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Intervención terapéutica multimodal en pacientes con sintomatología respiratoria crónica

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ÍNDICE

RESUMEN

Las enfermedades respiratorias crónicas siguen siendo una de las principales causas de muerte y discapacidad a nivel mundial, con un crecimiento anual de cifras absolutas. Se estima, que cada año mueren 4 millones de personas de manera prematura debido a estas patologías. Dentro de estas enfermedades, la enfermedad pulmonar obstructiva crónica (EPOC) es la más prevalente a nivel mundial.

A esta situación de gran importancia social y sanitaria, debemos sumar además la pandemia de enfermedad por coronavirus 2019 (COVID-19) que hasta el momento ha afectado a más de 763 millones de personas en todo el mundo, produciendo 6,9 millones de muertes.

Esta pandemia generará importantes repercusiones sanitarias a largo plazo, debido al desarrollo en los pacientes de la condición clínica denomina Long-COVID, caracterizada por la presencia de síntomas crónicos hasta tres meses después de la infección aguda.

El Long-COVID y la EPOC son patologías respiratorias con etiologías diferentes, y, por tanto, con curso clínico distintos. Sin embargo, en la base fisiopatológica de la sintomatología crónica de ambas enfermedades, se encuentra un proceso inflamatorio crónico que no solo se localiza a nivel del aparato respiratorio, sino que se expande a otras localizaciones.

De esta manera, ambas patologías cursan con síntomas respiratorios crónicos y una importante repercusión sistémica, generando sintomatología muy variada que da lugar a una importante repercusión función y deterioro de la calidad de vida de los pacientes.

Por lo tanto, el estudio de las patologías que generan sintomatología respiratoria crónica permitirá el establecimiento de perfiles clínicos específicos, estableciendo un marco de

referencia sobre el que desarrollar intervenciones terapéuticas multimodales ajustadas a las necesidades de estos pacientes.

El objetivo general de esta tesis doctoral fue la caracterización de los pacientes con patología respiratoria crónica y el estudio de las intervenciones terapéuticas multimodales que mejor se ajusten a sus necesidades clínicas.

El desarrollo de esta tesis doctoral se llevó a cabo en línea con estos objetivos. Para ello, se desarrollaron tres estudios con diferentes metodologías. El primer estudio consistió en un estudio transversal de casos y controles que tenía como objetivo evaluar la calidad de vida relacionada con la salud y las características del dolor en pacientes con Long-COVID. Los resultados muestran que los pacientes con Long-COVID presentan una mayor intensidad e interferencia del dolor, además de una peor calidad de vida en comparación con sujetos controles. El segundo estudio consistió en un estudio transversal de casos y controles que tenia como objetivo identificar el perfil clínico y psicosocial asociado al dolor en pacientes no hospitalizados con Long-COVID. Los resultados muestran que los pacientes con Long-COVID presentan alta intensidad e interferencia del dolor, sensibilización central, aumento de la gravedad del insomnio, miedo al movimiento, catastrofización, depresión, ansiedad y estrés. El tercer estudio consistió en una revisión sistemática y metaanálisis que tenía como objetivo identificar los efectos de intervenciones terapéuticas multimodales basadas en la telerehabilitación en la calidad de vida de los pacientes con EPOC. Lo resultados mostraron que las intervenciones de telerehabilitación pueden complementar o remplazar tratamientos presenciales en pacientes con EPOC, generando mejoras en su calidad de vida.

En conclusión, esta tesis muestra que los pacientes con enfermedades respiratorias presentan sintomatología crónica con importantes repercusiones a nivel sistémico, que limitan considerablemente la funcionalidad y calidad de vida influyendo en su pronóstico.

Además, se evidencia la eficacia de la telerehabilitación para desarrollar programas terapéuticos multimodales que se ajusten a las necesidades terapéuticas de estos pacientes.

ABSTRACT

Chronic respiratory diseases continue to be one of the main causes of death and disability worldwide, with an annual growth in absolute figures. It is estimated that 4 million people die prematurely each year due to these pathologies. Among these diseases, chronic obstructive pulmonary disease (COPD) is the most prevalent worldwide.

To this situation of great social and health importance, we must also add the 2019 coronavirus disease pandemic (COVID-19) that has so far affected more than 763 million people worldwide, resulting in 6.9 million deaths.

This pandemic will generate important long-term health repercussions, due to the development in patients of the clinical condition known as Long-COVID, characterized by the presence of chronic symptoms up to three months after acute infection.

Long-COVID and COPD are respiratory pathologies with different etiologies and, therefore, different clinical courses. However, at the pathophysiological basis of the chronic symptomatology of both diseases, there is a chronic inflammatory process that is not only localized at the level of the respiratory tract, but also spreads to other locations.

Thus, both pathologies have chronic respiratory symptoms and an important systemic repercussion, generating a wide variety of symptoms that result in a significant impact on function and deterioration of the quality of life of the patients.

Therefore, the study of the pathologies that generate chronic respiratory symptomatology will allow the establishment of specific clinical profiles, establishing a frame of reference on which to develop multimodal therapeutic interventions adjusted to the needs of these patients.

The general objective of this doctoral thesis was the characterization of patients with chronic respiratory pathology and the study of multimodal therapeutic interventions that best fit their clinical needs.

The development of this doctoral thesis was carried out in line with these objectives. To this end, three studies were developed with different methodologies. The first study consisted of a cross-sectional case-control study that aimed to evaluate health-related quality of life and pain characteristics in patients with Long-COVID. The results show that patients with Long-COVID have higher pain intensity and interference, as well as worse quality of life compared to controls. The second study consisted of a cross-sectional case-control study aimed at identifying the clinical and psychosocial profile associated with pain in non-hospitalized patients with Long-COVID. The results show that patients with Long-COVID present high pain intensity and interference, central sensitization, increased severity of insomnia, fear of movement, catastrophizing, depression, anxiety, and stress. The third study consisted of a systematic review and meta-analysis aimed at identifying the effects of telerehabilitation-based multimodal therapeutic interventions on the quality of life of COPD patients. The results showed that telerehabilitation interventions can complement or replace face-to-face treatments in COPD patients, generating improvements in their quality of life.

In conclusion, this thesis shows that patients with respiratory diseases present chronic symptomatology with important repercussions at a systemic level, which considerably limit their functionality and quality of life, influencing their prognosis. In addition, the efficacy of telerehabilitation to develop multimodal therapeutic programs that fit the therapeutic needs of these patients is evidenced.

INTRODUCCIÓN

Las enfermedades respiratorias crónicas siguen siendo una de las principales causas de muerte y discapacidad a nivel mundial, con un crecimiento anual de cifras absolutas(1). Algunas de las enfermedades respiratorias crónicas más comunes son el asma, la enfermedad pulmonar obstructiva crónica (EPOC) y las enfermedades pulmonares profesionales. Estas patologías contribuyen en gran medida al aumento de las enfermedades no transmisibles en todo el mundo.

Los factores de riesgo para el desarrollo de enfermedades respiratorias crónicas incluyen los efectos tóxicos del uso de combustibles de biomasa, la contaminación del aire exterior y el humo del tabaco(2). Se estima, que cada año mueren 4 millones de personas de manera prematura debido a enfermedades respiratorias crónicas(3).

Además, debemos tener en cuenta los importantes costes sanitarios derivados del tratamiento de los afectados con estas enfermedades. La Unión Europea estimó en el año 2019 unos costes anuales de 380 billones de euros dentro de los cuales se incluyen, los gastos derivados de la atención hospitalaria, los costes de la pérdida de productividad y el valor de los años de vida ajustados por discapacidad de estos pacientes(4).

A esta situación de gran importancia política y sanitaria, debemos sumar además la pandemia de COVID-19. Esta pandemia comenzó en la provincia de Wuhan en China, identificándose el primer paciente en noviembre de 2019. Desde entonces, la COVID-19 ha afectado a más de 763 millones de personas en todo el mundo, produciendo 6,9 millones de muertes(5).

Durante la pandemia de COVID-19 se generó una gran incertidumbre ante la posible repercusión sintomática y funcional que la enfermedad pudiera generar en los pacientes tanto a corto como a largo plazo.

Además, la investigación se vio gravemente limitada, impidiendo el desarrollo de estudios clínicos adecuados que dieran como resultado el establecimiento de perfiles clínicos concretos y el desarrollo de opciones terapéuticas ajustadas a sus necesidades(6).

De esta manera, se justifica el estudio de la enfermedad respiratoria crónica más frecuente hasta la fecha, la EPOC, como patología de referencia que nos permita estudiar y comparar la fisiopatología de base, así como las posibles repercusiones sintomáticas, funcionales y sistémicas de la COVID-19.

Enfermedad pulmonar obstructiva crónica

Definición

La Enfermedad Pulmonar Obstructiva Crónica (EPOC) es una patología pulmonar heterogénea que se caracteriza por la presencia de síntomas respiratorios crónicos como pueden ser la disnea, la tos y la producción de esputo. Se produce como consecuencia de anormalidades de las vías aéreas (bronquitis o bronquiolitis) y de los alveolos (enfisema) que dan lugar a una obstrucción del flujo aéreo persistente y a menudo progresiva(7).

La EPOC es una enfermedad prevenible y tratable, pero el infradiagnóstico de esta patología hace que muchas veces los pacientes no lleguen a recibir el tratamiento, o no reciban el tratamiento más adecuado a sus características clínicas(8).

Etiología y factores de riesgo

La EPOC es una enfermedad que se produce como consecuencia de un proceso acumulativo a lo largo de la vida del individuo, resultado de la factores genéticos y ambientales que aceleran el proceso normal de envejecimiento del pulmón(9).

Los principales factores ambientales que afectan al desarrollo de la enfermedad son el humo del tabaco y la inhalación de partículas y gases tóxicos de la contaminación atmosférica(10). Dentro de los factores genéticos de riesgo más importantes, aunque

epidemiológicamente poco frecuente, se encuentra la mutación del gen de la SERPINA1, que conduce a la deficiencia de α1-antitripsina, un importante inhibidor de las proteasas de serina(11).

Como factor ambiental más importante dentro de la etiología de la EPOC encontramos el humo del tabaco. Los pacientes fumadores tienen una mayor prevalencia de síntomas respiratorios y alteraciones funcionales pulmonares, además de presentar una mayor mortalidad que los pacientes no fumadores. Sin embargo, es importante remarcar que solo el 50% de los fumadores de grandes cantidades de tabaco anuales, acaban desarrollando EPOC, por lo tanto, no debemos subestimar otras causas etiológicas(10).

De esta manera, durante más de 50 años se ha considerado el tabaco como el factor de riesgo principal de la EPOC. Esto es así porque la mayoría de los estudios se realizaban en países desarrollados, donde el tabaco supone hasta el 70% de los casos de EPOC. Sin embargo, conforme se han incorporado datos de países en vía de desarrollo se ha visto que existen otra serie de factores que contribuyen al desarrollo del 50% de los casos a nivel mundial(12).

La exposición a combustibles de biomasa como pueden ser la madera, los residuos de cultivos o el carbón, que además suelen quemarse en fuegos abiertos o en cocinas poco eficientes, sobre todo en países en vías de desarrollo, suponen un importante factor de contaminación del aire en los hogares y se asocia a un mayor riesgo de desarrollo de la EPOC(13).

En cuanto a los factores ambientales es importante considerar las exposiciones ocupacionales como los polvos orgánicos e inorgánicos y los agentes químicos. Además, debemos tener en cuenta la contaminación atmosférica que suele consistir en óxidos de nitrógeno o azufre, metales pesados y otros gases de efecto invernadero, siendo estos

últimos, los responsables del 50% de los casos de EPOC en los países de ingresos medios y bajos.

Otros factores que contribuyen al desarrollo de la EPOC y que deben ser tenidos en cuenta, son el asma y las infecciones. En estudios de cohortes longitudinales se ha demostrado que los pacientes diagnosticados de asma tienen 12 veces mayor riesgo de desarrollar EPOC en comparación con controles sanos(14). Las infecciones respiratorias de repetición durante la infancia se han asociado a una capacidad pulmonar reducida y al incremento de la sintomatología respiratoria, con un mayor riesgo de desarrollar EPOC durante la etapa adulta(15).

En los pacientes con EPOC se pueden encontrar cambios fisiopatológicos en las vías respiratorias, el parénquima pulmonar y en los vasos pulmonares. Estos incluyen cambios inflamatorios y estructurales que progresan en el tiempo y persisten incluso después del cese del tabaquismo(16).

En la base de la fisiopatología de la EPOC se encuentra una respuesta inflamatoria anómala y exacerbada que ocurre tanto en las vías aéreas como en el parénquima y los vasos sanguíneos. Se caracteriza por un aumento en el número de macrófagos, neutrófilos y linfocitos, los cuales, producen una elevada cantidad de metabolitos proinflamatorios como factores quimiotácticos que atraen un mayor número de células inflamatorias y citoquinas que amplifican el proceso inflamatorio(17). De esta manera, el resultado es una respuesta inflamatoria exacerbada que dará lugar a cambios estructurales, con la posterior fibrosis y pérdida de la función fisiológica del tejido(18).

Derivado del daño a nivel de las vías pulmonares, los vasos sanguíneos y el parénquima pulmonar, se acaban generando, obstrucción del flujo aéreo y atrapamiento de gases, anomalías del intercambio gaseoso pulmonar e hipertensión pulmonar(19).

Prevalencia

Los datos de prevalencia sobre la EPOC varían enormemente entre diferentes regiones debido fundamentalmente a la falta de consenso en cuanto a los criterios diagnóstico y errores metodológicos en los métodos de encuesta(20).

Aun así, los datos publicados hasta la fecha ponen de manifiesto que la EPOC es mucho más prevalente en pacientes fumadores que en no fumadores, en pacientes mayores de 40 años que en pacientes menores de 40 años y en hombres en comparación con las mujeres(21).

En Europa, la prevalencia global es del 12,3% sin diferencias entre las diferentes regiones, encontrándose la prevalencia de la población española por debajo de la media con un 10%(22). Es importante remarcar que un porcentaje muy alto de la población con EPOC, cercano al 70% se encuentra infradiagnosticado(23).

Mortalidad y morbilidad

Las medidas de morbilidad incluyen tradicionalmente las visitas al médico, las visitas a urgencias y las hospitalizaciones. Los estudios realizados hasta le fecha indican que la morbilidad debida a la EPOC aumenta con la edad y que en los pacientes con EPOC el desarrollo de comorbilidades se produce a edades más tempranas(24).

Los últimos estudios publicados con respecto a la mortalidad de esta enfermedad nos dicen que en torno al 4,72% de todas las muertes a nivel mundial se producen por la EPOC. Los datos de la OMS indican que la EPOC llegará a ser la causa del 7,8% de todas las muertes en 2030(20).

Aspectos clínicos

El diagnóstico de esta enfermedad se considera en cualquier paciente que tenga disnea, tos crónica y producción de esputo y que además tenga historia de exposición a los

factores de riesgo de la enfermedad. Para confirmar el diagnóstico es necesario realizar una espirometría forzada post broncodilatadores con un valor de FEV1/FVC<0.7(7).

El síntoma más característico de la enfermedad es la disnea crónica, presentando tos crónica y producción de esputo únicamente el 30% de los pacientes. A pesar de que el diagnóstico se establece gracias a los valores espirométricos, todos los pacientes que se presenten con esta sintomatología deberán ser examinados para buscar las causas de la enfermedad(7).

La disnea es el síntoma más característico de la enfermedad causando en muchas ocasiones problemas psicológicos derivados, como la ansiedad. Es una disnea que un 40% de los pacientes clasifican como moderada o severa y que aparece sobre todo ante los esfuerzos físicos(25).

La tos crónica es en muchas ocasiones el primer síntoma de la enfermedad, pero los pacientes no se alarman ante su presencia pues la consideran una consecuencia del tabaquismo o la exposición a contaminantes. Puede ser una tos tanto productiva como improductiva y que se caracteriza por ser intermitente al inicio de la enfermedad, pero progresar hacia una tos continua(26).

La producción de esputo suele ser algo común entre los pacientes con EPOC. Se considera que el paciente tiene bronquitis crónica cuando presenta producción de esputo durante 3 o más meses en dos años consecutivos(27).

Otros síntomas que los pacientes presentan con frecuencia son las sibilancias, opresión torácica y fatiga. Los pacientes refieren a menudo una sensación de cansancio generalizado o falta de energía, que limita seriamente su capacidad funcional y su calidad de vida(28).

Es importante remarcar que los pacientes con EPOC sufren reagudizaciones frecuentes de la sintomatología conocidas como exacerbaciones. Estas exacerbaciones se producen como consecuencia de la exposición a factores de riesgo o de infecciones de las vías respiratorias, que cursan con inflamación de las vías respiratorias y una producción aumentada de esputo, dando lugar a un aumento de la disnea. Estas son un factor importante en el curso de la enfermedad pues repercuten negativamente en el estado de salud de los pacientes, favoreciendo la progresión de la enfermedad y aumentando las tasas de hospitalización y de reingreso(29).

Tras haber analizado la etiología, fisiopatología y clínica de la EPOC, podemos decir que se trata de una enfermedad crónica producida por la exposición continuada a partículas nocivas para las vías respiratorias. Esta enfermedad cursa además con procesos de reagudización conocidos como exacerbaciones. Sin embargo, en la base de su patogenia, se encuentra un proceso inflamatorio crónico que no solo se localiza a nivel del aparato respiratorio, sino que se expande a nivel sistémico(30).

Si sumamos esta inflamación sistémica a la hipoxia generada como consecuencia de la destrucción de las vías aéreas y el parénquima pulmonar, el paciente desarrollará importantes síntomas sistémicos, como, por ejemplo, el dolor, la ansiedad, la depresión, pérdida de fuerza de miembros inferiores, etc(31).

De esta forma, derivados de una patología inicialmente respiratoria, encontramos cuadros clínicos muy complejos, con una importante afectación sistémica, con la consecuente limitación de la funcionalidad de los pacientes y disminución de la calidad de vida de estos.

Abordaje terapéutico

Los objetivos fundamentales del tratamiento de los pacientes con EPOC se basan en reducir la sintomatología, el número de exacerbaciones e intentar mejorar el pronóstico de la enfermedad. Para ello se utiliza una combinación de tratamiento farmacológico y rehabilitación(32).

Para el tratamiento farmacológico de la EPOC se utilizan fundamentalmente una combinación de broncodilatadores, glucocorticoides y mucolíticos en aquellos pacientes con expectoración. Estos tratamientos consiguen una mejora sintomatológica, pero no existen tratamiento que permitan aumentar la capacidad pulmonar perdida debido a la enfermedad(33).

Los broncodilatadores de acción corta se recomiendan siempre que aparezca un aumento de la sintomatología. Han demostrado eficacia a la hora de aumentar la capacidad funcional y reducir la sintomatología de los pacientes con EPOC(34). Los glucocorticoides por su parte se han asociado a una reducción de las exacerbaciones y de la reactividad bronquial, no debiendo abusar de su uso debido a los efectos adversos de los mismo y a un aumento del riesgo de neumonía. Por último, debemos hablar de los mucolíticos, los cuales se prescriben con el objetivo de reducir la viscosidad del esputo, de manera que sea más fácil la expectoración(32).

Por otro lado, encontramos el tratamiento no farmacológico. Este se basa en una combinación de oxigenoterapia, con ejercicio físico, medidas de autocuidado y dieta adecuada. La oxigenoterapia se utiliza con el objetivo de mantener una saturación de oxígeno por encima del 90% en las diferentes situaciones del día a día, es decir, tanto en reposo como durante la actividad(35).

La base del tratamiento no farmacológico de estos pacientes es la rehabilitación pulmonar controlada por un profesional, que evite que entren en un círculo de fatiga, inactividad y disminución de la capacidad funcional. Dentro de los programas de rehabilitación pulmonar encontramos fundamentalmente ejercicio aeróbico controlado, pero también podemos encontrar otras modalidades como ejercicio de fuerza o entrenamiento respiratorio, así como combinaciones de estos(36).

Además, al tratarse de patologías crónicas que suponen una gran demanda a nivel sanitario, es importante que el paciente desarrolle habilidades de autocuidado. De esta manera cobran especial relevancia los programas de educación y automanejo de la enfermedad(37).

Debemos tener en cuenta que los pacientes con EPOC han sido considerados como pacientes de alto riesgo de infección durante la pandemia, lo que ha limitado seriamente las posibilidades de acceso a programas de rehabilitación adecuados a sus necesidades.

Los programas de telerehabilitación que han permitido a los pacientes continuar con la rehabilitación desde casa, evitando de esta manera un deterioro mayor de la funcionalidad y de la calidad de vida, han tenido especial relevancia(38). Por lo tanto, el estudio en profundidad de estos programas de telerehabilitación para adecuarlos a las necesidades terapéuticas de los pacientes con EPOC cobra especial relevancia en el contexto actual de pandemia.

Enfermedad por coronavirus 2019 (COVID-19)

Definición

La enfermedad por coronavirus (COVID-19) es una enfermedad infecciosa generada por el coronavirus 2 del síndrome respiratorio agudo severo (SARS-CoV-2)(39). La variabilidad clínica de la infección generada por la infección por SARS-CoV-2 es muy

amplia, pudiendo provocar desde una infección asintomática hasta una infección severa que derive en un síndrome de dificultad respiratoria aguda y la muerte del paciente(40).

Los factores de riesgo asociados a la hospitalización y mortalidad por la COVID-19 han sido identificados, siendo los más relevantes la edad, la obesidad, el sexo masculino y las comorbilidades previas, entre las que destacan las enfermedades cardiovasculares, la diabetes, el cáncer o las enfermedades respiratorias(41,42).

Etiología

El virus que genera la enfermedad por coronavirus (COVID-19) es un virus de la familia *Coronaviridae,* siendo los virus de esta familia encapsulados y con ARN monocatenario. Estos surgen a partir de virus que suelen afectar a animales, como consecuencia de alteraciones genéticas. Este es el caso del SARS-CoV-2, la mutación de un virus encontrado en los murciélagos, actuando estos últimos como reservorio antes de pasar al ser humano(43,44).

En la estructura de estos virus destaca una proteína que se encuentra en su membrana, la glicoproteína Spike. Esta proteína tiene la capacidad de unirse a determinadas células que cuenta con los receptores para la enzima convertidora de angiotensina II (ECA II)(44). Estos receptores se encuentran fundamentalmente en los neumocitos tipo II del pulmón, pero no son exclusivos de estas células, pudiendo encontrarlos también en el corazón, el cerebro, el riñón, el intestino y las paredes vasculares(45,46).

Una vez se produce el contacto entre la glicoproteína Spike y los receptores para la enzima convertidora de la angiotensina II, se produce la entrada del virus en el interior celular a través de la membrana celular por el mecanismo conocido como endocitosis. Cuando el virus se encuentra ya en el citoplasma, libera el genoma viral de ARN para empezar con su replicación. Además, el virus tiene la capacidad de usar la maquinaria celular para

elaborar nucleocápsides, que usará para formar nuevas partículas virales, liberadas posteriormente por mecanismos de exocitosis(47).

Todos estos cambios a nivel citoplasmático acabaran generando una grave alteración funcional de la célula que finalmente provocará la muerte celular programada(48).

En un primer momento, y antes de que ocurra la muerte celular, se produce la puesta en marcha de los mecanismos inmunológicos innatos. En concreto, la interacción de la célula con las proteínas víricas genera la producción de citoquinas. Estas a su vez, activaran las células del sistema inmune, como, por ejemplo, los linfocitos T, macrófagos y células dendríticas, que forman la primera barrera de defensa contra el virus(49).

A continuación, y de manera secundaria a la activación de la inmunidad innata, se pondrán en marcha los mecanismos de la inmunidad adaptativa y humoral. Se produce por tanto la formación de anticuerpos por parte de los linfocitos B, que intentarán eliminar el virus del organismo de manera definitiva(50). Lo descrito hasta el momento sería lo que ocurre en aquellos pacientes sin sintomatología o con una sintomatología leve. Sin embargo, en la etiopatogenia de la COVID-19 grave o severa se encuentra una desregulación inmunitaria para la cual se proponen muchos mecanismos sin aceptarse ninguno como el más indicado hasta el momento.

Por un lado, se propone una desregulación a nivel de los macrófagos y linfocitos T que darían lugar a una producción muy elevada de citoquinas. De hecho, existen pruebas claras de un aumento de los marcadores inflamatorios sistémicos como la interleucina IL-6 y la IL-8. Además, se han propuesto la activación de las vías de coagulación, la activación de trampas extracelulares de neutrófilos, la incapacidad de algunos pacientes de producir mediadores químicos de defensa antiviral y la autoinmunidad entre otros múltiples mecanismos(51,52).

Independientemente del mecanismo predominante en cada paciente, el resultado final es una respuesta inflamatoria alterada, que deriva en el evento fisiopatológico conocido como la “tormenta de citoquinas”. Esta se caracteriza por la producción exagerada y mal controlada de citoquinas en las células infectadas por SARS-CoV-2 y en las células del sistema inmune. Finalmente, se generan daños a nivel celular, dando lugar a las formas más graves de la enfermedad y pudiendo derivar en un síndrome de distrés respiratorio agudo y en la muerte del paciente(53,54).

Es importante destacar que los procesos patológicos descritos hasta el momento no se limitan únicamente al sistema respiratorio, sino que pueden llegar a tener una importante repercusión funcional como veremos más adelante cuando hablemos de la sintomatología que genera la COVID-19. La presencia de receptores ECA II en múltiples células del organismo, hace que el SARS-CoV-2 pueda infectar de manera directa otros órganos, generando una sintomatología muy variada. Este hecho se acrecienta aún más si tenemos en cuenta que muchos de los pacientes pueden presentar una patología de base en los diferentes órganos diana de este virus(55,56).

Además, es importante tener en cuenta dos factores más que pueden desencadenar una repercusión a nivel sistémico de la COVID-19. Por un lado, se encuentra el daño, inflamación y fibrosis secundaria que se genera en el parénquima pulmonar derivado de la infección por SARS-CoV-2. Este hecho genera una limitación de la ventilación de los pacientes, derivando en una menor cantidad de oxígeno a nivel sanguíneo, y, por lo tanto, de una menor cantidad de oxígeno a nivel tisular. En condiciones normales nuestro cuerpo cuenta con mecanismos suficientes para sobreponerse a este déficit de oxígeno, pero si se produce un aumento de los requerimientos metabólicos, se pueden generar daños a nivel de los diferentes tejidos afectados(57).

Por último, debemos tener en cuenta que la respuesta inflamatoria alterada que se produce de manera primaria a nivel pulmonar, pronto se extiende por todo el organismo. Esto da lugar a un ambiente proinflamatorio que puede derivar en daños importantes en aquellos órganos donde ya existiese un proceso inflamatorio de base(58,59). De esta forma vemos como la fisiopatología de esta enfermedad es mucho más compleja de lo que parece inicialmente.

Los cuadros clínicos que pueden llegar a presentarse derivados de la COVID-19 no se limitan únicamente a sintomatología respiratoria. La capacidad de infección directa del virus de determinados órganos, la hipoxia secundaria al daño del parénquima pulmonar y el ambiente proinflamatorio generado por una respuesta inmune alterada, acaban generando una importante repercusión sistémica de la enfermedad. La sintomatología tan variada que pueden presentar estos pacientes, así como la repercusión funcional derivada, suponen un reto importante a nivel clínico, siendo necesario el desarrollo de abordajes terapéuticos multidisciplinares, multimodales y ajustados a las necesidades concretas de cada paciente.

Prevalencia y mortalidad

La epidemiología de la enfermedad se ha modificado con el paso del tiempo, conforme aumentaba el número de contagios, permitiendo al virus causante de la COVID-19 generar nuevos factores de virulencia. De esta forma, ha sido capaz de aumentar la capacidad de transmisión, evasión del sistema inmune y severidad de la enfermedad(60,61).

La variante más prevalente en la actualidad es la variante ómicron, que ha mejorado sustancialmente la transmisibilidad y la capacidad del virus de evadir el sistema inmune, permitiendo de esta manera infectar a personas previamente infectadas y personas que ya hayan recibido la vacuna(62). Sin embargo, debemos tener en cuenta que esta variante

del virus genera una enfermedad de una severidad menor, con menor riesgo de hospitalización(63). Además, la vacunación contra el SARS-CoV-2 proporciona hasta un 90-95% de protección frente al riego de enfermedad severa y hospitalización, siendo esta protección mantenida en el tiempo y eficaz contra las nuevas variantes del virus(64).

Los datos aportados por la Organización Mundial de la Salud (OMS) a día 19 de abril de 2023 afirman que los casos confirmados de COVID-19 a nivel mundial alcanzan más de 763 millones, de los cuales 275 millones se han producido en Europa. Con respecto a la mortalidad por la COVID-19, se han producido 6,9 millones de muertes a nivel mundial, de las cuales 2,2 millones han sido en Europa(65).

En cuanto a las cifras de la pandemia en España, el número de casos confirmados de COVID-19 es de 13,8 millones, habiéndose alcanzado las 120.606 muertes(65).

Debemos tener en cuenta, que las cifras de la pandemia se han visto enmascaradas por muchos factores, no dando cuenta, quizás, de la repercusión real que ha alcanzado. Esto se debe, por ejemplo, a la falta de confirmación de casos en los primeros momentos de la pandemia, en los cuales todavía no se conocía la enfermedad ni la sintomatología que llevaba asociada. A esto debemos sumar la falta de test en los momentos iniciales de la pandemia(66).

Además, debemos tener en cuenta que muchas de las personas que se infectan no llegan a desarrollar sintomatología, por lo que es imposible conocer con exactitud el número de contagios reales que se han producido durante los meses que ha durado la pandemia(67).

Asimismo, las diferencias internacionales hacen que no todos los países dispongan de sistemas sanitarios lo suficientemente capacitados para aportar datos y cifras exactas de los contagios, siendo los países desarrollados los que más datos han aportado a los estudios epidemiológicos(68).

Los estudios epidemiológicos realizados a nivel mundial ponen de manifiesto que la COVID-19 tienen un tiempo de incubación de unos 6 días aproximadamente, habiendo un retraso de 5 días desde la aparición de los primeros síntomas hasta la primera visita médica(69). Los hallazgos radiológicos más frecuentes fueron la consolidación bilateral y la neumonía(70).

De media, la duración de la sintomatología es menor de 20 días(69). Es importante destacar que las tasas de incidencia acumulada fueron mayores en las mujeres y con el aumento de la edad. Por el contrario, la tasa de mortalidad acumulada fuer mayor en los varones y en las personas de 65 o más(71).

Las tasas de incidencia y mortalidad acumuladas variaron en función del nivel socioeconómico, con un claro gradiente que mostraba tasas de incidencia y mortalidad más elevadas en las personas más desfavorecidas(71,72). La hipótesis propuesta por los diferentes autores a estas diferencias socioeconómicas es multifactorial. En primer lugar, el bajo nivel socioeconómico lleva a las familias a vivir en casas más pequeñas, donde conviven muchas personas. Estas casas además suelen tener peores condiciones de ventilación.

En segundo lugar, las personas con menores recursos económicos suelen ser dependientes del transporte público para moverse o ser empleados de puestos de trabajo esenciales en los que el teletrabajo no es posible. Otro factor para tener en cuenta es la mayor prevalencia de enfermedades crónicas entre los estratos más desfavorecidos de la sociedad. Enfermedades como la obesidad, patologías cardiovasculares o la diabetes son más prevalentes entre los aquellos con bajo nivel socioeconómico y estas a su vez, predisponen una mayor gravedad de la COVID-19(73,74).

Con respecto a los datos de ingreso en las Unidades de Cuidados Intensivos (UCI), son los pacientes varones, con comorbilidades y de mayor edad, los que más frecuentemente necesitan ingreso en UCI. Los pacientes menores de 40 años representan el 5% aproximadamente de las muertes y los ingresos en UCI, mientras que los pacientes mayores de 70 años representan el 85% de las muertes por COVID-19 y el 40% de los ingresos en UCI(75).

Aspectos clínicos

Debido a la posibilidad de pasar la COVID-19 de manera asintomática, la OMS ha creado unos criterios para identificar no solo los casos confirmados de COVID-19, sino también los probables o sospechosos(75). De esta forma, se ha intentado fomentar las medidas higiénicas y de aislamiento no solo entre aquellos casos confirmados de COVID-19, sino también entre aquellos con un riesgo elevado(76).

Por lo tanto, podemos clasificar como sospechosos de estar contagiados aquellos pacientes que cumplen los criterios clínicos, es decir, la presencia de fiebre y tos aguda o la presencia tres o más de siguientes síntomas; fiebre, tos, debilidad, fatiga, dolor de cabeza, mialgia, dolor de garganta, disnea, anorexia, náuseas, vómitos, diarrea, o alteración del estado mental.

Además, para considerar a un paciente sospechoso de contagio es necesario que cumpla los criterios epidemiológicos: residir o trabajar en un área con un alto riesgo de trasmisión del virus como entornos residenciales cerrados o entornos humanitarios como campamentos para personas desplazadas, residir o viajar a una zona de transmisión comunitaria o ser profesional sanitario.

Para considerar a un paciente como caso probable de COVID-19 es necesario que cumpla los criterios clínicos y además sea contacto de un caso probable o confirmado. También

se consideran casos probables aquellos que presentan una imagen radiológica sugestiva de COVID-19 o una persona con anosmia o ageusia.

Por último, para considerar a un paciente como caso confirmado de COVID-19 es necesario tener confirmación por parte del laboratorio, independientemente de los signos y síntomas clínicos que presente.

Una vez la COVID-19 ha sido confirmada, la OMS ha desarrollado una clasificación en función de la severidad de la enfermedad(77). De esta manera, la severidad de la enfermedad se clasifica en:

- Leve: pacientes que cumplen la definición de caso confirmado, pero sin evidencia de neumonía viral o hipoxia.
- Moderada: paciente con signos clínicos de neumonía (fiebre, tos, disnea, respiración rápida) pero sin signos de neumonía grave, incluida una SpO2 mayor o igual a 90% con aire ambiente.
- Severa: paciente con signos clínicos de neumonía (fiebre, tos, disnea) más uno de los siguientes: SpO2 < 90% en aire ambiente, frecuencia respiratoria > de 30 respiraciones/min o dificultad respiratoria grave.
- Crítica: síndrome de distrés respiratorio agudo, sepsis, shock séptico, trombosis aguda, síndrome inflamatorio multisistémico.

Con respecto a las manifestaciones clínicas de la COVID-19 es necesario hacer un proceso exhaustivo de revisión de la literatura para identificar los síntomas más comunes que presentan los pacientes.

Respiratorios

De acuerdo con un estudio realizado en 55.924 casos confirmados de COVID-19, el síntoma más frecuente fue la fiebre con un 87,9%, seguida da la tos seca 67,7%, la fatiga

38,1%, la producción de esputo 33,4%, la dificultad respiratoria 18,6%, el dolor de garganta 13,9%, escalofríos 11,4%, congestión nasal 4,8%, y hemoptisis 0,9%(78).

Algunos pacientes pueden evolucionar rápidamente a una lesión pulmonar aguda y a síndrome respiratorio agudo severo (SARS) y shock séptico. El intervalo de tiempo entre la aparición de los síntomas y el desarrollo de SARS es de unos 8 días(44).

Un estudio radiológico que revisaba las radiografías de 2.814 pacientes demostró que los hallazgos radiológicos más frecuentes en la COVID-19 consistían en la opacidad en vidrio deslustrado y la consolidación. Sin embargo, debemos tener en cuenta que los hallazgos radiológicos pueden variar de manera importante entre pacientes y en diferentes estadios de la enfermedad(79). Además, es importante remarcar la alta prevalencia de alteraciones radiológicas, ya que solo el 18% de los pacientes con enfermedad no severa y el 3% de los pacientes con enfermedad severa presentan un estudio radiográfico sin ninguna alteración(54).

Otorrinolaringología

Las manifestaciones otorrinolaringológicas son uno de los síntomas más frecuentes encontrados en los pacientes con COVID-19. Se trata de una presentación clínica peculiar de estos pacientes que incluye el deterioro del gusto (disgeusia) y la pérdida del olfato (anosmia). Una revisión sistemática realizada en pacientes con 1.627 pacientes con deterioro olfativo y en 1.390 pacientes examinados con síntomas gustativos demostraron una prevalencia del 52,73% y del 43,93% respectivamente(80).

Estas características clínicas suelen presentarse a menudo en los inicios de la enfermedad y son de gran importancia a nivel diagnóstico pues nos permiten diferenciar la COVID-19 de otras enfermedades respiratorias con sintomatología similar.

Además, el dolor de garganta, la rinorrea, la congestión nasal, el edema de amígdalas y el aumento de tamaño de los ganglios linfáticos cervicales se observan con frecuencia entre las disfunciones otorrinolaringológicas de los pacientes(81).

Cardiovascular

Existen tres mecanismos por los cuales los pacientes COVID-19 pueden cursar con manifestaciones cardíacas. El primero, es la infección directa del virus de las células miocárdicas. El segundo, se caracteriza por la falta de oxigeno en el miocardio como consecuencia del daño tisular pulmonar e hipoxia secundarias. El último, es el proceso inflamatorio caracterizado por la tormenta de citoquinas(44).

Estos pacientes suelen cursar con alteraciones electrocardiográficas así como con elevaciones de marcadores inflamatorios cardíacos como la troponina cardíaca y el péptido natriurético(82).

Es importante remarcar que se han descrito importantes diferencias en cuanto a las necesidades terapéuticas de los pacientes con patología cardíaca y los pacientes que no la tienen. De esta manera el ingreso en UCI y necesidad de ventilación mecánica no invasiva es del 46,3% en pacientes con patología cardíaca en comparación a sujetos sanos, así como uso de ventilación mecánica invasiva fue de 22% en comparación el 4,2 de los sujetos sanos. Además, la mortalidad también ha demostrado porcentajes mayores en pacientes con alteraciones miocárdicas en comparación con sujetos sanos (51% vs 5%)(83).

Gastrointestinales

Dentro de los síntomas gastrointestinales presentes en los pacientes COVID-19 encontramos la anorexia, las náuseas o vómitos, la diarrea, el dolor abdominal agudo y de manera menos frecuente la hemorragia intestinal(84).

Una revisión sistemática demostró que la anorexia el síntoma más frecuente entre los adultos. Sin embargo, la diarrea es el síntoma más frecuente si sumamos los datos de adultos y niños, mientras que el síntoma más común entre los niños es el vómito(85).

Renales

La disfunción endotelial secundaria a la COVID-19 sumada a la invasión directa de las células renales por el virus, genera una serie de alteraciones anatomopatológicas a nivel renal. Estas se caracterizan por la invasión directa de podocitos y células tubulares proximales, así como vacuolización de las células renales(86).

Además, debemos tener en cuenta que la hipoxia secundaria a las lesiones pulmonares, la tormenta de citoquinas y la rabdomiólisis de células musculares secundarias a la invasión de estas por el virus, puede provocar o exacerbar una patología renal previa(87).

Neurológicos

Los síntomas neurológicos aparecen como algunos de los más limitantes para los pacientes con COVID-19. Estos síntomas pueden presentarse en combinación con los síntomas respiratorios, pero también ocurren en ocasiones de manera aislada(88).

El riesgo de sufrir una COVID-19 más severa aumenta de manera considerable en aquellos pacientes que han sufrido previamente una enfermedad cerebrovascular(89) o en pacientes con patologías neurológicas como pacientes con Parkinson(90).

Los síntomas neurológicos suelen aparecer en las fases iniciales de la enfermedad siendo los más frecuentes el dolor de cabeza, confusión, delirium, insomnio, disgeusia y ageusia, alteración del estado mental, ataxia y convulsiones(91).

Además, es importante remarcar las alteraciones de la salud mental que sufren estos pacientes. La situación pandémica, que deriva en asilamiento social, sumada a la COVID-

19, han generado en algunos pacientes importantes alteraciones de la salud mental como ansiedad y depresión(92).

Musculoesqueléticos

Las manifestaciones musculoesqueléticas también se encuentran dentro del amplio rango de manifestaciones clínicas que puede presentar la COVID-19. Durante las fases iniciales de la enfermedad la fatiga, la mialgia y la artralgia son los síntomas musculoesqueléticos más comunes(93). Sin embargo, debemos tener en cuenta que las diferentes manifestaciones clínicas presentes en estos pacientes siguen aumentando hoy en día debido al gran número de casos absolutos en los años acumulados de pandemia. De esta manera, cada vez son más los síntomas musculoesqueléticos descritos en estos en pacientes COVID-19(94).

Además, la etiología de estos síntomas puede ser diversa. Por un lado, se ha descrito la posibilidad de invasión directa de las células musculares por el virus, con la posible destrucción de estas. Por otro lado, la hipoxia secundaria a la inflamación, fibrosis y daños pulmonares puede llegar a generar alteraciones hipóxicas en las células musculares si los requerimientos de oxígeno aumentan. Además, el ambiente proinflamatorio global, caracterizado por una subida importante de los niveles de citoquinas en sangre, afectan negativamente a las células musculares(93).

Los síntomas musculoesqueléticos son algunos de los síntomas menos descritos dentro de la COVID-19. Esto se debe a que muchos de los estudios realizados hasta el momento se centran en pacientes en fase aguda de la enfermedad, en la cual se le da mayor importancia a los síntomas respiratorios como la disnea o la fatiga, que son considerados por los pacientes síntomas más urgentes o relevantes. Además, debemos tener en cuenta

que la medicación utilizada durante la fase aguda de la COVID-19 como pueden ser los corticoides, puede enmascarar en cierta medida las molestias musculoesqueléticas(93).

Abordaje terapéutico

La COVID-19 es una enfermedad con etapas bien diferenciadas(95). Derivadas de la etiología vírica de la enfermedad, podemos distinguir una fase inicial de la infección en la cual encontramos síntomas como fiebre, tos, pérdida del gusto y el olfato, cansancio y otros síntomas asociados a las altas cargas víricas que alcanza su máximo más altos a la semana de la enfermedad(96).

Otros síntomas que pueden presentar los pacientes son el dolor de garganta, el dolor de cabeza, diarrea, erupción cutánea o decoloración de los dedos de las manos y los pies, ojos rojos e irritados, dolores musculares y corporales, congestión o moqueo, náuseas o vómitos(97).

En la mayoría de los pacientes, los síntomas comienzan a mejorar después de la primera semana. Sin embargo, como hemos visto anteriormente, en otros pacientes comienza una segunda fase de la enfermedad caracterizada por una respuesta inflamatoria disfuncional y desarrollo de inflamación y lesión pulmonar(98).

Los pacientes que sufren estas lesiones pulmonares inflamatorias son los que desarrollan las formas más graves de la enfermedad requiriendo la mayoría de ellos hospitalización. Algunos de los síntomas que pueden presentarse en las formas más graves son la disnea o respiración entrecortada, la pérdida del habla o de la movilidad, la confusión y el dolor torácico(99).

La novedad que supuso la COVID-19 a nivel médico y farmacológico hizo que los responsables de salud tomasen de referencia la patogenia de la enfermedad para intentar al menos producir el alivio sintomático. La importancia de la carga vírica y de los

mecanismo inflamatorios secundarios al daño producido por el virus, han hecho que desde el principio de la pandemia se utilizaran como base del tratamiento fármacos antivirales e inmunosupresores(40). Derivado de la urgencia que suponía la situación de pandemia, se llevaron a cabo un gran número de ensayos clínicos a una gran velocidad que han confirmado el uso de estos tratamientos como los más efectivo(100).

Actualmente, solo existen tres tratamientos farmacológicos aprobados para el tratamiento de la COVID-19: plasma de convalecientes, remdesivir y casirivimab/imdevimab(46).

El plasma convaleciente (PC), obtenido de pacientes convalecientes, proporciona inmunidad pasiva en pacientes activamente infectados. El PC se ha utilizado en pandemias víricas anteriores demostrando eficacia y superioridad sobre el placebo en un estudio anterior con pacientes que sufrían infección por SARS-CoV(101).

Remdesivir es un análogo de nucleósido monofosforamida con actividad antivírica de amplio espectro. El remdesivir fue uno de los fármacos utilizados para tratar el primer caso de COVID-19 en Estados Unidos, con resultados notables. Desde entonces, ha habido numerosos informes de casos sobre el uso de remdesivir en la COVID-19 con mejoras documentadas en la carga viral y la sintomatología(102).

Casirivimab/Imdevimab se basa en una terapia de anticuerpos monoclonales humanos recombinantes que son capaces de dirigirse a la proteína responsable de la unión del virus a los receptores ACE II, la glicoproteína Spike. Este fármaco ha demostrado generar importantes reducciones de la carga viral de los pacientes(103).

Los corticosteroides, como la metilprednisolona y la dexametasona, son tratamientos estándar para los trastornos asociados a la inflamación. Las graves respuestas inflamatorias que suelen acompañar a la infección por SARS-CoV-2 han popularizado el uso de corticosteroides en el tratamiento de la COVID-19. Como era de esperar, el

tratamiento con corticosteroides en dosis altas y a corto plazo en las primeras fases de la insuficiencia respiratoria se ha asociado a un mejor pronóstico(104). Varios informes clínicos han demostrado que el uso de corticosteroides en la COVID-19 grave proporciona múltiples beneficios clínicos, incluyendo reducciones en la necesidad y duración de la ventilación invasiva(105).

Además del tratamiento farmacológico de la COVID-19, debemos tener en cuenta las medidas de soporte como la ventilación. Los principios básicos de proporcionar asistencia respiratoria para conservar unos niveles de saturación de oxígeno adecuados no han cambiado, aunque el uso de ventilación no invasiva (VNI) está más ampliamente aceptado(106).

Si tenemos en cuenta la sintomatología de los pacientes COVID-19 en una fase aguda, vemos como los síntomas respiratorios son los más frecuentes. El daño pulmonar genera de manera secundaria alteraciones de la función pulmonar, reducción de la capacidad de ejercicio físico y consecuentemente, pérdida de fuerza de los miembros inferiores(99). De esta forma, vemos que la COVID-19 puede llegar a tener una importante repercusión en la capacidad funcional de los pacientes, generando alteraciones de la calidad de vida de los mismo.

Por lo tanto, es razonable pensar en la indicación del tratamiento fisioterápico en estos pacientes durante la fase aguda de la enfermedad, con el objetivo no solo de recuperar la capacidad funcional perdida, sino de evitar mayores repercusiones en el futuro.

Intentar sintetizar la evidencia publicada hasta la fecha en lo que respecta a intervenciones de fisioterapia en pacientes COVID-19 resulta complejo. El principal motivo es que, hasta el momento, no se han realizado un número suficiente de ensayos clínicos aleatorizados que permitan extraer conclusiones claras de los mismos. Esto se debe a la gran

heterogeneidad de las poblaciones en las cuales se realizan los estudios. Por ejemplo, las revisiones sistemáticas que se han publicado hasta la fecha aúnan en una sola revisión pacientes con severidades muy diferentes de la enfermedad(107). De esta manera la extrapolación de los resultados a la población general puede derivar en la toma de decisiones clínicas erróneas.

Hasta el momento, las principales tendencias en cuanto a la rehabilitación de los pacientes COVID-19 se han centrado en programas de entrenamiento respiratorio(108) y reeducación ventilatoria(109), ya sea aislados o combinados con ejercicio terapéutico. El ejercicio terapéutico que se aplica puede ser aeróbico o de fuerza, mostrando ambos resultados similares en cuanto a la ganancia funcional.

Las revisiones sistemáticas realizadas hasta el momento que estudian el efecto de la rehabilitación pulmonar en los pacientes COVID-19 muestran una mejora significativa de los pacientes con respecto a la capacidad de ejercicio, la fatiga, la capacidad vital forzada y la disnea. Sin embargo, no se encuentran resultados concluyentes con respecto a la calidad de vida(107).

Estos programas de entrenamiento respiratorio se pueden realizar de manera presencial, pero la pandemia de COVID-19 ha hecho que los programas de telerehabilitación cobren especial relevancia. El miedo de los pacientes ya infectados a volver a infectarse, las limitaciones de movilidad instauradas durante los meses con más contagios, la facilidad que supone realizar los programas desde casa y el fácil acceso de los pacientes a las nuevas tecnologías, son algunos de los factores implicados. A estos factores hay que sumarle la ventaja que ofrecen en cuanto a tiempo, y, la capacidad de ofrecer intervenciones grupales que ayuden a lidiar con la incapacidad de los organismos sanitarios para gestionar el gran aumento de pacientes COVID-19 existentes.

Justificación

Como consecuencia de la segunda fase de la enfermedad caracterizada por una respuesta inflamatoria exacerbada cuyo evento fisiopatológico clave es la llamada “tormenta de citoquinas” algunos pacientes con COVID-19 padecen sintomatología crónica incluso 3 meses después del inicio de la enfermedad. A esta condición de salud se le ha denominado Long-COVID, y algunos metaanálisis realizados hasta la fecha hablan de que la prevalencia en pacientes que han pasado la COVID-19 podría ser de hasta el 60%(110).

Los síntomas más referidos por estos pacientes son principalmente síntomas respiratorios como la fatiga (53%) y la disnea (43%), secundarios a la destrucción y fibrosis del parénquima pulmonar. Sin embargo, además de la sintomatología respiratoria los pacientes refieren otros síntomas como debilidad muscular (63%), dificultades para dormir (26%) y ansiedad o depresión (23%)(111).

Algunos autores han informado de que el dolor es un síntoma persistente importante entre los supervivientes de la COVID-19 que puede llegar a convertirse en un importante problema a nivel sanitario(112,113). La prevalencia de este síntoma es cercana al 20% en los pacientes con Long-COVID(114).

Por lo tanto, vemos cómo, aunque la COVID-19 se trate de una enfermedad de etiología infecciosa que afecta fundamentalmente al sistema respiratorio, puede generar una importante repercusión sistémica conforme avanza la enfermedad, dando lugar a una amplia variedad de sintomatología, afectando negativamente a la funcionalidad y calidad de vida de los pacientes.

De esta manera y tras el estudio en profundidad tanto de la EPOC como de la COVID-19, podemos ver que, aunque son patologías con una etiología muy diferente, y por lo tanto con un curso clínico distinto, el proceso fisiopatológico que da lugar a las fases más

crónicas de ambas enfermedades se basa en un proceso inflamatorio exacerbado. Esta inflamación acabará generando un daño a nivel del parénquima, con la consiguiente disminución de la capacidad pulmonar e hipoxia secundaria, afectando a múltiples tejidos. Además, el proceso inflamatorio exacerbado genera una inflamación a nivel sistémico que dará lugar a sintomatología muy variada y no directamente relacionada con la sintomatología respiratoria(17).

Se entiende así que, aunque son dos patologías que en inicio pueden parecer muy diferentes, la sintomatología crónica que generan ambas están muy relacionadas. Las dos patologías generan una importante repercusión a nivel sistémico dando lugar a la disminución de la capacidad física y funcional del paciente, y afectando la calidad de vida de estos.

Por lo tanto, se justifica el estudio conjunto de ambas patologías en cuanto a la exploración de nuevos métodos de tratamiento que permitan el abordaje terapéutico multimodal de manera segura en el contexto actual de pandemia. Además, es necesario desarrollar nuevos estudios de los diferentes perfiles clínicos que podemos encontrar en las fases crónicas de estas enfermedades, facilitando de esta forma el desarrollo de futuros tratamientos adaptados a las necesidades de estos pacientes.

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HIPÓTESIS Y OBJETIVOS

Hipótesis

Los pacientes con sintomatología respiratoria crónica presentan una repercusión sistémica que afecta a la capacidad funcional y calidad de vida de estos. La caracterización de estos pacientes permitirá el diseño de intervenciones terapéuticas multimodales que mejoren sus variables clínicas.

Objetivos generales

Caracterización de los pacientes con patología respiratoria crónica y estudio de las intervenciones terapéuticas multimodales que mejor se ajusten a sus necesidades clínicas.

Objetivos específicos

Objetivo específico 1: evaluar la calidad de vida relacionada con la salud y las características del dolor (intensidad del dolor, interferencia del dolor y presentación clínica) en pacientes con Long-COVID.

Objetivo específico 2: identificar el perfil clínico y psicosocial asociado al dolor en pacientes no hospitalizados con Long-COVID.

Objetivo específico 3: identificar los efectos de intervenciones terapéuticas multimodales basadas en la telerehabilitación en la calidad de vida de los pacientes con EPOC.

HYPOTHESES AND OBJECTIVES

Hypothesis

Patients with chronic respiratory symptomatology present a systemic repercussion that affects their functional capacity and quality of life. The characterization of these patients will allow the design of multimodal therapeutic interventions to improve their clinical variables.

General objectives

Characterization of patients with chronic respiratory pathology and study of multimodal therapeutic interventions best suited to their clinical needs.

Specific objectives

Specific objective 1: to evaluate health-related quality of life and pain characteristics (pain intensity, pain interference and clinical presentation) in patients with Long-COVID.

Specific Objective 2: to identify the clinical and psychosocial profile associated with pain in non-hospitalized patients with Long-COVID.

Specific Objective 3: to identify the effects of multimodal therapeutic interventions based on telerehabilitation on the quality of life of patients with COPD.

ESTUDIO 1

Pain and clinical presentation: a cross-sectional study of patients with new-onset chronic pain in Long-COVID-19 syndrome.

Calvache-Mateo, A., López-López, L., Martín-Núñez, J., Heredia-Ciuró, A., Granados-Santiago, M., Ortiz-Rubio, A., & Valenza, M. C. (2023). Pain and Clinical Presentation: A Cross-Sectional Study of Patients with New-Onset Chronic Pain in Long-COVID-19 Syndrome. International Journal of Environmental Research and Public Health, 20(5), 4049.

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INTRODUCTION

The COVID-19 pandemic has impacted the lives and health of persons worldwide, with the potential for further effects in the future. The repercussion of this pandemic extends beyond physical illness, with relevant psychosocial consequences impacting significantly all health-related areas [1]. In this context of uncertainty, some of those who recovered from COVID-19 infection develop persistent or new symptoms lasting weeks or months; this has been called “Long-COVID-19” or “post-COVID-19 syn-drome” [2]. This new entity can be continuous or relapsing and remitting in nature [3] and can develop the persistence of one or more symptoms of acute COVID, or appearance of new symptoms.

The most common referred symptoms were fatigue (53%), dyspnea (43%), and pain (27%). In a large study evaluating the reported symptoms of Long-COVID-19 syndrome, 76% of patients reported at least one of a list of 17 symptoms, with the most frequent being fatigue and muscular weakness (63%), sleep difficulties (26%), and anxiety or depression (23%) [4]. However, the reviewed studies pooled prevalence rates without considering follow-up periods after symptoms [5].

According to the scientific literature, Long-COVID-19 syndrome is more prevalent in the working population. The evidence shows that the prevalence of symptoms was higher in people younger than 70 years old, specifically, in people among 35–49-year-olds and 50–69-year-olds, compared to the general population five weeks after testing positive for COVID-19 [6,7].

In addition to the health problems associated with their condition, people in the working-age population with Long-COVID-19 syndrome also report adverse effects and stressful situations that affect their quality of life and occupational well-being [8]. Fear of job loss and future job insecurity, quarantine, unsafe work environments, infection and/or

spreading the infection to those close to them for those working in “front-line” jobs, and COVID-19-related discrimination and/or stigma are all additional fac-tors that may worsen the psychological state, creating a societal burden in this population [9,10].

Another relevant Long-COVID-19 symptom that can generate a significant bur-den on society is chronic pain [11]. Some authors [12, 13] have reported pain as an important persistent symptom amongst COVID-19 survivors. Pain should be approached from the biopsychosocial model which understands this symptom as a com-plex dynamic interaction of biological factors with psychosocial factors, which influences in a determinant way the coping strategies of pain. Consequently, these factors impact on the chronification of pain, the development of disability, the appearance of fear of movement, decreased activity levels and, therefore, decisively modify the patient's prognosis [14, 15].

In a descriptive study of pain in survivors of COVID-19, the authors found a 19.6% of de novo chronic pain prevalence that interfered with their ability to function. Their pain was located primarily in the head and neck, but frequently occurred in the lower limbs, and often moved around the body [16]. While the data and clinical experience suggest that pain is common in survivors of COVID-19, only a few studies have provided information on the pain experience of these patients, and none compared Long-COVID-19 patients’ de novo pain with successfully recovered COVID-19 patients and healthy controls.

Therefore, the purposes of this study were to evaluate the health-related quality of life and characteristics of pain (i.e., pain intensity, pain interference, clinical presentation) in Long-COVID-19 patients and compare the location of pain with those successfully recovered COVID-19 patients and healthy matched controls.

MATERIALS AND METHODS

Study design and participants

A cross-sectional case-control study was performed. By the study design and with the recommended guidelines for the design of observational studies, the criteria and checklist of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were applied [17]. We conducted this study in accordance with the Declaration of Helsinki 1975, revised in 2013 [18]. Ethical approval for this study was obtained from the Biomedical Research Ethics Committee of Granada.

Three groups of patients were included in this study. The case group was com-posed of Long-COVID-19 patients meeting the WHO definition for this disease: "it is defined as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation". [19]. In addition, two additional groups of patients matched for age and gender were included, a group consisting of patients who successfully recovered from COVID-19 and, finally, a group of healthy controls who did not undergo SARS-CoV-2 infection. Patients in the Long-COVID-19 group were recruited from the autonomic Long-COVID-19 association. Control patients were recruited by word-of-mouth. Patients were recruited between May 2021 and April 2022.

Patients over 18 years of age, who agreed to sign the informed consent form were included in the study. Patients were excluded if they had any of the following conditions: neurological or orthopaedic pathologies that limited voluntary movement, a cognitive impairment that prevented them from understanding and answering the questionnaires, or if they suffered reinfection with SARS-CoV-2. In addition, all patients who had been hospitalized due to COVID-19 infection and those who had pre-existing chronic pain

according to the current IASP definition [20,21] before COVID-19 infection were excluded.

Outcome measures

Patients were initially contacted by telephone to inform them of the study and to arrange a face-to-face assessment. Once informed consent was obtained, an assessment of demographic characteristics, pain characteristics, and clinical presentation of pain were performed.

Comorbidities were assessed by the Charlson comorbidity index, one of the most widely used scoring systems for assessing comorbidities that has been validated in several disorders [22]. In addition, Charlson comorbidity index has been validated and previously used in other respiratory pathologies including patients infected by COVID-19 [23, 25].

Pain intensity and interference were measured with the Brief Pain Inventory (BPI). The pain intensity section of the BPI is composed of four items and the pain interference section is composed of seven items. For the intensity section, the responses range from 0 (no pain) to 10 (worst pain) and for the interference section, the responses range from 0 (no interference) to 10 (total interference). To obtain the severity and interference index, the mean of the corresponding items is calculated, obtaining values between 0 to 10, with a higher score reflecting greater pain intensity and interference. The BPI has been established as a reliable and valid tool for assessing pain severity and interference [26, 27] and has been previously used and validated in other respiratory pathologies [28, 29].

The Short Form McGill Pain Questionnaire (SF-MPQ) is a version of the original McGill Pain Questionnaire [30], developed by Melzak in 1987 [31]. This scale is divided into several parts. The first part consists of a list of 15 adjectives, including 11 sensory and 4 affective descriptors of pain (e.g., terrible, throbbing, etc.) on a scale ranging from 0

(none) to 3 (severe), giving an overall score ranging from 0 to 45, as well as two scores from 0 to 33 for the sensory subscale and 0 to 12 for the affective subscale. In addition, it includes a VAS scale that assesses the patient's pain in the last week. Final-ly, it includes a Present Pain Intensity Scale (PPI). The PPI is based on a single item measuring overall pain intensity. Patients are asked about their current level of pain on a 5-point Likert scale ranging from 0 (no pain) to 5 (unbearable). This scale has been shown to have excellent psychometric properties [31, 32, 33] and has been previously used in other respiratory pathologies [29, 34].

The Widespread Pain Index (WPI) [35, 36] assesses the body distribution of pain and specifically quantifies the degree of widespread body pain. The WPI assesses the presence of pain at 19 designated body sites over the past 7 days (e.g., neck, right lower arm, right upper leg). For each area with pain, the score is 1. The items are summed to give a total score ranging from 0 to 19 with higher scores indicating greater generalised pain. This questionnaire has been previously used and validated in other populations [37, 38].

In addition, the same pain drawings used for the WPI test were digitized with a commercial scanner and imported into an image analysis program. The procedure used to digitize the pain drawings was previously described and its reliability was con-firmed by Barbero et al. [39] This method of quantifying pain location and frequency is automated and does not rely on operator interpretation. This method allowed the generation of pain frequency and location maps that consisted of the overlay of all pain drawings and were analyzed in order to be able to illustrate where pain was most frequently perceived in the entire cohort. This was performed for both dorsal and ventral views. In this way, the pain drawings primarily provide us with information regarding pain frequency: the pain drawings of all participants were superimposed to illustrate where subjects refer pain most frequently, and pain localization: the body graph was divided into regions and the

percentage of participants referring pain in specific defined body regions is presented [40].

Health-related quality of life was assessed with the Euroqol-5 dimensions 5 Levels Visual Analogue Scale (EQ-5D-5L) [41]. This is a questionnaire consisting of 5 dimensions ("mobility", "self-care", "usual activities", "pain or discomfort", and "anxiety or depression") which is widely used. Each of the dimensions has 5 possible levels. In addition, a visual analogue scale (VAS) with values ranging from 0 (worst imaginable state of health) to 100 (best imaginable state of health) is included to assess the perceived health status. The EQ-5D-5L available value sets are accessible at https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/. This questionnaire has been previously used and validated in respiratory patients and COVID-19 patients [42, 44].

Statistical Analysis

The statistical power calculation (GPower version 3.1.9.2 for Windows) was per-formed at the design stage based on our previous pilot study that employed a similar methodology (unpublished). This suggested that a sample size of 64 in each group will have 95% power to detect a probability of 0.5. To allow for a dropout rate of 10%, we decided to have approximately 71 patients in each study group.

Data were analysed using the Statistical Package of Social Science (SPSS) program for Windows (version 26 IBM, Armonk, NY, USA). The normality of the data was first tested with the one-sample Kolmogorov-Smirnov test. For nominal variables, the chi-square test was used to identify differences. One-way analysis of variance (ANO-VA) was used to compare the three groups when the continuous variables were normally distributed, and Kruskal-Wallis when the continuous variables had a non-normal distribution. A 95%

confidence interval was used for statistical analysis. A p-value of ≤ 0.05 was set to indicate significant differences. No attempt at imputation was made for missing data.

RESULTS

A total of 213 participants agreed to participate in this study and were considered eligible. The distribution of participants is shown in Figure 1.

The descriptive characteristics of the sample are shown in Table 1.

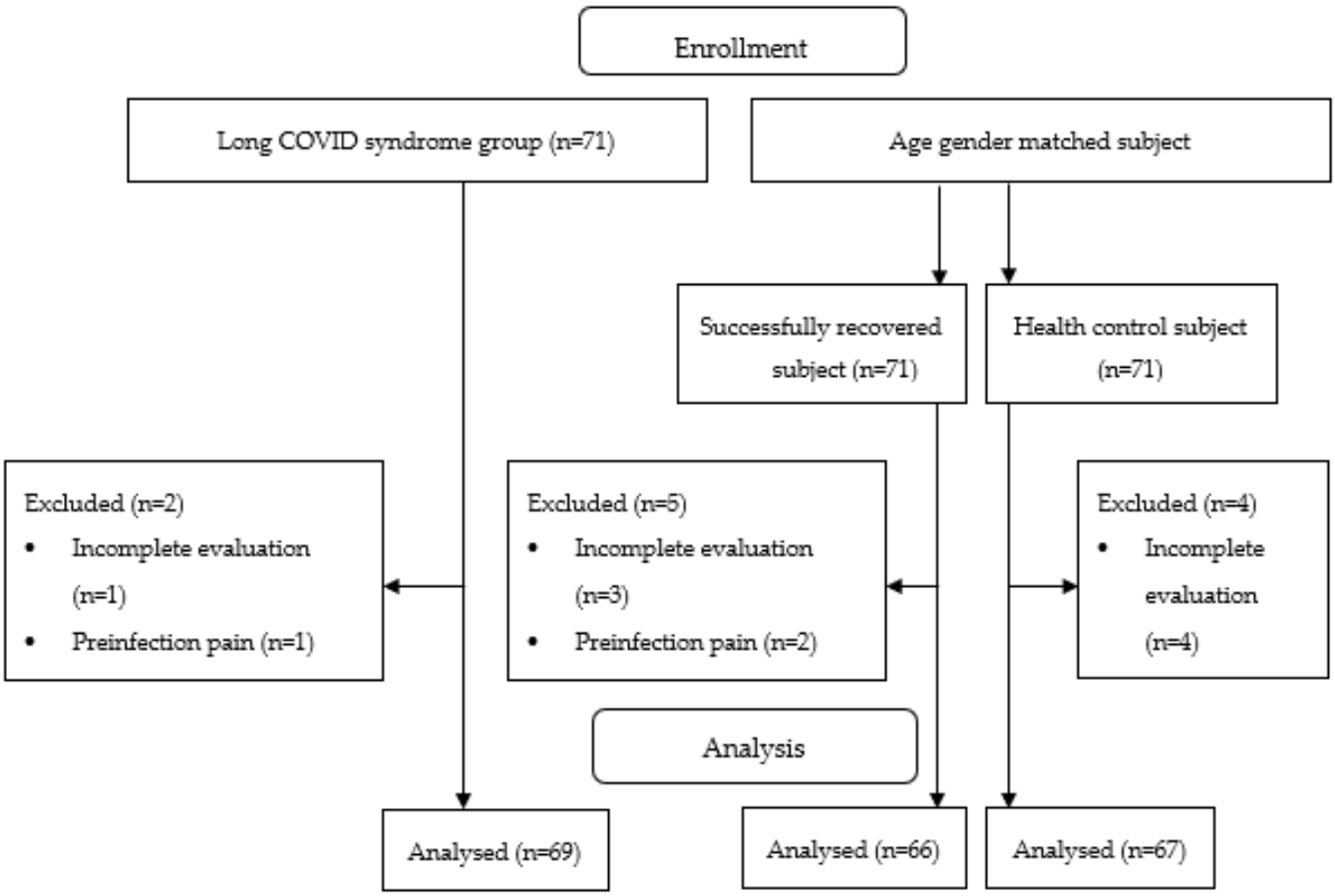


Figure 1. Flow diagram.

Table 1. Descriptive characteristics of the sample

Variables	Long-COVID-19 syndrome group (n=69)	Successfully recovered COVID-19 group (n=66)	Healthy controls group (n=67)	F
Age	44.99 ± 2.79	44.90 ± 2.94	44.67 ± 3.11	0.144
Sex (% female)	75.26	75.79	75.51	0.973
Weeks since infection	104.23 ± 11.36	103.26 ± 8.96		0.300
BMI (kg/m^2)	25.16 ± 3.07	25.19 ± 3.19	25.38 ± 3.6	0.052
Smoker (%)	13.0	22.9	17.2	0.432
Other diseases (%)	31.5	22.9	24.1	0.497
Charlson index	0.17 ± 0.38	0.15 ± 0.41	0.24 ± 0.51	0.488
Non-pharmacological treatment (%)	39.2	24.6	20	0.056
Physiotherapy	76.32	64.29	83.33	
Psychology	23.68	35.71	16.66	
Pharmacological treatment for pain (%)	74.2	14	13.3	<0.001**
NSAIDS	31.9	50	25	
Paracetamol	19.4	37.5	50	
Muscle relaxants	13.9	12.5	25	
Tramadol	12.5	0	0	
Codeine	2.8	0	0	
Metamizole	19.4	0	0	

BMI: Body Mass Index; NSAIDs: Nonsteroidal Anti-inflammatory Drugs. Descriptive data for each group are expressed as mean ± standard deviation and percentages when appropriate. **p<0,001.

No statistically significant differences were found in the demographic characteristics of the participants. Statistically significant differences were found regarding the use of pharmacological pain treatment. In the Long-COVID-19 syndrome group, women showed a 20% higher drug intake. The drugs most commonly consumed by women were NSAIDS and metamizole. On the other hand, the most consumed by men were NSAIDS and Paracetamol.

The pain characteristics are presented in Table 2.

Table 2. Pain characteristics.

Variables	Long-COVID-19 syndrome group	Successfully recovered COVID-19	Healthy controls group	F
Pain prevalence (%)	69.5	26.3	23.3	<0.001*
BPI-intensity	5.12 ± 2.28	0.93 ± 1.74	0.75 ± 1.48	101.88[bc]
BPI-interference	5.78 ± 2.77	0.82 ± 1.87	0.51 ± 1.41	107.73[bc]
SF-MPQ-sensory subscale	15.99 ± 6.89	2.94 ± 4.43	2.8 ± 5.54	108.79[bc]
SF-MPQ-affective subscale	5.75 ± 3.33	0.83 ± 1.29	0.67 ± 1.84	81.54[bc]
SF-MPQ-overall score	21.74 ± 9.51	3.77 ± 5.62	3.47 ± 6.96	114.46[bc]
SF-MPQ-VAS	65.11 ± 22.8	15.75 ± 22.92	11.62 ± 21.14	115.41[bc]
SF-MPQ-PPI	2.53 ± 1.35	0.49 ± 0.89	0.31 ± 0.66	78.36[bc]

BPI: Brief Pain Inventory; SF-MPQ: Short Form McGill Pain Questionnaire; VAS: Visual Analogue Scale; PPI: Present Pain Intensity Scale. Descriptive data for each group are expressed as mean ± standard deviation and percentages when appropriate. a= Significant differences between the healthy controls group and the successfully recovered group. b= Significant differences between the healthy controls group and Long-COVID-19 syndrome group. c= Significant differences between the successfully recovered group and Long-COVID-19 syndrome group.

Significant differences were found in pain intensity and pain interference between the Long-COVID-19 syndrome group, successfully recovered group, and healthy controls group. However, no significant differences were found in pain intensity and pain interference between successfully recovered group and healthy controls.

The SF-MPQ sensory and affective subscales also presented significant differences between groups, with poorer results in the Long-COVID-19 syndrome group. In addition, patients in the Long-COVID-19 syndrome group had greater pain in the last week measured with the VAS and at the time of evaluation measured with the PPI, com-pared to the group of successfully recovered patients and the healthy controls group.

Table 3 shows the health-related quality of life and widespread body pain results.

Table 3. Health-related quality of life.

Variables	Long-COVID-19 syndrome group (n=69)	Successfully recovered COVID-19 group (n=66)	Healthy controls group (n=67)	F
WPI	10.02 ± 5.93	1.16 ± 2.52	0.9 ± 1.68	86.297[bc]
EQ-5D-mobility	2.36 ± 1.07	1.00 ± 0.00	1.17 ± 0.46	65.61[bc]

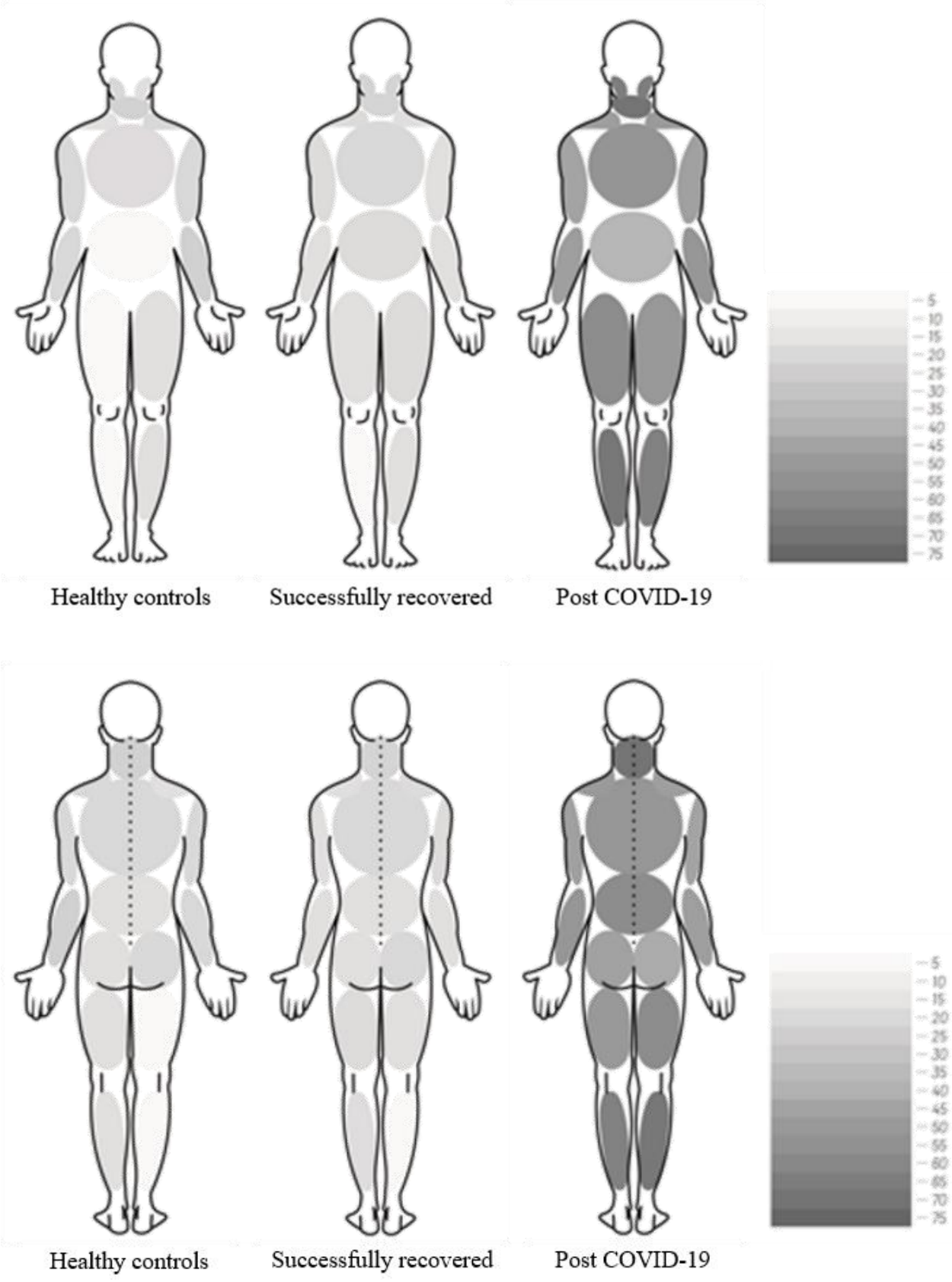
EQ-5D-self-care	1.80 ± 0.98	1.00 ± 0.00	1.03 ± 0.18	31.82[bc]
EQ-5D-usual activities	3.24 ± 0.95	1.04 ± 0.29	1.14 ± 0.44	225.40[bc]
EQ-5D-anxiety or depression	3.43 ± 0.76	1.26 ± 0.53	1.48 ± 0.68	216.35[bc]
EQ-5D-pain or discomfort	2.20 ± 1.17	1.47 ± 0.62	1.34 ± 0.61	18.98[bc]
EQ-5D VAS	42.05 ± 21.67	74.62 ± 28.31	70.76 ± 31.70	31.49[bc]

WPI: Widespread Pain Index; EQ-5D: Euroqol-5 dimensions; VAS: Visual Analogue Scale. Descriptive data for each group are expressed as mean ± standard deviation and percentages when appropriate. a= Significant differences between the healthy controls group and the successfully recovered group. b= Significant differences between the healthy controls group and Long-COVID-19 group. c= Significant differences between the successfully recovered group and Long-COVID-19 group.

Statistically significant differences were found, with poorer results for the Long-COVID-19 group compared to successfully recovered group and healthy controls group for the EQ-5D subscales, as well as for the VAS scale. Regarding the widespread body pain, the Long-COVID-19 group presented higher levels of widespread body pain, reaching statistically significant differences compared to successfully recovered group and healthy controls group.

Figures 2 show the location and frequency of pain. Specifically, it shows the percentage of patients presenting pain in each area of the body associated with a grey scale, where the higher the percentage, the darker the color of that area. The number of patients presenting pain in each area was much higher in the Long-COVID-19 group with the

Figure 2. Pain drawings.



most frequent locations being the neck (69.1%), followed by the legs (68%) and the head (63.9%).

Pain frequency maps were generated by superimposing the pain drawings of all patients included in the study. Pain frequency maps have been generated for both the dorsal and ventral views. The gray gradient indicates the percentage of people who reported pain in that specific area.

DISCUSSION

This study aimed to evaluate the characteristics of pain (i.e., pain intensity, pain interference, clinical presentation) in Long-COVID-19 patients and compare the location of pain with those of COVID-19 successfully recovered and healthy matched controls. Our results show that patients with Long-COVID-19 syndrome have higher levels of pain intensity and interference, as well as greater pain generalization compared to successfully recovered group and healthy controls group. In addition, these patients show worse levels of health-related quality of life.

The sample of subjects included in this study was representative of the general population with Long-COVID-19 syndrome, with similar sociodemographic charateristics [45-47]. The higher prevalence of Long-COVID-19 syndrome in the female gender has been previously demonstrated. These differences in prevalence are generated because of different symptomatic, inflammatory, and immune responses between men and women [48-50]. Differences in immune system function between women and men may be a differential factor in terms of the development of Long-COVID-19 syn-drome. Women's ability to develop a more rapid and robust innate and adaptive immune response protects them from initial infection and prevents the greater severity of acute infection, unlike men

who have a greater risk of acute infection severity [51]. However, this quality that may protect them during the acute phase of infection may make females more vulnerable to prolonged autoimmune disease [52, 53]. Another possible hypothesis to explain the sex differences is the hormonal difference, which may contribute to the asymmetry in risk and outcome between genders and may also be influenced by the overlap of symptoms of Long-COVID-19 syndrome with those of perimenopause and menopause [54].

With respect to differences in pharmacological treatment, although the pharmacological options tested so far to treat the different symptoms of COVID-19 have been numerous, they have demonstrated different levels of evidence in terms of efficacy and safety, with information on sex-related differences being limited. Sex-related differences in effectiveness are mainly explained by differences in the pharmacokinetic pro-file between men and women, as well as by the sexual hormonal status [55]. Future re-search into the pharmacological treatment of COVID-19 should focus on adequate knowledge of gender, and age as key factors in individual variation in drug responses [56].

To date, the exact causes that generate pain in Long-COVID-19 patients have not yet been found. The scientific evidence published to date supports the fact that pain is a very common symptom in Long-COVID-19 patients, with a prevalence that varies greatly between studies depending on the target population, the time since acute infection, and the treatments received. The proposed mechanisms to generate this pain are an inflammatory response induced by the virus and prolonged in time, associated to the increase of pro-inflammatory cytokines and hyperactivation of immune system cells [45]. Another proposed mechanism for the generation of pain is the direct entry of the virus into nervous system cells and muscle cells mediated by angiotensin-converting enzyme 2 (ACE2) receptors. Finally, Fernández-de-las-Peñas and collaborators propose the hyperexcitability of the central and peripheral nervous system induced by the virus as the

basis for pain of nociplastic characteristics, enhanced and prolonged in time by a series of negative psychosocial factors such as insomnia, stress, anxiety and social isolation [57].

Although previous studies [58, 59] have already reported a higher prevalence of pain in non-hospitalized patients than in hospitalized patients, few studies have so far focused on studying this symptom in non-hospitalized patients [60-65]. These studies focused on measuring the prevalence and main locations of pain, without measuring pain characteristics. In addition, these studies did not exclude patients who had pain previously. Therefore, to our knowledge and date, this is the first article that focuses on evaluating the characteristics of new-onset pain in non-hospitalized patients with Long-COVID-19 syndrome.

Many studies have demonstrated the presence of new-onset pain after infection with SARS-CoV-2, which can lead to chronic pain if not adequately studied and treat-ed [65-67]. This new-onset pain has a multifactorial etiology, the basis of which is the prolonged proinflammatory state due to the immune system response to SARS-CoV-2 infection [68–72]. To these physiological factors, we must add the alteration of the biopsychosocial factors [50, 73, 74] of the patients due to the pandemic situation, resulting in a new pattern of pain in these patients that needs to be defined and characterized [67].

The proportion of patients with Long-COVID-19 syndrome presenting with new-onset pain in this study is 69.5%, being quite high when compared with the prevalence of chronic pain in other populations with respiratory diseases; for example, in patients with COPD, the prevalence of chronic pain ranges from 32-62% [29, 75, 76]. Furthermore, the proportion of patients presenting with new-onset chronic pain in our study was also much higher than in previous studies in patients who had undergone COVID-19. For example, in the study of Soares et al., the prevalence of pain in COVID patients was 19.6% [16].

This may be because the patients included in the study were already diagnosed with Long-COVID-19 syndrome in contrast to previous studies [16, 44].

However, other studies previously performed at different clinical time points of SARS-CoV-2 infection already showed a similar prevalence of pain [32, 53, 54]. For example, studies performed during the acute phase of the disease, such as the study by Mural et al.[77] and Oguz-Akarsu et al. [78] showed a proportion of pain in their sample of 69.3% and 71.6%, respectively.

The results obtained from this study show a generalized pain pattern, with the most frequent location of pain being the neck, followed by the legs and head. These results do not agree with the results shown by other studies, where the most frequent lo-cation of the pain is back [79-81]. Concerning the generalized pain pattern, our results are consistent with previous [47, 82] studies, but not with other studies showing a more localized pain pattern [16, 64, 83, 84]. Concerning headaches, this study shows a higher prevalence than previously conducted studies in patients who had been hospitalized [85-90]. Concretely our results show 63.9% of patients with headaches, while the study by Fernández-de-las-Peñas et al. [85] and the study by González-Martínez et al. [90] showed 23.4% and 13%, respectively.

Although the exact mechanisms that generate pain in patients with Long-COVID syndrome at different body sites have not yet been elucidated, there are different theories that attempt to explain it. Regarding head and neck pain, it is believed that it may be a direct consequence of complications generated by the viral infection such as hypoxia, dehydration, and fever [91]. In addition, findings of increased IL-10 levels in COVID patients presenting with headaches seem to indicate that headaches may be a consequence of high cytokine levels [92, 93]. Finally, another hypothesis for the cause of headaches in these patients is the ability of SARS-CoV-2 to invade the central nervous system [94, 95].

Pain at the lower limb level could actually be explained by joint pains or by peripheral neuropathies, but these hypotheses remain theoretical so far [96, 97].

The mean pain intensity of the Long-COVID-19 syndrome patients included in this study measured with the BPI scale is 5.12. These results are in line with previously conducted studies showing moderate pain intensity [50, 98, 99]. The study by Soares et al. [16] in which new onset pain was evaluated showed levels of intensity and interference of this pain higher than those shown in our results, as well as a pain location similar to that of this study. However, we must consider that this study was performed on patients who had been hospitalized.

The results of this study demonstrate a lower health-related quality of life in Long-COVID-19 syndrome patients compared to successfully recovered group and healthy controls group. These results are in line with previously conducted research, which demonstrated that patients with COVID-19 [87] and Long-COVID-19 syndrome [47, 100-103] have worse levels of health-related quality of life.

The patient's perception of the disease are frameworks that patients construct in order to make sense of their symptoms and medical conditions. Thus, the patient's behavior and control of the disease will depend on the patient's cognitive representation of the disease. This cognitive representation of the disease will in turn be influenced by beliefs about the disease and what it means for the patient's life. The main factors that influence the patient's perception of the disease are the symptoms that form it, the control that the patient has over these symptoms, previous personal and family experiences, and the consequences that the disease generates in the life of the patient and his or her family. Numerous publications show that the perception of the disease is related to important health outcomes such as functionality and perceived state of health and can have a relevant influence on their measurement [104, 105]. Thus, patients who have undergone

an acute disease process in recent months may have a completely altered perception of the disease, leading to a more optimistic view of their health-related quality of life once they have recovered [106]. This would justify that patients who have had COVID-19 may have a better health-related quality of life than those who have never had the disease.

The differences shown by our results from previously conducted studies may be due to several factors. First, many of the studies performed so far had a positive anti-gen or polymerase chain reaction (PCR) test as an inclusion criterion. In our study, following the WHO definition of the Long-COVID-19 syndrome [19], patients with a probable or confirmed history of SARS-CoV-2 infection were included. In addition, we must take into account the differences in the patient sample in terms of time since infection, which was longer than in other studies, hospitalization, since only non-hospitalized patients were included, and new-onset chronic pain, since only patients without previous pain were included.

Several limitations of this study should be noted. First, it had a small sample size; larger sample sizes could improve the reliability of the result. However, previous studies in this population had used similar sample sizes [16, 47]. Another limitation of this study is the use of tests based on Classical Test Theory instead of Item Response Theory, which has less bias in the scores and better psychometric properties [107, 108]. As a limitation of this study, we could include the fact that the sample was obtained from an association of patients with the Long-COVID-19 syndrome, which makes the patients included more proactive in seeking help, perhaps because they have a greater intensity of symptoms. Despite having described several characteristics of new-onset chronic pain in patients with the Long-COVID-19 syndrome, there are still important pain-related aspects such as a more comprehensive assessment of patients' mood. It would also be interesting to include an evaluation of serum biomarkers in patients with the Long-COVID-19

syndrome to assess changes in these and compare them with the successfully recovered group and healthy controls group. In addition, a longitudinal design would allow us to observe changes in pain levels over time. Another limitation of this study is the use of scales that have not been specifically validated in the study population.

CONCLUSIONS

In conclusion, compared with healthy controls and patients who successfully re-covered from COVID-19, the results of this study show that health-related quality of life is significantly worse, and pain is significantly more prevalent in patients with the Long-COVID-19 syndrome. The pain of these patients is characterized by widespread pain, of moderate intensity and interference, with the most frequent locations being the neck, legs, and head, and significantly affecting the quality of life of these patients. These results will help inform the design of programs tailored to the needs of this population.

Authors' contributions: AOR had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, especially including any adverse effects. LLL contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. MCV had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MGS contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. JMN contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. AHC and ACM had full access to all of the data in the study and takes responsibility for the integrity. All authors read and approved the final version of the manuscript.

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ESTUDIO 2

Non-hospitalized post-covid patients with new-onset chronic pain 2 years after infection: cross-sectional study

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected the health and lives of people around the world, with the potential for further effects in the future (Hu et al., 2021; Haleem et al., 2020).

There is evidence of a second pandemic generated by all those patients who, after the acute phase of SARS-CoV-2 infection, continue to have long-lasting symptoms. This condition is called long-COVID (Fernández-de-las-Peñas, 2022) or post-COVID-19 syndrome (Soriano et al., 2022) and is generating increase burden on health systems (Menges et al., 2021).

Meta-analyses to date (Fernández-de-las-Peñas, Palacios-Ceña, et al., 2021; Lopez-Leon et al., 2021; Han et al., 2022; Cares-Marambio et al., 2021) show that about 60% of patients develop post-COVID symptoms, with fatigue and dyspnea being the most prevalent. Another relevant post-COVID symptom that can generate a significant burden (Bileviciute-Ljungar et al., 2022) on society is chronic pain (Cares-Marambio et al., 2021; López-León et al., 2021). A meta-analysis by Fernández-de-las-Peñas, Navarro-Santana, et al., 2022 recorded a post-COVID pain prevalence of 10%, however, studies focused on pain symptoms specifically show a prevalence of 45-70% (Herrero-Montes et al., 2022; Soares et al., 2021; Bakilan et al., 2021; Rubio-Rivas et al., 2020; Karaarslan et al., 2021; Fernández-de-las-Peñas, de-la-Llave-Rincón, et al., 2022; Fernández-de-las-Peñas, Cancela-Cilleruelo, et al., 2022). This suggests that it is an underestimated symptom in general post-COVID syndrome cohort studies (Fernández-de-las-Peñas, de-la-Llave-Rincón, et al., 2022).

The characterization of post-COVID pain will allow for a better understanding of the underlying mechanisms, the development of personalized treatment plans and the identification of patients with a higher predisposition (Clauw et al., 2020; Chou et al., 2007; Fernández-de-las-Peñas, Herrero-Montes et al., 2022). Pain should be approached from the biopsychosocial model (Gatchel et al., 2007; Uceyler et al., 2017; Bilgin et al., 2022) which understands this symptom as a complex dynamic interaction of biological factors with psychosocial factors, which influences in a determinant way the coping strategies of pain. Consequently, these factors impact on the chronification of pain, the development of disability, the appearance of fear of movement, decreased activity levels and, therefore, decisively modify the patient's prognosis (Nicholas et al., 2011; Overmeer et al., 2004; Lee et al., 2016; Rocha et al., 2021).

Evidence published to date suggests that post-COVID pain follows a nociplastic pain pattern (Fernández-de-las-Peñas, Ryan-Murua, et al., 2022; Pacho-Hernández et al., 2022) , which is characterized by an exaggerated response to pain associated with central nervous system-derived symptoms such as sleep problems, psychological disturbances and mood disorders (Nijs et al., 2021; Fitzcharles et al., 2021; Eccleston et al., 2020). The nociplastic pain pattern is created on the basis of a prolonged systemic inflammatory-immune response, which in turn generates a central sensitization process (Fernández-de-las-Peñas, Herrero-Montes et al., 2022; Cascella et al., 2021; Shanthanna et al., 2022; Fernández-de-las-Peñas, Ryan-Murua et al., 2022; Goudman et al., 2021; Nijs et al., 2021) that is enhanced and prolonged in time by a series of negative psychosocial factors that contribute to the chronification of pain and generate a worse prognosis (Huang et al., 2016; Knox et al., 2021).

Negative psychosocial factors such as anxiety, depression and insomnia appear in patients with post-COVID syndrome (Fernández-de-las-Peñas, Gómez-Mayordomo, et al., 2021;

López-León et al., 2021; Kind et al., 2019; Shanbehzadehet al., 2021; Bottemanne et al., 2021). However, the studies conducted so far have been carried out mainly in patients hospitalized during the acute phase of the disease (Fernández-de-las-Peñas, Gómez-Mayordomo, et al., 2021; Bottemanne et al., 2021). In these patients, in addition to the COVID-19-derived factors (Huang et al., 2016; Wang et al., 2021), there are hospitalization-derived factors for pain (Wu et al., 2020).

Therefore, it is necessary to conduct studies in the non-hospitalized population to help characterize the pain of these patients and develop treatment plans tailored to their needs. The aim of this study is to identify the clinical and psychosocial profile associated with pain in non-hospitalized patients with post-COVID-19 syndrome.

MATERIAL AND METHODS

Study design and participants

A cross-sectional case-control study was performed. Using the recommended guidelines Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were applied to develop the study design (Von Elmet al., 2014). We conducted this study in accordance with the Declaration of Helsinki 1975, revised in 2013 (World Medical Association, 2013). Ethical approval for this study was obtained from the Biomedical Research Ethics Committee of Granada.

Three groups of patients were included in this study. The case group was composed of post-COVID syndrome patients meeting the World health organization (WHO) definition for this disease (Soriano et al., 2022). In addition, two control groups of patients matched for age and gender were included, a group consisting of patients with a history of SARS-CoV-2 infection and successfully recovered and, finally, a group of healthy controls who

did not acquire SARS-CoV-2 infection. Patients in the post-COVID syndrome group were recruited from the "Covid Persistente Andalucía" association. Control patients were recruited by word-of-mouth. Patients were recruited between May 2021 and September 2022.

Patients over 18 years of age, who agreed to sign the informed consent form were included in the study. Patients were excluded if they had any of the following conditions: neurological or orthopaedic pathologies that limited voluntary movement, a cognitive impairment that prevented them from understanding and answering the questionnaires, or if they suffered reinfection with SARS-CoV-2. In addition, all patients who had been hospitalized due to COVID-19 infection and those who had pre-existing chronic pain according to the current IASP definition (Raja et al., 2020; Treede et al., 2019) before COVID-19 infection were excluded.

Outcome measures

Patients were initially contacted by telephone to inform them of the study and to arrange a face-to-face assessment. Once informed consent was obtained, an assessment of demographic characteristics, pain related clinical profile, and pain related psychosocial variables were performed.

The demographic characteristics included the anthropometric data, weeks since infection, percentage of smokers, percentage of patients with others diseases, comorbidities assessed with the Charlson comorbidities index (Charlson et al., 1987; Casas Duran et al., 2020) the quality of life evaluated by the Euroqol-5 dimensions 5 Levels (EQ-5D-5L) (Herdman et al., 2011; Hernández et al., 2018), and physical activity through the International Physical Activity Questionnaire Short Form (IPAQ-SF) (Craig et al., 2003; Roman-Viñas et al., 2010).

Pain related clinical profile included: pain intensity and interference, central sensitization, insomnia severity, and pain treatment. Pain intensity and interference were measured with the Brief Pain Inventory (BPI). The pain intensity section of the BPI is composed of four items and the pain interference section is composed of seven items. For the intensity section, the responses range from 0 (no pain) to 10 (worst pain) and for the interference section, the responses range from 0 (no interference) to 10 (total interference). To obtain the severity and interference index, the mean of the corresponding items is calculated, obtaining values between 0 and 10, with a higher score reflecting greater pain intensity and interference. The BPI has been established as a reliable and valid tool for assessing pain severity and interference (Keller et al., 2004; Tan et al., 2004. The Spanish version of this scale has a high internal consistency ($\alpha = 0.93$) (de Andrés Ares et al., 2015).

Central sensitization was measured with the Central Sensitization Inventory (CSI) (Roldán-Jiménez et al., 2021). The first part of the CSI is composed of 25 items that evaluate the frequency of presentation of the most common symptoms related to central sensitization syndrome. The score for each item ranges from 0 (never) to 4 (always) with a maximum score of 100. The higher the score, the greater the level of central sensitization. This questionnaire has a second part, which is not scored, that evaluates the presence of 7 disorders related to central sensitization. The Spanish version of this scale has a high internal consistency ($\alpha = 0.872$ (Cuesta-Vargas et al., 2016).

The Insomnia Severity Index (ISI) measured the severity of both nocturnal and daytime insomnia symptoms (Bastien et al., 2001). This index consists of 7 different items evaluating different aspect of insomnia in the past 2 weeks, each of which is a Likert point scale (0-4). The final score provides an overall index of insomnia severity and ranges from 0 to 28. The higher the score on this scale, the greater the severity of insomnia. The psychometric properties of this index have been shown to be good, including high

diagnostic accuracy (Bastien et al., 2001; Morin et al., 2011; Wong et al., 2017). The Spanish version of the ISI is a reliable and valid instrument with adequate internal consistency (α = 0.82) (Fernández-Mendoza et al., 2012).

In addition, patients were asked about the treatment they were currently receiving for pain. Data were collected on any type of treatment patients were receiving, both non-pharmacological and pharmacological treatment.

The assessment of pain related psychosocial variables included: fear of movement and (re)injury, catastrophizing, depression, anxiety, stress, and fear-avoidance beliefs.

The Spanish version of the Tampa Scale for Kinesiophobia (TSK) was used to measure fear of movement and (re)injury. The scale consists of 11 items which are a 4-point Likert scale (1-4). The final score ranges from 11 to 44 points, with higher scores expressing greater fear of movement and (re)injury. The Spanish version of this scale shows moderate internal consistency (α = 0.79) (Gómez-Perez et al., 2011).

Catastrophizing was measured with the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995). This scale consists of 13 items structured on a 5-point Likert scale ranging from 0 (not at all) to 4 (all the time). This scale assesses 3 components of catastrophizing: helplessness, magnification, and rumination (Osman et al., 1997; Van Damme et al., 2002). The items describe different thoughts and feelings that individuals can experience when they are in pain. The Spanish version of this scale used in this study showed appropriate internal consistency (α = 0.79) (García-Campayo et al., 2010).

The Depression, Anxiety and Stress Scale (DASS-21) (Lovibond et al., 1996) was used to measure stress, anxiety, and depression. The DASS-21 is a questionnaire composed of three subscales (stress, anxiety, and depression). These subscales consist of 7 items measured on a 4-point Likert-type scale. A final score is obtained for each subscale (0-

21) and for the final scale (0-63), the higher the score, the worse stress, anxiety and depression. The Spanish version of the DASS-21 has shown strong psychometric properties for the different subscales: depression (α = 0.93), anxiety (α = 0.86) and stress (α = 0.91) and for the total scoring (α = 0.96) (Daza et al., 2002).

Fear Avoidance Beliefs Questionnaire (FABQ) was used to measure fear avoidance and beliefs. This questionnaire consists of 16 items. The score for each item ranges from 0 (strongly disagree) to 6 (strongly agree). Within this questionnaire two subscales are defined, the FAB-work subscale reflects fear-avoidance beliefs about work, and the FAB-physical activity subscale reflects fear-avoidance beliefs about physical activities. The Spanish version shows high internal consistency (α = 0.93) (Kovacs et al., 2006).

Statistical Analysis

G*Power 3.1.9.2 software (3.1.9.2v; Statistical Power Analyses for Windows, Universität Düsseldorf, Germany) was used to perform a priori power analysis. This analysis was based on a pilot study (unpublished) of 15 subjects (effect size of 0.05). This suggested that a sample size of 53 in each group will have 95% power to detect a probability of 0.5. To allow for a dropout rate of 10%, we decided to have approximately 60 patients in each study group.

Data were analysed using the Statistical Package of Social Science (SPSS) program for Windows (version 26 IBM, Armonk, NY, USA). Nominal data were expressed as frequency (percentage). Continuous variables were presented as mean and standard deviation (SD). The normality of the data was first tested with the one-sample Kolmogorov-Smirnov test.

For nominal variables, the chi-square test was used to identify differences between groups. Normally distributed continuous variables were compared with a one-way

ANOVA. If the ANOVA analysis showed a significant interaction for each variable, the Bonferroni post hoc test was used to identify specific mean differences. A 95% confidence interval was used for statistical analysis. A p-value of ≤ 0.05 was set to indicate significant differences. The overall p-values were adjusted for multiplicity with the Bonferroni method. No attempt at imputation was made for missing data.

RESULTS

A total of 180 participants agreed to participate in this study and were considered eligible. The distribution of participants is shown in Figure 1.

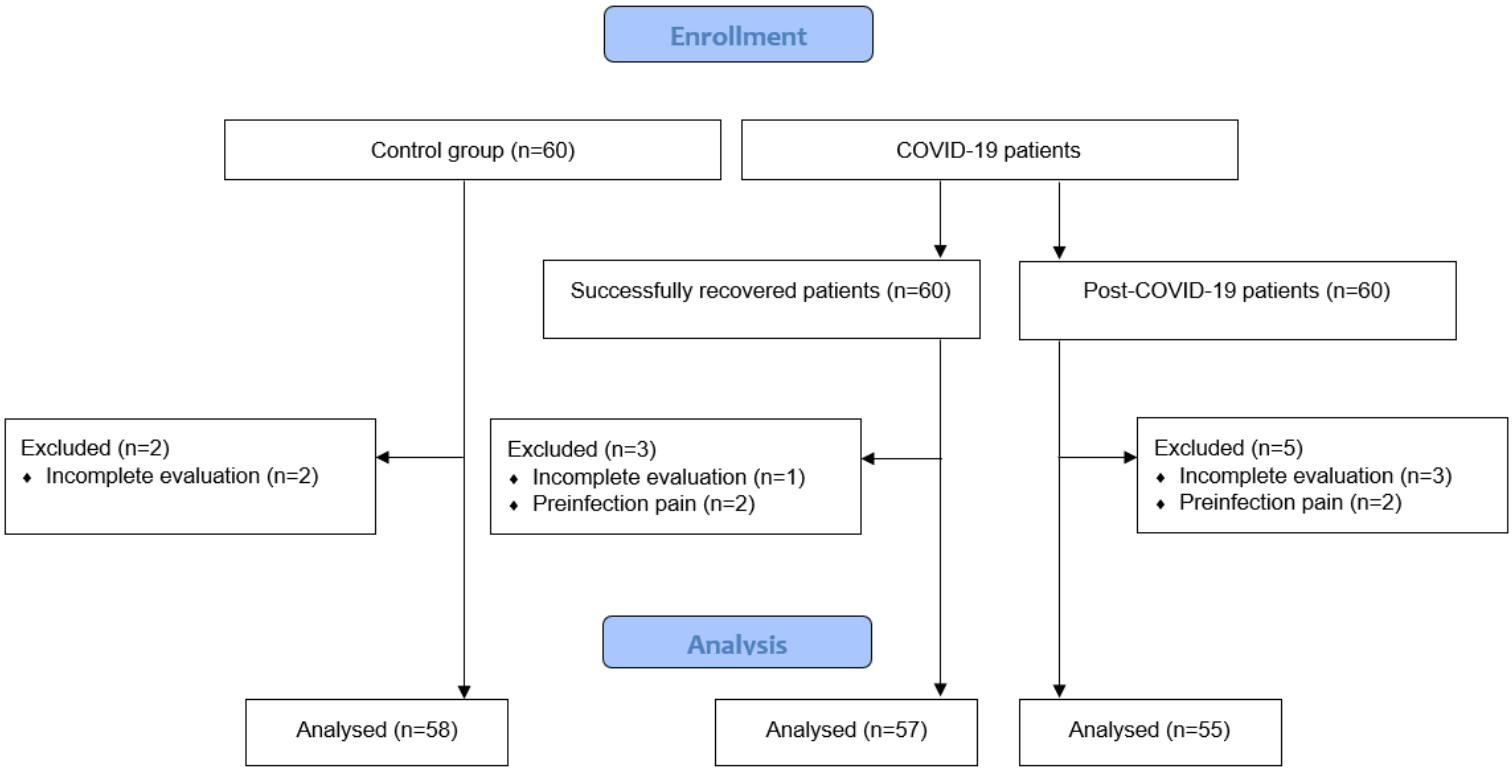

Figure 1. Flow diagram.

The demographic characteristics of the sample are shown in Table 1.

Table 1. Descriptive characteristic of the sample.

Variables	Healthy controls group (n=58)	Successfully recovered group (n=57)	Post-COVID group (n=55)	F/p
Age	45.43 ± 3.63	44.74 ± 3.04	45.51 ± 3.28	0.924
Sex (% female)	69	66.7	70.9	0.889
Weeks since infection		103.23 ± 9.04	104.98 ± 12.18	0.752
BMI (kg/m^2)	25.66 ± 3.12	25.15 ± 3.26	24.88 ± 3.09	0.901
Smoker (%)	15.5	21.1	25.5	0.275
Other diseases (%)	22.4	14	18.2	0.508
Charlson index	0.40 ± 0.70	0.19 ± 0.44	0.22 ± 0.42	2.454
EQ-5D-mobility	1.24 ± 0.54	1.11 ± 0.36	2.26 ± 1.21	35.85^{bc}
EQ-5D-self-care	1.05 ± 0.22	1.09 ± 0.29	1.87 ± 1.09	28.07^{bc}
EQ-5D-usual activities	1.17 ± 0.50	1.07 ± 0.32	3.00 ± 1.11	127.74^{bc}
EQ-5D-anxiety or depression	1.45 ± 0.68	1.25 ± 0.51	3.46 ± 0.77	191.43^{bc}
EQ-5D-pain or discomfort	1.31 ± 0.57	1.37 ± 0.56	2.46 ± 1.20	34.18^{bc}
EQ-5D VAS	83.60 ± 13.55	85.40 ± 13.97	42.71 ± 23.41	106.59^{bc}
IPAQ-walking	1170.53 ± 603.29	1026.68 ± 524.22	507.78 ± 465.59	23.76^{bc}
IPAQ-moderate	786.21 ± 599.86	731.23 ± 626.27	119.56 ± 269.90	27.52^{bc}

IPAQ-vigorous	1293.43 ± 878.04	1380.91 ± 570.23	185.18 ± 304.72	61.61[bc]
IPAQ-total	3250.17 ± 1253.65	3138.82 ± 958.98	812.53 ± 667.98	106.94[bc]

BMI: Body Mass Index; EQ-5D: Euroqol-5 Dimensions; VAS: Visual Analogue Scale; IPAQ: International Physical Activity Questionnaire. Data are expressed as mean ± standard deviation.
a= Significant differences between the healthy controls group and the successfully recovered group.
b= Significant differences between the healthy controls group post-COVID group.
c= Significant differences between the successfully recovered group and post-COVID group.

No statistically significant differences were found between groups in the anthropometric data, weeks since infection, percentage of smokers, percentage of patients with other diseases, and comorbidities. Statistically significant differences were found regarding the quality of life and physical activity. The group of post-COVID syndrome patients demonstrated worse results in quality of life and physical activity levels, with statistically significant differences with respect to the group of healthy controls and the group of successfully recovered patients.

The pain related clinical profile of the different groups is presented in Table 2.

Table 2. Pain related clinical profile.

Variables	**Healthy controls group (n=58)**	**Successfully recovered group (n=57)**	**Post-COVID group (n=55)**	**F/p**
BPI-intensity	0.66 ± 1.43	0.93 ± 1.74	5.07 ± 2.42	94.27[bc]
BPI-interference	0.56 ± 1.63	0.82 ± 1.87	5.78 ± 3.14	91.76[bc]
SC	17.69 ± 14.30	18.81 ± 16.24	54.53 ± 17.10	96.99[bc]
ISI	6.03 ± 5.13	6.35 ± 7.34	14.06 ± 7.12	26.53[bc]

Non-pharmacological treatment (%)	24.1	22.8	40	0.083
Physiotherapy	78.57	69.23	72.73	
Psychology	21.43	30.77	27.27	
Pharmacological treatment for pain (%)	10.3	14	76.4	<0.001**
NSAIDS	50	50	26.2	
Paracetamol	33.3	37.5	21.4	
Muscle relaxants	16.7	12.5	19	
Tramadol	0	0	14.3	
Codeine	0	0	4.8	
Metamizole	0	0	14.3	

BPI: Brief Pain Inventory; ISI: Insomnia Severity Index; NSAIDS: Nonsteroidal Anti-Inflammatory Drugs. Data are expressed as mean ± standard deviation.**p<0,001.
a= Significant differences between the healthy controls group and the successfully recovered group.
b= Significant differences between the healthy controls group and post-COVID group.
c= Significant differences between the successfully recovered group and post-COVID group.

Statically significant differences in pain intensity and pain interference were found between the post-COVID syndrome group and both control groups, with the post-COVID syndrome group showing higher levels of pain intensity and pain interference. The CSI and ISI score also indicated higher levels of central sensitization and insomnia severity in the post-COVID syndrome group compared to the control groups, with these differences being statistically significant.

No significant differences were found with respect to the proportion of patients who treated their pain non-pharmacologically, although the results did show that the proportion of patients in the three groups who went to physiotherapy was higher than the

percentage of patients who went to a psychologist. When comparing the proportion of pain pharmacologically, statistically significant differences were found, being considerably higher in the post-COVID syndrome group of patients (76.4%) compared to the healthy control group (10.3%) and the successfully recovered group (14%). The most commonly used drugs in the three groups were nonsteroidal anti-inflammatory drugs (NSAIDS), followed by paracetamol, and muscle relaxants.

The assessment of pain related psychosocial variables included fear of movement and (re)injury, catastrophizing, depression, anxiety, stress, and fear-avoidance beliefs.

Table 3 shows the assessment of pain related psychosocial variables results.

Table 3. Pain related psychosocial variables.

Variables	**Healthy controls group (n=58)**	**Successfully recovered group (n=57)**	**Post-COVID group (n=55)**	**F**
TSK	16.55 ± 9.44	13.81 ± 7.20	25.06 ± 6.67	30.86[bc]
PCS-helplessness	2.90 ± 3.42	2.16 ± 3.09	9.93 ± 5.70	57.93[bc]
PCS-magnification	1.59 ± 1.97	2.09 ± 3.15	5.15 ± 2.72	29.38[bc]
PCS-rumination	2.47 ± 2.97	1.91 ± 3.14	7.02 ± 3.91	38.85[bc]
PCS-total	6.95 ± 7.71	6.16 ± 8.89	22.09 ± 10.64	53.95[bc]
DASS-depression	2.76 ± 4.00	2.14 ± 3.76	7.02 ± 5.41	19.98[bc]
DASS-anxiety	2.60 ± 4.11	2.54 ± 3.45	9.11 ± 3.98	53.35[bc]

DASS-stress	4.35 ± 4.41	4.79 ± 5.12	9.26 ± 5.27	16.88[bc]
DASS-total	9.71 ± 11.66	9.47 ± 11.06	25.38 ± 12.56	33.50[bc]
FABQ-physical activity	5.38 ± 6.75	4.25 ± 5.95	9.91 ± 6.40	12.30[bc]
FABQ-work	5.05 ± 7.08	3.74 ± 5.79	18.95 ± 10.77	60.14[bc]
FABQ-total	10.43 ± 12.64	7.98 ± 9.34	28.86 ± 13.76	50.07[bc]

TSK: Tampa Scale for Kinesiophobia; PCS: Pain Catastrophizing Scale; DASS: Depression Anxiety and Stress Scales; FAB: Fear-Avoidance Beliefs Questionnaire. Data are expressed as mean ± standard deviation.
a= Significant differences between the healthy controls group and the successfully recovered group.
b= Significant differences between the healthy controls group and post-COVID group.
c= Significant differences between the successfully recovered group and post-COVID group.

Patients in the post-COVID syndrome group had higher levels of fear of movement and (re)injury, as well as catastrophizing. The results of the TSK, the different subscales, and the total PCS score indicated greater scores in the post-COVID syndrome group of patients, reaching a statistically significant difference with respect to the group of healthy controls and the successfully recovered group.

With respect to depression, anxiety and stress, the DASS-21 scale demonstrated significantly worse results in the post-COVID syndrome group with respect to both control groups in the three subscales and in the total score.

Finally, with respect to fear-avoidance beliefs, measured with the FABQ, it was noted that the results shown by both control groups were significantly better than the results found in the post-COVID syndrome group of patients, both in the physical activity subscale, the work subscale and in the total scoring.

No statistically significant differences were found between the group of healthy controls and the group of successfully recovered patients in any variable.

DISCUSSION

The aim of this study was to identify the clinical and psychosocial profile associated with pain in non-hospitalized patients with post-COVID-19 syndrome. The results have shown that patients with post-COVID-19 syndrome have obtained higher scores in pain intensity and interference, central sensitization, insomnia severity, fear of movement, catastrophizing, fear-avoidance beliefs, depression, anxiety and stress, compared to the control groups.

The sample of subjects included in this study was representative of the general population with the post-COVID-19 syndrome, with similar sociodemographic characteristics (Fernández-de-las-Peñas et al. de-la-Llave-Rincón, 2022; Seang et al., 2022). The higher prevalence of post-COVID-19 syndrome in the female gender has been previously demonstrated. These differences in prevalence are generated because of different symptomatic, inflammatory and immune responses between men and women (Pelà et al., 2022; Bilgin et al., 2022).

Pain has been previously studied in post-COVID patients. Khoja et al., 2022 concluded that musculoskeletal pain was one of the most common symptoms in post-COVID patients. They also affirmed that the majority of the published studies reported the prevalence of pain, but literature exploring the characteristics and the profile of patients is needed. Our results not only have concluded that pain intensity and severity was significantly higher in the post-COVID syndrome group, we have also explored the pain-clinical and psychosocial profile of these patients. Significant poor results were found in

post-COVID syndrome group in central sensitization, fear of movement, catastrophizing, and fear-avoidance beliefs, compared to the control groups. It is well documented in the pain literature that all of these factors exacerbate the experience of pain and predispose individuals to pain chronification (Asmundson et al., 2009).

Our results have demonstrated a decreased quality of life in the post-COVID syndrome group compared to the other two control groups. Malik et al., 2022 carried out a systematic review with the aim of evaluating the prevalence of poor quality of life in post-COVID-19 syndrome, and they concluded that post-COVID syndrome was related to poor quality of life. They thought that a possible reason was the fact that post-COVID patients have higher stress levels and psychological issues inhibiting them from relaxing and may result in sleep disturbances (Bellan et al., 2021). These results are in line with those found in our study. We have found significant levels of insomnia as well as stress, anxiety and depression in the post-COVID syndrome group.

One limitation of this study could be the fact that the sample was obtained from an association of patients with the post-COVID-19 syndrome, which makes the patients included more proactive in seeking help, perhaps because they have a greater intensity of symptoms. In future studies, it would also be interesting to include an evaluation of serum biomarkers in patients with the post-COVID-19 syndrome to assess changes in these and compare them with both control groups. Additionally, a longitudinal design would allow us to observe changes in pain levels over time. Finally, we have collected some information about the specific description of the pain in the participants. Nevertheless, the information collected is not sufficient to identify a more specific profile. In future studies, it could be improved.

CONCLUSION

Identification of the COVID-19 aftermaths will be crucial for healthcare professionals. This study has revealed that patients with post-COVID-19 syndrome have shown high pain intensity and interference, central sensitization, insomnia severity, fear of movement, catastrophizing, fear-avoidance beliefs, depression, anxiety and stress. These findings have important implications for the development of future interventions to improve the management of these patients.

Conflict of interest

The authors declared that there is no conflict of interest.

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ESTUDIO 3

Efficacy of web-based supportive interventions in quality of life in COPD patients, a systematic review and meta-analysis

Calvache-Mateo, A., López-López, L., Heredia-Ciuró, A., Martín-Núñez, J., Rodríguez-Torres, J., Ortiz-Rubio, A., & Valenza, M. C. (2021). Efficacy of web-based supportive interventions in quality of life in COPD patients, a systematic review and meta-analysis. International Journal of Environmental Research and Public Health, 18(23), 12692.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a non-reversible inflammatory disease that causes progressive obstruction of the airways. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 report, COPD is the leading lung disease in terms of mortality and morbidity worldwide [1,2]. Due to the increase in smoking and the progressive ageing of the population, the prevalence of COPD will increase in the coming years [3].

As the disease progresses, the symptoms become increasingly severe and complex. Often the combination of psychological, emotional and social factors with physical symptoms makes it difficult for patients and professionals to deal with the disease [4]. As a result, COPD patients experience significant impairment of disease-related quality of life as well as social isolation [5] that generates a significant burden of disability [6] and demands continuous health care [7].

Unfortunately, COPD patients face significant barriers when seeking access to appropriate health services to manage the disease, including living in medically un-derserved regions [8], language barriers [9], reduced mobility due to the disease itself or other comorbidities, ageing and limited time [10]. In addition, due to the respiratory status of these patients and the potentially serious medical consequences for them, the risk of COVID-19 infection should be minimized [11]. Despite all these obstacles, there are not many interventions to support COPD patients in dealing with their disease [8].

Technological development is a great opportunity to generate new tools to sup-port COPD patients [8]. These technologies have enabled existing treatments to be de-livered online and also allow for the development of new interventions tailored to patients' needs [12]. New technologies are increasingly being investigated with the aim of developing

interventions that can adequately complement or replace interventions al-ready provided in health services [13,14].

Rapid advances towards a more digitalized society as well as the rapid development of today's electronic devices have caused a significant rise in the availability of communication technologies applied to health services [15]. The different online health communication tools allow patients to access personalized content, disease self-management tools and communication with healthcare professionals from the comfort and security of their own home [16,17].

The most recent systematic reviews and meta-analyses [18–21] on telehealthcare have analyzed teleassessment, telephone assistance, mobile app development and website assistance in depth, but they need to be analyzed separately [8].

Previous studies show chronic disease patients' need for personalized web-based interventions [21,22]. COPD patients demand access to information about their health status, related to the disease itself and to the improvement of quality of life [8]. Different mechanisms related to a perception of health-related needs, such as health education, self-management [23] and family and social support, have a significant influence on the quality of life of patients using web-based interventions [17,24–26].

The advantages offered by web-based interventions such as easy and on-demand access to health information content, interactive support with other patients and tools for symptom self-management may have the potential to influence the different variables and symptoms of a COPD patient. There is a need to investigate whether these web-based interventions have an impact on the quality of life of COPD patients and which are the most appropriate contents. The aim of this systematic review and me-ta-analysis was to

identify the effects of web-based supportive interventions in the quality of life outcomes of patients with COPD.

MATERIALS AND METHODS

Search strategy and eligibility criteria

This review was conducted using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement guidelines [27] and its registration number in the International Prospective Register of Systematic Review (PROSPERO) is CRD42020211978. The Cochrane Collaboration guidelines for reviewing interventions were also closely followed [28]. Three databases were used for the electronic search: PubMed, Web of Science and Scopus. The screening and analysis of the studies was conducted between November and March 2021. Relevant publications from inception to 1 March 2021 were included. A search strategy was created for MEDLINE and then modified to be specific to each of the databases. The following Medical Subject Headings (MeSH) terms were used (Appendix 1).

To adequately define the research question, the PICOS strategy [29] was applied.

(P) Population: COPD patients over 18 years of age.

(I) Interventions: Studies that used web-based supportive interventions.

(C) Comparison: Any other intervention not administered through a web.

(O) Outcome: Studies that included an outcome reporting quality of life (e.g., St George Respiratory Questionnaire, EuroQol 5- Dimension Questionnaire).

(T) Timing: At any time.

(S) Setting: No restriction of setting.

Only full-text randomized controlled trials written in English, Spanish and French were included in the review. Systematic reviews and meta-analyses, observational studies, clinical practice guidelines, letters, abstracts, editorials, conference papers, theses or dissertations were excluded. Studies in other languages were also considered for inclusion, when translation was possible.

Study selection and data extraction

After all studies had been retrieved from the three databases, duplicates were re-moved. To determine if the articles met the inclusion criteria for this review, two independent investigators performed a first assessment of the title and abstract of all studies. If the article met the inclusion criteria, it was selected for a second phase in which the full text was analyzed and reviewed.

The Cochrane guidelines for systematic reviews were followed for data extraction [28]. A third reviewer was responsible for resolving any disagreement between the two main reviewers. The information extracted from the articles was: year of publication, main author, sample size, sample age, treatment status, severity of COPD, specific intervention for the control and experimental groups, web content elements, intervention duration, outcome measures and main results. If the reviewers did not find any data during the analysis and review of the articles, they contacted the authors of the articles.

Assessment of risk of bias

The Downs and Black quality assessment method was used to assess the methodological quality of the studies included in the review. This assessment was carried out independently by the two principal investigators [30]. This method contains 27 items divided into 5 subscales (study quality, external validity, study bias, confounding and

selection bias, and study power). Due to its high reliability and validity this scale is considered one of the 6 most appropriate scales to measure the quality of the studies included in a systematic review. Studies are classified into four categories according to the score obtained: it will be classified as poor if its score is less than or equal to 14, fair if the score is between 15 and 19, good if the score is between 20 and 25 and excellent if the score is between 26 and 28 [31,32].

In addition to the quality of the articles, the risk of bias was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials [28]. This measurement tool is divided into 7 items that are subdivided into 6 subscales. The first subscale corresponds to the selection bias and is the only one with two items. The remaining sub-scales are called performance bias, detection bias, attrition bias, reporting bias and other bias and have only one item. When the reviewer determines that there is a low risk of bias for each of the items, the study is classified as high quality. When the re-viewer determines that one of the items is not met because there is a high risk of bias or two of the items cannot be answered clearly, the study is classified as fair quality. When the reviewer determines that one of the items is not met because there is a high risk of bias or two of the items cannot be answered clearly and there are important limitations that may invalidate the results, the study is classified as of poor quality. The study is also classified as poor quality when two or more items are not met.

Data synthesis and analysis

Meta-analysis was undertaken using Review Manager (RevMan v.5.3; Cochrane Collaboration, Oxford UK). All variables included were continuous data. Study authors were contacted whenever data were insufficient for the purposes of me-ta-analysis (e.g., neither means nor standard deviation were provided). The embedded Review Manager

calculator was used to calculate standard deviations whenever p-values or 95% confidence intervals were given [33].

Because all of the studies measured outcomes on the same scale, the results were then analyzed using weighted mean differences, and 95% confidence intervals were calculated for all outcomes [34].

The Q and I2 statistics were calculated in order to examine statistical heterogeneity, and a visual inspection of the forest plots was also performed to identify outlier studies. The I2 is a statistical value that is interpreted as the percentage of the total variation observed between studies that is due to the difference between them and not to sampling error (chance). An I2 of ≥50 %; I2 >25 % and <50 %; I2 of ≤25 % were considered to indicate high, moderate and low heterogeneity respectively. When the I2 value is greater than 50%, the meta-analysis is considered heterogeneous and, there-fore, a random effects analysis had to be used. Statistical significance was established as $p<0.05$, which means that the effects differ significantly between the control and intervention groups. We also explored sources of heterogeneity and performed a sensitivity analysis excluding trials with high risk of attrition or detection bias [33].

RESULTS

An initial search of the databases found 3089 records. After eliminating duplicates, a total of 1,319 studies were selected. In the end, an overall total of 9 studies that analyzed a total of 1,168 participants were included in the review. The PRISMA flow diagram is shown in Figure 1.

Table 1 shows the main characteristics of the studies included in the review. The included studies have a publication date ranging from 2013 to 2020. The analyzed participants

ranged in age from 66.1 [35] to 71.9 years [36]. All of the studies except the study of Wang et al. (47.5%) [36] had a higher proportion of males than females in the study sample. In regard to the COPD severity, five studies [37–41] included mild to very severe patients and four studies [35,36,42,43] included moderate to very severe patients. All studies included clinically stable patients with the exception of Wang et al. [36] and Jiménez-Reguera et al. [43] that included patients after discharge.

The web-based supportive intervention of each study was covered in Table 2 by the content of the comparison group approach, the content of the experimental interventions, the intervention duration, the outcome measures and main results. Table 2 also includes six web content elements that were identified as important to the technical characteristics of internet-supported therapeutic interventions [44] as well as for evidence-based web interventions (E= educational content, M= symptom and mood monitoring, F= personalized feedback, SM= education in self-management skills, CH= web-based communication with healthcare professionals and CP= web-based communication with patients) [45,46].

One study compared the usual care with a comparator group who received the usual care with the addition of the web-based supportive program [36]. Four studies compared a web-based supportive pedometer walking intervention with a pedometer walking intervention without the support of the web [38–41] and four studies com-pared the web-based supportive intervention with a face-to-face program [35,37,42,43].

Regarding intervention duration, for each study mean duration of intervention was 7.9 months (range 6 weeks to 15 months). Most of the studies conducted an intervention over one year [36,37,39,41]. One study conducted an intervention for 10 months [43] and four studies conducted an intervention of less than 4 months [35,38,40,42].

Most repeated web content elements were educational content, self-management skills training and web-based communication with healthcare professionals. Only one study [39] excluded the educational content. Education in self-management skills and web-based communication with healthcare professionals were excluded by Jiménez-Reguera et al. [43].

The included studies evaluated quality of life using different tools, e.g. the Chronic Respiratory Questionnaire (CRQ), Short Form 36-Item Health Survey (SF-36), St George's Respiratory Questionnaire (SGRQ), Chronic Obstructive Pulmonary Disease Assessment Test (CAT), EuroQol 5-Dimension Questionnaire (EQ- 5D). The most commonly re-ported outcome was SGRQ, which was followed by CAT and CRQ.

Other variables repeated in several studies are: Self-efficacy, functional capacity, dyspnoea, physical activity, lung function and anxiety and depression. Self-efficacy was measured in four studies, with the most commonly used tool being the Exercise Self-Regulatory Efficacy Scale (Ex-SRES). Functional capacity was the second most frequently measured variable after quality of life. Five studies measured functional capacity with the 6MWT being the most commonly used tool. Four studies measured dyspnoea and physical activity, three studies measured anxiety and depression and two studies measured lung function.

The modified Downs and Blacks scale scores are presented in Table 1. The average score of the included studies in the review was 21.6. In accordance with the suggested cut-off points to grade studies according to quality, one article was rated as "fair" (15-19 points) and eight were categorized as "good" (20-25 points). Figure 2 shows in detail the scoring of the studies on the different items of the Cochrane Risk of Bias Tool for randomized trials.

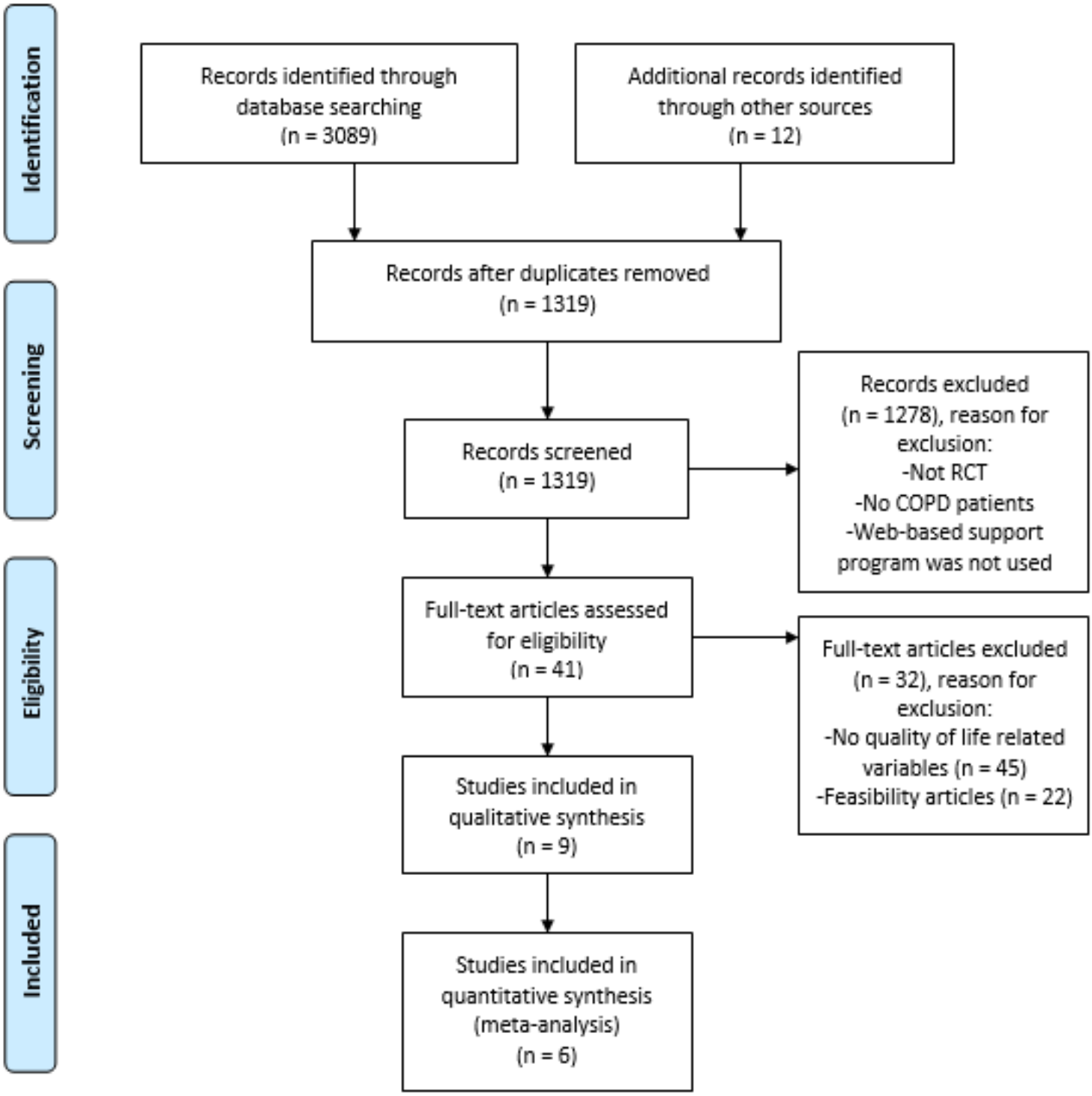

Figure 1. PRISMA flow chart of the literature screening process and results.

Data from 6 RCTs were included [36,38–40,42,43]. All studies that did not provide sufficient data on quality of life (means and standard deviations at baseline or after the intervention) and in which no response was received from the authors were excluded.

Finally, the analysis was performed on a total of 873 patients (359 for control and 514 for intervention).

Figure 3 depicts the forest plot of SGRQ change. Due to the statistical heterogeneity of the results (I2 = 89 %, $p < 0.001$), a statistical random effects model was applied. Patient quality of life was not significantly improved in the intervention groups in comparison with controls (MD = -4.68, 95 % CI = -11.97, 2.62).

When compared to usual care, the mean difference (MD) showed significant overall effect with the addition of the web-based supportive program to usual care (MD = -26.57, 95% CI = -34.09, -19.05; $p<0.001$, one study [36]). When compared a web-based supportive pedometer walking intervention with a pedometer walking intervention without the support of the web (MD = -0.68, 95% CI = -4.11, 2.75; p=0.70, three studies [38–40]) or a web-based supportive intervention with a face-to-face intervention (MD = 0.33; 95% CI= -6.65, 7.30; p=0.93, two studies [42,43]), the pooled MD showed no significant overall effect.

Table 1. Characteristics of the included studies

Study (year)	**Sample size, distribution and sample age** **N (% men): (Mean ± SD)**	**Treatment Status**	**Severity**	**Downs and Black** (Risk of bias)
Nguyen et al. (2013) (115)	125 (54%) allocated randomly into: **EG**: 68.5 ± 11.0 **CG1**: 68.2 ± 9.9 **CG2**: 69.3 ± 8.0	Clinically stable	Mild to very severe	22 (Poor quality)
Moy et al. (2015) (116)	238 (93.7%) allocated randomly into: **EG**: 67.0 ± 8.6 **CG**: 66.4 ± 9.2	Clinically stable	Mild to very severe	22 (Poor quality)

Moy et al. (2016) (117)	238 (93.7%) allocated randomly into: **EG**: 67.0 ± 8.6 **CG**: 66.4 ± 9.2	Clinically stable	Mild to very severe	23 (Poor quality)
Wang et al. (2017) (118)	120 (47.5%) allocated randomly into: **EG**: 69.3 ± 7.8 **CG**: 71.9 ± 8.1	After discharge	Moderate to very severe	20 (Fair quality)
Wan et al. (2017) (119)	109 (98,2%) allocated randomly into: **EG**: 68.4 ± 8.7 **CG**: 68.8 ± 7.9	Clinically stable	Mild to very severe	23 (Fair quality)
Bourne et al. (2017) (120)	90 (65.56%) allocated randomly into: **EG**: 69.1 ± 7.9 **CG**: 71.4 ± 8.6	Clinically stable	Moderate to very severe	22 (Fair quality)
Chaplin et al (2017) (121)	103 (68.93%) allocated randomly into: **EG**: 66.4 ± 10.1 **CG**: 66.1 ± 8.1	Clinically stable	Moderate to very severe	22 (Fair quality)
Wan et al. (2020) (122)	109 (98.17%) allocated randomly into: **EG**: 68.4 ± 8.7 **CG**: 68.7 ± 7.9	Clinically stable	Mild to very severe	23 (Fair quality)
Jiménez-Reguera et al. (2020) (123)	36 (61.11%) allocated randomly into: **EG**: 68.1 ± 6.6 **CG**: 68.1 ± 7.0	After discharge	Moderate to very severe	18 (Poor quality)

Notes: EG: experimental group; CG: control group.

Table 2. Characteristics of the included studies

Study	Interventions	Web content elements						Experimental intervention content	Intervention duration	Outcomes measures	Main results
		E	M	F	SM	CH	CP				
Nguyen et al. (2013) (115)	**EG**: Internet-based dyspnea self-management program. **CG1**: Face-to-face dyspnea self-management program. **CG2:** General health education.	x	x	x	x	x	x	Intervention included a personalized education program, dyspnea self-management training, exacerbation guidelines, personalized exercise with biweekly feedback and support, personal symptom and exercise log, real-time follow-up, convenient access to	12 months	Quality of life measure(s): CRQ, SF-36. Other outcomes (measure(s)): Self-efficacy (validated question); functional capacity (6MWT, ITT); dyspnea with activities (CRQ-D);	Quality of life results: No significant differences were found between group in quality of life. EG participants had significant improvement in CRQ compared with baseline. Other outcomes results: Self-efficacy for managing dyspnea improved for the EG and CG1 compared with CG2. No

								information and support materials.		arm endurance; adherence; satisfaction.	significant differences were found in dyspnea and functional capacity between groups.
Moy et al. (2015) (116)	**EG**: Web based pedometer walking intervention. **CG**: Pedometer walking intervention.	x	x	x	x	x	x	Step counting allowed for patient self-monitoring, new personalized weekly objectives were established, educational and motivational content to improve patient self-management, social support through an online forum.	4 months	Quality of life measure(s): SGRQ. Other outcomes (measure(s)): Physical activity (pedometer); adherence; safety.	Quality of life results: No significant differences were found between group in SGRQ total score. However, a significantly higher proportion of intervention participants than controls had at least a 4-unit improved SGRQ total score the minimal difference that is clinically important. EG had significant improvement

										on symptoms and impact subscales compared to the CG. Other outcomes results: EG had significant improvement on physical activity compared to the CG.
Moy et al. (2016) (117)	**EG**: Web based pedometer walking intervention. **CG**: Pedometer walking intervention.	x	x	x	x	x	Step counting allowed for patient self-monitoring, new personalized weekly objectives were established, motivational content to improve patient self-management, social	12 months	Quality of life measure(s): SGRQ. Other outcomes (measure(s)): Physical activity	Quality of life results: No significant differences were found between group in quality of life. Other outcomes results: No significant differences were

					support through an online forum.		(pedometer); adherence; safety.	found in physical activity between groups.
Wang et al. (2017) (118)	**EG**: Web based coaching program + Routine care **CG**: Routine care	x	x	x	These were used to manage patients' clinical and demographic variables and have communication between health care providers and patients. The patient was able to access disease information, pulmonary rehabilitation instructions and particular management of the participant according to	12 months	Quality of life measure(s): SGRQ. Other outcomes (measure(s)): Functional capacity (6MWT); dyspnea (MRC); lung function (spirometry).	Quality of life results: EG had significant improvement in the SGRQ total score, SGRQ symptoms, SGRQ activity and SGRQ impact compared to the CG. Other outcomes results: EG had significant improvement of lung function, functional capacity and degree of dyspnea compared to CG.

								the evolution of the disease.			
Wan et al. (2017) (119)	**EG**: Web based pedometer walking intervention. **CG**: Pedometer walking intervention.	x	x	x	x	x	x	Step counting allowed for patient self-monitoring, new personalized weekly objectives were established, educational and motivational content to improve patient self-management, social support through an online forum.	3 months	Quality of life measure(s): SGRQ. Other outcomes (measure(s)): Self-efficacy (Ex-SRES); functional capacity (6MWT); physical activity (pedometer); dyspnea (MRC); depression (BDI-II); COPD knowledge (BCKQ); social	Quality of life results: No significant differences were found between group in quality of life. Other outcomes results: No significant differences were found between group in functional capacity, self-efficacy, dyspnea, depression, COPD knowledge, social support motivation and confidence to exercise. EG

									support (MOS-SSS); motivation and confidence to exercise; adherence.	participants had significant improvement of daily step count compared with baseline.
Bourne et al. (2017) (120)	**EG**: Online supportive pulmonary rehabilitation. **CG**: Face-to-face-supportive pulmonary rehabilitation.	x	x	x	x	Intervention included pulmonary online rehabilitation and educational videos to promote self-management.	6 weeks	Quality of life measure(s): SGRQ, CAT. Other outcomes (measure(s)): Functional capacity (6MWT); dyspnea (MRC); anxiety and depression (HADS); adherence; safety.	Quality of life results: No significant differences were found between group in quality of life. Other outcomes results: No significant differences were found between group in exercise capacity, anxiety and depression.

Chaplin et al. (2017) (121)	**EG**: Web based pulmonary rehabilitation program. **CG**: Face-to-face pulmonary rehabilitation program.	x	x	x	x	x	Intervention included education content, exacerbation guidelines, a home exercise program and goal setting, record of the progress, motivational interviewing techniques and convenient access to information and support.	6-8 weeks	Quality of life measure(s): CRQ, CAT, EQ-5D. Other outcomes (measure(s)): Self-efficacy (PRAISE); exercise capacity (ISWT, ESWT); anxiety and depression (HADS); COPD Knowledge (BCKQ).	Quality of life results: No significant differences were found between group in quality of life. EG and CG participants had significant improvement in quality of life compared with baseline. Other outcomes results: No significant differences were found between group in any other outcome. EG and CG participants had significant improvement in functional

											capacity compared with baseline.
Wan et al. (2020) (122)	**EG**: Web based pedometer walking intervention. **CG**: Pedometer walking intervention.	x	x	x	x	x	x	Step counting allowed for patient self-monitoring, new personalized weekly objectives were established, educational and motivational content to improve patient self-management, social support through an online forum.	15 months	Quality of life measure(s): SGRQ. Other outcomes (measure(s)): Self-efficacy (Ex-SRES); physical activity (pedometer); acute exacerbations.	Quality of life results: No significant differences were found between group in quality of life indicating no significant decline from baseline. Other outcomes results: No significant differences were found between group in daily step count and self-efficacy. EG participants had significant

							improvement of acute exacerbations compared with baseline.
Jiménez-Reguera et al. (2020) (123)	**EG**: Web-based follow-up program. **CG**: Usual care follow-up program.	x	x	Intervention included an educational program and data collection relate to disease and physical activity, daily reminders of daily exercise, record medication intake, daily mood and level of tiredness.	10 months	Quality of life measure(s): SGRQ, CAT, EQ- 5D. Other outcomes (measure(s)): Functional capacity (6MWT); lung function (spirometry); adherence (CAP	Quality of life results: No significant differences were found between group in quality of life Other outcomes results: No significant differences between the two groups were observed in functional capacity and lung function. EG participants had significant improvement of

		FISIO); adherence to physical activity (Morisky-Green Test).	adherence to the program and adherence to physical activity.

Notes: E, educational content; M, symptom and mood monitoring; F, personalized feedback; SM, education in self-management skills; CH, web-based communication with healthcare professionals; CP, web-based communication with patients; EG, Experimental Group; CG, Control Group; CRQ, Chronic Respiratory Questionnaire; SF-36, Short Form 36 survey tool version 1; 6MWT, 6-Minute Walk Test; ITT, Incremental Treadmill Test; CRQ-D, Chronic Respiratory Questionnaire Dyspnea subscale; SGRQ, St George's Respiratory Questionnaire; MRC, Medical Research Council scale; ; Ex-SRES, Exercise Self-Regulatory Efficacy Scale; ; BDI-II, Beck Depression Inventory-II; BCKQ, Bristol COPD Knowledge Questionnaire; MOS-SSS, Medical Outcomes Study Social Support Survey; CAT, COPD Assessment Test; HADS, Hospital Anxiety and Depression Scale; EQ- 5D, EuroQol 5-Dimension questionnaire; PRAISE, PR Adapted Index of Self-Efficacy; ISWT, Incremental Shuttle Walk Test; ESWT, Endurance Shuttle Walk Test; CAP FISIO, Respiratory Physiotherapy Adherence self-report questionnaire.

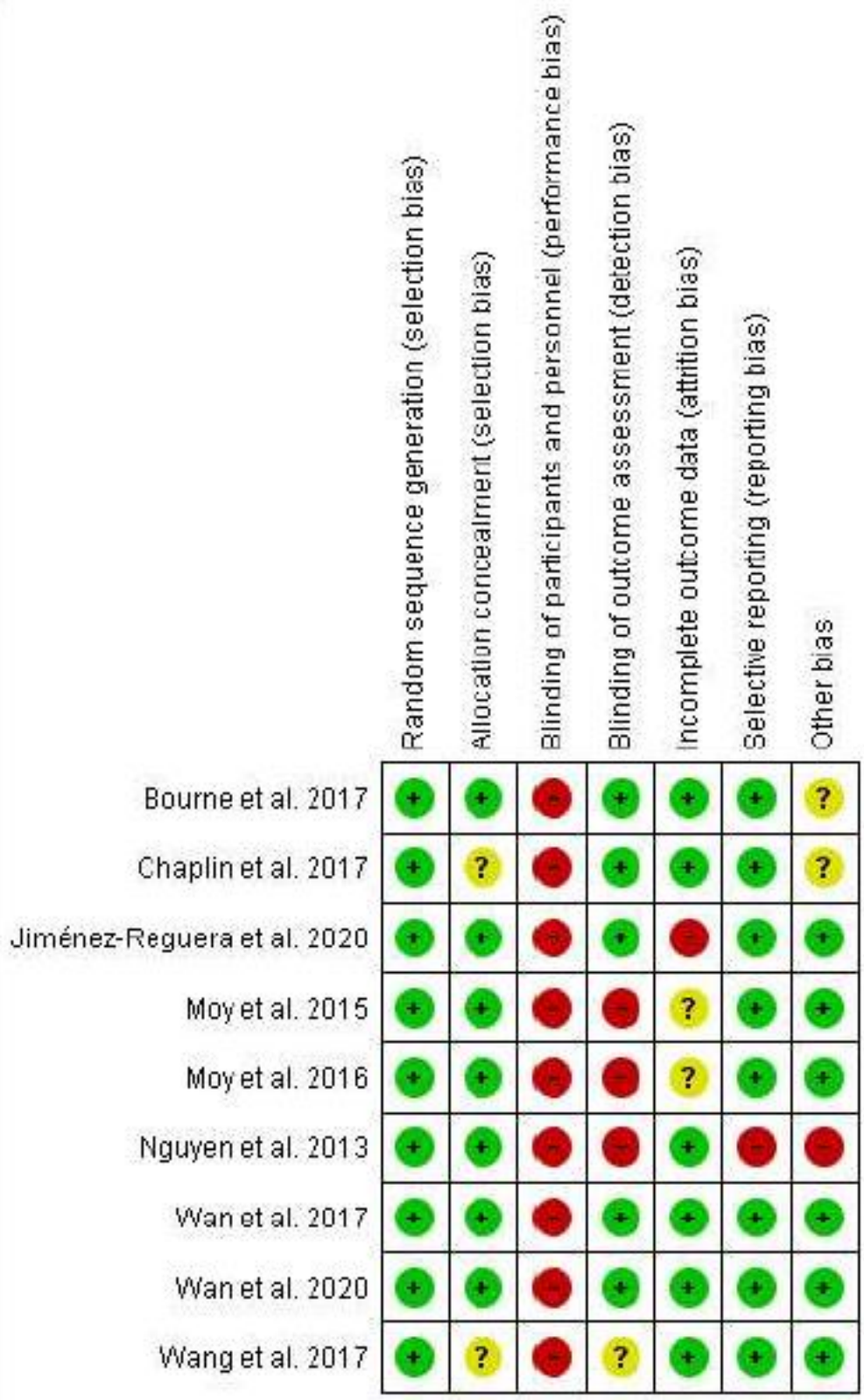

Fig. 2. Risk of bias assessment of included studies. Notes: Red, high risk of bias: Yellow, moderate risk of bias: Green, low risk of bias.

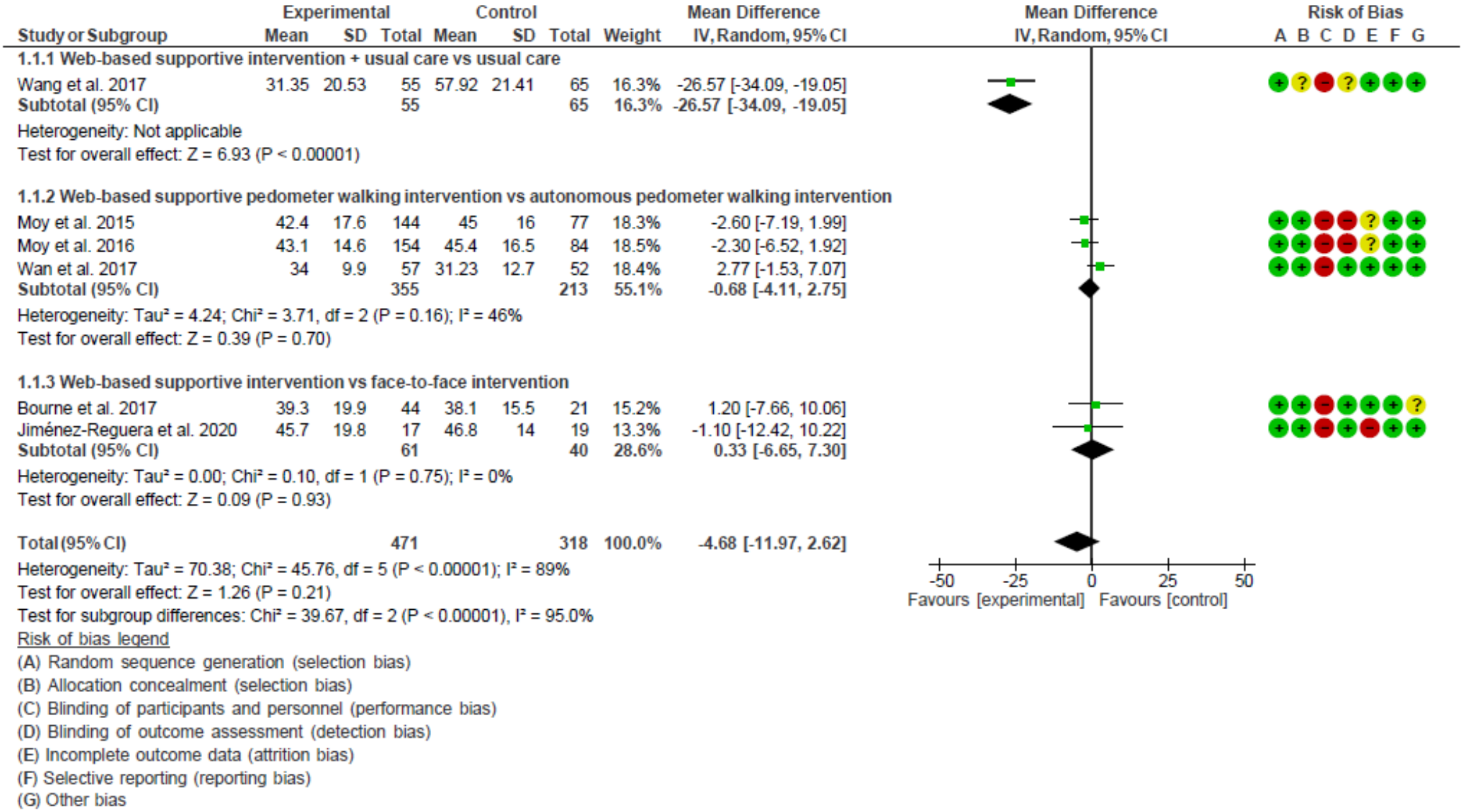

Fig. 3. Forest plot of the effect of web-based supportive interventions on quality of life in COPD patients compared with the control group.

DISCUSSION

The continuous technological growth of today's society, the increasing use of online services, and the patients' need for new supportive initiatives have facilitated the creation of new web-based interventions that have not been properly tested. This is the first systematic review specifically evaluate the effects of web-based supportive interventions on quality of life in COPD patients.

Our results support the idea that web-based supportive interventions can improve the quality of life in COPD patients. Nevertheless, it is important to note that the systematic review of the literature related to the design of web-based supportive interventions must be correctly interpreted, considering the different sample sizes of the studies, the differences in length of therapy and follow-up and the differences in effect size of the include studies.

Our systematic review is the first one exploring specifically the effects of web-based supportive interventions in quality of life in COPD patients, with 9 RCTs [35–43] included. Our results are consistent with those of previous systematic reviews performed in COPD patients and other telehealth systems [18,21,47–50].

Regarding the web components, Sobnath et al. [51] describe the possible features that a potential supporting tool for COPD patients should have in their systematic re-view. The tools must be easily accessible for both patients and health professionals and should be adapted to elderly patients with limited experience in the use of technology and have an user-friendly interface. The tool should include a customized education section for each patient, with disease-specific information and self-management mate-rial, phycological motivation to encourage good adherence, electronic coaching, comment section and social networks to share information with medical professionals [51,52].

Among the web-based supportive interventions analyzed, the education and motivational content was the most used alone or in combination with other contents, and the most frequent comparison treatment was the same in a face-to-face format. When compared, web-based supportive interventions showed similar results in all measured variables.

The web-based support interventions analyzed in this systematic review utilized a variety of components of COPD patients support tools, that were described by Sobnath et al. [51], such as personalized educations section and social networks to share information with medical professionals. Our results are in line the previous systematic re-views conducted in patients with cancer in which the most common and promising interventions include a combination of effective communication with healthcare providers, customized educational strategies based on the patient's disease and condition, ongoing symptom monitoring, disease self-management tools, and automated feed-back [53,54].

It is difficult to determine exactly which web elements are most important in designing an effective disease management tool, and to determine whether the effects are due to one or some of the elements or to all of them together. Effective communication with healthcare providers is a highly recommended content for a web-based support intervention since patients have different characteristics, preferences and needs [44,55] as seen in the Norwegian WebChoice study [56].

A Cochrane review identified that in improving the quality of life of COPD patients, the effects of technology-based interventions attenuated over time. Support interventions based on new technologies were found to be more effective in improving the quality of life of COPD patients than interventions based on face-to-face education and support materials even at 6 months, but not at 1 year. This is probably due to the fact that

educational and motivational content were not updates during the maintenance phase [49,57], highlighting the importance of these elements.

Given the great heterogeneity and diversity of the studies included in this systematic review, it may not be recommended to perform a meta-analysis. However, a random-effects model was chosen to allow the pooling of more clinically heterogeneous studies [58]. Furthermore, in order to adequately answer the question posed in this re-view, i.e., whether web-based support interventions are effective in improving the quality of life of COPD patients, and due to the great diversity of the studies published to date, it was necessary to use a wide range of studies in which these types of interventions have been used. It is therefore required to adequately justify our findings.

The findings of our meta-analysis of pooled data do not identify statistically significant differences in the quality of life outcomes. Even though the results of this me-ta-analysis suggested that there is no evidence that web-based support interventions are effective in increasing the quality of life of COPD patients, the results should be analyzed by subgroups.

The findings from this meta-analysis demonstrate that web-based supportive interventions can be effective in improving quality of life when compared with usual care, but not when compared to a podometer walking intervention or face-to-face treatment. These results are in line with the increasing evidence in the literature on the success of telehealth interventions [46–49].

Four included studies used diffused wearable systems like the pedometer included in the web-based supportive programs [38–41]. Those programs have shown similar results in quality of life to those using autonomous interventions. Those results can be due to the

theory of self-regulation [59] in which the use, web-based or autonomous, of pedometer guide the patients to his own feelings, thoughts, and behaviors to achieve specific goals.

Armstrong et al. [60] showed that when baseline physical activity levels are >4000 steps per day patients benefit more from physical activity promotion. Consequently, it should be noted that the baseline mean of steps per day of the population of the pooled studies in this subgroup was <4000 steps per day. In addition, it should be noted that the most severe patients have great potential for improving compared to less severe patients, as they are further from their maximal capacity [61,62] and the most patients included in this subgroup had mild to moderate severity on the GOLD scale. In addition, blinding patients from the web-based supportive podometer walking interventions would require to give a pedometer to the control group, this may cause the results of the control group to be altered, since the simple fact of having control of their daily steps may promote an increase in the physical activity of the patients.

Other studies have used web-based pulmonary rehabilitation programs compared to the same program developed face-to-face. The results obtained by Bourne et al. [42] show no significant differences between groups in quality of life. In the study by Jiménez-Reguera et al. [43] the results show statistically significant improvement on the quality of life of the web-based group, but no differences between groups after intervention. Both studies support the argument that results comparable between web-based and face-to-face interventions or the absence of impairment can be considered a success as seen in previous reviews [18,63], due to the opportunities for new technologies for at risk COPD patients [18,64]. In this line, web-based supportive interventions may complement or replace routine care as no significant differences were found between the face-to-face and online modalities [51].

This meta-analysis supports the promising role and the feasibility for web-based supportive interventions in COPD patients to improve quality of life when added to the usual care, reaching the currently minimum significant established difference for SGRQ results in a mean COPD sample population of -4 points [65], but not when compared to an autonomous pedometer walking intervention or face-to-face treat-ment. Our results are consistent with the increasing evidence in the literature on the efficacy of telehealth supportive interventions [18,21,47–49].

The use of web-based supportive interventions for COPD patients is not strong based on quality of life data alone, but neither is it an argument against the use of the-ses interventions. Some further advantages should be derived from the uses of tele-health interventions for this argument to be valid and the extensive literature on this topic leaves no doubt about it. Telehealth intervention groups show better results than the control group in risk of exacerbation [66], costs of health care [67], length of bed days [66], risk of hospitalizations and risks of the emergency department visit, without the need for travel [68].

Strengths and limitations

The strengths of this study are the following. First, to increase the quality of envidence we only included RCTs. Second, it was possible to pool data from 6 studies in a meta-analysis.

Thirdly, in previous studies on the effects of ehealth's intervention, web-based supportive intervention was not separately analyzed. In this study, web-based supportive intervention was first taken as a primary intervention.

The major weakness of this systematic review is due to the limited number of RCTs focused on web-based support interventions. However, the inclusion criteria en-abled us

to include articles with this type of intervention even if quality of life was not the main variable. There are no obvious reasons for the lack of research on COPD web-based supportive interventions but the issue of possible facilitators such as de-creased burden of web-based interventions [69] and the personalized nature and possible barriers such as security and technical issues should be addressed when performing these types of health interventions.

Some more limitations need to be reported. First, one subgroup in our me-ta-analysis have only one study. Second, we should note that the diversity of the pro-posed interventions makes it difficult to distinguish whether or not the web-based supportive intervention was solely responsible for the observed effects. Third, since the authors were only fluent in French, English and Spanish, they were only possible to re-view the research published or translated into these languages, but not for studies in other languages.

With regard to the methodological quality the 6 RCTs included in the me-ta-analysis [36,38–40,42,43] were classified as “poor quality”. The main reason for the low evidence of the studies presented in this review lies in methodological issues. For example, it has been shown in previous studies that selection bias in interventions based on technological tools is evident. The reason for this is that some patients are al-ready used to the use of new technologies and the Internet, leading to the automatic preference of these over other tools [70].

In addition, web-based interventions appear to be not suitable for all patients be-cause the level of follow-up and adherence to treatments is often low [71]. Other that also increase the risk of bias and should be taken into account involve the lack of patient blinding and not adequately describing the randomization method.

CONCLUSIONS

This review and meta-analysis show the promising potential of web-based supportive interventions for improving quality of life in COPD patients. Our results sup-port the idea that web-based supportive interventions can improve the quality of life in COPD patients when added to the usual care. In addition, web-based supportive interventions may complement or replace face-to-face interventions. Because of the methodological limitations and the limited number of studies on this field, the results should be treated with caution. Further randomized controlled studies are needed to evaluate the effect of web-based supportive interventions on quality of life in COPD patients, with larger populations and using appropriate placebo interventions to blind the control group, thus increasing the evidence in this field of research.

Practical implications

Our findings suggest that the most common and promising web-based supportive intervention content are the education and motivational content as well as communication with health professionals. This systematic review and meta-analysis suggests that web-based supportive interventions may complement or replace treatments in COPD patients due to the advantages of online interventions.

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and editing, A.C.M., J.R.T and M.C.V.; visualization, L.L.L., A.H.C. and J.M.N; supervision, M.C.V.; project administration, M.C.V.; funding acquisition, M.C.V. All authors have read and agreed to the published version of the manuscript.

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

Appendix A

("Chronic Obstructive Lung Disease" OR Airflow Obstruction, Chronic" OR "Chronic Airflow Obstructions" OR "Chronic Airflow Obstruction" OR "COPD" OR "Chronic Obstructive Pulmonary Disease" OR "COAD" OR "Chronic Obstructive Air-way Disease" OR "Airflow Obstructions, Chronic") AND ("eHealth" OR "ehealth" OR "e-Health" OR "e-health" OR "telemedicine" OR "tele-medicine" OR "Mobile Health" OR "Health, Mobile" OR "mHealth" OR "m-Health" OR "m-health" OR "telehealth" OR "tele-health" OR "telecare" OR "tele-care" OR "telemonitoring" OR "tele-monitoring" OR "teleconsultation" OR "tele-consultation" OR "health informatics" OR "internet" OR "mobile") AND ("Life Quality" OR "Health-Related Quality Of Life" OR "Health Related Quality Of Life" OR "HRQOL" OR "quality of life" OR "management" OR "adherence" OR "healthy lifestyle" OR "well-being").

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DISCUSIÓN

Estudio 1

En comparación con los controles sanos y los pacientes que se recuperaron con éxito de la COVID-19, los resultados de este estudio muestran que la calidad de vida relacionada con la salud es significativamente peor y que el dolor es significativamente más prevalente en los pacientes con el síndrome de COVID-19 prolongado. El dolor de estos pacientes se caracteriza por ser generalizado, de intensidad e interferencia moderadas, siendo las localizaciones más frecuentes el cuello, las piernas y la cabeza, y afectando significativamente a la calidad de vida de estos pacientes. Estos resultados ayudarán a diseñar programas adaptados a las necesidades de esta población.

Estudio 2

La identificación de las secuelas del COVID-19 será crucial para los profesionales sanitarios. Este estudio ha revelado que los pacientes con síndrome post-COVID-19 han mostrado una elevada intensidad e interferencia del dolor, sensibilización central, gravedad del insomnio, miedo al movimiento, catastrofismo, creencias de evitación del miedo, depresión, ansiedad y estrés. Estos hallazgos tienen importantes implicaciones para el desarrollo de futuras intervenciones que mejoren el manejo de estos pacientes.

Estudio 3

Esta revisión y metaanálisis muestran el prometedor potencial de las intervenciones de apoyo basadas en la web para mejorar la calidad de vida de los pacientes con EPOC. Nuestros resultados apoyan la idea de que las intervenciones de apoyo basadas en la web pueden mejorar la calidad de vida de los pacientes con EPOC cuando se agregan a la atención habitual. Además, las intervenciones de apoyo basadas en la web pueden complementar o sustituir a las intervenciones presenciales. Debido a las limitaciones

metodológicas y al número limitado de estudios en este campo, los resultados deben tratarse con cautela. Se necesitan más estudios controlados aleatorios para evaluar el efecto de las intervenciones de apoyo basadas en la web sobre la calidad de vida de los pacientes con EPOC, con poblaciones más grandes y utilizando intervenciones placebo apropiadas para cegar al grupo de control, aumentando así las pruebas en este campo de investigación.

CONCLUSIÓN

Específicas

Específica 1: los pacientes con Long-COVID presentan una mayor intensidad e interferencia del dolor, además de una peor calidad de vida en comparación con sujetos controles.

Específica 2: los pacientes con Long-COVID presentan alta intensidad e interferencia del dolor, sensibilización central, aumento de la gravedad del insomnio, miedo al movimiento, catastrofización, depresión, ansiedad y estrés.

Específica 3: las intervenciones de telerehabilitación pueden complementar o remplazar tratamientos presenciales en pacientes con EPOC, generando mejoras en su calidad de vida.

General

En conclusión, esta tesis muestra que los pacientes con enfermedades respiratorias presentan sintomatología crónica con importantes repercusiones a nivel sistémico, que limitan considerablemente la funcionalidad y calidad de vida influyendo en su pronóstico. Además, se evidencia la eficacia de la telerehabilitación para desarrollar programas terapéuticos multimodales que se ajusten a las necesidades terapéuticas de estos pacientes.

CONCLUSION

Specific

Specific 1: patients with Long-COVID present higher pain intensity and interference, as well as worse quality of life compared to control subjects.

Specific 2: the results show that patients with Long-COVID present high pain intensity and interference, central sensitization, increased severity of insomnia, fear of movement, catastrophizing, depression, anxiety and stress.

Specific 3: the results showed that telerehabilitation interventions can complement or replace face-to-face treatments in COPD patients, generating improvements in their quality of life.

General

In conclusion, this thesis shows that patients with respiratory diseases present chronic symptomatology with important repercussions at a systemic level, which considerably limit their functionality and quality of life, influencing their prognosis. In addition, the efficacy of telerehabilitation to develop multimodal therapeutic programs that fit the therapeutic needs of these patients is evidenced.

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