de salud en el contexto de los déficits del SNS (197). En consecuencia, este rechazo social puede conducir al

aislamiento social de estos pacientes y afecta negativamente a su salud física y mental. Además, esta discriminación puede reducir su probabilidad de buscar atención médica y tratamiento, por temor a ser avergonzados y estigmatizados (196,198), tal y como han verificado las personas participantes.

Este mismo estudio ha identificado que el apoyo social supone un sustento y motivación para los afectados por COVID persistente. La mayoría de las personas participantes en este estudio han reconocido a sus familiares y amigos como una de sus principales fuentes de apoyo. Macpherson et al. (2021), en su revisión sistemática de estudios cualitativos, confirman que los pacientes con COVID persistente buscan la comprensión y aceptación de sus allegados, incluyendo familiares, amigos y también de sus profesionales de la salud (57). Además, el estudio cualitativo de Ireson et al (2022) muestra cómo las personas más cercanas han sido el apoyo principal para la realización de actividades de la vida diaria, aunque en ocasiones estas acciones iban acompañadas de incomprensión y desconocimiento sobre la enfermedad (56). Macpherson et al. (2022) agregan que los familiares más cercanos de los pacientes también requieren apoyo, a partir de la necesidad de comprender la enfermedad (57). En este sentido, algunas de las personas participantes refieren sentirse únicamente comprendidos por otros pacientes que viven el impacto de la enfermedad en primera persona. En definitiva, los hallazgos del estudio cualitativo resultan coincidentes con la investigación de Humphreys et al (2022), concluyendo que la familia y los amigos son acompañantes importantes que influyen positivamente en el bienestar emocional de los pacientes, generando tranquilidad ante diversas adversidades (163)**.** En población general, las personas con apoyo social adecuado tienen un menor riesgo de mortalidad en comparación con las que no lo tienen (199). Por lo tanto, el aislamiento social se considera un factor de riesgo de mortalidad por cualquier causa (200,201). Este dato destaca el impacto que tienen las redes sociales

deficientes en las enfermedades mentales (201). En términos generales, el apoyo social puede ser un moderador de síntomas mentales a través de otros factores psicosociales, como la integración social y la participación en comunidad (202,203). Otras fuentes de apoyo identificadas han sido la atención por parte de profesionales de la salud mental y la participación en asociaciones de afectados. En algunos casos las situaciones vitales derivadas tras la enfermedad hacen necesaria la intervención de profesionales de la salud mental (163). Las personas participantes han descrito esta atención como un elemento fundamental para su bienestar emocional. Además, otras de las personas participantes han buscado terapias o tratamientos alternativos, y grupos de ayuda mutua, como la asociación de pacientes afectados "Long COVID Aragón", que ha contribuido positivamente su salud mental. Algunas de las personas participantes aseguran que si no hubiesen podido hablar con otras personas con COVID persistente nunca se habrían sentido comprendidos, ni habrían mostrado esperanza por su recuperación.

Otra fortaleza identificada por las propias personas participantes ha sido el empleo de recursos comunitarios. La principal motivación reportada por las personas participantes para emplear recursos comunitarios fue buscar una mejora de su sintomatología persistente. La literatura científica ha demostrado los beneficios de los recursos comunitarios para mejorar la salud física y mental (204,205). De hecho, la recomendación de activos para la salud implementada desde APS tiene el potencial de mejorar la salud y el bienestar emocional de la población general (206). Algunos autores concluyen que los pacientes con problemas generales de salud y que acuden regularmente a consultas de APS podrían beneficiarse de la recomendación de activos para la salud, disminuyendo así el uso del SNS, convirtiéndolo en una alternativa costo-efectiva (207–209). Los recursos comunitarios más empleados por las personas participantes con COVID persistente fueron principalmente espacios verdes, equipamientos locales,

actividades físicas y culturales y sociedades. Estos tipos de recursos se encuentran entre los principales tipos (210). Con respecto a la disponibilidad de recursos comunitarios, las personas que viven en ambientes urbanos reportan una mayor disponibilidad de recursos que las que viven en áreas rurales. Es decir, además de desigualdades en salud también existe desigualdad geográfica. Los que viven en áreas urbanas tienen ventajas sobre las poblaciones rurales, viéndose obligadas estas últimas a viajar a localidades cercanas. No obstante, los participantes que residían en áreas rurales formaban un pequeño porcentaje del total de participantes, por lo que estas desigualdades geográficas deben interpretarse con cautela.

La mayoría de los recursos comunitarios se adecuaban parcialmente a las necesidades de las personas participantes. Las actividades de estimulación cognitiva fueron una excepción, ya que atienden a pacientes de edad avanzada con diferentes necesidades. Otro hallazgo del estudio, ya presente en literatura previa (204,207), es que las personas con mayor vinculación y participación en su comunidad tienen mayor conocimiento de los recursos a su disposición y hacen mayor uso de ellos. Por lo tanto, fortalecer estos dos aspectos entre la población general podría tener un impacto positivo en la forma en que las personas manejan su propia salud. El empleo de recursos comunitarios parece tratarse de una herramienta útil para mejorar algunos síntomas persistentes de estos pacientes y contribuir en su recuperación. Las experiencias de este grupo de pacientes muestran que todavía queda por profundizar en este campo. Esto requiere infraestructuras comunitarias adecuadas, de tal forma que se necesita la implicación y colaboración de las instancias gubernamentales. Sin embargo, sería una estrategia rentable que podría aliviar las listas de espera del SNS, especialmente después de la pandemia de COVID-19 (205).

5.3 Efectividad de una intervención de telerehabilitación destinada a pacientes con COVID persistente

Los primeros hallazgos de este estudio indicaron que, en un periodo de tiempo de tres meses, la intervención para mejorar la calidad de vida de pacientes con COVID persistente no fue efectiva, en comparación con el grupo control. Es decir, la diferencia pre-intervención y post-intervención (diferencia pre-post) del instrumento usado para medir la calidad de vida (SF-36) no fue significativamente mayor para el grupo intervención en comparación con la diferencia pre-post del grupo control. Lo mismo ocurrió en el seguimiento de los 6 meses, la diferencia pre-post del grupo intervención no fue significativamente mayor en comparación con el grupo control.

Los análisis de efectividad, post 3 meses, revelaron mejoras superiores a favor del grupo de intervención en términos de salud mental (SF-36), estado cognitivo (MoCA), estado físico (SST-30), apoyo social comunitario (PCSQ) y activación del paciente (PAM). Los análisis de efectividad post 6 meses demostraron que dichas mejoras se mantenían a favor del grupo intervención, además de sumar otras. En concreto, presentaron mejoras superiores a favor del grupo intervención en términos de: salud mental (SF-36), número de síntomas, estado cognitivo (MOCA), estado físico (IPAQ-SF), estado ansioso-depresivo (HADS), activación del paciente (PAM) y alfabetización en salud (HLS-EUQ16). Estos datos indican que las personas participantes en el grupo intervención están sufriendo una mejoría mayor que las asignadas al grupo control. Sin embargo, en ninguna de estas mediciones dichas mejoras fueron significativas. Otro aspecto destacable es que todos los participantes, independientemente de su grupo de asignación mejoraron de manera significativa su salud física y mental (SF-36), además de su número de síntomas persistentes, estado cognitivo (MoCA), rendimiento físico

(SST-30) y bienestar emocional (HADS). Estos datos resultan esperanzadores, dado que indican que la variable tiempo favorece la recuperación de este colectivo de pacientes.

El gran impacto sufrido por estos pacientes hace que ya se hayan implementado ECAs que han evaluado la efectividad de una intervención rehabilitadora sobre la calidad de vida de los pacientes Post-COVID-19 y COVID persistente (211–213). Al contrario, algunas investigaciones lograron mejoras significativas en la calidad de vida de estos pacientes. El ECA de Nambi et al. (2022) identificó mejoras significativas en el componente físico de la escala SF-12, a favor de un grupo de actividad aeróbica de baja intensidad frente al de alta intensidad (211). Liu et al. (2020) encontraron mejoras en todas las dimensiones vitales del SF-36 tras seis semanas de entrenamiento basado en rehabilitación respiratoria (212). Además, el estudio piloto de Abodonya et al. (2021), mediante el entrenamiento de los músculos inspiratorios durante 2 semanas, verificó una mejora significativa en la calidad de vida a favor del grupo de intervención según el cuestionario EQ-5D-3L (213). Estos estudios, sin embargo, se han basado en un pequeño número de participantes (211,213) o tienen ciertas limitaciones potenciales con respecto a la validez interna (212). Además, es crucial destacar que muchos de estos ECAs, según sus criterios de inclusión, permitieron participar a personas contagiadas por COVID-19 desde hace menos de tres meses. De esta forma, es necesario diferenciar y recalcar que no serían pacientes con COVID persistente, dado que la sintomatología persistente debe de darse al menos tres meses posteriores a la infección inicial (20). En este sentido, los pacientes con COVID persistente pueden presentar un mayor deterioro, dado que el periodo de evolución es mayor (37). De hecho, dependiendo del estado del paciente, algunas intervenciones pueden causar daños importantes, como se ve en el ECA de Mohamed et al. (2021), en el que una intervención basada en la actividad aeróbica supuso una disminución de la calidad de vida de los pacientes Post-COVID-19 (214). Por lo

tanto, se debe considerar que los síntomas crónicos de los pacientes con COVID persistente pueden requerir un período de rehabilitación más prolongado.

Así, la telerehabilitación en pacientes Post-COVID-19 (posiblemente en las primeras semanas tras la infección) es factible para mejorar su calidad de vida (215). Todavía se necesitan estudios a gran escala con pacientes con síntomas persistentes durante al menos doce semanas después de la infección. De hecho, el caso clínico de Mayer et al. (2021), en el que un paciente con COVID persistente participó en sesiones de fisioterapia durante ocho semanas, consiguió mejoras en algunas variables físicas estudiadas, pero no en su calidad de vida (216). Con respecto a la telerehabilitación, la revisión sistemática de Valverde-Martínez et al. (2023). afirma que parece ser útil para pacientes con COVID persistente. Sin embargo, dicho estudio advierte que un subgrupo de pacientes presentó efectos adversos durante la intervención (episodios de mareos) (215). En esta misma línea, el estudio de Vieira et al. (2022) sugiere investigar modelos mixtos de rehabilitación clásica y telerehabilitación, con elementos presenciales y a distancia, de manera que profesionales capacitados puedan ajustar y/o parar la actividad en determinados momentos (98). Como antecedente de esta realidad, cabe señalar el estudio de Lau et al. (2005), en el que se utilizó una intervención de entrenamiento físico para la recuperación de pacientes infectados por SARS-CoV en 2002 (217). Dicha intervención no ofreció una mejora significativa en la calidad de vida de las personas participantes.

Las mejoras no significativas en este estudio hacen necesario considerar la adherencia a ReCOVery. La adherencia a la APP fue baja, dado que sólo el 25 % de las personas participantes del grupo intervención realizaron un uso significativo de la APP durante las primeras doce semanas. No se sabe si la adherencia al APP disminuyó con el transcurso de dichas semanas. Además, alrededor del 90% de las personas participantes

realizaron un uso mínimo de la APP a partir de las doce semanas. El estudio de Deng et al. (2022) comprueba que la adherencia al tratamiento es un problema común para las personas con problemas emocionales, como la depresión o la ansiedad (218), lo que puede ocurrir con los pacientes con COVID persistente, dado el impacto negativo en su bienestar emocional, según lo verificado el análisis de datos secundarios del ECA (SF-36; HADS) y evidencias previas (42,55). Contrario a estos resultados, la revisión sistemática de Vieira et al. (2022), basada en telerehabilitación Post-COVID-19, afirma que la telerehabilitación puede aumentar la adherencia del paciente en comparación con la rehabilitación presencial, dada su conveniencia y accesibilidad (98). Además, mencionan que la comunicación diaria a través de una plataforma de software o recordatorios aumentaría la adherencia de las personas participantes (98). La baja adherencia a ReCOVery APP sigue siendo un misterio que posiblemente podría resolverse mediante futuras investigaciones cualitativas a las personas participantes. En relación, el modelo de regresión lineal del ECA a medio plazo identificó modelos significativos que explican una mejor calidad de vida general (SF-36) y una mejor salud mental (SF-36), predichos por un mayor uso de ReCOVery APP y mayor autoeficacia (GSES-12). Por ello, mención destacada merece también el constructo personas de autoeficacia, correlacionado con una mejor calidad de vida general y salud mental. La autoeficacia se trata de un factor con potencial de incluir en la capacidad de los pacientes con enfermedades crónicas para autogestionar sus síntomas (219). Aquellas personas con alta autoeficacia para hacer frente a su enfermedad crónica muestran más capacidad para manejar los desafíos derivados de su patología y mayor sensación de control sobre sus vidas (220). Estas evidencias estarían en concordancia con los resultados obtenidos. Esta realidad también se ha visto en otras patologías como esclerosis múltiple (221), procesos oncológicos (222) o tras las secuelas de un accidente cerebrovascular(223). Por ello, el papel de la

autoeficacia debe de ser contemplado en futuras investigaciones como un importante elemento en la recuperación de los pacientes con COVID persistente.

Además, este estudio permitió identificar mejoras de variables relacionadas con otras variables analizadas. El modelo de regresión lineal post 3 meses identificó modelos significativos que explican la mejora en el funcionamiento cognitivo (MoCa), el funcionamiento físico (SST-30) y el apoyo social comunitario (PCSQ), así como la disminución del número de síntomas, en relación con el tiempo de uso de la APP y la mejora de otras variables secundarias del estudio.

Una mayor alfabetización en salud predice una disminución en el número de síntomas persistentes. Como señalan Liu et al. (2020), la alfabetización en salud se refiere no sólo al conocimiento de la salud y el cuidado del sistema de salud, sino que se define como la capacidad de un individuo para obtener y procesar conocimientos e información para mantener y mejorar la salud a través de la autogestión en colaboración con proveedores de salud (212). El estudio de Sorensen et al. (2015) ha comprobado que la alfabetización en salud tiene un impacto positivo en los pacientes con enfermedades crónicas, especialmente en aquellos que tienen un menor nivel de educación o conocimiento de la salud (115). De esta forma, las personas participantes que presentan mayor alfabetización en salud pueden haber gestionado mejor sus síntomas persistentes, posiblemente haciendo un mejor uso de los servicios de salud y reduciendo así dichos síntomas. A su vez, el aumento de la alfabetización en salud y un mayor uso de ReCOVery APP son predictores de un mayor apoyo social comunitario autopercibido. Una reciente revisión sistemática establece que las asociaciones entre la alfabetización en salud autoinformada y la adherencia a la medicación son bastante consistentes (224), por lo que, en esta intervención, una mejor alfabetización en salud y un mayor uso de ReCOVery APP harían que las personas siguieran las recomendaciones para iniciar

procesos de rehabilitación en la comunidad, además de asistir a asociaciones de afectados, como refleja el estudio cualitativo.

La mejora del funcionamiento cognitivo se predice mediante un aumento en el constructo de autoeficacia (GSES-12). Coincidente con este hallazgo, el estudio observacional prospectivo multicéntrico de Jongen et al. (2015) concluyó que la autoeficacia puede afectar positivamente el rendimiento cognitivo de los pacientes con esclerosis múltiple (225). De hecho, la autoeficacia tiene el potencial de reducir los factores estresantes cognitivos (226).

La mejora del funcionamiento físico (SST-30) se predice por los minutos de uso de la APP y por ser hombre. La puntuación inicial del grupo intervención en la prueba SST-30 mejoró, mientras que la del grupo control empeoró, aunque no significativamente. Una revisión sistemática que incluye ECAs con pacientes con secuelas Post-COVID-19 basados en rehabilitadores físicos también verificó la mejoría de estos pacientes en la escala SST-30 (227). Más concretamente, el estudio de De Souza et al. (2021), basado en la rehabilitación pulmonar de baja intensidad para supervivientes de la COVID-19, vio mejoras en esta prueba, además de su actividad física diaria y fatiga (228). Por ello, los ejercicios de rehabilitación, tanto físicos como respiratorios, así como las recomendaciones diarias de la APP han podido suponer mejoras en este ámbito. Además, la evidencia previa apoya la idea de que los hombres con enfermedades crónicas tienen una mayor predisposición genética que las mujeres a mejorar su funcionamiento físico (229), dado el mayor desgaste óseo y muscular que sufren las mujeres con el proceso de envejecimiento (230). Por lo tanto, se esperaría que las mejoras en el funcionamiento físico fueran mayores en los hombres participantes.

Finalmente, las personas participantes de la presente intervención no notificaron de ningún efecto adverso no contemplado, durante la intervención, ni meses posteriores.

Además, no existieron dificultades de ningún tipo durante su transcurso. Por ello, se puede afirmar que se trata de una intervención segura, coherente y factible.

Se requieren ECAs futuros para evaluar la eficacia de las intervenciones basadas en telerehabilitación en pacientes con COVID persistente. En cuanto al uso del APP, se deben realizar estudios basados en metodologías mixta para investigar las causas específicas de la mala adherencia al APP y determinar cómo mejorar las tasas de adherencia y cumplimiento. Estos estudios son necesarios para identificar nuevos modelos significativos que contribuyan a mejorar la calidad de vida y los síntomas de estos pacientes, además de promover evidencias sobre su manejo clínico para apoyar a los profesionales de APS.

4.6 Fortalezas

- La primera fortaleza de esta tesis fue el diseño del estudio principal: un ECA pragmático con homogeneidad muestral entre el grupo intervención y control. Dado que la aleatorización, las evaluaciones y el análisis estadístico fueron ciegos, los resultados poseen mayor validez. Esto se ve fundamentado en que los ECAs con asignación aleatoria se encuentran en el nivel 1b de evidencia según la clasificación propuesta por el OCEBM (136).
- Como novedad, se ha creado una APP ad hoc para esta investigación, destinada a personas con COVID persistente, y con contenido rehabilitador basado en evidencias científicas.
- Los cuestionarios administrados fueron instrumentos validados y ampliamente usados, y se obtuvo una adecuada validez interna de los mismos en nuestra muestra.

- Los hallazgos de esta investigación son fácilmente transferibles a la práctica clínica, dado que las intervenciones se realizaron con pacientes originarios de APS.
- Un importante número de personas participantes han podido ser evaluadas a corto y medio plazo. Se alcanzó el tamaño muestral establecido durante todo el seguimiento y los análisis se realizaron por intención de tratar.

4.7 Limitaciones

- Los datos de uso de la APP se encontraban por debajo del tiempo recomendado, por lo que la adherencia no fue la recomendada. Se necesita profundizar sobre futuras estrategias para fomentar la adherencia.
- A todas las personas participantes se les solicitó que no iniciaran ninguna actividad rehabilitadora ajena a la intervención, hasta su finalización. Sin embargo, no podemos asegurar que se haya cumplido este requisito, especialmente por parte de las personas asignadas al grupo control.
- La propia sintomatología de estos pacientes y sus situaciones vitales pueden suponer una limitación para realizar un proyecto de investigación.
- Otra limitación fue la coincidencia del estudio con la pandemia de la COVID-19. Desde diciembre de 2021 a marzo de 2022 fueron los meses en los que mayores tasas de contagios se contabilizaron en la Comunidad Autónoma de Aragón (116). Hasta agosto de 2022 dicha Comunidad Autónoma registró un elevado número de casos. Este contexto podría haber generado dificultades en las personas participantes, dado que muchos de ellos expresaron el miedo a la reinfección y un consecuente aislamiento social.

- La muestra era predominantemente femenina, en consonancia con las tasas de prevalencia de la COVID persistente, por lo que no se pudo realizar un análisis por género.
- El análisis de datos secundarios del ECA, a pesar de ser una estrategia adecuada, capaz de hacer inferencias causales (231), que deben ser interpretadas con cautela (232). Debido a la naturaleza exploratoria de este análisis, no se realizaron estimaciones del tamaño de la muestra ni ajustes del valor de *p*.

4.8 Futuros estudios

- ECAs futuros podrían considerar otras estrategias de adherencia a la intervención para fomentar un mayor uso y evitar el abandono. Por ejemplo, se ha demostrado que el envío de mensajes de texto es eficaz para aumentar la actividad física (233). Además, se podrían ofrecer sesiones en diferido. Por otro lado, convendría realizar estudios cualitativos para analizar más a fondo las razones de baja adherencia y abandono de la intervención.
- Se necesitan más estudios para determinar cómo mejorar las tasas de adherencia a las tecnologías, para que los pacientes con COVID persistente puedan gestionar su propia telerehabilitación.
- Trabajar con tamaños de muestra más grandes podrían permitir diversos subanálisis. Por ejemplo, permitiría analizar la efectividad de la intervención según los diferentes grados de afectación, meses de evolución desde la infección o según diferentes características sociodemográficas, como por género. También, se podría analizar qué perfiles de personas podrían beneficiarse más de la intervención.

- La efectividad de la telerehabilitación para mejorar la calidad de vida de pacientes con COVID persistente debe estudiarse más a fondo, por ejemplo, probando otros tipos de análisis como la mediación.

6. CONCLUSIONES GENERALES

La evidencia científica demostrada en la presente tesis permite extraer las siguientes conclusiones:

-Primero, a corto y a medio plazo, el uso de ReCOVery APP no fue efectivo para mejorar la calidad de vida de pacientes con diagnóstico de COVID persistente.

-Segundo, a corto plazo, la mayoría de las personas participantes asignadas al grupo intervención realizaron un uso de ReCOVery APP por debajo del recomendado, presentando una baja adherencia.

-Tercero, a medio plazo, el uso de ReCOVery APP y autoeficacia fue predictor de una mejor calidad de vida general y de una mejor salud mental.

-Cuarto, a medio plazo, todas las personas participantes mejoraron significativamente su salud física y mental, independientemente del grupo de asignación.

-Quinto, la calidad de vida de las personas pacientes con COVID persistente está relacionada con el número de síntomas persistentes, funcionamiento físico, calidad del sueño y afectación emocional.

-Sexto, se obtuvo que la mala salud física está predicha por un mayor número de síntomas, un peor funcionamiento físico y peor calidad del sueño. Además, una mala salud mental está predicha por un mayor nivel educativo, menor número de síntomas y mayor afectación afectiva.

-Séptimo, las personas participantes con COVID persistente identificaron bajos niveles en su estado emocional, principalmente causados por su propia sintomatología y el estigma autopercibido.

-Octavo, el apoyo de personas cercanas y profesionales de la salud resultó importante, aunque en muchos casos la comprensión sólo es recibida de otras personas con la misma patología.

-Noveno, las personas participantes expresaron tener miedo a una posible reinfección que suponga un retroceso en su recuperación, por lo que su vida se encuentra parcialmente limitada y existe una tendencia al aislamiento social.

-Décimo, los pacientes con COVID persistente que emplearon recursos comunitarios reportaron que los beneficios son aparentemente escasos y que todavía es necesaria una mayor adaptación.

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ANEXOS

ANEXO I. Manuscrito VI

Manuscrito VI. Effectiveness of ReCOVery APP to improve the quality of life of Long COVID patients: a 6-month follow-up randomized clinical trial.

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Effectiveness of ReCOVery APP to improve the quality of life of Long COVID patients: a 6-month follow-up randomized clinical trial.

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ABSTRACT

The main objective of this study is to analyse the clinical efficacy of medium-term telerehabilitation in the recovery of patients with Long COVID using ReCOVery APP, administered in the Primary Health Care (PHC) setting. The second objective is to identify significant patterns associated with an improvement in their quality of life predicted by other study variables. To this end, a randomised clinical trial was conducted with two parallel groups of a total of 100 patients with Long COVID. The control group continued with their usual treatment (TAU), established by their primary care physician. The intervention group, in addition to continuing with their TAU, attended three sessions based on motivational methodology and used ReCOVery APP for six months. The main variable was quality of life. The results of this study concluded that ReCOVery APP was not significantly more effective in improving the quality of life of patients with Long COVID. There was low adherence of participants. However, linear regression analyses revealed significant patterns of improvement in overall quality of life and mental health predicted by time of use of the APP and the personal construct of self-efficacy. In addition, all participants significantly improved their physical and mental health over the duration of the intervention. In conclusion, meaningful use of the ReCOVery APP may contribute to improving the quality of life of patients with Long COVID, but strategies to improve adherence need to be encouraged.

Trial Registration No.: ISRCTN91104012.

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.

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INTRODUCTION

The severe and global impact of COVID-19 has generated a pandemic of consequences. Among them, since 2020 many infected people continue to have persistent and debilitating symptoms for months after infection (1). It was in October 2021 when the World Health Organization (WHO) defined these persistent symptoms as a new pathology, calling it as Post COVID-19 Condition (2). It consists of symptoms typical of a probable or confirmed SARS-CoV-2 infection that continue or develop three months after the infection, and that do not correspond to an alternative diagnosis. The scientific society refers to this pathology as "Long COVID" or "persistent COVID", among others.

According to the WHO (3), approximately 145 million people have been affected by Long COVID during the first two years of the pandemic worldwide. The etiology of Long COVID is still a great unknown, including its origin, duration, or possible treatments. This fact represents a gap for the society of the moment, especially for the scientific and health community. Emerging evidence seems to indicate a high prevalence of persistent COVID among people hospitalized for COVID-19 (4). In fact, Ceban et al., (2022) estimated this prevalence of 10-30% of non-hospitalized COVID-19 patients, compared to 50-70% in hospitalized COVID-19 patients (5). Also, this high prevalence has been reflected in the female sex and in ages around 50 years, although often based on cross-sectional studies of small samples (6). More recently, several hypotheses state that comorbidities (7) and the immune response (8) could be behind the development of Long COVID illnesses.

The symptoms of persistent COVID can affect multiple organ systems (9), mainly: respiratory, cardiovascular, gastrointestinal, neurological, musculoskeletal, dermatological, visual, and olfactory, in addition to chronic fatigue and a negative impact on their emotional well-being (10). Davis et al. (2021) has come to count 203 symptoms of this disease (11). The development and evolution of these persistent symptoms supposes a total alteration of their organism (11). They are disabling, altering their personal, family, social and work environment and, consequently, their quality of life (12).

These sequelae require multidisciplinary rehabilitation, which makes it possible to address the multisystem symptoms that these patients present (13). Along these lines, given the need to continue offering general rehabilitation during the pandemic,

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telerehabilitation underwent an unprecedented boost that persists to this day (14,15). Even so, prior to the COVID-19 pandemic, the benefits of telerehabilitation compared to traditional rehabilitation had already been demonstrated, not only for therapeutic benefits but also in terms of cost-effectiveness (16). In this way, telerehabilitation is positioned as a real and possible alternative to help patients with long-term or chronic diseases, such as Long COVID patients. In fact, the qualitative study by Reis et al., (2022), based on the perception of nurses, considers telerehabilitation programs a fundamental strategy for recovery programs aimed at Long COVID patients (17). A meta-analysis of randomized controlled trials conducted by Hung et al., (2022), considers telerehabilitation as an effective option to improve dyspnea or muscle strength, among others, in Long COVID patients (18). Thus, a quasi-experimental pre-post study evaluated the functional capacity of Long COVID patients after four weeks of digital physiotherapy, obtaining significant improvements (19). An online seven-weeks course aimed at "Recovery from COVID" obtained significant improvements in the quality of life in the seventy-six participants who completed it (20). Also, a systematic review of exercise interventions through telerehabilitation in patients with Post COVID-19 symptoms confirms their efficacy in the short and long term (21). However, all the studies mentioned above suggest the need for large-scale randomized clinical trials to be able to extrapolate their results. Therefore, it seems that the effectiveness of telerehabilitation in this group of patients still needs to be investigated.

Given the need for multidisciplinary management of patients with persistent COVID and the growing momentum for telerehabilitation, this study developed an APP called ReCOVery. It is a digital tool with rehabilitation content based on clinical guidelines and evidence (11,22–25). An RCT with two parallel groups was conducted to assess its short-term clinical effectiveness (26). However, it is necessary to know the effectiveness of this intervention in the medium term.

Therefore, the main objective is to deepen the clinical efficacy of rehabilitation (ReCOVery APP) for people with a diagnosis of Long COVID for six months, compared to the treatment as usual (TAU) administered in the context of Primary Health Care (PHC). The second objective is to identify significant models associated with an improvement in their quality of life and other study variables.

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METHODOLOGY

Study design

This research study is an open-label randomized clinical trial (RCT) through two parallel groups of Post COVID-19 patients infected twelve weeks or more ago and with persistent symptoms. First group participants have continued to receive their TAU established by their GP of PHC (control group). Second group participants have also continued with their TAU and have also had access to ReCOVery APP, as an adjuvant treatment in the form of telerehabilitation, and to three motivational sessions to increase adherence to the APP (intervention group).

This research was carried out in the territory of Aragon, located in the northeast of Spain. This RCT was registered in February of 2022 (ISRCTN91104012). The recruitment of patients was carried out from January 2022 to March 2022. The baseline evaluation and start of the intervention were carried out in March-April 2022, the follow-up evaluation in June-July 2022 (26), and the final evaluation was carried out in October 2022. In addition, the original protocol article of this investigation was published (27).

Sample size

The sample size was established and detailed in the protocol article of this RCT study (27). The pre-post score difference of the Short Form-36 Health Survey Questionnaire (SF-36) instrument was used, considering the value of the highest possible standard deviation (SD) and a minimum expected difference of 19.3 points for the pre-post rating. A risk of 0.05 was accepted as well as a power of 95% in a two-sided contrast, and a maximum dropout rate of 10%. The minimum required sample size was 78 subjects.

Given the demand of the potentially interested participants, the final sample size included 100 participants, 22 more than the required sample size.

Recruitment of participants

The study population were patients with Post COVID-19 condition, over eighteen years of age, infected for twelve weeks or more and with a positive diagnostic test for COVID-19. The exclusion criteria were: not having a positive COVID-19 diagnostic test for more than the previous twelve weeks; participation in a clinical trial in the last six months; pregnancy and lactation; have a diagnosis of severe uncontrolled illness; significant risk

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of suicide; existing structured psychotherapeutic or rehabilitative treatment by health professionals and the presence of any medical, psychological or social problems that may significantly interfere with the study.

Patients originating from the consultation of GPs of PHC and who met the inclusion criteria were included in the study. Also, some interested patients from the association for those affected "Long COVID Aragón" were redirected to their GP to be eligible to participate if they met the established criteria.

An informative document with the study criteria was provided to the GPs. In this way, when they identified potential patients, and after obtaining their informed consent, they contacted one of the researchers to facilitate contact with the potential patient. Subsequently, the researcher contacted the probable participant again to reconfirm if they met the criteria, their interest in the study, and to resolve any possible doubts. Recruitment was carried out consecutively until reaching the estimated sample size, from January to March 2022. Prior to carrying out the baseline evaluation of the participants, it was necessary for them to offer their written consent to participate.

Randomization and assignment and blinding of study groups

The individual randomization process was performed using an alphabetical list of participants and computer-generated blind sequence. An independent investigator, and therefore blinded, was commissioned to carry out this task. The assignment to both groups was not blind, due to the very nature of the intervention. The same independent investigator made a phone call to each participant to confirm the assigned group and to ask her not to inform third parties about her assignment. On the one hand, the participants assigned to the control group were required to continue with their TAU and not start rehabilitation-type activities that could affect the intervention. On the other hand, the participants of the intervention group were summoned in person and individually at a nearby health center. The latter were asked to bring their personal mobile device with a battery, to install the APP.

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Development and evaluation the APP and interventions

Prior to the design of the APP, a qualitative study was carried out through individual interviews and focus groups with Long COVID patients (28). Some of the main themes were persistent symptoms, identified needs or possible treatments followed. Subsequently, the available scientific evidence on health recommendations and rehabilitation for Long COVID patients was also collected (11,22–25). In this way, a human-centered design was chosen (29), a technique that seeks to solve problems and needs by understanding the users themselves, in this case Long COVID patients. A native APP with Java language was created using the Android Studio platform. The design of a native APP was chosen, instead of a hybrid one, to allow the use of the device's own tools, such as notifications. All its contents must be graduated and personalized according to the needs and characteristics of each patient, as indicated in the available instructions. All the details about the contents and bibliographic references of ReCOVery APP were collected in the protocol article of this RCT (26,27). ReCOVery APP consists of six main modules:

- 1) Food. Recommendations based on adherence to the Mediterranean diet are provided, with the aim of supplying possible nutritional deficiencies of vitamin D, vitamin B12, B complex, folic acid and omega-3 fatty acids.

- 2) Rest and sleep. Recommendations are provided as tips that can be carried out daily, to improve the quality of sleep and rest. The need to achieve an average of between 7 and 8 hours of sleep each night is promoted, to achieve a restful and satisfactory rest.

- 3) Physical exercises. In this section, physical rehabilitation exercises are provided through graphic representations. All the contents and indications in this section were based on guidelines on the management of this disease or other pathologies with similar symptoms.

- 4) Breathing exercises. Various video tutorials on respiratory physiotherapy are provided following the indications and symptoms of these patients.

- 5) Cognitive exercises. Three levels of cognitive stimulation exercises are provided, aimed at working on cognitive skills focused on executive function, difficulty maintaining attention, decreased processing speed, verbal fluency, and short-term memory deficits.

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- 6) Participation in the community. The objective is to promote participation in the local development process through different services, associations, or cultural activities, as well as groups affected by the same pathology, seeking to improve their emotional well-being.

All the participants continued with their TAU, being cared for by their GP and other PHC professionals. However, participants assigned to the intervention group also had access to ReCOVery APP for twenty-four weeks. In addition, at the beginning of the intervention, this group of patients attended three sessions based on motivational methodology, APP management, and strengthening of their personal constructs (health literacy, self-efficacy, and personal activation) in relation to their disease. All the sessions were carried out in person, based on the guidelines of Miller and Rollnick (30). The first two sessions were individual and the third group session (in groups of 8-10 participants). The individual sessions were guided by a clinical psychologist, lasting 20-30 minutes, in which the APP was installed and doubts about its use and management were resolved. The group sessions were guided by two clinical psychologists, lasting 50-60 minutes. The sessions were carried out during three consecutive weeks, so all the participants completed the sessions in the same weeks.

Follow-up of the intervention and adverse events

Prior to the start of the intervention, the group of researchers established as possible adverse events: reinfection by COVID-19, use of emergency medical services, hospitalization, or surgical interventions, as well as any other circumstance that could affect the development of the intervention. In addition, all participants were provided with a telephone number, where they could report adverse events at any time during the study. All reported adverse events were assessed by two independent investigators, blinded to group assignment. In case of discrepancies, a third investigator would evaluate the situation. There were no adverse events other than those mentioned above or discrepancies during the intervention.

Despite being a remote and uncontrolled intervention, two follow-up calls were made, at six weeks and eighteen weeks from the start. Information on possible adverse events was also requested on these calls.

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Measures and variables

A total of three measurements were made: baseline evaluation (T0), follow-up evaluation carried out twelve weeks from the beginning (T1) and final evaluation carried out forty-two weeks from the beginning of the intervention (T2).

All the evaluations were carried out face-to-face and individually in a health center in their city for two consecutive weeks. They were asked to come with sports or comfortable clothes. In addition, it was necessary to go with prescription glasses, hearing aids or any functional element in case of need. The evaluations were carried out by two blinded researchers with experience in similar research projects. However, both were instructed to do so through theoretical and practical sessions, avoiding biases in said process.

The main study variable is quality of life. The SF-36 (31) was selected to be evaluated. This instrument measures eight dimensions of health (physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, vitality, and emotional well-being) that are grouped into two main components: physical health and mental health, with whom we will work in the statistical analysis. The eight scales and the two components are scored from zero to one hundred, with scores above or below fifty indicating better or worse health, respectively. Cronbach's alpha obtained in this study was 0.89.

Regarding the secondary variables, a total of eight validated scales have been selected. The official versions in Spanish of all scales were used. Moreover, an ad hoc questionnaire was designed for variables: sociodemographic, clinical and use of ReCOVery APP.

-The sociodemographic variables have been gender (man/woman/other), age, civil status (married or in couple/single, separated, divorced or widowed), education (no studies or primary studies/secondary or university studies) and occupation (employee/ unemployed/employee with temporary work disability (TWD)/retired/others).

-The clinical variables studied have been time since infection (months) and number of self-reported persistent symptoms at the time of each evaluation, using a list of thirty

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persistent symptoms typical of Long COVID patients according to previous literature (7,25,32,33).

-The use variable of ReCOVery APP has been the time of use of the APP, expressed in minutes. Regarding adherence to the APP, significant use was estimated from fifteen minutes a day, five days a week, for twenty-four weeks (1,800 minutes or more).

Emotional well-being, in relation to depression and anxiety, was measured using the Hospital Anxiety and Depression Scale (HADS) questionnaire (34). It includes fourteen items, each item corresponding to a four-point Likert scale, with scores ranging from zero to forty-one for its total score. Higher scores indicate more severe symptoms. Cronbach's alpha obtained in this study was 0.93.

-Cognitive status was assessed using the Montreal Cognitive Assessment (MoCA) questionnaire (35). It assesses cognitive domains such as memory, attention, language or working memory. The maximum score obtained is 30 points, indicating mild cognitive impairment for scores below twenty-six points, the deterioration being progressive the lower the score. Cronbach's alpha obtained in this study was 0.49.

-Physical functioning was assessed using the thirty-second Sit to Stand Test (36). The test assesses endurance at high power, speed in terms of strength, or muscular strength, recording the number of times a person can fully stand up and sit down. It has good test-retest reliability (0.84 <R< 0.92).

- Habitual physical activity was measured using the International Physical Activity Questionnaire-Short Form (IPAQ-SF) (37). The minutes' walked score was used in the analysis of this study. It consists of seven items and records activity at four levels of intensity. Cronbach's alpha obtained in this study was 0.71.

- The quality of sleep and rest was measured using the Insomnia Severity Index (ISI) questionnaire (38). This scale has seven items, with a Likert Scale from zero to four, and an overall score ranging from zero to twenty-eight. A higher score indicates a greater severity of insomnia. Cronbach's alpha obtained in this study was 0.89.

-Personal constructions. Three validated questionnaires were selected to know the personal factors related to their behaviour:

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a) Self-efficacy was assessed using the Self-efficacy Scale-12 (GSES-12) (39). It is a questionnaire with twelve items, with a Likert Scale from one to five. The resulting scores range from twelve to sixty, with a higher score indicating better self-efficacy. Cronbach's alpha obtained in this study was 0.81.

b) The activation of the patient in his own health was measured using the Patient Activation Measure questionnaire (PAM) (40). This questionnaire on managing your own health contains thirteen items with a Likert Scale from one (strongly disagree) to four (strongly agree). The scores obtained range from thirteen to fifty-two, with the highest indicating better activation. Cronbach's alpha obtained in this study was 0.78.

c) Health literacy will be measured using the Health Literacy Europe Questionnaire (HLS-EUQ16) (41). It contains sixteen elements, ranging from one to four. The resulting score ranges from sixteen to sixty-four. A higher score indicates worse health literacy. Cronbach's alpha obtained in this study was 0.87.

Statistical analysis

Statistical analyzes were performed using IBM SPSS Statistics version 22.0.0.0 and Microsoft Excel software. Normality of the sample distribution was assumed when there are more than 50 participants (42).

First, a descriptive analysis of the sample was made, calculating frequencies and % for the qualitative variables and mean and standard deviation for the quantitative variables. Secondly, a univariate and bivariate analysis was performed (comparison at baseline and differences in measurements at three months and six months) calculating Chi-Square for qualitative variables and T-Student for quantitative ones.

Second, to analyze the effectiveness of ReCOVery APP, a per-protocol analysis was performed, comparing the differences at baseline (T0), at three months (T1), at six months (T2) and at six months (T2-T0) between both groups using T-Student.

Third, it was examined whether there had been a significant improvement in all subjects over the six months, regardless of their allocation group. For this, baseline (T0) and post-intervention (T2) comparisons were made, using T-Student for the related samples for the ten selected scales and the number of symptoms.

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Finally, to analyze the variables associated with the effectiveness of ReCOVery APP, a linear regression model was developed for SF-36 quality of life, SF-36 physical health, and SF-36 mental health as dependent variables. The time of use from the beginning to the end of the intervention and the three personal constructs (GSES-12, PAM and HLS-EUQ16) of all the participants in the control group and intervention group who completed the study by performing the tests were included as independent variables. three measurements, and a final model was obtained. In addition, a multicollinearity test was performed. Linear regression was used since the model residuals had a finite mean, constant variance, and normal distribution. However, a bootstrapping analysis was also performed with 2000 samples.

Ethical approval

Ethical approval was granted by the Aragon Clinical Research Ethics Committee (PI21/454), complying with all the ethical standards of the recently mentioned committee. In addition, the procedures carried out for the creation of this work also complied with the Declaration of Helsinki of 1975. All the participants signed an informed consent prior to the start of the intervention. All the data obtained in this research were anonymized and will only be used for the purposes of the study. Any change or modification relevant to the research will be notified to the corresponding ethics committee.

RESULTS

Initially, a total of 182 people were included in the study (Figure 1). 72 (39.56%) were discarded for not meeting the inclusion criteria and 10 (5.49%) refused to participate. 100 people were randomly assigned to the study, 52 participated in the intervention group and 48 in the control group. Subsequently, in the evaluation carried out at 6 months, 20 people were discarded (8 were reinfected by COVID19 and 12 refused to continue in the study). Finally participating in the evaluation of the 6 months a total of 80 people.

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Figure 1. Flowchart of the study

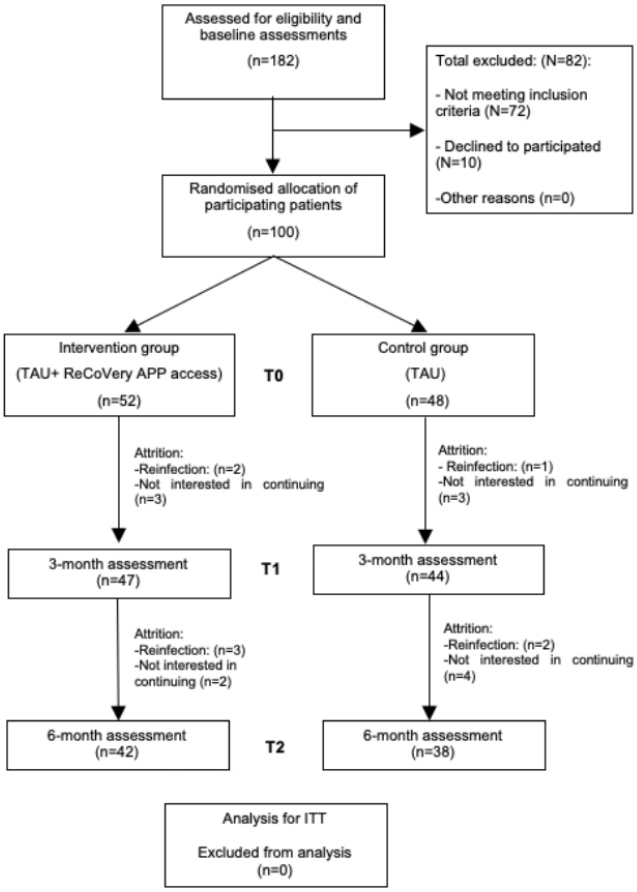

Figure 1.
Flowchart of the study: randomization, sampling and monitoring of patients. TAU, Treatment as Usual; ITT, Intention-to-treatment

The general characteristics of the patients recruited for this study are presented in Table 1, as well as their comparison by assigned group on the variables collected at baseline. The descriptive analysis at baseline yielded a total of 100 participants (80 women and 20 men). The general profile corresponds to a woman with a mean age of 48.28 years (SD: 9.26), with secondary or university education and with active employment or TWD. The participants have a low quality of life (both physical and mental), according to the results of the SF-36. In addition, they have a mean of 16.47 (SD: 5.99) persistent symptoms. This is consistent with their limited physical functioning (reflected in the Sit

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to Stand Test and IPAQ-SF score), cognitive impairment (MoCA), high levels of anxious-depressive symptoms (HADS) and insomnia (ISI). In terms of personal constructs, these participants are characterised by acceptable levels of self-efficacy (GSES-12), high activation and self-management (PAM), but low levels of health literacy (HLS-EUQ16). As for the comparison by assigned group, this analysis subsequently revealed no significant differences between the groups.

Table 1. Description of sociodemographic and clinical variables of the total sample and comparing by assigned group.

Variables	**Total sample** N(%)/Median (IQR) N=100	**Intervention gr.** N(%)/Median (IQR) N=52	**Control gr.** N(%)/ Median (IQR) N=48	**P-value**
Gender (%)				
Men	20 (20%)	8 (15,4%)	12	0,230
Women	80 (80%)	44 (84,5%)	33	
Age	48,28 (9,26)	48,25 (10,36)	48,31 (8,01)	0,963
Perceived age	58,10 (14,69)	59,69 (15,02)	56,38 (14,27)	0,260
Marital status (%)				
Married or in couple	70 (70%)	35 (67,3%)	35 (72,9%)	0,541
Single, separated, widowed	30 (30%)	17 (32,7%)	13 (27,1%)	
Educational level (%)				
Without studies or primary studies	9 (9%)	5 (9,6%)	4 (8,3%)	0,823
Secondary or university studies	91 (91%)	47 (94,4%)	44 (91,7%)	
Ocupación (%)				
Employee	46 (46%)	20 (38,5%)	26 (54,2%)	0,350
Unemployed	5 (5%)	4 (7,7%)	1 (2,1%)	
TWD	37 (37%)	21 (40,4%)	16 (33,3%)	
Retired	9 (9%)	6 (11,5%)	3 (6,3%)	
Others	3 (3%)	1 (1,9%)	2 (4,2%)	
Time since the contagious	16,12 (6,34)	15,75 (6,56)	16,52 (6,14)	0,545
Number of persistent symptoms	16,47 (5,99)	17,50 (5,29)	15,35 (6,55)	0,074
SF-36				
SF-36 Physical Health	32,19 (16,61)	29,06 (13,67)	35,58 (18,86)	0,053
SF-36 Mental health	34,77(19,31)	32,64 (17,98)	37,09 (20,59)	0,254
MoCA	23,64 (3,85)	23,48 (4,20)	23,81 (3,46)	0,667
Sit to Stand Test	10,37 (3,49)	9,87 (3,77)	10,92 (3,10)	0,131
IPAQ-SF				
HADS	17,61 (8,31)	17,86 (7,98)	17,33 (8,74)	0,752
ISI	11,34 (6,58)	11,13 (7,21)	11,56 (5,89)	0,745
GSES-12	44,66 (7,51)	44,57 (6,49)	44,75 (8,55)	0,910
PAM	39,82 (6,16)	38,92 (7,24)	40,79 (4,61)	0,210
HLS-EUQ16	32,10 (7,03)	32,94 (7,84)	31,18 (5,98)	0,125

Significant differences ($p \leq 0.05$) are highlighted in bold. *A total of thirty symptoms were included. Chi-Square test for the variables gender, marital status, educational level and occupation, and one-way ANOVA for the rest of the variables. TWD, temporary work disability; SF-36, Short Form-36 Health Survey Questionnaire; SF-36 Physical Health= physical function + physical role + bodily pain + general health; SF-36 Mental Health= vitality + social function + emotional role + mental health; MoCA, Montreal Cognitive Assessment; HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; IPAQ-SF, Physical Activity Questionnaire-Short Form; GSES-12, Self-efficacy Scale-12; PAM, Patient Activation Measure Questionnaire; HLS-EUQ16, Health Literacy Europe Questionnaire.

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When analyzing the use of ReCOVery APP in the intervention group, the range of use during the 6 months ranged from 10.95 min to 5,764.81 min. The mean use was 839.65 min (SD: 1,090.57) during the 6 months. Only 7 participants (13.4%) in the intervention group made significant use of the APP. More than 90% used the APP during the first three months, but not afterwards, which explains the low adherence in the medium term.

Table 2 shows a comparison between the intervention group and the control group, using data obtained from three different measurements, from the beginning to the end of the intervention. As shown, no significant differences in favour of the intervention group were identified between the end (T2) and the beginning of the intervention (T0). However, the SF-36 Physical Health variable did show statistically significant differences between the intervention and control groups at three months (p: 0.021; CI: -16.30, -1.40) and six months (p: 0.022; CI: -2.18, -3.18), with better levels of physical health in favour of the control group. The intervention group has improved (T2-T0) in the variables: mental health, number of persistent symptoms, cognitive status, emotional well-being, habitual physical activity, activation and health literacy, compared to the control group.

Table 2: Outcome data at baseline, three and six month follow-up, and their comparting by assigned groups.

VARIABLES	INTERVENTION GROUP* N (%) Mean (SD)	CONTROL GROUP** N (%) Mean (SD)	SIGNIFICANCE p-value (CI)
PRIMARY OUTCOMES			
SF-36 Physical Health			
Baseline (T0)	29.06 (13.67)	35.58 (18.86)	0.053 (-13.12; 0.07)
3 months (T1)	33.80 (12.19)	42.30 (20.31)	**0.021 (-16.30; -1.40)**
6 months (T2)	32.53 (18.11)	41.88 (22.40)	**0.022 (-2.18;-3.18)**
T2-T0	5.33 (14.03)	7.50 (17.37)	**0.106 (-9.16;4.84)**
SF-36 Mental health			
Baseline (T0)	32.64 (17.98)	37.09 (20.59)	0.252 (-12.16; 3.24)
3 months (T1)	37.35 (20.01)	40.29 (19.59)	0.491 (-11.38; 5.50)
6 months (T2)	44.45 (24.07)	48.57 (24.30)	0.845 (-14.89;6.66)
T2-T0	14.48 (19.85)	11.87 (19.92)	0.902 (-6.25;11.48)
SECONDARY OUTCOMES			
Number of persistent symptoms			
Baseline (T0)	17.50 (5.29)	15.35 (6.55)	0.074 (-0.23; 4.52)
3 months (T1)	16.48 (4.65)	14.00 (6.64)	0.090 (-0.44; 5.41)
6 months (T2)	13.92 (6.40)	12.13 (7.06)	0.318 (-1.19; 4.79)
T2-T0	-0.84 (3.18)	-1.67 (3.80)	0.485 (-0.98; 2.66)
MoCA			
Baseline (T0)	23.48 (4.20)	23.81 (3.46)	0.667 (-1.85; 1.19)
3 months (T1)	24.13 (4.45)	24.14 (3.84)	0.991 (-1.78; 1.76)
6 months (T2)	25.48 (2.99)	25.39 (2.98)	0.773 (-1.37; 1.53)

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T2-T0	1.00 (4.67)	0.11 (2.87)	0.249 (-0.86; 2.65)
Sit to Stand Test			
Baseline (T0)	9.87 (3.77)	10.92 (3.10)	0.131 (-2.42; 0.31)
3 months (T1)	10.65 (3.66)	11.28 (3.89)	0.462 (-2.30; 1.05)
6 months (T2)	11.00 (4.05)	12.60 (4.77)	0.269 (-3.62; 0.42)
T2-T0	0.48 (3.23)	0.21 (2.28)	0.390 (-1.04; 1.57)
IPAQ-SF			
Baseline (T0)	341.04 (443.87)	308.68 (233.48)	0.325 (-127.59;192.32)
3 months (T1)	344.09 (338.65)	303.76 (244.52)	0.325 (-129.72;212.42)
6 months (T2)	355.48 (491.631)	271.32 (480.38)	0.853 (-132.61-300,93)
T2-T0	-224.89 (485.61)	-194.13 (51.47)	0.813 (-218.51;157.12)
HADS			
Baseline (T0)	17.86 (7.98)	17.33 (8.74)	0.752 (-2.80; 3.86)
3 months (T1)	17.20 (8.72)	16.00 (9.95)	0.553 (-2.80; 5.20)
6 months (T2)	15.42 (9.18)	16.90 (8.62)	0.398 (-2.48; 5.44)
T2-T0	-1.09 (4.96)	-0.97 (6.28)	0.489 (-2.65; 2.40)
ISI			
Baseline (T0)	11.13 (7.21)	11.56 (5,89)	0.745 (-3.03; 2.17)
3 months (T1)	10.50 (5.53)	10.33 (5,94)	0.893 (-2.30; 2.63)
6 months (T2)	13.69 (7.47)	11.18 (7.23)	0.901 (-0.77; 5.78)
T2-T0	-0.95 (5.52)	-1.65 (6.10)	0.340 (-1.91; 3.33)
GSES-12			
Baseline (T0)	44.57 (6.49)	44.75 (8.55)	0.910 (-3.21; 2.86)
3 months (T1)	43.31 (9.10)	44.92 (8.69)	0.399 (-5.41; 2.17)
6 months (T2)	43.14 (8.48)	43.74 (8.21)	0.915 (-4.31; 3.12)
T2-T0	-0.85 (6.67)	0.44 (6.06)	0.265 (-4.16; 1.56)
PAM			
Baseline (T0)	38.92 (7.24)	40,79 (4.61)	0.210 (-4.26; 0.52)
3 months (T1)	40.24 (6.90)	39,92 (5.72)	0.816 (-2.39; 3.02)
6 months (T2)	40.17 (6.17)	40.79 (4.76)	0.101 (-3.09; 1.85)
T2-T0	18.26 (53.25)	17.97 (50.81)	0.906 (-23.23;23.83)
HLS-EUQ16			
Baseline (T0)	32.94 (7.84)	31.18 (5.98)	0.125 (-1.00; 4.51)
3 months (T1)	32.00 (7.35)	30.32 (7.16)	0.291 (-1.46; 4.81)
6 months (T2)	30.00 (6.34)	32.79 (8.24)	0.767 (-0.51;6.08)
T2-T0	-0.84 (3.18)	-1.67 (3.80)	0.485 (-0.98;2.66)

Significant differences ($p \leq 0.05$) are highlighted in bold. *Intervention group had 52 participants in T0, 47 participants in T1 and 42 participants in T2. **Control group had 48 participants in T0, 44 participants in T1 and 38 participants in T2. SF-36, Short Form-36 Health Survey Questionnaire; MoCA, Montreal Cognitive Assessment; HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; IPAQ-SF, Physical Activity Questionnaire-Short Form; GSES-12, Self-efficacy Scale-12; PAM, Patient Activation Measure Questionnaire; HLS-EUQ16, Health Literacy Europe Questionnaire.

Table 3 shows the evolution of both the control and intervention groups in the different quality and health constructs analysed after a six-month follow-up period. All participants significantly improved in physical health, mental health, number of persistent symptoms, cognitive status, physical performance, as well as levels of depression and anxiety ($p<0.001$).

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Table 3. General description of the evolution of all study participants who were evaluated in the three measurements in a period of six months.

VARIABLES	RESULTS T0 N=80 Mean (SD)	RESULTS T2 N=80 Mean (SD)	SIGNIFICANCE p-value	Confidence interval 95%	
				Inf.	Sup.
PRIMARY OUTCOMES					
SF-36 Physical health	30,61 (14.401)	36,97 (20.679)	**p < 0.001**	-9.847	-2.883
SF-36 Mental health	33,16 (18.352)	46,40 (24.120)	**p < 0.001**	-17.652	-8.836
SECONDARY OUTCOMES					
N. º of persistent symptoms	16,81 (6.084)	12,83 (6.649)	**p < 0.001**	2.80	5.148
MoCA	23,59 (3.946)	25,48 (3.241)	**p < 0.001**	-2.563	-1.215
Si-to-Stand Test	10,22 (3.606)	11,74 (4.446)	**p < 0.001**	-2.311	-0.715
IPAQ-SF	326,43 (361.277)	315,50 (485.089)	0.805	-76.960	98.835
HADS	18,26 (8.316)	16,20 (8.868)	**p < 0.001**	0.980	3.144
ISI	12,02 (6.408)	12,05 (7.424)	0.475	-1.792	0.842
GSES-12	43,70 (7.925)	43,43 (8.306)	0.703	-1.154	1.705
PAM	39,75 (6.327)	31,46 (5.523)	0.320	-2.129	0-704
HLS-EUQ16	31,98 (7.299)	31,46 (7.490)	0.426	-0.781	1.831

Significant differences ($p \leq 0.05$) are highlighted in bold. SF-36, Short Form-36 Health Survey Questionnaire; MoCA, Montreal Cognitive Assessment; HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; IPAQ-SF, Physical Activity Questionnaire-Short Form; GSES-12, Self-efficacy Scale-12; PAM, Patient Activation Measure Questionnaire; HLS-EUQ16, Health Literacy Europe Questionnaire.

Table 4 shows the regression models in relation to improvements in quality of life and mental health in both the control and intervention groups. No significant results were observed to help explain the improvement in physical health (SF-36 physical health). Results showed how increases in quality of life and mental health were predicted by an increase in time spent using the ReCOVery APP (p:0.009; p:0.003, respectively) and personal self-efficacy constructs (GSES-12) (p:0.025, p:0.012, respectively), explaining 17.8% of the variance in quality of life and 20.4% in mental health.

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Table 4: Linear regression model in relation to the improvements of quality of life and mental health

Quality of life (SF-36 physical and mental health)	**Coefficient**	**P-Value**	**Confidence interval 95%**		**Collinearity analysis**	
			SUPERIOR	**INFERIOR**	**TOLERANCE**	**VIF**
Minutes of ReCOVery APP use	0.001	**0.009**	0.000	0.000	0.920	1.088
Increase of in self-efficacy (GSES-12)	0.675	**0.025**	0.088	1.262	0.879	1.138
R2	0.178					
R2adj	0.134					
Mental Health (SF-35 Mental health)	**Coefficient**	**P-value**	**CI 95%**		**Collinearity analysis**	
			SUPERIOR	**INFERIOR**	**TOLERANCE**	**VIF**
Minutes of ReCOVery APP use	0.001	**0.003**	0.000	0.000	0.920	1.088
Increase of in self-efficacy (GSES-12)	0.860	**0.012**	0.194	1.527	0.879	1.138
R2	0.204					
R2adj	0.162					

Significant differences ($p \leq 0.05$) are highlighted in bold. SF-36, Short Form-36 Health Survey Questionnaire; GSES-12, Self-efficacy Scale-12.

DISCUSION

For the scientific community, understanding the aetiology of Long COVID is proving much more complex than in the case of COVID-19 (43). Research has created evidence, but there are still many unknowns surrounding the disease. The disparity of symptoms, coupled with the presence of comorbidities, has created great difficulty in understanding the condition (44). In the last two years, several medical guidelines have been published focusing on the diagnosis and management of Long COVID (22–24). However, these guidelines lack potentially useful rehabilitation interventions, which is understandable given the paucity of RCTs conducted in this patient group. In the same vein, official sources highlight the need for interventions based on a personalised care plan, from a multidisciplinary perspective (45). In this context and given that Long COVID patients have experienced a reduction in their quality of life, functional capacities, and well-being (46), this intervention has designed ReCOVery, an APP with a multidisciplinary rehabilitative approach, focused on improving the quality of life of patients with persistent COVID.

The results of this study concluded that ReCOVery APP was not significantly more effective in improving the quality of life of patients with Long COVID over a six-month period. Effectiveness analyses have revealed a greater improvement in the intervention

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group compared to the control group in terms of their mental health (SF-35 mental health and HADS), cognitive ability (MoCA), physical ability (IPAQ-SF), activation ability (PAM) and health literacy (HLS-EUQ16), as well as a greater decrease in the number of persistent symptoms. However, these were non-significant improvements compared to the control group. However, linear regression analyses have revealed significant patterns of improvement in the quality of life of these patients predicted by time of APP use and self-efficacy (GSES-12).

It was from 2021 onwards that the first telerehabilitation and digital health interventions began to appear, aimed at the recovery of post-COVID-19 and persistent COVID patients. An example of this was the pilot study by Fowler-Davis et al. (2021), which identified improvements in quality of life, including through a virtual consultation to offer advice on their needs, albeit with only eight participants (47). In contrast, the telerehabilitation programme of Dalbosco-Salas et al. (2021) had a large number of Post-COVID-19 participants with persistent dyspnoea, although there was no control group. This intervention was based on 24 supervised home-based exercise training sessions for patients and achieved significant improvements in fatigue, dyspnoea, physical function and quality of life as measured by the SF-36. However, they did not report improvements in their physical complaints, nor in their perceived mental health through telerehabilitation (48). Harenwall et al (2021) conducted an intervention based on a course of recovery after COVID infection, and reported an increase in their general health after the intervention. It appears that the inclusion criteria allowed for self-diagnosis by self-suspicion of the participants and no inclusion criteria were set so that the sample has low validity (49). Thus, early research would point towards telerehabilitation as a viable option for the recovery of patients with Long COVID, but had several of the biases already mentioned.

In 2022, the first RCTs started to be implemented, such as the one by Li et al. (2022), based on a 6-week unsupervised home-based post-COVID-19 exercise programme. This study did obtain significant improvements in favour of the intervention group in their quality of life (SF-12), although both groups improved lung function in a similar way but no long-term effects were obtained (50). The RCT by McNarry et al (2022) verified that after eight weeks of inspiratory muscle training in Post-COVID-19 patients there was no

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improvement in quality of life in favour of the intervention group (51). The cohort study by Kortianou et al. (2022) studied the clinical effects of a home-based telerehabilitation exercise programme after discharge from hospital for COVID-19. Their results showed significant improvements in perceptions of health and well-being (measured through the SF-36 and HADS), however, they did not show significant improvements in physical health. In addition, more than half of their participants dropped out of the intervention before completion (52). On the other hand, the clinical trial by Estébanez-Pérez achieved a significant improvement in the functional capacity of patients with Long COVID after a 4-week digital physiotherapy intervention. However, this study did not have a control group of participants (53). Finally, the qualitative study by Ruckser-Scherb et al. (2022) analysed the experiences of post-COVID-19 patients after two weeks of using an APP, initially for oncology patients (54). In response, more than 80 % of participants found some of the content useful, more than 70 % liked the exercises, and all participants recommended its use to post-COVID-19 and persistent COVID patients.

Regarding the most recent evidence, the systematic review by Chuang et al. (2023) affirm that therapies based on physical exercise are fundamental for the recovery of Long COVID, including the telerehabilitation modality (55). In addition, I recommend early management that should begin with a comprehensive and individualized evaluation (55). In this sense, De Mars et al. (2023) publish recommendations to implement a safe rehabilitation for this group of patients (56). Among them, the RCT by Del Corral et al. (2023), in which, through a supervised 8-week inspiratory/expiratory muscle program carried out from home, he managed to improve the quality of life of the 88 post-COVID-19 participants. No improvements in exercise tolerance were achieved (57). The RCT by Santana et al. (2023) investigated the potential therapeutic effects of high-definition transcranial direct current stimulation in conjunction with a rehabilitation program for the management of post-COVID-19 fatigue. This intervention was effective in reducing fatigue and anxiety, as well as improving quality of life (58). The Jimeno-Almazán RCT demonstrated the benefits of a supervised exercise program in people with post-COVID-19 conditions, for people with mild COVID-19 (59). In this line, the recent systematic review by Burnett et al. (2023) show promise for exercise interventions in Long COVID patients for improving functional exercise capacity,

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dyspnea, and fatigue (60). The scoping review by Rinn et al. (2023) believe that digital interventions have the potential to help control some persistent symptoms, both physical and psychological (61).

Thus, the use of digital interventions, such as telerehabilitation, is being progressively implemented for a multitude of pathologies, and reported research suggests that this is also the case for Long COVID (61). Current evidence demonstrates the potential of digital interventions to help control some physical and psychological symptoms. Several studies on telerehabilitation that evaluated quality of life obtained significant improvements in favor of the intervention group (62–65). However, its inclusion criteria allowed access to patients infected for less than twelve weeks, so it could not be considered that the total sample was made up of Long COVID patients, as some indicate. Thus, the limited research on effective digital tools for patients with Long COVID still requires the implementation of large-scale RCTs with a high degree of clinical evidence. An important aspect to consider in future research has turned out to be adherence. Various investigations have reported numerous dropouts of a notable percentage of participants (48,52,62), as well as poor adherence as shown in this study. However, in the short term, the time of use of ReCOVery APP was not found to be correlated with the improvement of the general quality of life and mental health of the participants (26). Therefore, these medium-term analyzes are promising given the effectiveness of APP.

Of particular note is the construct of self-efficacy, which is also correlated with better overall quality of life and mental health. Self-efficacy is a factor with potential for inclusion in the ability of patients with chronic diseases to self-manage their symptoms (66). Thus, patients with high self-efficacy in coping with their chronic diseases show more perceived ability to manage the challenges related to their diseases and a greater sense of control over their lives (67). This evidence would be consistent with the findings that higher self-efficacy correlates with better overall quality of life and mental health. This reality has also been seen in other pathologies such as multiple sclerosis (68), oncological processes (67) or after the sequelae of a stroke (69). Therefore, the role of self-efficacy should be considered as an important element in the recovery of patients with persistent COVID.

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Finally, participants in the present intervention did not report any unanticipated adverse effects, either during the intervention or months later. Furthermore, there were no difficulties of any kind during the course of the intervention. Therefore, it can be affirmed that this is a safe, consistent and feasible intervention. Our research team intends to carry out a qualitative analysis to further investigate the low adherence of the participants, as well as to be able to offer technical and content improvements in the future.

Our study has some limitations. First, the context in which the study was carried out, during the vaccination process and an increase in the number of infections. Second, due to the nature of the intervention, all participants were aware of their group assignment during the RCT. Third, the symptomatology itself (physical and mental) and its fluctuation may be limiting for rehabilitation interventions. Fourth, the Montreal Cognitive Assessment (MoCA) questionnaire obtained a Cronbach's alpha of 0.49, thus reporting low reliability. Finally, the study variables are based on participants' self-perceptions; therefore, we must rely on their statements, even if they cannot be objectively verified. This study also has several strengths. Unlike other research, a specific APP has been designed for persistent COVID, which is easy to use and access from any location with an internet connection. In addition, to our knowledge, there are no studies in our country with a similar number of Long COVID participants and a long follow-up time, using a telerehabilitation intervention for this disease.

CONCLUSIONS

After a six-month telerehabilitation intervention for patients with persistent COVID, some non-significant improvements were observed. However, linear regression analyses revealed that longer use of ReCOVery APP and higher self-efficacy lead to better overall quality of life and mental health of these patients. Possibly, low adherence to the APP justifies the lack of significant improvements. Therefore, future large-scale research is needed to further investigate strategies to increase adherence to telerehabilitation in patients with persistent COVID. Ultimately, the development of this research increases the knowledge available on the effectiveness of telerehabilitation for patients with persistent COVID as a promising tool to improve their quality of life.

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DECLARATIONS

Acknowledgements

We wish to thank the University of Zaragoza, the Aragonese Primary Care Research Group (GAIAP, B21_23R) that is part of the Department of Innovation, Research and University at the Government of Aragón (Spain); the Institute for Health Research Aragón (IIS Aragón); the Research Network on Chronicity, Primary Care, and Health Promotion (RICAPPS) that received a research grant from the Carlos III Institute of Health, Ministry of Science and Innovation (Spain), awarded on the call for the creation of Health Outcomes-Oriented Cooperative Research Networks (RICORS), with reference RD21/0016/0005, co-funded with European Union – NextGenerationEU funds, which finance the actions of The Recovery and Resilience Facility (RRF); the University of Zaragoza; and Feder Funds “Another way to make Europe”.

Authors' contributions

M.S.-P., B.O.-B. and S.L.-H. elaborated the research design. M.S.-P., B.O.-B. and S.L.-H. Developed the study and coordinated the field work. R.S.-R and M.S.-P did the analysis. R.S.-A., V.C.-V and R.S.-R. have helped with the coordination of the project. M.S.-P. and B.O.-B. wrote the manuscript. B.O.-B. is the principal investigator of the project. All authors reviewed the content of the manuscript and approved the final version for submission. Not applicable as the data are anonymised and no individual images are presented.

Funding

This work is supported by grant number PI21/01356 from the Instituto de Salud Carlos III. In adittion, This work was supported by the Aragonese Primary Care Research Group (GAIAP, B21_23R) that is part of the Department of Innovation, Research and University at the Government of Aragón (Spain); the Institute for Health Research Aragón (IIS Aragón); the Research Network on Chronicity, Primary Care, and Health Promotion (RICAPPS) that received a research grant from the Carlos III Institute of Health, Ministry of Science and Innovation (Spain), awarded on the call for the creation of Health Outcomes-Oriented Cooperative Research Networks (RICORS), with reference RD21/0016/0005, co-funded with European Union – NextGenerationEU funds, which

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finance the actions of The Recovery and Resilience Facility (RRF); the University of Zaragoza; and Feder Funds "Another way to make Europe".The funding body will carry out an audit test once a year.

Conflict of interest

The authors declare that they have no conflicts of interest.

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ANEXO II. Información adicional sobre los manuscritos que componen esta tesis

Manuscrito I

Samper-Pardo, M., León-Herrera, S., Oliván-Blázquez, B., Benedé-Azagra, B., Magallón-Botaya, R., Gómez-Soria, I., Calatayud, E., Aguilar-Latorre, A., Méndez-López, F., Pérez-Palomares, S., Cobos-Rincón, A., Valero-Errazu, D., Sagarra-Romero, L., & Sánchez-Recio, R. (2022). Development and Validation of a Mobile Application as an Adjuvant Treatment for People Diagnosed with Long COVID-19: Protocol for a Co-Creation Study of a Health Asset and an Analysis of Its Effectiveness and Cost-Effectiveness. International journal of environmental research and public health, 20(1), 462. https://www.mdpi.com/1660-4601/20/1/462

Factor de Impacto (JCR 2021): 4,614 (Q2)

Área temática: SALUD PÚBLICA, AMBIENTAL Y OCUPACIONAL

Justificación de la contribución del doctorando: Tal y como se menciona en el manuscrito publicado, el doctorando hizo una contribución significativa en la investigación, encargándose del diseño de la investigación, el desarrollo del estudio, la coordinación del trabajo, la redacción del borrador original y posterior revisión y edición de éste.

Manuscrito II

Samper-Pardo, M., León-Herrera, S., Oliván-Blázquez, B., Méndez-López, F., Domínguez-García, M., & Sánchez-Recio, R. (2023). Effectiveness of a telerehabilitation intervention using ReCOVery APP of long COVID patients: a randomized, 3-month follow-up clinical trial. Scientific reports, 13(1), 7943. https://doi.org/10.1038/s41598-023-35058-y

Factor de Impacto (JCR 2022): 4,6 (Q2)

Área temática: CIENCIAS MULTIDISCIPLINARIAS

Justificación de la contribución del doctorando: Tal y como se menciona en el manuscrito publicado, el doctorando hizo una contribución significativa en la investigación, encargándose del diseño de la investigación, el desarrollo del estudio, la coordinación del trabajo, la redacción del borrador original y posterior revisión y edición de éste.

Manuscrito III

Samper-Pardo, M., León-Herrera, S., Oliván-Blázquez, B., Gascón-Santos, S., & Sánchez-Recio, R. (2023). Clinical characterization and factors associated with quality of life in Long COVID patients: Secondary data analysis from a randomized clinical trial. PLoS ONE, 18(5), e0278728. https://doi.org/10.1371/journal.pone.0278728

Factor de Impacto (JCR 2022): 3,7 (Q2)

Área temática: CIENCIAS MULTIDISCIPLINARIAS

Justificación de la contribución del doctorando: Tal y como se menciona en el manuscrito publicado, el doctorando hizo una contribución significativa en la investigación, encargándose del diseño de la investigación, el desarrollo del estudio, la coordinación del trabajo, la redacción del borrador original y posterior revisión y edición de éste.

Manuscrito IV

Samper-Pardo, M., Oliván-Blázquez, B., Magallón-Botaya, R., Méndez-López, F., Bartolomé-Moreno, C., & León-Herrera, S. (2023). The emotional well-being of Long COVID patients in relation to their symptoms, social support and stigmatization in social and health services: a qualitative study. BMC Psychiatry, 23(1), 68. https://doi.org/10.1186/s12888-022-04497-8

Factor de Impacto (JCR 2022): 4,4 (Q2)

Área temática: PSIQUIATRÍA

Justificación de la contribución del doctorando: Tal y como se menciona en el manuscrito publicado, el doctorando hizo una contribución significativa en la investigación, encargándose del diseño de la investigación, el desarrollo del estudio, la coordinación del trabajo, la redacción del borrador original y posterior revisión y edición de éste.

Manuscrito V

Samper-Pardo, M., Formento-Marín, N., Oliván-Blázquez, B., León-Herrera, S., & Benedé-Azagra, B. (2023). Use of community resources as health assets for rehabilitation of people with Long COVID in northeastern Spain two years after the outbreak of the COVID-19 pandemic: qualitative study. Archives of public health, 81(1), 125. https://doi.org/10.1186/s13690-023-01139-7

Factor de Impacto (JCR 2022): 3,3 (Q2)

Área temática: SALUD PÚBLICA, AMBIENTAL Y OCUPACIONAL

Justificación de la contribución del doctorando: Tal y como se menciona en el manuscrito publicado, el doctorando hizo una contribución significativa en la investigación, encargándose del diseño de la investigación, el desarrollo del estudio, la coordinación del trabajo, la redacción del borrador original y posterior revisión y edición de éste.