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Ana Lear Claveras

Repercusiones de la pandemia por COVID-19 en las enfermedades crónicas que se manejan desde Atención Primaria de Salud

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Tesis Doctoral

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REPERCUSIONES DE LA PANDEMIA POR COVID-19 EN LAS ENFERMEDADES CRÓNICAS QUE SE MANEJAN DESDE ATENCIÓN PRIMARIA DE SALUD

ANA LEAR CLAVERAS

Directoras: Rosa Magallón Botaya y Bárbara Oliván Blázquez

Tutora: Bárbara Oliván Blázquez

A mi familia y en especial, a mi abuela Abundia.

"La satisfacción radica en el esfuerzo, no en el logro. El esfuerzo total es la victoria total."

Gandhi.

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Zaragoza, 26 de febrero de 2023.

La Tesis Doctoral que se presenta en este documento, está compuesta por un compendio de trabajos previamente publicados en revistas de impacto científico.

A continuación, se enuncian las referencias completas de los artículos que conforman el cuerpo de esta Tesis.

1er manuscrito:

Lear-Claveras A, Oliván-Blázquez B, Clavería A, Couso-Viana S, Botaya R.M. Analysis of Clinical Parameters, Drug Consumption and Use of Health Resources in a Southern European Population with Diabetes That Did Not Contract COVID-19: A Longitudinal Big Data Study. Int J Environ Res Public Health. 2022;19(11): 6835. DOI: 10.3390/ijerph19116835. Factor de impacto (JCR 2021): 4,614 (Q1).

2º manuscrito:

Lear-Claveras A, Oliván-Blázquez B, Clavería A, Couso-Viana S, Puente-Comesaña J, Magallón Botaya R. Sex Differences in Clinical Parameters, Pharmacological and Health-Resource Utilization in a Population With Hypertension Without a Diagnosis of COVID-19. Int J Public Health 2022;67:1604913. DOI: 10.3389/ijph.2022.1604913. Factor de impacto (JCR 2021): 5,100 (Q1).

3er manuscrito:

Lear-Claveras A, González-Álvarez B, Couso-Viana S, Clavería A, Oliván-Blázquez B. Analysis of Clinical Parameters, Drug Consumption and Use of Health Resources in a Southern European Population with Alcohol Abuse Disorder during COVID-19. Pandemic. Int J Environ Res Public Health. 2022;19(3): 1358. DOI: 10.3390/ijerph19031358. Factor de impacto (JCR 2021): 4,614 (Q1).

4º manuscrito:

Lear-Claveras A, Clavería A, Couso-Viana S, Nabbe P, Oliván-Blázquez B. Analysis of Drug and Health Resource Use Before and After COVID-19 Lockdown in a Population Undergoing Treatment for Depression or Anxiety. Front Psychol. 2022;13:861643. DOI: 10.3389/fpsyg.2022.861643. Factor de impacto (JCR 2021): 4,232 (Q1).

5º manuscrito:

Lear-Claveras A, Aguilar-Latorre A, Oliván-Blázquez B, Couso-Viana S, Clavería-Fontán A. Evolution of Anxiety and Depression in Men during the First Six Month of the COVID-19 Pandemic and Factors Associated with Worsening of Mental Health: Retrospective Longitudinal Study. J Mens Health 2022;18(9):182. DOI: 10.31083/j.jomh1809182. Factor de impacto (JCR 2021): 0,789 (Q4).

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RESUMEN

Introducción: El envejecimiento de la población secundario al aumento de la esperanza de vida, supuso un cambio histórico en los riesgos de mortalidad por causas específicas, convirtiendo a las enfermedades no transmisibles (ENT) en la principal causa de mortalidad y morbilidad en el mundo. La atención y cuidado de los pacientes con condiciones crónicas, se realiza desde los servicios de Atención Primaria de Salud (APS), donde según la Sociedad Española de Medicina de Familia y Comunitaria (SemFYC), las ENT son el motivo de atención en ocho de cada diez consultas. A finales de 2019, la aparición de una nueva enfermedad infecciosa (COVID-19) y su declaración como pandemia mundial, colapsaron los servicios de APS (que en nuestro país atendieron al 90% de los casos de infección durante la primera ola). Este colapso provocó la interrupción de la atención habitual a los pacientes crónicos, quienes además retrasaron las consultas presenciales en sus centros de salud por temor a un posible contagio. Adicionalmente, las medidas de confinamiento domiciliario impuestas para frenar el avance del virus, podrían haber tenido repercusiones particularmente negativas entre los pacientes con enfermedades crónicas. Según algunos estudios, los pacientes crónicos experimentaron niveles de estrés más altos durante la pandemia que la población general. Del mismo modo, la interrupción de las rutinas diarias pudo conllevar la adquisición de hábitos poco saludables, los cuales podrían haber exacerbado la morbilidad de sus enfermedades crónicas, creando así un círculo vicioso. El **objetivo** de esta Tesis Doctoral fue conocer las consecuencias de la pandemia por COVID-19 en algunas enfermedades crónicas que se manejan desde APS en la Comunidad Autónoma (C. A.) de Aragón. Para ello, se analizó la existencia de empeoramiento o deterioro entre los pacientes con trastornos crónicos físicos (diabetes mellitus e hipertensión arterial: objetivos 1 y 2) y psíquicos (trastorno por abuso crónico de alcohol y ansiedad y/o depresión: objetivos 3-5) que durante el confinamiento y en los seis meses posteriores a su finalización, no presentaron infección documentada de SARS-CoV-2. Esta línea de investigación fue abordada a través de una única **metodología.** Para analizar cada uno de los objetivos, se realizaron estudios observacionales retrospectivos pre-post de grupo único con Datos del Mundo Real (RWD por sus siglas en inglés). En cada manuscrito, se incluyó a la población mayor de 16 años de Aragón con historia clínica electrónica (HCE) en los centros de Atención Primaria del Servicio Aragonés de Salud y diagnóstico de: diabetes mellitus (n = 86.615), hipertensión arterial (n = 245.979), trastorno por abuso crónico de alcohol (n = 9.184) y ansiedad y/o depresión (n = 105.554; n = 28.294), que durante el periodo de estudio no presentaron diagnóstico positivo de COVID-19 mediante prueba PCR. Para cada individuo, se recogieron **variables** clínicas, farmacológicas

(Dosis Diaria Definida [DDD], y DDD por 1.000 habitantes y día [DHD] dispensadas en farmacia) y de utilización de recursos sanitarios (visitas a APS, pruebas diagnósticas de imagen o laboratorio y visitas a atención especializada) en los seis meses previos al inicio del confinamiento (del 14/09/2019 al 15/03/2020) y, en los seis meses posteriores a su finalización (desde el 03/05/2020 al 04/11/2020). El **análisis estadístico** se realizó con IBM® SPSS® Statistics 21 y R versión 4.0.5, estableciéndose en todos los estudios un nivel de significación de 5%. Estadísticos descriptivos (frecuencias, medias y desviación estándar) fueron calculados para conocer las características sociodemográficas y las comorbilidades crónicas más frecuentes entre las muestras a estudio. Para calcular las variaciones en los parámetros clínicos y en la utilización de recursos sanitarios entre los dos periodos a estudio, se utilizaron pruebas T de Student para muestras dependientes o pareadas y, pruebas de rangos con signos de Wilcoxon cuando el número de observaciones fue menor de 100. Las variaciones en los patrones de consumo de fármacos, se evaluó a través del cálculo de las DDD o las DHD dispensadas en farmacia en los dos periodos de tiempo. Los **resultados** obtenidos sugieren que seis meses después de la finalización del confinamiento domiciliario, en Aragón gran parte de los servicios sanitarios de APS y de atención especializada, no han recuperado los niveles de prestación de atención pre pandémicos (consultas a enfermería, realización de pruebas diagnósticas, atención hospitalaria, etc.). El número de consultas a medicina de familia y a atención médica continuada, se vio en cambio incrementado entre los pacientes con diabetes mellitus y con trastornos mentales subyacentes durante los meses siguientes. Este incremento en el número de visitas podría sugerir un mayor impacto de la pandemia por COVID-19 entre los pacientes con diabetes mellitus más frágiles y entre aquellos con trastorno por abuso crónico de alcohol y con ansiedad y/o depresión. Este posible mayor impacto, no parece reflejarse sin embargo en los parámetros clínicos. Gran parte de los pacientes con condiciones crónicas físicas (diabetes mellitus e hipertensión arterial), no experimentaron cambios clínicos importantes entre mayo y noviembre de 2020. De igual manera, tampoco se evidenciaron cambios clínicamente significativos en los marcadores biológicos de los pacientes con trastorno por abuso crónico de alcohol. Respecto a la dispensación de medicamentos, las variaciones observadas en la dispensación de fármacos para el tratamiento de los dos trastornos psíquicos analizados (abuso crónico de alcohol y ansiedad y/o depresión), podrían indicar también mayores niveles de malestar psicológico entre los pacientes con problemas mentales preexistentes. Simultáneamente, la pandemia por COVID-19 podría haber tenido entre los pacientes crónicos de Aragón un gran impacto en la mortalidad con origen no COVID. En el periodo posterior al fin del confinamiento, en todos los trastornos analizados, se observó un incremento en la tasa bruta de mortalidad por otras causas. **Conclusiones:** Seis meses después de la finalización del confinamiento estricto domiciliario, no

se evidenciaron cambios clínicamente significativos en los parámetros analizados. No obstante, preocupa el impacto de la crisis sanitaria en algunos grupos más vulnerables (los pacientes crónicos de alto riesgo y los pacientes con problemas mentales subyacentes), así como la contribución de la pandemia al exceso de mortalidad por otras causas distintas a la infección.

ABSTRACT

Introduction: The aging of the population, secondary to the increase in life expectancy, led to a historic change in mortality risks from specific causes, making non-communicable diseases (NCDs) the leading cause of mortality and morbidity in the world. The attention and care of patients with chronic conditions is carried out from the Primary Health Care (PHC) services, where NCDs are the reason for care in eight out of ten consultations according to the Spanish Society of Family and Community Medicine (SemFYC). At the end of 2019, the appearance of a new infectious disease (COVID-19) and its declaration as a global pandemic, collapsed PHC services (which in our country attended 90% of the cases of infection during the first wave). This collapse caused the interruption of the usual care for chronic patients. These patients also could have delayed face-to-face consultations at their health centers for fear of possible exposure to the virus. Additionally, lockdown imposed to stop the spread of the virus could have had particularly negative repercussions among patients with chronic diseases. According to some studies, chronic patients experienced higher stress levels during the pandemic than the general population. In the same way, the interruption of daily routines could lead to the acquisition of unhealthy habits, which could have exacerbated the morbidity of their chronic diseases, creating a vicious cycle. The **objective** of this doctoral thesis was to know the consequences of the COVID-19 pandemic in some chronic diseases that are managed from PHC in the Autonomous Region of Aragon. To this end, the existence of worsening or deterioration was analyzed among patients with chronic physical disorders (diabetes mellitus and hypertension: objectives 1 and 2) or with mental disorders (chronic alcohol abuse disorder and anxiety and/or depression: objectives 3-5) that during the lockdown and in the six months after its end, they did not have a documented SARS-CoV-2 infection. This line of research was approached through a single **methodology**. To address each of the objectives, single group pre-post retrospective observational studies with real world data (RWD) were conducted. In each manuscript, the population over 16 years of age from Aragon with electronic medical record (EMR) in Primary Care centers of the Aragonese Health Service and a diagnosis of diabetes mellitus (n = 86,615), arterial hypertension (n = 245,979), chronic alcohol abuse disorder (n = 9,184) and anxiety and/or depression (n = 105,554; n = 28,294) without a positive diagnosis of COVID-19 by PCR test during the study period was included. For everyone, clinical, pharmacological (Defined Daily Dose [DDD] and DDD per 1,000 inhabitants per day [DHD] dispensed at the pharmacy) and health resources utilization **variables** (visits to PHC, imaging or laboratory diagnostic tests, and visits to specialized care) were collected in the six months prior to the start of lockdown (from 09/14/2019 to 03/15/2020) and in the six months after its end (from 05/03/2020 to 11/04/2020). In all studies **statistical analysis**

was performed with IBM® SPSS® Statistics 21 and R version 4.0.5 with a significance level of 5%. Descriptive statistics (frequencies, means, and standard deviation) were calculated to find out the most frequent sociodemographic characteristics and chronic comorbidities among the study samples. To calculate the variations in clinical parameters and in the use of health resources between the two study periods Student's T tests were used for dependent or paired samples and when the number of observations was less than 100 Wilcoxon signed rank tests were used. Variations in drug consumption patterns were evaluated by calculating the DDD or DHD dispensed in the pharmacy in the two time periods. The **results** obtained suggest that six months after the end of lockdown, a large part of the PHC health services and specialized care have not recovered the pre-pandemic levels of care provision in Aragon (consultations to nursing, performing diagnostic tests, hospital care, etc.). On the other hand, the number of visits to general practitioner and the continuing medical care increased during the following months among patients with diabetes mellitus and with underlying mental disorders. This increase in the number of visits could suggest a greater impact of the COVID-19 pandemic among the most fragile patients with diabetes mellitus and among those patients with chronic alcohol use disorder and with anxiety and/or depression. This possible greater impact does not seem to be reflected, however, in the clinical parameters. A large part of the patients with chronic physical conditions (diabetes mellitus and arterial hypertension) did not experience important clinical changes between May and November 2020. Similarly, there were no clinically significant changes in the biological markers of patients with chronic alcohol use disorder. Regarding the dispensing of drugs, the variations observed in the dispensing of drugs for the treatment of the two psychic disorders analyzed (chronic alcohol abuse and anxiety and/or depression) could also indicate higher levels of psychological discomfort among patients with pre-existing mental problems. Simultaneously, the COVID-19 pandemic could have had a great impact on mortality of non-COVID origin among chronic patients in Aragon. In the period after the end of lockdown, in all the disorders analyzed, an increase in the crude mortality rate from other causes was observed. **Conclusions:** Six months after the end of strict home lockdown, there were no clinically significant changes in the parameters analyzed. However, the impact of the health crisis on some of the most vulnerable groups is worrying (high-risk chronic patients and patients with underlying mental health problems) as well as the contribution of the pandemic to excess mortality from other causes than infection.

LISTADO DE ABREVIATURAS Y ACRÓNIMOS

APS	Atención Primaria de Salud
ATC	Anatómica Terapéutica Química
AUDIT	Alcohol Use Disorders Identification Test
AVAD	Años de Vida Ajustados por Discapacidad
BDCAP	Base de Datos Clínicos de Atención Primaria
CAP	Centro de Atención Primaria
C. A	Comunidad Autónoma
CC. AA	Comunidades Autónomas
CIAP	Clasificación Internacional de Atención Primaria
COVID – 19	Enfermedad por Coronavirus 2019
DDD	Dosis Diarias Definidas
DHD	Dosis Diarias Definidas por 1.000 Habitantes Día
DM	Diabetes Mellitus
DS	Desviación Estándar
DSS	Determinantes Sociales de la Salud
EADG	Escala de Depresión y Ansiedad de Goldberg
ECDC	Centro Europeo para la Prevención y el Control de Enfermedades
EES	Encuesta Europea de la Salud
ENT	Enfermedades No Transmisibles
EPIs	Equipos de Protección Individual
EPOC	Enfermedad Pulmonar Obstructiva Crónica
ERTE	Expediente de Regulación Temporal de Empleo
EVN	Esperanza de Vida al Nacimiento
GBD	Global Burden of Disease
GMA	Grupos de Morbilidad Ajustados
GOT	Transaminasa Glutámico-Oxalacética
GPT	Transaminasa Glutamato-Piruvato
HbA1c	Hemoglobina Glicosilada
HCE	Historia Clínica Electrónica
HDL	Lipoproteínas de Alta Densidad
HTA	Hipertensión Arterial
IC 95%	Intervalo de Confianza al 95%

IECAS	Inhibidores de la Enzima Convertidora de Angiotensina
IMC	Índice de Masa Corporal
INE	Instituto Nacional de Estadística
ISRS	Inhibidores Selectivos de la Recaptación de la Serotonina
ITS	Series de Tiempo Interrumpido
JIFE	Junta Internacional de Fiscalización de Estupefacientes
LDL	Lipoproteínas de Baja Densidad
MAC	Médico de Atención Continuada
MERS	Síndrome Respiratorio de Oriente Medio
MF	Médico de Familia
OCDE	Organización para la Cooperación y el Desarrollo Económico
OMS	Organización Mundial de la Salud
OR	Odds Ratio
PCC	Paciente Crónico Complejo
PIB	Producto Interior Bruto
POP	Plataforma de Organización de Pacientes
RIQ	Rango Intercuartílico
R_0	Número Básico de Reproducción
RWD	Real World Data
SARS	Síndrome Respiratorio Agudo Grave
SARS-CoV-2	Síndrome Respiratorio Agudo Severo Coronavirus 2
SemFYC	Sociedad Española de Medicina de Familia y Comunitaria
SIG	Sistemas de Información Geográfica
SNS	Sistema Nacional de Salud
TAC	Tomografía Axial Computerizada
TAD	Tensión Arterial Diastólica
TAS	Tensión Arterial Sistólica
UBE	Unidades de Bebida Estándar
UCC	Unidades de atención a enfermos Crónicos Complejos
UCI	Unidad de Cuidados Intensivos
WONCA	World Organization of Family Doctors
ZBS	Zona Básica de Salud

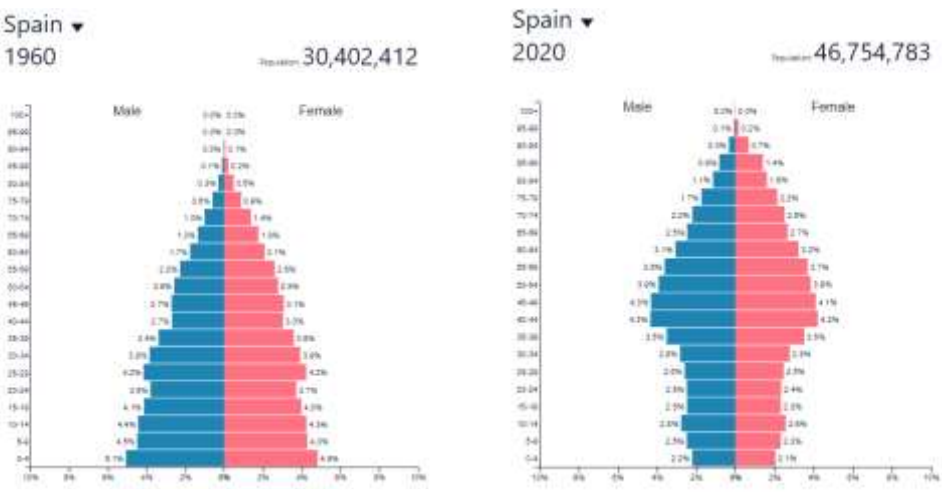
INTRODUCCIÓN

1.1 Enfermedades crónicas o enfermedades no trasmisibles (ENT):

La esperanza de vida al nacer (EVN) entendida como el número medio de años que esperaría seguir viviendo una persona de una determinada edad en caso de mantenerse el patrón de mortalidad por edad observado, ha experimentado un considerable incremento en las últimas seis décadas[1].

De 1960 a 2020, la EVN de la población mundial aumentó 20 años (de 53 a 73 años), encontrándose las cifras más altas de este indicador en regiones desarrolladas como Japón (85 años), Singapur (84 años), Suiza (83 años) o España (82 años)[2]. Los avances médicos, tecnológicos y científicos de los últimos siglos (medicamentos, vacunas, medidas de higiene y saneamiento, etc.) permitieron, especialmente en los países occidentales, aumentar la longevidad al disminuir la mortalidad (fundamentalmente la infantil y la ocasionada por epidemias y hambrunas)[1]. Este descenso inicial de la mortalidad fue posteriormente acompañado de la caída progresiva de la natalidad, dando como resultado, la denominada transición demográfica[3]; que poco a poco fue reflejando un envejecimiento progresivo de la sociedad y un crecimiento natural estancado. La Figura 1, muestra la transición demográfica a través de las pirámides de población española de 1960 y 2020.

Figura 1. Pirámides demográficas España 1960 – 2020.



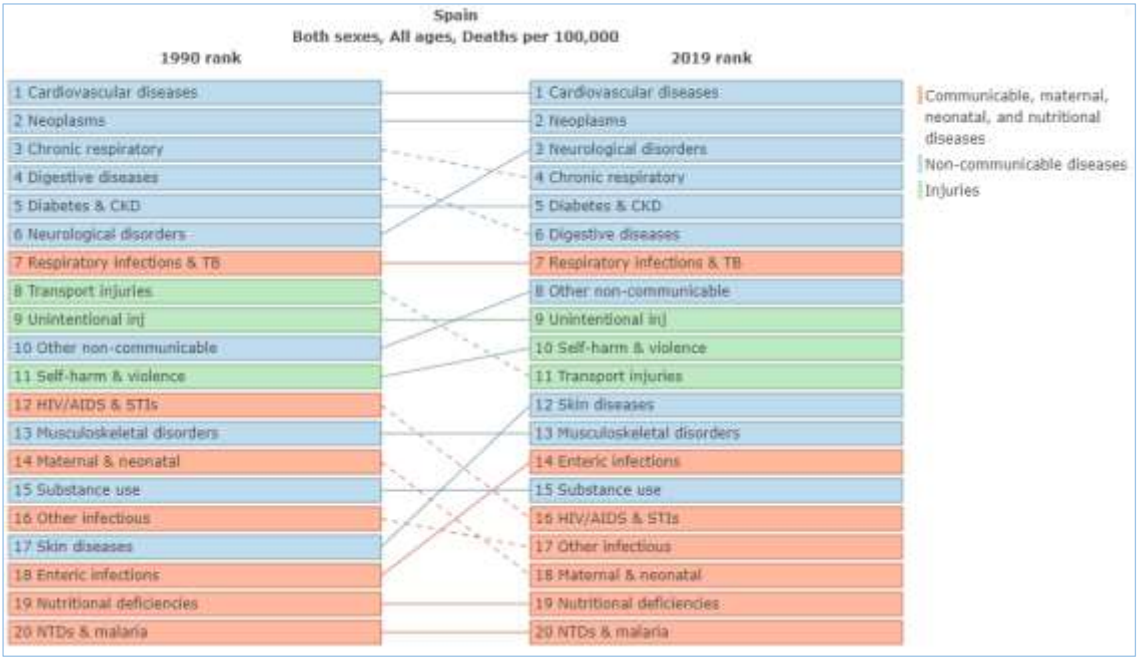
Pirámide demográfica progresiva

Pirámide demográfica regresiva

Fuente: Population Pyramids of the World from 1950 to 2100. PopulationPyramid.net. 2022.

Esta transición demográfica supuso un cambio histórico en los riesgos de mortalidad por causas específicas, transformando así los patrones de salud y enfermedad[4]. Las causas de muerte a consecuencia de enfermedades infecciosas dieron paso a un patrón de causas de muerte dominado por enfermedades crónicas (Figura 2), tal y como postuló Omran en 1971 en su teoría de la transición epidemiológica[5].

Figura 2. Causas de muerte por cada 100.000 habitantes. España 1990 – 2019.



Fuente: Institute for Health Metrics and Evaluation. Global Burden of Disease (GBD) Compare. 2020.

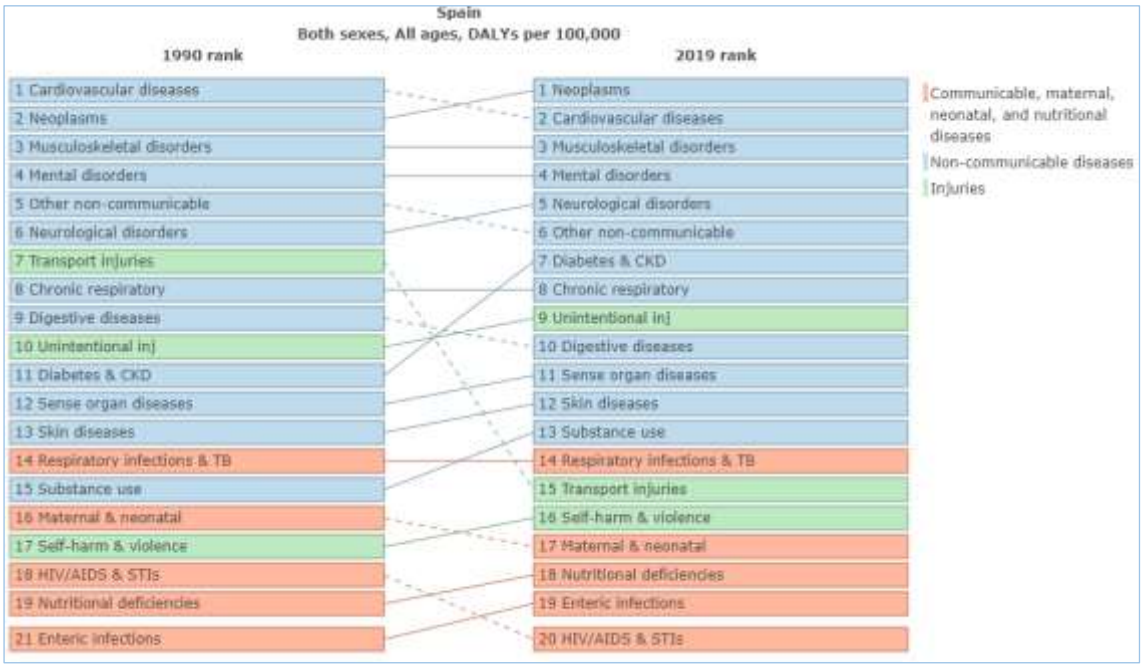
En la actualidad, las enfermedades crónicas o enfermedades no transmisibles (ENT), son la principal causa de mortalidad y discapacidad en el mundo[6]; convirtiéndose su prevención y manejo en una prioridad mundial[7]. Según la Organización Mundial de la Salud (OMS), las enfermedades crónicas son la causa del 74% de todos los fallecimientos a nivel mundial. Cada año, se cobran la vida de 41 millones de personas. Casi la mitad, 17 millones, antes de los 70 años. El 80% de las muertes por ENT en el mundo, son atribuidas a cuatro grupos de enfermedades: las enfermedades cardiovasculares (con 17,9 millones de fallecimientos al año), las neoplasias (con 9,3 millones), las enfermedades respiratorias (con 4,1 millones) y la diabetes mellitus (con 2,0 millones)[8]. En nuestro país, estos cuatro grupos de enfermedades fueron en el año 2017 responsables de casi el 60% del total de fallecimientos[9].

En cuanto a la prevalencia de ENT, según la Encuesta Europea de Salud 2020 (EES,2020)[10], en España el 59,1% de mujeres y el 49,3% de hombres de 15 años y más tiene alguna enfermedad o problema de salud crónico. Estos porcentajes muestran un incremento progresivo en los grupos etarios de mayor edad (alcanzando prevalencias superiores a 90% en

mujeres y 80% en hombres en la categoría de 75 años y más). En cuanto a las diferencias por sexo, las mujeres presentan mayores prevalencias para todos los grupos de edad. La comorbilidad con uno o más trastornos crónicos está presente en uno de cada tres adultos a nivel mundial[11]; siendo también ellas quienes presentan mayores prevalencias de comorbilidades físicas y psicológicas[12,13], a pesar de que viven de media más años que los varones[14].

De acuerdo con la Global Burden of Disease (GBD), las ENT no solo causan el mayor número de muertes, sino que también provocan el mayor número de años de vida saludable perdidos[15] (Figura 3). Entre estas patologías crónicas, los trastornos mentales como la ansiedad y la depresión contribuyen de forma importante a la carga mundial de morbilidad[16].

Figura 3. Causas de años de vida ajustados por discapacidad (AVAD) por 100.000 habitantes. España 1990 – 2019.



Fuente: Institute for Health Metrics and Evaluation. Global Burden of Disease (GBD) Compare. 2020.

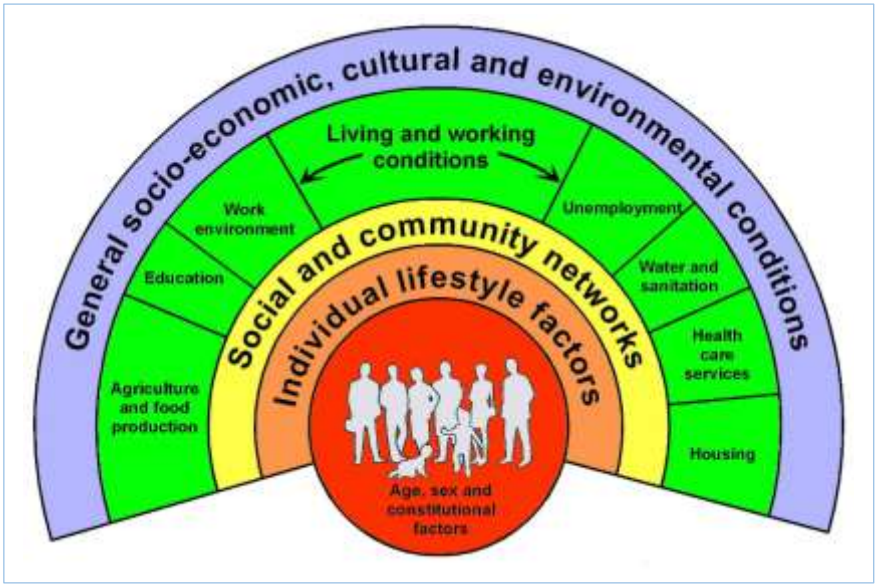
De la misma forma, las enfermedades crónicas no sólo suponen una importante carga para la salud de la población, sino también para el desarrollo económico y social. El elevado coste de su tratamiento supone una carga económica directa para los sistemas sanitarios y la sociedad (en España el 80% del gasto sanitario está dedicado a los pacientes crónicos), generando además una significativa carga económica indirecta a través de pérdidas de productividad[17-19].

No obstante, las enfermedades crónicas pueden prevenirse reduciendo algunos factores de riesgo conductuales (como la inactividad física, la alimentación poco saludable, el consumo nocivo de tabaco o alcohol, etc.), a los que podemos estar expuestos ya desde los primeros años

de vida[18]. Algunos estudios[20,21] han puesto de manifiesto la influencia de estos y otros factores en los niveles de salud de los individuos y comunidades. Ya en 1974 Marc Lalonde, Ministro de Sanidad Canadiense, enunció los cuatro grandes grupos de determinantes sociales de la salud (DSS): i) estilos y hábitos de vida, ii) biología humana, iii) medio ambiente, iv) sistema sanitario. Estos determinantes, según Lalonde, contribuían a reducir la mortalidad en un 50%, 20%, 20% y 10% respectivamente[22].

Otro de los modelos de DSS ampliamente utilizado en el mundo, es el modelo de Dahlgren y Whitehead (Figura 4). Este modelo presenta los DSS como un arcoíris donde cada capa externa determina las capas sucesivas en dirección al centro, donde se encuentra el individuo y factores no modificables como el sexo, la edad y la carga genética[23].

Figura 4. Modelo de determinantes sociales de la salud de Dahlgren y Whitehead (1991).



Fuente: Dahlgren G, Whitehead M. The Dahlgren-Whitehead model of health determinants: 30 years on and still chasing rainbows. 2021.

Las intervenciones básicas de gran impacto contra las enfermedades crónicas pueden realizarse mediante un enfoque de Atención Primaria de Salud (APS) para reforzar la promoción de estilos de vida saludables, la detección temprana y el tratamiento oportuno[8].

1.2 Atención Primaria de Salud y enfermedades crónicas:

En nuestro país, el Sistema Nacional de Salud (SNS) está basado en los principios de universalidad y libre acceso. Su financiación depende principalmente de los impuestos.

Inicialmente el SNS estaba centralizado en una única gestión estatal. Con el desarrollo de las autonomías, está gestión se fue transfiriendo progresivamente a las CC. AA., culminándose este proceso en el año 2001[24].

El organismo encargado de las prestaciones sanitarias en la Comunidad Autónoma de Aragón es el Servicio Aragonés de Salud, que está organizado territorialmente en ocho sectores de salud: Zaragoza I, II y III, Huesca, Teruel, Calatayud, Barbastro y Alcañiz. Cada uno de los sectores están subdivididos en zonas básicas de salud (ZBS), concretamente en 123[25].

La base donde se asienta el Sistema Nacional de Salud, y por lo tanto el Servicio Aragonés de Salud, está constituida por la Atención Primaria de Salud y los equipos encargados de su provisión. La APS constituye el primer punto de contacto con el sistema sanitario y es considerada un elemento fundamental[24]. Así se puso ya de manifiesto en 1978, en la Conferencia Internacional sobre Atención Primaria de Salud de Alma-Ata donde se asentaron los valores y principios de la APS (derecho a la salud, solidaridad, equidad, justicia social, etc.); y donde se definió ésta como la estrategia esencial para conseguir la meta de "Salud para todos en el año 2000"[26,27]. Este objetivo está, cuarenta años después, lejos de alcanzarse. La mitad de la población mundial carece de acceso a servicios sanitarios básicos, y las intervenciones sanitarias continúan centradas en modelos biomédicos que priorizan los servicios curativos frente a la promoción y prevención de la salud[27].

La provisión de servicios de APS parte de la premisa de que éste es el nivel básico que garantiza la continuidad de la atención durante todas las etapas de la vida del paciente. La cartera de servicios sanitarios en APS comprende, además de la asistencia sanitaria (a demanda, concertada o urgente en la consulta o en el domicilio), la indicación y prescripción de procedimientos terapéuticos, actividades de promoción de la salud, prevención de la enfermedad, educación sanitaria, y servicios específicos relativos a la mujer, la infancia, la adolescencia, los adultos mayores, los enfermos crónicos y los grupos de riesgo[28]. Además de estas actividades, existen otras como asistencia social, rehabilitación o salud bucodental. Otros servicios, como la atención a la salud mental y a los pacientes terminales se prestan en estrecha colaboración con otros niveles de asistencia especializada[24,28].

Entre los motivos de consulta a los servicios de APS, los trastornos crónicos son, según la Sociedad Española de Medicina de Familia y Comunitaria (SemFYC), responsables de ocho de cada diez consultas[29]. Dentro de estos trastornos, la hipertensión arterial (HTA) y la diabetes mellitus (DM) son por su elevada prevalencia e incidencia, algunos de los motivos más frecuentes de consulta[30]. Asimismo, su considerable aportación al aumento del riesgo de

enfermedades cardiovasculares los convierte en problemas de salud de gran trascendencia a nivel individual y también de salud pública.

Estudios previos realizados en nuestro país[31-33] estiman prevalencias de HTA de más del 40%. Datos más recientes (EES de 2020) revelan que el 19% y el 20,5% de la población española y aragonesa padecieron HTA en los últimos 12 meses[10] (Tabla 1). En cuanto a la DM, trabajos anteriores[33,34] estimaron prevalencias en España del 14% (siendo el 90% de estos casos, DM tipo 2). La EES (2020) mostró porcentajes de DM en los últimos 12 meses, en el 7% de la población de España y Aragón[10] (Tabla 2).

Tabla 1. Porcentajes HTA en los últimos 12 meses.

	España	Aragón
Hombres	19	21,4
Mujeres	19,1	19,6
Total	19	20,5

Tabla 2. Porcentajes DM en los últimos 12 meses.

	España	Aragón
Hombres	8,2	7,3
Mujeres	6,9	6
Total	7,5	6,6

Fuente: Ministerio de Sanidad, Gobierno de España. Encuesta Europea de Salud. 2020.

Los trastornos de salud mental, son otro de los principales motivos de consulta a los servicios de APS. Algunos estudios afirman que el 25-30% de las visitas al centro de atención primaria (CAP) las realizan pacientes que presentan alguna condición psiquiátrica (mayoritariamente ansiedad y/o depresión)[35]; y que solamente el 5-10% de estos pacientes son derivados a servicios especializados de salud mental[36].

Los estilos de vida de los países occidentales (estrés, competitividad, inconformidad, etc.), podrían estar contribuyendo a las elevadas cifras de estos trastornos[37,38]. En el mundo, 301 millones de personas sufrieron ansiedad en 2019 y, 280 millones depresión[39]. En España, según el informe sobre salud mental de la Base de Datos Clínicos de Atención Primaria (BDCAP) del SNS, en 2021 el trastorno mental más frecuente fue el de ansiedad, que afectó al 6,7% de la población (8,8% de mujeres y 4,5% de hombres). La depresión, presentó menores porcentajes (4,1% de la población; 5,9% de mujeres y 2,3% de hombres)[40]. Los datos de la EES de 2020 muestran cifras algo más reducidas en Aragón, siendo la prevalencia de ansiedad en los últimos 12 meses de 4,7% (6,7% en mujeres y 2,7% en hombres) y de 3,6% para la depresión (4,9% en mujeres y 2,2% en hombres)[10] (Tabla 3).

Tabla 3. Porcentajes de ansiedad y depresión en los últimos 12 meses.

	Ansiedad		Depresión	
	España	Aragón	España	Aragón
Hombres	3,5	2,7	3,2	2,2
Mujeres	8,1	6,7	7,2	4,9
Total	5,8	4,7	5,3	3,6

Fuente: Ministerio de Sanidad, Gobierno de España. Encuesta Europea de Salud. 2020.

Todas estas patologías, presentan mayores porcentajes en las categorías de mayor edad (de 65 y más años)[10]. Sin embargo, aunque la longevidad es un factor esencial en el aumento de la cronicidad, no debemos asociar exclusivamente enfermedad crónica con persona mayor. Algunas estimaciones, confirman que el 60% de los años de vida ajustados por discapacidad (AVAD) atribuidos a las enfermedades crónicas, fueron en personas de menos de 60 años[41]. Según la EES (2020), en la población menor de 24 años, el 13,6% ha sido diagnosticado de alergia crónica, el 4,5% de asma, el 2,6% de ansiedad o el 0,4% de diabetes mellitus[10].

El incremento de las enfermedades crónicas, está convirtiendo su abordaje en un importante reto para los sistemas sanitarios; donde la APS, como se ha comentado, desempeña un rol decisivo en el adecuado manejo de las mismas[42]. El desafió que supone la lucha contra estos trastornos fue trastocado por la aparición de una enfermedad infecciosa emergente a finales del año 2019: la enfermedad por Coronavirus (COVID-19).

1.3 Enfermedad por Coronavirus 2019 (COVID-19):

La COVID-19 es una enfermedad infecciosa causada por un nuevo coronavirus llamado Síndrome Respiratorio Agudo Severo Coronavirus 2 (SARS-Cov-2).

Los coronavirus son virus ARN pertenecientes a la familia *Coronaviridae* que fueron descubiertos por primera vez en los años 60[43]. Reciben este nombre ya que, cuando se observan al microscópico electrónico, presentan una forma esférica de la que sobresalen unas espículas que le dan la apariencia de una corona solar[44]. Hasta la fecha, se conocen siete tipos de coronavirus; cuatro de ellos (229E, NL63, OC43 y HKU1) son muy habituales entre los humanos y algunos están presentes en el resfriado común[45]. Los coronavirus pueden también infectar a un huésped animal y así, evolucionar y convertirse en un nuevo coronavirus humano. Ejemplos recientes de estas zoonosis son el SARS-CoV y el MERS-CoV que dieron lugar en 2002 y 2012 a

las epidemias de Síndrome Respiratorio Agudo Grave (SARS) y Síndrome Respiratorio de Oriente Medio (MERS)[45,46].

La tercera epidemia zoonótica del siglo XXI causada por un coronavirus, se detectó el 31 de diciembre de 2019 en la ciudad China de Huwan. Semanas más tarde del inicio del brote de neumonía de etiología desconocida, se aisló un nuevo coronavirus de los pacientes enfermos, el cual fue designado por la OMS como SARS-CoV-2[46]. Un mes después de la detección del brote, el virus fue declarado una emergencia de salud pública de importancia internacional, al presentarse casos confirmados de la enfermedad en dieciocho países[47]. El SARS-CoV-2, que se transmite de una persona a otra principalmente mediante la inhalación de las gotas y aerosoles respiratorios emitidos por un enfermo[48], tenía al inicio de la pandemia una infectividad o número básico de reproducción (R_0) de 2,2[49]. Con un $R_0 > 1$, la infección se propagó rápidamente entre la población, llegando al continente Europeo a finales del mes de febrero de 2020 cuando nueve países, entre ellos España, habían notificado casos[50]. Los alarmantes niveles de propagación de la enfermedad y la gravedad de la misma, llevaron a la OMS a declarar la COVID-19 como pandemia mundial el 11 de marzo[47]. Para frenar el ritmo de contagios, los gobiernos de numerosos países promulgaron medidas excepcionales. En España, tres días más tarde de la designación de la COVID-19 como pandemia mundial, se declaró el estado de alarma en todo el territorio nacional (R.D 463/2020)[51]. Las estrategias para reducir la transmisión del virus incluyeron el confinamiento domiciliario, el distanciamiento social, el cierre de negocios no esenciales y la recomendación de comportamientos como el lavado de manos[51,52]. A pesar de la puesta en marcha de estas políticas, el incesante goteo de casos positivos y fallecimientos, convirtieron a nuestro país en una de las regiones más afectadas por el nuevo virus durante la primera ola (con casi 250.000 contagios y más de 28.000 fallecimientos a 21 de junio de 2020)[53,54]. Más de dos años después del fin del confinamiento y de seis oleadas de contagios, en nuestro país las cifras a 30 de diciembre de 2022 superan los 13 millones de casos confirmados y los 117.000 fallecimientos[55].

En cuanto a los contagios, la mayoría de las personas infectadas (80%) experimentaron síntomas leves-moderados[56] (dolor de garganta, tos, mialgias, fiebre, dolor de cabeza, náuseas o vómitos, diarrea, anosmia o ageusia)[43,56]. Entre los casos graves de la infección, la neumonía con fiebre, tos, disnea, taquipnea, desaturación de oxígeno e infiltrados pulmonares fueron las manifestaciones más comunes según el Centro Europeo para la Prevención y el Control de Enfermedades (ECDC)[56]. Los casos más graves de la infección, así como las complicaciones respiratorias letales fueron, según numerosos estudios[57-61], más frecuentes en pacientes hombres, más longevos y con comorbilidades subyacentes (obesidad, diabetes mellitus,

hipertensión arterial, enfermedad pulmonar obstructiva crónica [EPOC], enfermedad renal crónica, etc.). Dos de estas características (longevidad y comorbilidad) convirtieron a las personas mayores y especialmente a aquellas institucionalizadas, en un grupo especialmente vulnerable a la COVID-19[62]. Durante la pandemia, y especialmente durante la primera ola, el impacto del nuevo virus fue notable en los centros residenciales de nuestro país, los cuales experimentaron altas tasas de contagios y fallecimientos[63].

1.4 Impacto directo e indirecto de la COVID-19:

La pandemia causada por el SARS-CoV-2 ha impactado directamente en la mortalidad y en la morbilidad, actuando las patologías crónicas como un importante factor de riesgo para ambos indicadores de salud. Varios estudios y revisiones han expuesto una mayor probabilidad de desarrollar formas graves de la infección[64,65] e incluso de morir por COVID-19[66] entre aquellos pacientes con enfermedades crónicas preexistentes. Especialmente entre ellos, el contagio también se ha asociado con importantes secuelas no solo a nivel respiratorio[67], también a nivel neurológico[68] (encefalopatía, accidentes cerebrovasculares isquémicos o cefaleas) y cardiovascular[69] (síndrome coronario agudo, miocarditis o insuficiencia cardíaca). De igual manera, entre quienes superaron la infección, incluso sin condiciones médicas crónicas subyacentes o con síntomas leves, la enfermedad ha podido no remitir, persistiendo algunas características clínicas (tos, fatiga, disnea, mialgias, etc.) más de tres meses después de la primoinfección[70,71]. Esta persistencia de los síntomas ha sido denominada como “Long COVID” o “COVID persistente” y contribuye, junto con las secuelas graves, al aumento de la carga de las enfermedades no transmisibles al crear un nuevo grupo de pacientes crónicos[71].

Por otra parte, la pandemia ha tenido igualmente un impacto directo en las afecciones mentales. La aparición del nuevo virus y su rápida progresión expusieron a la población mundial, sobre todo al inicio de la pandemia, a situaciones angustiosas[72]. El incremento progresivo de los casos positivos y del número de fallecimientos, la imposibilidad de acompañar a familiares enfermos de COVID-19 en sus últimos momentos de vida y el desconocimiento de tratamientos efectivos o vacunas frente al SARS-CoV-2, generó sentimientos negativos en parte de la población, repercutiendo éstos en su bienestar psicológico[72,73]. Algunos estudios[74-76], han mostrado un incremento de la incidencia de síntomas de ansiedad, depresión y estrés postraumático entre la población general española durante los primeros meses de pandemia; siendo las mujeres quienes declararon mayores niveles en todos ellos. Entre quienes pasaron la infección, las secuelas psicológicas también están presentes. Según un estudio realizado por

Taquet M et al[77], en uno de cada cinco pacientes el diagnóstico de COVID-19 se asoció con un diagnóstico psiquiátrico (trastorno de ansiedad e insomnio principalmente) entre los catorce y los noventa días posteriores. A su vez, los casos graves hospitalizados parecen presentar un mayor riesgo de desarrollar trastorno por estrés postraumático[78]. El impacto directo de la pandemia sobre la salud mental de los profesionales sanitarios de primera línea ha sido también objeto de estudio de números trabajos[79,80]. El enfrentamiento al nuevo virus con Equipos de Protección Individual (EPIs) insuficientes, el temor al contagio y el desbordamiento del sistema sanitario ante la creciente demanda asistencial, expusieron a estos trabajadores a largas jornadas de duro trabajo, las cuales parecen haber contribuido a la aparición de estrés, ansiedad y agotamiento físico y emocional (síndrome de Burnout) entre este colectivo.

Sin embargo, el impacto de la COVID-19 va mucho más allá del propio virus, ya que las medidas impuestas para frenar su propagación han tenido también repercusiones indirectas en la población general y, en la población con patologías crónicas en particular[81].

El confinamiento domiciliario y la interrupción de la actividad económica no esencial durante varias semanas, modificaron los hábitos familiares y las rutinas laborales y de ocio. Esta extraordinaria situación pudo afectar al bienestar de la población y, derivar en problemas emocionales y físicos[82].

El aislamiento en el domicilio y el distanciamiento social motivados por la COVID-19, han sido asociados con la presencia de estrés y síntomas de ansiedad y depresión[82-84]. Para las personas con trastornos crónicos y mentales preexistentes, este efecto negativo parece haber sido todavía mayor según algunos estudios[57,85,86]. Del mismo modo, la interrupción de las rutinas diarias, la soledad derivada del aislamiento y la incertidumbre ante el futuro, pudieron exacerbar la morbilidad de sus enfermedades crónicas, creando así un círculo vicioso[87]. Trabajos previos realizados en población general, ponen de manifiesto cambios en los estilos de vida y, algunos de ellos, la adquisición de hábitos poco saludables durante los meses del confinamiento domiciliario estricto (inactividad física[88-90], dietas insanas[88,89], ingesta de tabaco y alcohol[90,91] o deterioro de la calidad y duración del sueño[90,92]). Aunque son menos, los estudios llevados a cabo en población con patologías crónicas[93-95] también arrojan resultados en esta misma línea.

En referencia a la capacidad de respuesta y adaptación de los sistemas sanitarios, el aumento de la demanda asistencial durante la pandemia y especialmente durante la primera ola de COVID-19, sometió a los sistemas de salud de todo el mundo a una gran presión[96]. Este hecho obligó a interrumpir servicios de atención esenciales (inmunización, planificación familiar y anticoncepción, atención prenatal, etc.), tal y como muestran los resultados de la encuesta

realizada por la OMS[97] entre mayo y julio de 2020, donde el 90% de los países encuestados (n = 105) informó de la paralización de estos servicios en mayor o menor medida. La rápida propagación del virus impacto también en la capacidad de abordar y responder a las enfermedades crónicas. El 61% de los países encuestados declaró interrupciones en el tratamiento de los trastornos mentales y el 69% en el diagnóstico y tratamiento de las patologías crónicas.

Como se mencionó anteriormente, la atención y cuidado de los pacientes con problemas crónicos son competencias de los profesionales sanitarios que conforman los equipos de APS. Especialmente al inicio de la pandemia, los equipos de APS se vieron obligados a adoptar cambios bruscos en su organización[98], afectando estos a la calidad y continuidad de la atención de los pacientes con patologías crónicas[99]. Sin tener una orientación clara y sin EPIs adecuados, las funciones de estos equipos pasaron a centrarse en la detección de casos positivos de la infección, el seguimiento activo de los mismos y el rastreo de los contactos estrechos. Según la SemFYC, hasta el 90% de los casos de infección por COVID-19 durante la primera ola en España, fueron atendidos y resueltos en APS[98]. Esto derivó en una falta de atención y control a los pacientes crónicos. En el mejor de los casos, la atención se realizó a través de consultas remotas[87], a pesar de la importancia que tiene en este tipo de pacientes realizar un seguimiento personal estrecho para reducir el riesgo de resultados de salud adversos[87,95]. Entre los trastornos más castigados por la interrupción de la atención, algunos estudios[99-101] señalan a la diabetes mellitus, la EPOC, la hipertensión arterial, las enfermedades cardíacas, el asma, el cáncer y la depresión como las patologías más afectadas.

La reorganización de los servicios de APS y las restricciones gubernamentales a visitas médicas electivas no urgentes, interrumpieron innegablemente la atención y el seguimiento a estos pacientes[87]; además, según algunos estudios[87,97,102], se postergaban o evitaban las consultas presenciales en los CAP por temor a una posible exposición al SARS-CoV-2. Este retraso y disminución en el acceso a la atención, pudo tener un impacto negativo en el manejo y pronóstico de los problemas crónicos a medio y largo plazo, anticipando complicaciones y reagudizaciones[102,103]. El temor al contagio cambió la percepción de lo considerado como urgencia médica, reduciéndose también la demanda de atención especializada entre estos pacientes[87]. Varios estudios[104-108] han reportado un descenso en el número de hospitalizaciones y visitas al servicio de urgencias por patologías no relacionadas con COVID-19, pero también un exceso de mortalidad por estas mismas causas durante los primeros meses de la pandemia.

Por último, la emergencia sanitaria y las medidas adoptadas por los gobiernos para proteger la salud de la población, han tenido también un efecto perjudicial en la economía y en la sociedad en general[109]. Según el Banco Mundial, estos efectos son particularmente negativos en los países más afectados por la pandemia, entre los cuales se encuentra España[110]. Nuestro país, ya fue uno de los más castigado por la crisis económica de 2008, y experimentó entonces las nefastas consecuencias de la gran recesión en la salud mental de la población (trastornos del estado de ánimo, ansiedad, trastornos por abuso de alcohol)[111]. Aunque han tenido un origen distinto, las consecuencias de ambas recesiones podrían asemejarse. Según la Organización para la Cooperación y el Desarrollo Económico (OCDE), la crisis de salud pública ha desembocado en una crisis económica que tiene consecuencias sobre el bienestar individual y social en la actualidad y también en el futuro[112].

Por todo ello, las consecuencias directas e indirectas de la pandemia por COVID-19 ponen de manifiesto el gran desafío que esta crisis sanitaria supone para el manejo y control de las enfermedades crónicas, poniendo a prueba la capacidad de respuesta y adaptación de los gobiernos y los sistemas sanitarios[113].

1.5 El concepto de sindemia:

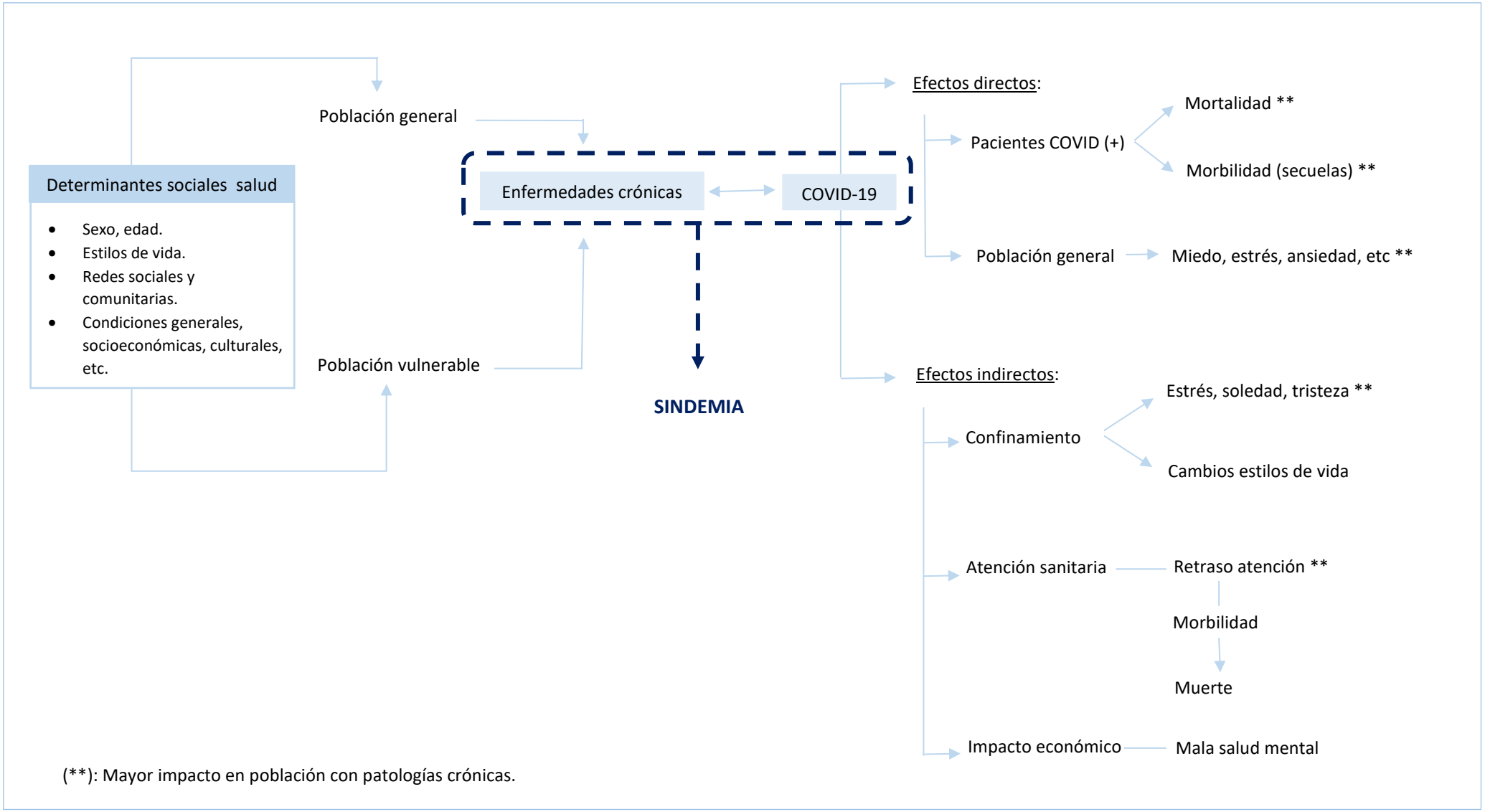
La pandemia por COVID-19 ha afectado directa e indirectamente a poblaciones y comunidades de todo el mundo. El desarrollo y progreso de la misma, hizo evidente su interacción con otras enfermedades no transmisibles que ya representaban, antes del inicio de la crisis sanitaria, una parte importante de la carga de morbilidad y mortalidad[6,114]. Como ya ha sido comentado, las enfermedades crónicas suponen un factor de mal pronóstico e incrementan el riesgo de mortalidad derivado de la infección y, viceversa, la COVID-19 y las medidas para frenar su propagación han impactado en la atención y la salud de las personas con patologías crónicas preexistentes[114].

Ambos procesos (el virus emergente y las enfermedades crónicas), se presentan hoy en día como una sindemia[114-116] (Figura 5). Este término epidemiológico acuñado por el antropólogo Merill Singer, es definido en su nivel más simple como la presencia de dos o más estados de enfermedad que interactúan adversamente entre sí, afectando negativamente el curso mutuo de la trayectoria de cada enfermedad[114]. El concepto no se limita al enfoque de la comorbilidad como simple sumatorio de enfermedades[116,117]. Va más allá, ya que amplía la mirada a los procesos biosociales en los que se dan estas enfermedades, además de entender los contextos, las condiciones de vida y las desigualdades como los posibilitadores de estas interacciones entre

distintas patologías[117]. Históricamente, las pandemias se han experimentado de manera desigual. Por ello, la COVID-19 no puede definirse como una enfermedad socialmente neutra, ni tampoco como un sindemia global, ya que la pandemia ha tenido expresiones diferentes en distintos contextos[115,117]. La prevalencia y la gravedad de la COVID-19 se han magnificado debido a la epidemia preexistente de enfermedades crónicas, que en sí mismas tienen un patrón social y están asociadas con los determinantes sociales de la salud. El gradiente social de las enfermedades crónicas surge como resultado de las desigualdades en la exposición a los determinantes sociales de la salud (DSS): las condiciones en las que las personas viven, trabajan, crecen y envejecen, incluidas las condiciones laborales, el desempleo, el acceso a bienes y servicios esenciales, la vivienda y el acceso a la salud[118].

La consecuencia más importante de ver la COVID-19 como una sindemia es pues subrayar sus orígenes sociales. Si las causas de las desigualdades en salud son sociales, las soluciones deben ser sociales e integrar los DSS en la forma de entender los procesos de salud y enfermedad. Abordar la COVID-19 como una sindemia implica abordar las enfermedades crónicas como requisito previo, pero también abordar la educación, el empleo, la vivienda, la alimentación y el medio ambiente[114].

Figura 5. Marco conceptual: Efectos directos e indirectos de la sindemia por COVID-19 en la salud de la población.



Fuente: Elaboración propia a partir de World Health Organization. Strengthening monitoring of population health to signal and address the wider effects of the COVID-19 pandemic. 2020.

JUSTIFICACIÓN Y OBJETIVOS

La línea de investigación de esta Tesis Doctoral se ha centrado en el estudio del impacto de la pandemia por COVID-19 en los pacientes con enfermedades crónicas que, durante el confinamiento y en los seis meses posteriores a su finalización, no presentaron una infección por SARS-CoV-2 documentada (en su historia clínica electrónica [HCE] o en el aplicativo informático de Atención Primaria: OMI AP).

Dada la importancia y necesidad de atención continuada a estos pacientes para lograr un buen control de su patología y prevenir la aparición de complicaciones, resulta fundamental conocer las repercusiones clínicas que han tenido las interrupciones en su atención a consecuencia del confinamiento estricto domiciliario y del colapso de los servicios de APS.

De igual manera, la enorme carga económica que supone para los sistemas sanitarios el control de estos trastornos, hace necesario conocer cómo ha variado la utilización de los servicios sanitarios (tanto de APS como de atención especializada), y el consumo de fármacos por parte de estos pacientes tras el fin del confinamiento.

El estudio de la sinergia de dos crisis sanitarias globales (la COVID-19 y las enfermedades crónicas), tiene mucho interés en el ámbito de la Salud Pública[117,119]. Generar evidencias en este campo es muy necesario, ya que la pandemia ha puesto a prueba el sistema sanitario español, poniendo de manifiesto necesidades de mejora[97,119]. Este conocimiento ayudará a identificar formas de aumentar la resiliencia del sistema de salud, las cuales permitirán no solo mitigar o evitar el impacto de futuras pandemias, sino también, planificar y gestionar adecuadamente los recursos para proporcionar a los pacientes crónicos servicios de salud de calidad y equitativos.

En base a ello, se enunciaron los siguientes objetivos:

<u>Objetivo general:</u>

- Conocer las consecuencias de la pandemia por COVID-19 en algunas enfermedades crónicas que se manejan desde APS en la C. A. de Aragón, en pacientes sin infección por el SARS-CoV-2 documentada durante el confinamiento y en los seis meses posteriores a su finalización.

Objetivos específicos:

- Analizar si existe empeoramiento o deterioro en los seis meses posteriores a la finalización del confinamiento, entre los pacientes con trastornos crónicos físicos **(diabetes mellitus e hipertensión arterial)** y psíquicos **(trastorno por abuso crónico de alcohol y ansiedad y/o depresión)**, considerando variables clínicas, farmacológicas y de utilización de recursos sanitarios.

    - **Diabetes mellitus:**
        - ✓ Objetivo 1: Identificar variaciones en parámetros clínicos, de dispensación de medicamentos y de utilización de recursos sanitarios entre los pacientes con diabetes mellitus que no presentaron diagnóstico positivo de COVID-19 durante el confinamiento y en los seis meses posteriores (manuscrito 1).
    - **Hipertensión arterial:**
        - ✓ Objetivo 2: Conocer las diferencias (por sexo) en los parámetros clínicos, de dispensación de medicamentos y de utilización de recursos sanitarios de los pacientes con hipertensión arterial sin infección por SARS-CoV-2 documentada, entre los seis meses previos al inicio del confinamiento y los seis meses posteriores a su finalización y, explorar la proporción de hombres y mujeres que han mantenido, empeorado o mejorado sus parámetros clínicos en los seis meses siguientes (manuscrito 2).
    - **Trastorno por abuso crónico de alcohol:**
        - ✓ Objetivo 3: Determinar, seis meses después del fin del confinamiento, cambios en parámetros clínicos, de dispensación de medicamentos y de utilización de recursos sanitarios entre los pacientes con trastorno por abuso crónico de alcohol que no presentaron diagnóstico positivo de COVID-19 y, evaluar las variaciones en los parámetros clínicos entre los pacientes no diagnosticados de COVID-19 y aquellos con diagnostico positivo de la infección (manuscrito 3).
    - **Ansiedad y/o depresión:**
        - ✓ Objetivos 4: Explorar los cambios en los patrones de consumo de fármacos y en la utilización de recursos sanitarios, entre los pacientes

en tratamiento activo de ansiedad y/o depresión sin infección por SARS-CoV-2 documentada (manuscrito 4).

- ✓ Objetivo 5: Determinar los cambios en los patrones de consumo de fármacos y en la utilización de recursos sanitarios, entre los pacientes varones en tratamiento activo de ansiedad y/o depresión que no presentaron diagnóstico positivo de COVID-19 y, conocer los factores asociados al posible deterioro de estos trastornos mentales en el género masculino (manuscrito 5).

Las variaciones en los parámetros clínicos no pudieron ser examinadas en los objetivos 4 y 5, ya que no fue posible el acceso a los resultados de escalas validadas utilizadas en APS: Escala de Depresión y Ansiedad de Goldberg (EADG), Escala de Depresión Geriátrica de Yesavage, Escala de Ansiedad de Hamilton o Inventario de Ansiedad de Beck. Finalmente, el último objetivo se centró en el impacto del confinamiento específicamente en los hombres con ansiedad y/o depresión, ya que son menos los estudios sobre estos trastornos entre los varones, al presentar ellos menos riesgo de desarrollarlos que las mujeres[120,121].

METODOLOGÍA

3.1 Diseño y población de estudio:

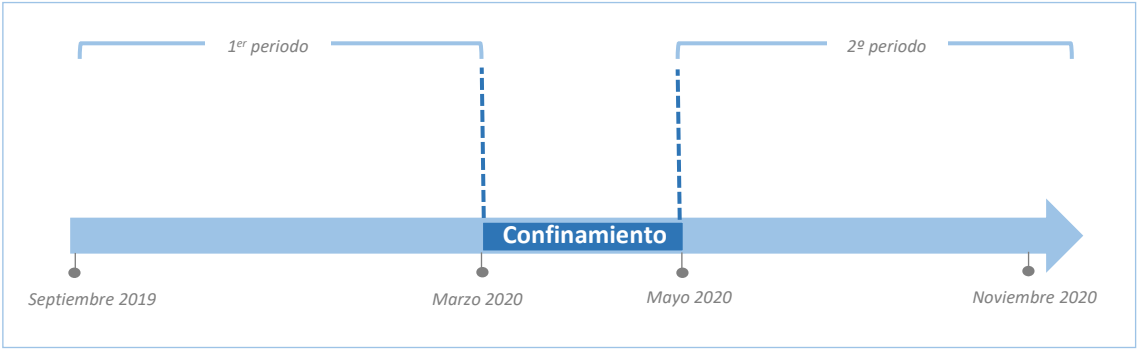
La región objeto de estudio tiene una superficie de 47.720,3 km^2 y una densidad de población de 28 habitantes/km^2. Con más de 1.319.000 habitantes (a fecha de 01/01/2019), Aragón tiene una estructura de población envejecida (al representar el grupo etario de 85 y más años el 4,29% de la población total, frente al 3,21% a nivel nacional). Este envejecimiento está más concentrado en áreas rurales, presentando las capitales de provincia estructuras de población más jóvenes. Zaragoza, capital de la región, concentra a la mitad de la población, existiendo solo trece municipios que superan los 10.000 habitantes. Los núcleos rurales con menos de 2.000 habitantes albergan al 16% de la población a pesar de representar el 92,3% de los municipios[122].

La investigación global que conforma esta Tesis Doctoral presenta el mismo diseño. Para cada uno de los objetivos se realizó un estudio observacional retrospectivo pre-post de grupo único, de la población mayor de 16 años de Aragón con HCE en los centros de Atención Primaria del Servicio Aragonés de Salud (n = 1.122.000 personas ≥ 16 años).

En el análisis, se incluyó la totalidad de personas mayores de 16 años con HCE en los CAP del Servicio Aragonés de Salud y diagnóstico de: diabetes mellitus (n = 86.615), hipertensión arterial (n = 245.979), trastorno por abuso crónico de alcohol (n = 9.184), ansiedad y/o depresión (n = 105.554; n = 28.294), que durante el periodo de estudio no presentaron diagnóstico positivo documentado de COVID-19 detectado mediante prueba PCR.

A partir de la HCE, se recogió para cada individuo información en los seis meses previos al inicio del confinamiento (del 14/09/2019 al 15/03/2020) y en los seis meses posteriores a su finalización (desde el 03/05/2020 al 04/11/2020) (Figura 6). El 15 de marzo de 2020, el gobierno español, declaró el estado de emergencia nacional, limitando la movilidad y obligando a la población a quedarse en casa hasta el 3 de mayo. Los registros recogidos durante este periodo de confinamiento estricto no fueron considerados por la escasez de los mismos.

Figura 6. Diseño del estudio.



Fuente: Elaboración propia.

3.2 Variables:

- ***Variables sociodemográficas:*** sexo, edad, tipo de prestación farmacéutica[123] (<18.000€, entre 18.000 y 100.000€, >100.000€, exentos de pago, mutualista y no asegurados) y zona básica de salud (definida como: rural [con menos de 10.000 habitantes] o urbana [con más de 10.000 habitantes]). También se consideró el número de decesos en los dos periodos de medición para las diferentes poblaciones a estudio.

- ***Variables relacionadas con la COVID-19:*** diagnóstico de COVID-19 documentado (si/no).

- ***Patologías y comorbilidades crónicas:*** para cada uno de los objetivos se abordó una patología. Según la Clasificación Internacional de Atención Primaria (CIAP-2) desarrollada por la World Organization of Family Doctors (WONCA)[124], se incluyeron los siguientes códigos.
    - Diabetes mellitus (códigos T89 y T90).
    - Hipertensión arterial (códigos K86 y K87).
    - Trastorno por abuso crónico de alcohol (código P19).
    - Ansiedad y/o depresión (códigos P82, P85 y P86).

  En cuanto a las comorbilidades crónicas, se incluyeron los códigos de la CIAP-2 de aquellas patologías con prevalencias superiores al 5% según los resultados del estudio de Calderón-Larrañaga et al[125].

Tabla 4. Comorbilidades crónicas y códigos CIAP-2.

	Códigos CIAP-2
Comorbilidades físicas	
Arritmia	K78, K79, K80, A84
Insuficiencia cardíaca	K77
Cardiopatía isquémica	K74, K75, K76
Dislipemia	T93
Sobrepeso	T83
Obesidad	T82
Enfermedad de las venas y arterias	K92 – K99
Enfermedad cerebrovascular	K89, K90, K91
Bronquitis crónica	R79
EPOC	R95
Asma	R96
Enfermedad renal crónica	U99
Hipo e hipertiroidismo	T81, T85, T86, T99
Anemia	B78, B80, B81, B82
Neoplasia	A79, B72, D74 – D78, F74, H75, K72, L71, L97, N74 – N76, R84 – R86, R92, S77 – S80, T71 – T73, U75 – U79, X75 – X81, Y77 - Y79.
Hipoacusia	H86
Cataratas	F92
Glaucoma	F93
Artrosis	L89, L90, L91
Osteoporosis	L95
Dorsalgia, lumbalgia	L84, L85, L86
Comorbilidades psicológicas	
Tabaquismo	P22, P27
Insomnio	P06
Intento autolítico	P98
Demencia	P70, P78

Fuente: Elaboración propia a partir de Gervás J. Clasificación Internacional de la Atención Primaria. Comité Internacional de Clasificación de la Wonca©.

Para la consecución del objetivo 5 se incluyó la variable "número de comorbilidades", la cual fue categorizada como: i) una comorbilidad y ii) dos o más comorbilidades.

- ***Variables clínicas:*** para cada patología abordada fueron seleccionados diferentes parámetros clínicos.
    - Diabetes mellitus:
        - ✓ Nivel de glucosa en sangre (mg/dL), hemoglobina glicosilada (HbA1c) (%), creatinina en sangre (mg/dL), filtrado glomerular (ml/min), tensión arterial sistólica (TAS) y diastólica (TAD) (mmHg), colesterol total

(mg/dL), lipoproteínas de baja densidad (LDL) (mg/dL), lipoproteínas de alta densidad (HDL) (mg/dL), peso (kg) e índice de masa corporal (IMC).

- Hipertensión arterial:
  - ✓ TAS y TAD, creatinina en sangre, filtrado glomerular, colesterol total, LDL, HDL, triglicéridos (mg/dL), circunferencia de la cintura (centímetros), peso e IMC.
- Trastorno por abuso crónico de alcohol:
  - ✓ Transaminasa glutámico-oxalacética (GOT) y transaminasa glutamato-piruvato (GPT) (UI/L), creatinina en sangre, filtrado glomerular, TAS y TAD, colesterol total, LDL, HDL, triglicéridos e IMC.
- Ansiedad y/o depresión: no fue posible acceder a los resultados de las escalas validadas utilizadas en APS, por lo que para ambas patologías, no se consideró ninguna variable clínica.

- ***Variables farmacológicas:*** el consumo de fármacos se midió a través del número de Dosis Diarias Definidas (DDD) y del número de DDD por 1.000 Habitantes Día (DHD) dispensadas en farmacia (Anexo 1). Se consideraron las DDD y DHD dispensadas en farmacia y no las prescritas ya que las unidades dispensadas proporcionan una información más fiable sobre el consumo.

  En base a las Dosis Diarias Definidas estipuladas por la OMS[126] (DDD_{OMS}), el cálculo de las DDD y las DHD prescritas en cada periodo se realizó según las siguientes fórmula[127]:

$$\text{DDD} = \frac{\text{nº envases} * \text{nº ff env} * \text{contenido ff}}{\text{DDD OMS}}$$

$$\text{DHD} = \frac{(\text{nº envases} * \text{nº ff env} * \text{contenido ff}) * 1.000 \text{ habitantes}}{\text{DDD OMS} * \text{nº habitantes de la población a estudio} * 182{,}5 \text{ días}}$$

nº envases: número de envases dispensados.
nº ff env: número de formas farmacéuticas por envase.
Contenido ff: contenido en principio activo por forma farmacéutica.
182,5 días = seis meses.

Para el cálculo de las DHD, se utilizó la población de Aragón a mitad de cada uno de los periodos. Para el periodo pre (del 14/09/2019 al 15/03/2020) se calculó la población a 12/2019, y para el periodo post (del 03/05/2020 al 04/11/2020) se calculó para 08/2020.

Con respecto al análisis específico de los fármacos consumidos, y teniendo en cuenta el sistema de clasificación Anatómica Terapéutica Química (ATC [Anatomical, Therapeutic, Chemical classification system])[126], para cada patología se incluyeron los siguientes grupos farmacológicos:

Tabla 5. Fármacos y códigos ATC incluidos para abordar el objetivo 1 (Diabetes Mellitus).

	Principio activo ATC	DDD (mg)
Insulinas y análogos	A10A	
Acción rápida	A10AB	
Insulina Humana	A10AB01	40
Insulina Lispro	A10AB04	40
Insulina Aspart	A10AB05	40
Insulina Glulisina	A10AB06	40
Acción intermedia	A10AC	
Insulina Humana	A10AC01	40
Acción intermedia o combinada con rápida	A10AD	
Insulina Humana	A10AD01	40
Insulina Lispro	A10AD04	40
Insulina Aspart	A10AD05	40
Acción prolongada	A10AE	
Insulina Glargina	A10AE04	40
Insulina Determir	A10AE05	40
Insulina Degludec	A10AE06	40
Antidiabéticos orales	A10B	
Metformina	A10BA02	2000
Glibenclamida	A10BB01	10
Glipizida	A10BB07	10
Gliclazida	A10BB09	60
Glimepirida	A10BB12	2
Glisentida	A10BB19	10

Fuente: Elaboración propia a partir de World Health Organization. Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2022.

Tabla 6. Fármacos y códigos ATC incluidos para abordar el objetivo 2 (Hipertensión Arterial).

	Principio activo ATC	DDD (mg)
Diuréticos	C03	
Tiazídicos	C03A	
Hidroclorotiazida	C03AA03	25
Clortalidona	C03BA04	25
Xipamida	C03BA10	20
Indapamida	C03BA11	2,5
De asa	C03C	
Furosemida	C03CA01	40
Bumetanida	C03CA02	1
Torasemida	C03CA04	15
Antagonistas de los canales de calcio	C08	
Amlodipino	C08CA01	5
Felodipino	C08CA02	5
Nicardipino	C08CA04	90
Nifedipino	C08CA05	30
Nimodipino	C08CA06	300

Nisoldipino	C08CA07	20
Nitrendipino	C08CA08	20
Lacidipino	C08CA09	4
Manidipino	C08CA11	10
Barnidipino	C08CA12	10
Lercanidipino	C08CA13	10
Verapamilo	C08DA01	240
Diltiazem	C08DB01	240
Inhibidores enzima convertidora angiotensina (IECAS)	C09	
Captopril	CO9AA01	50
Enalapril	CO9AA02	10
Lisinopril	CO9AA03	10
Perindopril	CO9AA04	4
Ramipril	CO9AA05	2,5
Quinapril	CO9AA06	15
Benazepril	CO9AA07	7,5
Cilazapril	CO9AA08	2,5
Fosinopril	CO9AA09	15
Trandolapril	CO9AA10	2
Imidapril	CO9AA16	10

Fuente: Elaboración propia a partir de World Health Organization. Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2022.

Tabla 7. Fármacos y códigos ATC incluidos para abordar el objetivo 3 (Trastorno por abuso crónico de alcohol.

	Principio activo ATC	DDD (mg)
Otros medicamentos del sistema nervioso	N07	
Vareniclina	N07BA03	2
Disulfiram	N07BB01	200
Acamprosato	N07BB03	2000
Naltrexona	N07BB04	50
Nalmefeno	N07BB05	18
Psicolépticos	N05	
Ansiolíticos	N05B	
Diazepam	N05BA01	10
Clorazepato	N05BA05	20
Lorazepam	N05BA06	2,5
Bromazepam	N05BA08	10
Clobazam	N05BA09	20
Ketazolam	N05BA10	30
Alprazolam	N05BA12	1
Hipnóticos y sedantes	N05C	
Flurazepam	N05CD01	30
Triazolam	N05CD05	0,25
Lormetazepam	N05CD06	1
Midazolam	N05CD08	15
Brotizolam	N05CD09	0,25
Quazepam	N05CD10	15
Loprazolam	N05CD11	1
Antidepresivos	N06A	
Inhibidores no selectivos recaptación monoaminas	N06AA	
Imipramina	N06AA02	100
Clomipramina	N06AA04	100

Amitriptilina	N06AA09	75
Nortriptilina	N06AA10	75
Doxepina	N06AA12	100
Maprotilina	N06AA21	100
Inhibidores selectivos recaptación serotonina	N06AB	
Fluoxetina	N06AB03	20
Citalopram	N06AB04	20
Paroxetina	N06AB05	20
Sertralina	N06AB06	50
Fluvoxamina	N06AB08	100
Escitalopram	N06AB10	10

Fuente: Elaboración propia a partir de World Health Organization. Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2022.

Tabla 8. Fármacos y códigos ATC incluidos para abordar los objetivos 4 y 5 (Ansiedad y/o depresión).

	Principio activo ATC	DDD (mg)
Psicolépticos	N05	
Ansiolíticos	N05B	
Diazepam	N05BA01	10
Clorazepato	N05BA05	20
Lorazepam	N05BA06	2,5
Bromazepam	N05BA08	10
Clobazam	N05BA09	20
Ketazolam	N05BA10	30
Alprazolam	N05BA12	1
Pinazepam	N05BA14	20
Clotiazepam	N05BA21	10
Bentazepam	N05BA24	75
Hipnóticos y sedantes	N05C	
Flurazepam	N05CD01	30
Triazolam	N05CD05	0,25
Lormetazepam	N05CD06	1
Midazolam	N05CD08	15
Brotizolam	N05CD09	0,25
Quazepam	N05CD10	15
Loprazolam	N05CD11	1
Antidepresivos	N06A	
Inhibidores no selectivos recaptación monoaminas	N06AA	
Imipramina	N06AA02	100
Clomipramina	N06AA04	100
Trimipramina	N06AA06	150
Amitriptilina	N06AA09	75
Nortriptilina	N06AA10	75
Doxepina	N06AA12	100
Maprotilina	N06AA21	100
Inhibidores selectivos recaptación serotonina	N06AB	
Fluoxetina	N06AB03	20
Citalopram	N06AB04	20
Paroxetina	N06AB05	20
Sertralina	N06AB06	50
Fluvoxamina	N06AB08	100
Escitalopram	N06AB10	10

Fuente: Elaboración propia a partir de World Health Organization. Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2022.

- ***Variables de utilización de recursos sanitarios:***
    - Visitas a APS:
        - ✓ Nº de visitas a enfermería en el CAP o por teléfono.
        - ✓ Nº de visitas de enfermería en el domicilio.
        - ✓ Nº de visitas a enfermería en el CAP (atención continuada).
        - ✓ Nº de visitas de enfermería en el domicilio (atención continuada).
        - ✓ Nº de visitas a medicina de familia (MF) en el CAP o por teléfono.
        - ✓ Nº de visitas de medicina de familia en el domicilio.
        - ✓ Nº de visitas a medicina de familia en el CAP (atención continuada).
        - ✓ Nº de visitas de medicina de familia en el domicilio (atención continuada).
        - ✓ Nº visitas a otros profesionales del CAP: fisioterapeuta, matrona, odontólogo/a y trabajador/a social.
    - Pruebas diagnósticas de imagen y laboratorio:
        - ✓ Nº de radiografías, ecografías, resonancias, tomografía axial computerizada (TAC), otras pruebas de imagen, retinografías (solo en manuscrito 3: diabetes mellitus).
        - ✓ Nº de hemogramas, bioquímicas, microbiología, inmunología, pruebas de coagulación, pruebas de orina.
    - Visitas a atención especializada:
        - ✓ Nº visitas a atención especializada (1ª consulta).
        - ✓ Nº visitas a atención especializada (consultas sucesivas).
        - ✓ Nº visitas al servicio de urgencias hospitalarias.
        - ✓ Nº ingresos hospitalarios.
        - ✓ Nº de días de estancia hospitalaria.
        - ✓ Nº de ingresos en una Unidad de Cuidados Intensivos (UCI).
        - ✓ Nº de días de estancia en una UCI.

3.3 Fuentes de información:

Todos los manuscritos están basados en datos clínico-administrativos provenientes de las HCE de Atención Primaria.

La historia clínica, constituye un instrumento fundamental para la comunicación entre los diferentes profesionales que forman parte del sistema sanitario. Su contenido, estructura y funciones están regulados por el artículo 3 de la *Ley 41/2002 del 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica.* En ella, la historia clínica *se* define como: el conjunto de documentos que contienen los datos, valoraciones e informaciones de cualquier índole sobre la situación y la evolución clínica de un paciente durante el proceso asistencial.

La HCE permite el almacenamiento sistemático de datos sociales y médicos de un paciente a través de un sistema informático. La puesta en funcionamiento de la HCE en el SNS se llevó a cabo paulatinamente en las 17 CC. AA. sin una planificación conjunta[128]. En Aragón, se inició en la primera década de este siglo, finalizando su implementación total en algunas zonas de difícil cobertura en el año 2011[129].

La digitalización de los sistemas de salud produce una cantidad enorme de datos electrónicos que son conocidos con el término de macrodatos o big data. Estos macrodatos generados por el sistema de salud durante el seguimiento habitual de los pacientes son también conocidos como datos del mundo real (Real World Data o RWD) y, a diferencia de los obtenidos por los ensayos clínicos, tienen gran validez externa y contribuyen a establecer evidencias de la vida real. Este conjunto de datos masivos, complejos y variados requieren, en cambio, del uso de herramientas tecnológicas para ser procesados[130]. El sistema de gestión de datos clínicos del Servicio Aragonés de Salud (BIGAN), recoge todos los datos que genera el sistema sanitario y los anonimiza[131]. Esta herramienta de big data, permitió construir una base de datos que incluyera información sociodemográfica y clínica de aquellos pacientes mayores de 16 años con HCE en Atención Primaria y con alguno de los diagnósticos estudiados (diabetes mellitus, hipertensión arterial, trastorno por abuso crónico de alcohol, ansiedad y/o depresión) que durante el confinamiento y los seis meses posteriores a su finalización no presentaron prueba diagnóstica positiva documentada de COVID-19.

3.4 Análisis estadístico:

El gran tamaño muestral permitió la utilización de estadísticos paramétricos[132].

Con la finalidad de conocer las características sociodemográficas y las comorbilidades crónicas más frecuentes entre las muestras estudiadas, se realizó un análisis descriptivo en cada estudio. Para la descriptiva de las variables cualitativas se utilizaron medidas de frecuencia absolutas (n) y relativas (%). Para las variables cuantitativas se utilizaron medidas de tendencia central (media) y de dispersión (desviación estándar o DS).

La mortalidad por causas distintas a la COVID-19 (sin confirmación mediante PCR) se evaluó a través del cálculo de la tasa bruta de mortalidad y de sus intervalos de confianza al 95% (IC 95%) para cada uno de los periodos: pre (14/09/2019 al 15/03/2020) y post (03/05/2020 al 04/11/2020).

$$\text{Tasa bruta de mortalidad } = \frac{\text{nº defunciones}}{\text{nº habitantes}} * 1000$$

Calculo IC 95%[133]:

- Límite superior: *(100/n) * (d + (1,96 * $\sqrt{d}$))*
- Límite inferior: *(100/n) * (d - (1,96 * $\sqrt{d}$))*

Donde (n) = nº habitantes y (d) = nº defunciones

Al igual que en el cálculo de las DHD, para el cálculo de las tasas se utilizó como denominador la población de Aragón a mitad de cada uno de los periodos: pre (12/2019) y post (08/2020).

Para conocer las variaciones en los parámetros clínicos, para cada uno de ellos se calculó inicialmente la media y la DS en cada periodo. Si para un mismo individuo había más de una medición del mismo parámetro en un periodo, se calcularon además otras medidas de tendencia central y de dispersión, como la mediana y el rango intercuartílico (RIQ). Finalmente, para comparar la diferencia entre la media del periodo pre y post, se realizó una prueba T de Student para muestras dependientes o pareadas.

En el objetivo 2 (Hipertensión arterial), las variaciones (pre/post) en las medias de los parámetros clínicos fueron presentadas por sexos. Además, se calculó la proporción de personas que habían empeorado, mejorado o mantenido sus valores de presión arterial en rango (TAS <140 mmHg y TAD < 90 mmHg). Considerando:

- Empeoramiento: aquellos que antes del confinamiento presentaban valores en rango y después de éste, valores fuera de rango.
- Mejora: aquellos que antes del confinamiento presentaban valores fuera de rango y después de éste, valores en rango.
- Mantenimiento: aquellos que i) antes y después del confinamiento presentaron valores en rango o ii) aquellos que antes y después del confinamiento presentaron valores fuera de rango.

Para valorar la distribución de estas frecuencias se utilizó la prueba Chi cuadrado (X^2) de Pearson.

En el objetivo 3 (Trastorno por abuso crónico de alcohol), se valoraron también para cada uno de los periodos, las diferencias en las medias de los parámetros clínicos entre pacientes con trastorno por abuso crónico de alcohol con diagnóstico positivo de COVID-19 y sin diagnóstico de la infección. El gran tamaño de la muestra permitió asumir la distribución normal de las variables clínicas y, tras realizar el contraste de homogeneidad de varianzas de Levene, utilizar la prueba T de Student. En aquellas variables clínicas con un número menor de 100 observaciones, no se pudo suponer normalidad y se utilizó la prueba de rangos con signo de Wilcoxon.

En cuanto a las diferencias en los patrones de consumo de fármacos, éstas fueron evaluadas a través del cálculo de las DHD dispensadas en farmacia para las distintas muestras en los dos periodos de tiempo. En el objetivo 5 (Ansiedad y/o depresión), las diferencias en las DDD se calcularon utilizando la prueba T de Student para muestras pareadas y la prueba de rangos con signo de Wilcoxon en los casos en las que las observaciones estaban por debajo de 100. En éste mismo manuscrito, también se utilizaron modelos de regresión logística multivariada para analizar los factores asociados al posible deterioro de los trastornos mentales.

Por otro lado, la media y la DS de cada variable relacionada con la utilización de recursos sanitarios (acceso a servicios de APS así como especializada y realización de pruebas diagnósticas), también fue calculada para cada periodo. El cálculo de la diferencia de medias se realizó utilizando nuevamente la prueba T de Student para muestras dependientes. En los casos con menos de 100 observaciones, se aplicó también la prueba de rangos con signos de Wilcoxon.

En todos los estudios el nivel de significación fue establecido en 5% ($p < 0,05$). Todos los análisis estadísticos fueron realizados con IBM® SPSS® Statistic 21[134] y R versión 4.0.5[135] en un ordenador con 16 MB de RAM.

3.5 Consideraciones éticas:

Los datos de los pacientes que se incluyeron en todas las muestras analizadas, se obtuvieron mediante procesos de anonimización a partir de la HCE facilitada por el Servicio Aragón de Salud. Ningún dato disponible de los pacientes permitía su identificación, por lo que no se requirió su consentimiento para ser incluidos en los estudios. El tratamiento, la comunicación y transferencia de los datos personales se realizó de conformidad con lo dispuesto en el Reglamento (UE) 2016/679 del Parlamento Europeo y Ley Orgánica de Protección de Datos de Carácter Personal y garantía de derechos digitales 03/2018.

Además, los procedimientos que se realizaron en esta Tesis Doctoral cumplen con las normas éticas y fueron aprobados por el Comité Ético de Investigación Clínica de Aragón (PI20-175. Anexo 2), perteneciente al Departamento de Salud del Gobierno de Aragón, y con la Declaración de Helsinki de 1975, y su versión revisada en 2008.

PUBLICACIONES DE LA TESIS

Para la consecución de los objetivos de esta Tesis Doctoral, se elaboraron cinco manuscritos que ya han sido publicados en revistas de impacto científico. Los cinco artículos completos se presentan a continuación.

1er manuscrito:

Lear-Claveras A, Oliván-Blázquez B, Clavería A, Couso-Viana S, Botaya R.M. Analysis of Clinical Parameters, Drug Consumption and Use of Health Resources in a Southern European Population with Diabetes That Did Not Contract COVID-19: A Longitudinal Big Data Study. Int J Environ Res Public Health. 2022;19(11): 6835. DOI: 10.3390/ijerph19116835. Factor de impacto (JCR 2021): 4,614 (Q1).

2º manuscrito:

Lear-Claveras A, Oliván-Blázquez B, Clavería A, Couso-Viana S, Puente-Comesaña J, Magallón Botaya R. Sex Differences in Clinical Parameters, Pharmacological and Health-Resource Utilization in a Population With Hypertension Without a Diagnosis of COVID-19. Int J Public Health 2022;67:1604913. DOI: 10.3389/ijph.2022.1604913. Factor de impacto (JCR 2021): 5,100 (Q1).

3er manuscrito:

Lear-Claveras A, González-Álvarez B, Couso-Viana S, Clavería A, Oliván-Blázquez B. Analysis of Clinical Parameters, Drug Consumption and Use of Health Resources in a Southern European Population with Alcohol Abuse Disorder during COVID-19. Pandemic. Int J Environ Res Public Health. 2022;19(3): 1358. DOI: 10.3390/ijerph19031358. Factor de impacto (JCR 2021): 4,614 (Q1).

4º manuscrito:

Lear-Claveras A, Clavería A, Couso-Viana S, Nabbe P, Oliván-Blázquez B. Analysis of Drug and Health Resource Use Before and After COVID-19 Lockdown in a Population Undergoing Treatment for Depression or Anxiety. Front Psychol. 2022;13:861643. DOI: 10.3389/fpsyg.2022.861643. Factor de impacto (JCR 2021): 4,232 (Q1).

5º manuscrito:

Lear-Claveras A, Aguilar-Latorre A, Oliván-Blázquez B, Couso-Viana S, Clavería-Fontán A. Evolution of Anxiety and Depression in Men during the First Six Month of the COVID-19 Pandemic and Factors Associated with Worsening of Mental Health: Retrospective Longitudinal Study. J Mens Health 2022;18(9):182. DOI: 10.31083/j.jomh1809182. Factor de impacto (JCR 2021): 0,789 (Q4).

Manuscrito 1: Analysis of Clinical Parameters, Drug Consumption and Use of Health Resources in a Southern European Population with Diabetes That Did Not Contract COVID-19: A Longitudinal Big Data Study.

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Article

Analysis of Clinical Parameters, Drug Consumption and Use of Health Resources in a Southern European Population with Diabetes That Did Not Contract COVID-19: A Longitudinal Big Data Study

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Abstract: The lockdown measures imposed to stop the spread of the virus have affected the general population, but particularly people with chronic diseases such as diabetes. An observational real world data pre-post study of 86,615 individuals over the age of 16, having a medical history in the Aragon (Spain) Health Service and diagnosed with diabetes, without COVID-19 infection was undertaken. Clinical, pharmacological and health resource use variables were collected during the six months prior to the onset of the lockdown and during the six months after the lockdown ended. The Student's *t*-test was used to analyse differences in means. Our study does not show clinically relevant changes six months following the end of the strict lockdown. The consumption, by these patients, of hypoglycaemic drugs and the use of health resources continue at below pre-pandemic levels, six months later. The interruption in care for these patients and the lifestyle change resulting from the pandemic do not appear to have had a significant impact on the health of the diabetic population.

Keywords: COVID-19; diabetes; lockdown; lifestyle; health resources

1. Introduction

The current COVID-19 pandemic has tested the response and ability of people, governments and health systems around the world to adapt [1]. Its impact on essential health services is of great concern. According to the results of the PULSE survey carried out by the World Health Organisation (WHO) in 105 countries, the majority (90%) have suffered interruptions in essential healthcare services since the beginning of the pandemic [2]. These interruptions are likely to have serious adverse effects on the health of the most vulnerable populations, such as those with chronic diseases who need regular assistance and care, especially Primary Care (PC) [2,3].

These PC services, which helped people to manage chronic diseases before COVID-19, were modified with the arrival of the pandemic. Since then, they have been focused on detecting mild cases of the infection, following up positive cases and contact tracing. This interrupted their care of patients with chronic diseases to a greater or lesser extent. In addition, to reduce the risk of COVID-19 transmission, medical appointments were postponed and follow-up appointments were mostly carried out by telephone [4].

The restrictions imposed under the state of emergency to stop the spread of the virus has also had a direct impact on people with chronic diseases, and especially on those with diabetes. The global prevalence of diabetes was 9.3% in 2019 [5]. In Spain, the figure was 13.8%, counting type 2 diabetics alone [6]. The home lockdown measures applied have affected the diabetic population's ability to lead a healthy lifestyle (balanced diet, physical activity, etc.), which plays a very important role in the proper management and control of this disease [7].

Previous studies about the impact that lifestyle modifications have had on patients with diabetes have had varying results. Some suggest that lockdown has not had a negative impact on the disease's clinical parameters [8,9], while others report the deterioration of patients during the time when restrictions were imposed [10,11].

The deterioration of the clinical parameters of diabetes, and other non-communicable diseases such as cardiovascular diseases or cancer during the pandemic, could further increase the risk of poor prognosis and mortality from COVID-19 [12]. An association between the presence of diabetes and a more serious COVID-19 disease has been found by many studies [13,14].

Most studies on diabetes and COVID-19 have investigated the influence of this disease on the prognosis of infected patients, but fewer have analysed the impact of the pandemic on the uninfected diabetic population. These latest studies also mostly have cross-sectional designs and small sample sizes, and it is, therefore, necessary to carry out large-scale studies that provide a longitudinal perspective.

Accordingly, this paper aims to study and conduct a longitudinal analysis of the possible changes in the clinical parameters, as well as in the hypoglycaemic drug consumption and the use of health resources, between the six months prior to the start of lockdown and the six months after the end of strict lockdown, in a southern European population with diabetes who did not contract COVID-19.

2. Materials and Methods

2.1. Design and Study Population

Observational real world data pre-post study of the population aged over 16 registered in the Autonomous Region of Aragon, in the north of Spain, with medical records in Primary Healthcare Centres (n = 1,122,151 people).

This study's final sample is made up of individuals aged over 16 with a clinical history in the Aragon Health Service and a diagnosis of type 1 or type 2 diabetes, according to the International Classification of Primary Care (ICPC-2) criteria [15], who have not been infected with COVID-19 (n = 86,615). This last criterion was established to analyse changes in health status due exclusively to the measures imposed to control the pandemic. On 15 March 2020, the Spanish Government declared a state of national emergency, limiting mobility and requiring the population to stay at home until 3 May.

Data were collected from each individual at different time periods. The baseline measurement was taken in the six months prior to the start of lockdown (from 14 September 2019 to 15 March 2020), and the second measurement in the six months after the end of strict lockdown (until 4 November 2020).

2.2. Data Sources

This study is based on data from Aragon Primary Care centre's longitudinal electronic health records.

Given that the healthcare system is universal, with practically no other Primary Care providers, it is considered that the data obtained in this study are representative of practically 100% of the population that met the study's inclusion criteria.

2.3. Variables

The sociodemographic variables included in this study were: sex, age, pharmaceutical delivery and rurality of the health zones (defined as: rural—with less than

10,000 inhabitants—or urban—with more than 10,000 inhabitants). The number of deaths in the study population was also considered for each of the measurement periods.

Comorbidity with other chronic diseases was also considered. Those chronic conditions with a prevalence greater than 5% [16] were also collected (arrhythmias, heart failure, ischaemic heart disease, hypertension, dyslipidaemia, obesity, overweight, vein and artery disease, cerebrovascular disease, chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease, hypo and hyperthyroidism, smoking, alcoholism, insomnia, anxiety and depression, autolytic attempt, anaemia, neoplasia, dementia, hearing loss, cataracts, glaucoma, osteoarthritis, osteoporosis and dorsopathy).

The variables of interest in our study are related to the clinical parameters of diabetes and its possible complications. The clinical parameters collected were: blood glucose level, glycated haemoglobin (HbA1c), blood creatinine and glomerular filtration. In addition, blood pressure measurements (systolic and diastolic), total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides, weight and body mass index (BMI) were collected.

Patient drug use in the 6 months prior to the start of lockdown and in the 6 months after the end of strict lockdown was assessed through variations in the number of patients with diabetes who do not use hypoglycaemic drugs vis-à-vis those who consume one or more, and through the total number of defined daily doses (DDD) per 1000 inhabitants per day (DHD), dispensed by the pharmacy during each of the two periods. For the calculation of DHD, the Aragon population at the middle of each of the periods was used.

$$\mathrm{DHD} = \frac{\text{Registered consumption of the active ingredient} * 1000 \text{ inhabitants}}{\text{Standard DDD} \times \text{ninhabitants/period} * 365 \text{ days}}$$

It was decided to take the dispensed DHD and not the prescribed one, as some prescribed drugs may not be dispensed. According to the Anatomical Therapeutic Chemical classification system (ATC), the following pharmacological groups were assessed: A10A (insulins and analogues) and A10B (oral antidiabetics).

Finally, these patients' use of health system resources during the period under study was assessed using variables related to the use of PC services (number of nurse and general practitioner—GP—visits for ordinary or continuous care at a health centre or at home, and number of visits to other health centre professionals), and the use of specialised hospital services (number of visits to hospital's specialised care, number of diagnostic tests performed, number of visits to accident and emergency—A&E—department, hospitalisations and admissions to intensive care unit—ICU—as well as the duration of these stays).

2.4. Statistical Analysis

Given our large sample size, we used parametric statistics [17]. To determine the characteristics of the population, and the total number of patients who take one or more hypoglycaemic drug, or none at all, a descriptive analysis of the study variables was carried out using frequencies (percentages) to summarise the categorical variables and measures of central tendency and dispersion (mean and standard deviation) for the continuous variables.

For the study population, mortality due to causes other than COVID-19 was assessed by calculating the crude mortality rate for each of the two periods. The Aragon population at the middle of each of the two periods was used as the denominator.

In order to ascertain the variations in clinical variables, if in any of the different periods of time (6 months prior to the start of lockdown or 6 months later) there was more than one measurement collected for the same clinical parameter, the median and the interquartile range (IQR) were calculated. For the two time periods, the mean and standard deviation (SD) of each of the clinical variables were calculated. To compare the difference of means between the two measurements a paired samples *t*-test was performed.

Differences in drug consumption were assessed through the DHDs dispensed in the pharmacy to the study population in each of the periods.

The mean and standard deviation of each variable of resource use (primary and hospital specialised care) were also calculated. A paired samples *t*-test was used to compare the difference of means too. For those variables with a fewer number of observations than 100, a Wilcoxon rank test was used.

The level of significance was established at 5% ($p < 0.05$). The statistical analysis was carried out using IBM SPSS Statistic 21 (IBM Corporation, New York, NY, USA) and R version 4.0.5 (IBM Corporation, New York, NY, USA) in a PC with 16 MB of RAM.

3. Results

On 14 September 2019, there were 86,615 people over 16 years of age, with a diagnosis of diabetes (type 1 or type 2) in their PC history, who, as of 3 November 2020, had not been infected with COVID-19. It should be noted that for the population aged over 16, the prevalence of diabetes was 7.72% at the beginning of 2019. The mean age of the sample was 69.5 years (SD: 13.7), with 48,436 men (55.9%) and 38,179 women (44.1%). Two-thirds (69.5%) had annual incomes below 18,000 euros, and more than half (51.2%) resided in urban areas (with more than 10,000 inhabitants) (Table 1). Hypertension (66.1%), followed by dyslipidaemia (58.2%) and dorsopathies (28.9%) were the most prevalent comorbid diseases among the population with diabetes under study.

Table 1. Sociodemographic data and chronic comorbidities in diabetic patients not infected with COVID-19.

		N (%)
Age	Mean (SD)	69.5 (13.7)
Sex		
	Men	48,436 (55.9)
	Women	38,179 (44.1)
Pharmaceutical delivery		
	<18,000	60,182 (69.5)
	Between 18,000 and 100,000	22,140 (25.6)
	>100,000	336 (0.4)
	Free pharmacy	3189 (3.7)
	Mutualist	706 (0.8)
	Uninsured	62 (0.1)
Rurality of health zones		
	Urban	44,321 (51.2)
	Rural	42,293 (48.8)
Chronic comorbidities (Yes %)		
	Arrhythmias	9266 (10.7)
	Heart failure	5023 (5.8)
	Ischaemic heart disease	9633 (11.1)
	Hypertension	57,295 (66.1)
	Dyslipidaemia	50,431(58.2)
	Obesity	20,200 (23.3)
	Overweight	1374 (1.6)
	Vein/artery disease	4705 (5.4)
	Cerebrovascular disease	7784 (9)
	Chronic bronchitis	1354 (1.6)
	COPD	5853 (6.8)
	Asthma	4901 (5.7)
	Chronic kidney disease	11,309 (13.1)
	Hypothyroidism	9983 (11.5)
	Hyperthyroidism	3932 (4.5)
	Smoking	12,192 (14.1)
	Alcoholism	1661 (1.9)
	Insomnia	12,828 (14.8)
	Anxiety and depression	23,289 (26.9)
	Autolytic attempt	200 (0.2)

Table 1. *Cont.*

	N (%)
Anaemia	16,927 (19.5)
Neoplasia	23,682 (27.3)
Dementia	3725 (4.3)
Hearing loss	8914 (10.3)
Cataracts	15,300 (17.7)
Glaucoma	9838 (11.4)
Osteoarthritis	10,124 (11.7)
Osteoporosis	7772 (9.0)
Dorsopathy	25,051 (28.9)

(SD) Standard deviation; (COPD) Chronic Obstructive Pulmonary Disease.

Of the individuals included in the study, 1887 died over the six months prior to the declaration of the state of emergency, and 2019 during the six months following the end of the lockdown. Taking into account the Aragon population during these two periods, the mortality rate per 1000 individuals was 1.4 [95%CI 1.4–1.5] and 1.5 [95%CI 1.5–1.6], respectively.

The variation in the clinical variables when comparing the two measurements, can be seen in Table 2. HbA1c parameters [$p < 0.001$, 95%CI: 0.04–0.11], total cholesterol [$p < 0.001$, 95%CI: 2.39–5.00], LDL cholesterol [$p < 0.001$, 95%CI: 2.61–4.84], weight [$p < 0.001$, 95%CI: 0.54–0.65] and BMI [$p < 0.001$, 95%CI: 0.17–0.24] show a significant trend towards a slight improvement. This is in contrast to the improvement observed in blood glucose and HDL cholesterol, which is only statistically significant for this last parameter [p 0.032, 95%CI: 0.04–0.94]. In the same table, we can observe a subtle deterioration for other variables such as blood creatinine [$p < 0.001$, 95%CI: −0.04–−0.02] and a decrease in the glomerular filtration rate [$p < 0.001$, 95%CI: 1.28–1.95]; both are statistically significant variations. For blood pressure six months after lockdown ended, only diastolic blood pressure experienced a statistically significant deterioration [$p < 0.001$, 95%CI: −0.42–−0.22].

Table 2. Clinical parameters 6 months before and 6 months after lockdown.

		6 Months Before	6 Months After	Paired Samples *t*-Test	
	N	Mean (SD)		95%CI	*p*
Blood glucose level	2910	137.2 (38.6)	135.8 (41.2)	−0.06; 2.87	0.06
HbA1c (%)	2518	7.0 (1.1)	6.9 (1.1)	0.04; 0.11	<0.001
Blood creatinine	2688	0.9 (0.4)	1.0 (0.4)	−0.04; −0.02	<0.001
Glomerular filtration	2688	75.5 (22.0)	73.8 (22.5)	1.28; 1.95	<0.001
Systolic blood pressure	26,685	136.1 (14.3)	136.2 (15.4)	−0.33; 0.01	0.073
Diastolic blood pressure	26,691	75.6 (8.8)	75.9 (9.3)	−0.42; −0.22	<0.001
Total cholesterol	2708	179.6 (39.3)	175.9 (38.9)	2.39; 5.00	<0.001
LDL	2459	100.2 (33.3)	96.5 (31.6)	2.61; 4.84	<0.001
HDL	2638	50.8 (16.0)	50.3 (13.2)	0.04; 0.94	0.032
Triglycerides	2669	145.9 (84.0)	147.5 (84.5)	−4.08; 0.94	0.211
Weight	17,095	78.3 (15.0)	77.7 (15.2)	0.54; 0.65	<0.001
BMI	10,800	29.9 (5.0)	29.7 (5.1)	0.17; 0.24	<0.001

(HbA1c) Glycated haemoglobin; (LDL) Low density lipoprotein; (HDL) High density lipoprotein; (BMI) Body mass index; (SD) Standard deviation; (95%CI) Confidence interval.

In terms of drug use by patients with diabetes in the six months before the start of the lockdown and six months after lockdown, Table 3 shows an increase in the total number of patients who did not take any hypoglycaemic drugs [38,032 (43.9) vs. 40,568 (46.8)], and a decrease in the total number of patients who took one or more drugs. Table 4 also reveals a decrease in the total number of DHDs dispensed by pharmacies for all drugs

included in the study, except for the insulins Aspart, Glargine and Degludec and the oral antidiabetic Metformin.

Table 3. Number of patients who do not use insulins or oral antidiabetics or who consume one or more.

	6 Months Before	6 Months After
	N (%)	N (%)
No hypoglycaemic drug	38,032 (43.9)	40,568 (46.8)
One hypoglycaemic drug	36,360 (42.0)	34,461 (39.8)
Two hypoglycaemic drugs	10,325 (12.0)	9968 (11.5)
Three or more hypoglycaemic drugs	1898 (2.1)	1618 (1.9)

Table 4. Number of DHDs 6 months before and 6 months after lockdown.

		6 Months Before	6 Months After
	N	DHD	
Insulins			
Insulin (human) fast acting	655	0.63	0.61
Lispro fast acting	2106	4.15	4.15
Aspart fast acting	5490	9.13	9.34
Glulisine	1179	2.05	1.76
Insulin (human) intermediate acting	448	1.01	0.98
Insulin (human) intermediate acting + fast acting	255	0.70	0.65
Lispro intermediate acting	922	2.71	2.61
Aspart intermediate acting	1591	5.10	4.73
Glargine	14,491	22.70	23.10
Determir	1620	3.26	3.18
Degludec	3060	4.44	4.74
Oral antidiabetics			
Metformin	31,076	39.96	42.30
Glibenclamide	289	0.46	0.42
Glipizide	110	0.21	0.18
Gliclazide	2369	4.25	3.90
Glimepiride	1951	7.26	6.57
Glisentide	5	0.01	0.01

(DHDs) Defined Daily Doses per 1000 inhabitants per day.

The use that the population with diabetes made of health resources can be seen in Table 5. Between the two measurement periods, the number of nurse and general practitioner visits decreased; with only the decrease in the number of nurse visits (continuous care), including those at the health centre and home visits, not being statistically significant. On the other hand, the same table shows an increase in the number of general practitioner visits (continuous care) at the health centre [$p = 0.014$, 95%CI: −0.14—0.02], and the number of visits to other professionals, such as social workers [$p = 0.020$, 95%CI: −0.71—0.06]. As for physiotherapy services, visits were considerably reduced compared to the baseline measurement [$p = 0.006$, 95%CI: 0.34–2.04].

Table 5. Number of visits and diagnostic tests prescribed 6 months before and 6 months after lockdown.

		6 Months Before	6 Months After	Paired Samples *t*-Test	
	N	Mean (SD)		95%CI	*p*
No. of nursing visits (ordinary care) at health centre or by telephone	54,995	5.26 (5.27)	4.53 (4.85)	0.68; 0.76	<0.001
No. of nursing visits (ordinary care) at home	4985	7.03 (9.94)	6.70 (9.80)	0.04; 0.60	0.023
No. of nursing visits (continuous care) at health centre	2108	2.31 (3.53)	2.19 (3.57)	−0.03; 0.27	0.112
No. of nursing visits (continuous care) at home	621	2.30 (2.99)	2.28 (3.67)	−0.30; 0.35	0.861
No. of general practitioner visits (ordinary care) at health centre or by telephone	68,803	5.36 (4.24)	5.29 (4.72)	0.03; 0.10	<0.001
No. of general practitioner visits (ordinary care) at home	2811	3.44 (3.67)	2.80 (3.33)	0.51; 0.77	<0.001
No. of general practitioner visits (continuous care) at health centre	4458	1.85 (1.82)	1.93 (2.19)	−0.14; −0.02	0.014
No. of general practitioner visits (continuous care) at home	682	1.84 (1.63)	1.68 (1.38)	0.03; 0.28	0.014
No. of visits to other professionals					
Physiotherapist	294	5.63 (6.13)	4.43 (6.16)	0.34; 2.04	0.006
Midwife	141	2.45 (2.16)	2.52 (2.06)	−0.53; 0.37	0.732
Dentist	257	2.15 (1.82)	2.41 (1.88)	−0.55; 0.04	0.092
Social worker	426	2.75 (2.65)	3.13 (3.45)	−0.71; −0.06	0.020
No. of visits to specialised care (first consultation)	3105	1.49 (0.87)	1.53 (0.93)	−0.08; 0.00	0.067
No. of visits to specialised care (successive consultations)	26,307	2.71 (2.27)	2.61 (2.38)	0.07; 0.12	<0.001
No. of diagnostic tests performed					
X-rays	12,895	1.18 (1.34)	1.03 (1.26)	0.12; 0.18	<0.001
Ultrasound	12,895	0.33 (0.58)	0.30 (0.54)	0.01; 0.04	<0.001
Resonance	12,895	0.11 (0.36)	0.12 (0.35)	−0.01; 0.00	0.148
CT scans	12,895	0.36 (0.67)	0.37 (0.68)	−0.03; −0.00	0.028
Retinographies	41	1.02 (0.16)	1.15 (0.65)	−0.33; 0.09	0.257 [a]
Other imaging test	12,895	0.15 (0.43)	0.14 (0.41)	0.00; 0.02	0.019
Haemograms	22,398	0.31 (0.54)	0.22 (0.48)	0.08; 0.09	<0.001
Biochemistry	22,398	1.05 (0.65)	0.98 (0.64)	0.05; 0.07	<0.001
Microbiology	22,398	0.18 (0.56)	0.24 (0.64)	−0.07; −0.05	<0.001
Immunology test	22,398	0.14 (0.40)	0.13 (0.38)	0.01; 0.02	<0.001
Coagulation	22,398	0.03 (0.17)	0.04 (0.20)	−0.01; −0.00	<0.001
Urine test	22,398	0.40 (0.61)	0.36 (0.60)	0.03; 0.05	<0.001
No. of visits to the emergency department	4333	1.78 (1.50)	1.66 (1.29)	0.06; 0.16	<0.001
No. of hospital admissions	1335	1.54 (1.04)	1.54 (1.05)	−0.07; 0.06	0.926
No. of days of hospital stay	1335	18.70 (56.44)	17.37 (45.54)	−0.30; 2.95	0.111
No. of ICU admissions	5	1 (0)	1 (0)		(*) [a]
No. of days of ICU stay	5	22.20 (27.36)	18.60 (27.59)	−5.20; 12.40	0.465 [a]

(*) The correlation and t cannot be calculated because the standard error of the differences is 0. [a] Wilcoxon signed-rank test. (ICU) Intensive care unit; (SD) Standard deviation; (95%CI) Confidence interval.

In relation to hospital specialised care, we observe the opposite trend. While the number of first visits to specialised care increased in the six months after the end of strict lockdown, the number of follow-up consultations decreased; this was the only statistically significant decrease [$p < 0.001$, 95%CI: 0.07–0.12].

The performance of diagnostic tests also changed during the months under study. These variations were statistically significant for all tests [$p < 0.05$], except for resonances and retinographies.

Among these patients, the number of visits to A&E also decreased [$p < 0.001$, 95%CI: 0.06–0.16]. In terms of hospitalisations and ICU admissions, no statistically significant differences were observed in terms of the number of visits or the duration of these stays.

4. Discussion

Unlike the results published by other studies [10,11], our longitudinal, large-scale study does not show clinically relevant changes in the clinical parameters of diabetes, despite the observed interruptions in these patients' care. These findings are consistent with the results of some previous studies that also report a neutral [18,19], or even a positive [7] influence of restrictive measures on glycaemic control in these patients.

When patients with type 1 and 2 diabetes are analysed separately, the results are more heterogeneous. A systematic review that analysed 33 studies which included patients with type 1 ($n = 33$) and 2 ($n = 8$) diabetes showed significant improvements in glycaemic values, mainly in patients with type 1 diabetes [20]. In our study, we were unable to differentiate between patients with type 1 or type 2 diabetes, but we assumed that the vast majority of patients were type 2 diabetics because: (a) in Spain type 1 diabetes accounts for 1 in 10 cases of diabetes [21] and (b) the mean age of the sample was high.

One of the factors that could explain the slight impact of lockdown in the clinical parameters shown in our study is the knowledge the patients with diabetes themselves have of the influence that their disease has on their prognosis if infected with COVID-19 [22]. This could have promoted better disease management among patients with diabetes (more frequent glycaemic control, awareness of taking medication, etc.) [23], and greater self-care [19]. This last would be reflected in the significant improvement in the total cholesterol, LDL, HDL, weight and BMI showed in our study. Some previous studies in this area have pointed to the possible improvement of dietary habits [24] and physical exercise [23,24] due to the lockdown in patients with diabetes.

This subtle improvement in clinical parameters could in turn explain the decrease in the consumption of hypoglycaemic drugs in the six months after the end of lockdown. Previous studies showed the same trend in terms of diabetes drug prescriptions [25,26].

The decrease in the consumption of these drugs could also be explained by the difficulty of accessing them. According to the results of the study carried out in our country by a Patient Organisation Platform (POP) [27], during the first wave of the pandemic, 79.3% of patients with chronic diseases found it difficult to access treatment. In the second wave, this percentage fell to 25.2%.

During the first months of the pandemic, to avoid the spread of the new virus, people with diabetes in Aragon (as in other places [2,28]) had interruptions in primary health care. Nevertheless, they continued to have telephone consultations. This allowed these patients' condition to be controlled and monitored [29], which could have prevented any short-term deterioration. Very similar results were reported by two studies [30,31] carried out in patients with type 2 diabetes.

However, not all care for these patients can be done properly remotely. Patients with diabetes (especially elderly patients with type 2 diabetes) have a high prevalence of metabolic risk factors and comorbid conditions and, therefore, require regularly, face-to-face attention [32,33]. For these most fragile patients, telematic attention could have been more difficult during the months of the pandemic [30]. As shown in another work [34], the decrease in the number of nursing visits observed in our study could have represented a challenge in the nursing management of diabetic foot care during the COVID-19 pandemic.

According to the results of a study [35] carried out in Catalonia (Spain), diabetic foot screening was the most affected indicator among the quality standards that decreased the most during the pandemic.

Likewise, six months after the end of the strict home lockdown, the number of visits to specialised care and diagnostic tests conducted on patients with diabetes had not yet reached pre-pandemic levels. These results, are consistent with the results of other published works [2,28]. Diabetic retinopathy screening also showed a significant decrease in the study carried out in Catalonia [35]. In our study, the number of retinographies performed showed an opposite trend, however, these results were not statistically significant. According to the decrease in the number of visits to specialised care (successive consultations), another study conducted in England, showed a decrease in lower-limb major and minor amputation and revascularisation procedures among patients with diabetes in 2020 [36].

A mix between supply and demand was responsible for the disruption of services [2].

These interruptions could have caused a delay in the diagnosis and in the start of treatment, causing a worsening in clinical outcomes (decompensations or acute or chronic complications) in those more fragile individuals [2,28,33]. This fact could explain the increase in the number of deaths during the second measurement period, although this study does not include patients with diabetes who also contracted COVID-19, the excess of mortality due to other causes could have been caused by the concentration of resources in the fight against COVID-19. Another study also carried out in Spain reported similar results, showing a reduction in this trend in the first half of 2021 [37].

Our study has some limitations. Firstly, the dataset includes patients with both type 1 and type 2 diabetes, which means that it is dealing with patients with different clinical profiles. Secondly, for certain clinical variables, a limited number of records are available, because the GP must validate those results. Therefore, they are a sample of the real data. We cannot rule out the existence of a bias, although it is reasonable to consider that it would have the same size and direction in each of the periods considered. Thirdly, we do not know how long these patients have been diabetic. We also do not have information about the acute (hypoglycaemia, hyperglycaemia, diabetic ketoacidosis) and chronic (microvascular and macrovascular) complications of diabetes or the decompensation of other chronic diseases. Finally, this study also does not include self-reported data on disease management (glycaemic control, medication intake) and the lifestyle habits (diet, physical activity, work routine, etc.) maintained by the population under study during the months of lockdown. Conducting studies with a qualitative approach would provide information about the subjective perception that individuals have of the impact of lockdown on maintaining healthy lifestyles and managing their disease. Likewise, it would be interesting to evaluate the changes 12 months after the end of strict lockdown, to verify whether or not the clinical parameters follow the same trend over time.

Episodes, use of health resources and drug consumption, are routinely collected from a variety of sources for the total population. Greater knowledge about the health demand and the real consequences of pandemics and their secondary effects, may improve health planning and resource management. A more detailed analysis of geographic variations will allow the identification of vulnerable populations.

5. Conclusions

Our study contributes to the knowledge of the consequences of lockdown for the population of diabetes patients not infected with COVID-19 in a medium-size Spanish Health Authority. It offers a longitudinal perspective, considering variables related to clinical parameters, drug consumption and the use of health resources together.

Our results suggest that diabetes patients without COVID-19 have been able to cope adequately with the restrictions imposed, with no clinically significant impact on their diabetes control.

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Institutional Review Board Statement: The procedures that constitute this work comply with the ethical standards of the Aragón Clinical Research Ethics Committee (belonging to the Department of Health of the Government of Aragón, Spain), and with the Declaration of Helsinki of 1975, and its version revised in 2008. The Study Protocol was approved by the Aragón Clinical Research Ethics Committee (PI20–175).

Informed Consent Statement: The data of the participating patients were obtained anonymously from the medical records provided by the Aragón Health Service. This report does not contain patient identifiable data. Consent from individuals involved in this study was not required. The treatment, communication and transfer of this personal data was in accordance with the provisions of Regulation (EU) 2016/679 of the European Parliament and Organic Law on the Protection of Personal Data and guarantee of digital rights 03/2018.

Data Availability Statement: This report does not contain patient identifiable data. Consent from individuals involved in this study was not required. Requests for any underlying data cannot be granted by the authors because the data was acquired under a license/data sharing agreement with the Aragon Health Services, under which conditions of use (and further use) apply.

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Manuscrito 2: Sex Differences in Clinical Parameters, Pharmacological and Health-Resource Utilization in a Population With Hypertension Without a Diagnosis of COVID-19.

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Sex Differences in Clinical Parameters, Pharmacological and Health-Resource Utilization in a Population With Hypertension Without a Diagnosis of COVID-19

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Objectives: Determine the changes in clinical, pharmacological and healthcare resource use parameters, between the 6 months prior to the lockdown and the 6 months following its end, in a population with hypertension who did not have a diagnosis of COVID-19.

Methods: Real world data observational study of 245,979 persons aged >16 years with hypertension in Aragon (Spain). Clinical (systolic-diastolic blood pressure, estimated glomerular filtration rate (eGFR), blood creatinine, cholesterol, triglycerides and anthropometric measures); pharmacological (diuretics, calcium channel antagonists, and ACE inhibitors); and utilization of healthcare resources were considered. We performed the Student's T-test for matched samples (quantitative) and the Chi-squared test (qualitative) to analyze differences between periods.

Results: SBP, DBP, parameters of renal function and triglycerides displayed a significant, albeit clinically irrelevant, worsening in women. In men only DBP and eGFR showed a worsening, although to a lesser extent than in women. Certain antihypertensive drugs and health-resource utilization remained below pre-pandemic levels across the 6 months post-lockdown.

Conclusion: Changes in lifestyles, along with difficulties in access to routine care has not substantially compromised the health and quality of life of patients with hypertension.

Keywords: utilization, lockdown, pharmacoepidemiology, lifestyle behaviours, hypertension (HTN), COVID-19 epidemic

INTRODUCTION

Cardiovascular diseases are the leading cause of morbidity and mortality globally, and in 2019 accounted for 17.9 million deaths, almost one third of the sum total [1]. Among these diseases, complications of arterial hypertension (AHT) (defined as systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg measured in a doctor's office) cause 9.4 million deaths each year [2, 3].

AHT is one of the most prevalent chronic diseases, affecting over one billion persons worldwide [4]. In Spain, some 14 million adults have high blood pressure (BP) (33%), with prevalence of this disease rising to double (66%) among persons over 60 years of age [3]. According to the Aragon Regional Health Authority, in 2018, 19% of men and 20% of women had a diagnosis of AHT, percentages that rose to 60% among those over the age of 65 [5]. With over 1,300,000 inhabitants, Aragon has a rapidly aging population, with this phenomenon being more pronounced in rural than in urban areas. The capital, Zaragoza, concentrates over 80% of the population, while rural towns with fewer than 2,000 inhabitants, which represent 92% of the region's urban centers, account for only 16% of the population [6].

A number of chronic conditions, including AHT [7], have been associated with a worse COVID-19 disease course. Even so, this relationship would not seem to be altogether clear for this disease, i.e., although there are several studies which suggest that persons with high blood pressure present with a higher risk of poor prognosis and mortality in the case of COVID-19 [8, 9], this association could well be confounded by age [7, 10]. AHT is very frequent among advanced age groups, which have undeniably proven to be especially vulnerable to the new virus SARS-CoV-2. There is, however, sufficient evidence to show a higher risk of hospital mortality due to COVID-19 among patients with underlying complications stemming from high blood pressure levels (such as heart failure, kidney disease or stroke) [11–13].

Good management and control of blood pressure during the pandemic is fundamental to reduce both the burden of this disease, and any ensuing cardiovascular complications and worse prognosis among infected patients [7]. Prior to the COVID-19 outbreak, health professionals at primary care (PC) centers played an important role in the promotion of healthy lifestyles [14], by trying to ensure the prevention, early detection and control of this and other chronic diseases [15]. Once BP levels have been successfully stabilized, the standard follow-up recommended for such patients is a check by nursing staff every 3–6 months, and an annual examination by the physician or a joint examination by both professionals [16]. The outbreak of the pandemic in March 2020 modified the functions of PC teams, a development that possibly had an impact on the follow-up of patients with AHT. Since healthcare services were forced to focus their resources on diagnosis and treatment of COVID-19 [17], this entailed a reduction in routine face-to-face care of persons with AHT and other chronic diseases [18].

Furthermore, AHT is strongly influenced by virus control measures [19]. On 15 March 2020, the Spanish government declared a nationwide state of alarm, thereby placing the public under home confinement until 3 May. By limiting the possibility of engaging in physical activity, these measures could thus have increased sedentary behaviors among these patients [20]. Similarly, isolation could generate feelings of loneliness and increase levels of anxiety or stress [21], negative feelings which are associated with developing unhealthy lifestyles, such as the intake of hypercaloric diets [22], or tobacco and alcohol consumption [23, 24].

The implications of COVID-19 therefore go beyond the harm related with the infection itself. Less rigorous control of blood pressure, coupled with the adoption of unhealthy lifestyles during strict lockdown, could increase the likelihood of suffering some complication or cardiovascular event, something that would translate as an increase in the burden of these diseases in the medium term.

The great majority of studies on AHT and COVID-19 have investigated the influence exerted by this disease on the prognosis of infected patients [7–10], as well as the association between antihypertensive drugs and risk of infection [25]. Far fewer studies have analyzed the impact of the pandemic on the uninfected population with AHT [26–28]. Hence, the aim of this study was to analyze changes in clinical parameters, use of antihypertensive drugs, and health-resource utilization between the 6 months pre-lockdown and the 6 months post-lockdown, among patients older than 16 years in Aragon who were shown to be diagnosed with AHT in their electronic medical records (EMR) but who did not have a diagnosis of COVID-19 during the study period.

METHODS

Study and Design Population

A real world data observational study of the population over the age of 16 years in a region in the north of Spain, Aragon (n = 1,122,151). To ascertain the repercussions of lockdown measures on the health of the population with hypertension (n = 259,808), we decided to include only those patients >16 whose EMR showed diagnosis of AHT as per the International Classification of Diseases 10th Revision [29], who during the months of study, did not have a diagnosis of COVID-19 (n = 245,979).

For each individual, we obtained EMR data across the 6 months immediately before lockdown (14 September 2019–15 March 2020) and the 6 months immediately after lockdown (03 May 2020–04 November 2020).

Data-Sources

This study was based on data sourced from longitudinal EMR of primary care in Aragon.

EMR are widely established in Spain; and in the case of Aragon, implementation of EMR in the region's health system concluded in 2011. All data generated in the healthcare process (PC and hospital) of patients enrolled in Spain's national health system, which has a population coverage of over 90%, are pooled and shared by all the professionals in the system.

Variables

The following sociodemographic variables were included in this study: sex, age, pharmaceutical services and rurality of the health zones (rural or urban with less or more than 10,000 inhabitants). In addition, we also considered the number of deaths in the study population for each of the periods measured.

For study purposes, we recorded the number of comorbidities and chronic comorbid conditions with prevalences higher than 5% [30] 1) somatic comorbidities: arrhythmias, heart failure, ischemic heart disease, dyslipidemias, obesity, overweight, vascular diseases, cerebrovascular disease, diabetes, chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease, hypo- and hyperthyroidism, anemia, neoplasm, hearing loss, cataracts, glaucoma, osteoarthritis, osteoporosis, dorsopathy and 2) psychological comorbidities: smoking habit, alcoholism, insomnia, anxiety and depression, autolytic attempt, and dementia.

We selected clinical and analytical parameters related with AHT (SBP, DBP, estimated glomerular filtration rate (eGFR), blood creatinine, total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, waist circumference, body weight, and body mass index (BMI)).

Variations in drug treatment were evaluated by reference to changes in the daily human doses (DHD) for each period, as shown by retail pharmacy dispensing. DHD are calculated on the basis of the standard daily defined dose (DDD) [a measure stipulated by the World Health Organization (WHO)] and other parameters, in accordance with the following formula:

$$DHD = \frac{Registered\ consumption\ of\ the\ active\ ingredient * 1000\ inhabitants}{Standard\ DDD * n^{o}inhabitants/period * 365\ days} \quad (1)$$

Taking into account the Anatomical Therapeutic Chemical (ATC) Classification System, we analyzed the following codes of the drugs of choice for treatment of this disease, as indicated by the Spanish Society for Family and Community Medicine (Sociedad Española de Medicina de Familia y Comunitaria – semFYC –) [31]: C03 (diuretics); C08 (calcium channel antagonists); and C09A (angiotensin-converting enzyme inhibitors – ACE inhibitors –).

Lastly, health-resource utilization by these patients was evaluated using variables linked to use of PC services (number of patients, and number of nursing and general practitioner (GP) visits for routine or continued care, at the health center or home; and number of patients and number of visits to other health center professionals, such as social workers, physiotherapists or midwives) and specialized services (number of visits to specialized care, number of diagnostic tests performed, number of visits to emergency services, hospitalizations and admissions to intensive care units (ICU), and duration of such stays), for each of the periods covered.

TABLE 1 | Sociodemographic data and chronic comorbidities in patients with hypertension, without diagnosis of COVID-19 (Aragon, Spain. November 2020).

	N (%)
Age	
Mean (SD)	70.0 (13.6)
Sex	
Men	117,924 (47.9)
Women	128,065 (52.1)
Pharmaceutical services	
<18,000	167,611 (68.1)
18,000–100,000	67,958 (27.6)
>100,000	1,147 (0.5)
Free drug prescriptions	6,835 (2.8)
Mutual insurance	2,294 (0.9)
Uninsured	134 (0.1)
Rurality of the health zones	
Urban	125,327 (51.0)
Rural	120,661 (49.0)
Number of comorbidities	
One	27,978 (11.4)
Two	40,629 (16.5)
Three	43,971 (17.9)
Four	40,529 (16.5)
Five	31,466 (12.8)
Six	21,486 (8.7)
Seven	13,556 (5.5)
More than seven	14,475 (5.9)
Chronic comorbidities (Yes %)	
Arrhythmias	25,122 (10.2)
Heart failure	10,661 (4.3)
Ischemic Heart disease	18,669 (7.6)
Dyslipidemia	131,948 (53.6)
Obesity	47,859 (19.5)
Overweight	4,568 (1.9)
Vascular diseases	9,794 (4.0)
Cerebrovascular disease	19,421 (7.9)
Diabetes	57,295 (23.3)
Chronic bronchitis	3,749 (1.5)
COPD[a]	13,590 (5.5)
Asthma	15,104 (6.1)
Chronic kidney disease	28,762 (11.7)
Hypothyroidism	27,333 (11.1)
Hyperthyroidism	12,313 (5.0)
Anemia	38,482 (15.6)
Neoplasm	68,870 (28.0)
Hearing loss	24,660 (10.0)
Cataracts	40,586 (16.5)
Glaucoma	24,938 (10.1)
Osteoarthritis	31,807 (12.9)
Osteoporosis	31,575 (12.8)
Dorsopathy	75,172 (30.6)
Smoking habit	30,368 (12.3)
Alcoholism	3,848 (1.6)
Insomnia	38,183 (15.5)
Anxiety and depression	71,792 (29.2)
Autolytic attempt	458 (0.2)
Dementia	9,853 (4.0)

[a]Chronic obstructive pulmonary disease.

Statistical Analysis

Owing to the large sample size, parametric tests were used for analysis purposes [32]. We performed a descriptive analysis of the study variables, using frequencies, means and standard deviation.

For the clinical variables we calculated the mean and standard deviation (SD) of the parameters for each of the study time points (pre-lockdown and post-lockdown) by sex. If there was more than one measurement of the same parameter for the same

individual, the median and interquartile range (IQR) were calculated. To compare differences in means between the baseline measurement and the measurement at 6 months post-lockdown, we used the Student's T-test for matched samples.

To determine variations in clinical parameters, the proportion of people who had maintained, worsened or improved their BP values were calculated. People who had remained stable were defined as those who: 1) before and after lockdown presented values in range (I-I) or 2) before and after lockdown presented values out of range (O-O). Those who presented values in range before lockdown and after it presented values out of range were considered as worsening (I-O). Lastly, we considered as improvements those who had values out of range before lockdown and values in range after lockdown (O-I). Values greater than 140 and 90 mmHg for systolic and diastolic blood pressure, respectively, were considered out of range.

We use Chi-squared test for calculate the proportion of people who had maintained, worsened or improved by sex.

To ascertain variations in drug use, we calculated the DHD of the study population for each period, and transformed it into its annual equivalent.

To compares differences in the utilization of healthcare resources, we used the Student's T-test for matched samples in the case of quantitative variables, and the Chi-squared test in the case of qualitative variables. For those variables with less than 100 observations, a Wilcoxon rank test was used.

RESULTS

Six months after the end of strict lockdown in Aragon, a total of 245,979 persons over the age of 16 years with diagnosis of AHT in their EMR did not have a diagnosis of COVID-19 during the study period.

The descriptive analysis showed that: 52.1% of the population were women, mean age 70 years (SD: 13.6); over two thirds (68.1%) had an income of under 18,000 euros per year, and a little over half (51%) lived in urban areas. 95.2% of patients with AHT presented with some associated comorbidity, with the category of three related comorbidities being the one that embraced the highest number of individuals (17.9%). Among the chronic comorbidities, the most prevalent were dyslipidemias (53.6%), dorsopathies (30.6%), anxiety and depression (29.2%), neoplasms (28%), and diabetes (23.3%) (**Table 1**).

Of the 259,808 patients older than 16 years with a diagnosis of hypertension 13,829 were not included in the study. 4,485 because they had a diagnosis of COVID-19 during the study period and 9,344 because they died. Of these 4,352 died in the 6 months preceding the declaration of the state of emergency (14 September 2019 through 15 March 2020), and a further 4,992 in the 6 months following the end of lockdown (03 May 2020 through 04 November 2020). Taking into account the Aragon population in the middle of the period in each of the two measurement moments, the mortality rate per 1000 individuals was 3.3 (95%CI 3.2–3.4) and 3.7 (95%CI 3.6–3.9), respectively.

Changes in clinical parameters observed on comparing the baseline measurement with the measurement in the 6 months post-lockdown by sex, can be seen in **Table 2**. In women the parameters of SBP [$p < 0.001$ (95%CI: −0.69 to −0.37)], DBP [$p < 0.001$ (95%CI: −0.78 to −0.59)], eGFR [$p < 0.001$ (95%CI: 1.62–2.35)] blood creatinine [$p < 0.001$ (95%CI: −0.04 to −0.03)] and triglycerides [p 0.016 (95%CI: −4.64 to −0.48)] showed a slight, though significant, worsening with respect to the baseline measurement. In men only DBP [p 0.010 (95%CI: −0.24 to −0.03)] and eGFR [$p < 0.001$ (95%CI 0.83–1.64)] showed a worsening, although to a lesser extent than in women. For the rest of variables (total cholesterol, LDL, body weight and BMI) both sexes appeared to undergo a slight but equally significant ($p < 0.001$) improvement. The same trend was observed in HDL only in women [$p < 0.001$ (95%CI: 0.52 – 1.11)] and in triglycerides in men [p 0.001 (95%CI 2.19 – 7.95)].

Number and percentage of women and men with a stable evolution, deterioration or improvement in clinical parameters at 6 months is shown in **Table 3**. For SBP approximately 2/3 remain unchanged (I-I or O-O), with no differences according to sex. For individuals who improve (O-I) there are significant differences between the clinical evolution of the parameters and sex, therefore improvements in SBP and DBP depends on sex. The same differences can be seen in SBP for individuals who worsened (I-O).

With respect to drug use (**Table 4**), in the 6 months post-lockdown the total number of DHD of diuretics dispensed at pharmacies showed a slight increase in comparison with the previous 6 months, with the exception of two thiazide diuretics (Chlorthalidone and Xipamide) which registered a decrease in this same period. In the case of calcium channel antagonists, the number of DHD of all Dihydropyridines (except Nicardipine and Lercardipine) and Bencilalquilaminas/Phenylalkylamines (Verapamil) fell, in contrast to Benzothiazepines (Diltiazem) which saw a rise in the last 6 months. As regards ACE inhibitors, the total number of DHD also decreased in all the drugs in this group (except Quinapril, Fosinopril and Trandolapril).

In terms of health-resource utilization, as **Table 5** shows, the total number of patients with AHT but without a diagnosis of COVID-19 who visited PC services in the 6 months after the end of strict lockdown, fell as compared to the 6 months before the beginning of lockdown ($p < 0.001$). Only the number of patients who received home nursing visits (routine care) rose in comparison with the previous 6 months ($p < 0.001$).

Table 6 shows a decrease in the number of visits to nursing and family medicine services, both in routine and continued care, across the 6 months following the end of lockdown ($p < 0.05$), a decrease that was only significant in terms of the number of home nursing visits made to provide continued care (p 0.655, 95%CI: −0.17–0.27). With respect to the number of visits to other health center professionals, these fell solely in the case of physiotherapists ($p < 0.001$, 95%CI: 0.99–1.93), and rose in the case of midwives (p 0.003, 95%CI: −0.67 to −0.14) and social workers (p 0.002, 95%CI: −0.58 to −0.14).

When it came to the number of visits to specialized care, opposite but statistically significant trends were in evidence.

TABLE 2 | Clinical parameters 6 months pre-lockdown and 6 months post-lockdown (Aragon, Spain. September 2019–November 2020).

	Women					Men				
	N	6 months before	6 months after	95% CI	p	N	6 months before	6 months after	95% CI	p
		Mean (SD)	Mean (SD)				Mean (SD)	Mean (SD)		
SBP[a]	33,769	135.7 (13.9)	136.3 (15.4)	(−0.89; −0.37)	<0.001	26,126	136.2 (14.0)	136.0 (15.2)	(0.05; 0.40)	0.010
DBP[b]	33,763	75.6 (8.7)	76.3 (9.4)	(−0.78; −0.59)	<0.001	26,124	76.6 (9.3)	76.8 (9.7)	(−0.24; −0.03)	0.010
eGFR[c]	2429	72.8 (21.4)	70.8 (21.9)	(1.82; 2.35)	<0.001	1951	73.3 (20.8)	72.0 (21.5)	(0.83; 1.64)	<0.001
Blood creatinine	2452	0.8 (0.3)	0.9 (0.3)	(−0.04; −0.03)	<0.001	1984	1.1 (0.36)	1.1 (0.4)	(−0.04; −0.02)	<0.001
Total cholesterol	2446	199.0 (41.4)	195.1 (40.3)	(2.48; 5.26)	<0.001	1944	179.7 (40.2)	174.9 (39.5)	(3.26; 6.23)	<0.001
LDL[d]	2252	115.9 (36.3)	112.3 (35.1)	(2.38; 4.84)	<0.001	1781	103.6 (35.5)	100.1 (34.5)	(2.17; 4.84)	<0.001
HDL[e]	2322	56.8 (13.2)	56.0 (12.9)	(0.52; 1.11)	<0.001	1872	48.6 (16.2)	48.2 (12.3)	(−0.19; 0.99)	0.180
Triglycerides	2391	134.3 (68.3)	136.9 (71.2)	(−4.64; −0.48)	0.016	1921	138.3 (83.6)	133.2 (78.0)	(2.19; 7.95)	0.001
Waist circumference	931	100.9 (12.3)	100.9 (12.3)	(−0.29; 0.24)	0.853	857	106.4 (13.0)	106.3 (13.0)	(−0.16; 0.29)	0.563
Body weight	18,978	71.2 (13.2)	70.9 (13.5)	(0.23; 0.33)	<0.001	15,720	83.5 (13.9)	82.7 (14.1)	(0.69; 0.82)	<0.001
BMI[f]	11,689	29.8 (5.2)	29.7 (5.3)	(0.06; 0.12)	<0.001	9824	29.8 (4.4)	29.6 (4.5)	(0.19; 0.26)	<0.001

[a]Systolic blood pressure.
[b]Diastolic blood pressure.
[c]Estimated glomerular filtration rate.
[d]Low-density lipoproteins.
[e]High-density lipoproteins.
[f]Body mass index.

TABLE 3 | Number and percentage of patients with hypertension with a maintain get better or get worse evolution at 6 months (Aragon, Spain. September 2019–November 2020).

	Remain unchanged: (I-I[a] or O-O[b])			(I-O)[c]			(O-I)[d]		
	Women	Men	p	Women	Men	p	Women	Men	p
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
SBP[e]	31856 (73.5)	25014 (73.6)	0.573	6294 (14.5)	4604 (13.6)	<0.001	5219 (12.0)	4353 (12.8)	0.001
DBP[f]	40808 (93.7)	31538 (92.8)	<0.001	1708 (3.9)	1396 (4.1)	0.216	1014 (2.3)	1122 (3.3)	<0.001

[a]In range before and after lockdown.
[b]Out of range before and after lockdown.
[c]In range before lockdown and out of range after it.
[d]Out of range before lockdown and in range after it.
[e]Systolic blood pressure.
[f]Diastolic blood pressure.

Among patients with AHT, the number of first visits to specialized care rose in the 6 months after the end of lockdown ($p < 0.001$, 95%CI: −0.08 to −0.02), while the number of control visits to these same services fell across the same period ($p < 0.001$, 95%CI: 0.06–0.10).

In comparison with the previous 6 months, the number of X-rays, ultrasound, blood count, biochemistry, immunology and urine tests decreased among patients with AHT. In contrast, the number of resonances, CAT scans, microbiology and coagulation tests increased among these patients in the 6 months after the end of lockdown, with all these variations being statistically significant ($p < 0.05$).

Lastly, the number of visits to emergency services ($p < 0.001$, 95%CI: 0.08–0.13) and the number of hospitalizations ($p < 0.001$, 95%CI: 0.99–1.03) also decreased, with no statistically significant differences being found between the number of ICU admissions and the duration of hospital stay.

DISCUSSION

The results of our study suggest a clinically irrelevant slight worsening in blood pressure levels in the 6 months after the end of the lockdown, especially in women. These results are similar to the results of other articles [26, 27] that also show small variations or even improvement in blood pressure levels after lockdown.

Another longitudinal study [28] conducted in China from October 2019 through March 2020 showed that the hypertensive population in one of the areas hardest hit by the pandemic (Wuhan) experienced a higher increase in SBP during the growth phase of the epidemic in comparison with other less affected areas (with differences between 2.1 and 3 mmHg). However, these parameters again returned to normal or even reached values below pre-pandemic limits within a short period of time.

TABLE 4 | Number of daily human doses 6 months pre-lockdown and 6 months post-lockdown. (Aragon, Spain. September 2019–November 2020).

	6 months before	6 months after
	DHD[a]	
Diuretics		
Chlorthalidone	10.45	10.12
Xipamide	0.60	0.58
Indapamide	9.11	9.27
Furosemide	71.86	74.65
Bumetanide	0.11	0.11
Torasemide	13.05	13.45
Calcium channel antagonist		
Amlodipine	59.06	58.78
Felodipine	0.33	0.33
Nicardipine	0.10	2.16
Nifedipine	4.44	3.62
Nimodipine	0.43	0.41
Nisoldipine	0.04	0.03
Nitrendipine	0.35	0.26
Lacidipine	0.51	0.50
Manidipine	20.0	19.58
Barnidipine	5.62	4.91
Lercanidipine	10.77	10.78
Verapamile	1.89	1.67
Diltiazem	10.03	10.55
ACE[b] inhibitors		
Captopril	2.15	2.09
Enalapril	91.92	88.82
Lisinopril	13.35	13.0
Perindopril	1.96	1.84
Ramipril	63.20	61.10
Quinapril	0.04	1.69
Benazepril	0.06	0.05
Cilazapril	0.06	0.06
Fosinopril	0.02	0.56
Trandolapril	0.17	0.21
Imidapril	5.03	4.84

[a]*Daily human doses.*
[b]*Angiotensin–converting enzyme inhibitors.*

Spain was one of the European countries hardest hit by the virus. The slight increase in BP parameters observed in our study might be accounted for, in part, by this severity and by the particular susceptibility which persons with AHT, as a risk group, appear to show to the psychological consequences of the pandemic (anxiety, anguish, stress, etc.) [33, 34]. Some previous studies suggest that these stressful situations, the result of home lockdown and isolation, could have increased the activity of the sympathetic nervous system [33–35] and altered the quality of sleep [35, 36], with this in turn having particularly negative consequences on BP. As some works showed [37] the psychological consequences of the pandemic are more likely to be suffer by women, which could explain the greater worsening of blood pressure levels among the female gender in our study.

The nationwide lockdown imposed by the government to halt the propagation of the novel virus, has had an important impact, not only on people's psychological wellbeing, but also on their lifestyles and daily routines [38, 39]. These restrictive measures have hindered physical activity, thereby increasing exposure to sedentariness, something that could have contributed to the worsening of BP figures [40, 41]. Similarly, the development of unhealthy habits, such as high consumption of alcohol [42] and tobacco [43], during the months of lockdown, might have favored the increase in BP levels. As regards the slight improvements observed in cholesterol and anthropometric measurements, previous studies undertaken in this country during the months of lockdown [44], report healthy dietary changes in the Spanish population (with a higher consumption of fruit and vegetables, and a lower consumption of processed meat and sugar-sweetened beverages).

Control and follow-up of patients with hypertension after the introduction of drug treatment was already inadequate well before the pandemic, according to some studies [45, 46]. The successive waves of the pandemic in Spain have at times overwhelmed the healthcare services, which have destined a great deal of their resources to the diagnosis and treatment of positive cases, and additionally, to the immunization of the population [47]. This state of affairs, taken together with changes in social dynamics resulting from the decision to extend the restrictive measures, may well have delayed the normalization of BP parameters to pre-pandemic levels, as observed in the study by S. Zhang et al [28].

With respect to use of antihypertensive drugs in the 6 months following the end of lockdown, the reduction observed in the total number of DHD dispensed at pharmacies might be partly accounted for by difficulties in access to drug treatments, especially during the first wave [48]. Furthermore, at the

TABLE 5 | Number of patients who used Primary Care services 6 months pre-lockdown and 6 months post-lockdown (Aragon, Spain. September 2019–November 2020).

	6 months before		6 months after		*p*
	N	%	N	%	
No. of nursing patients (routine care) at health center or by telephone	166,214	67.57	152,034	61.81	<0.001
No. of nursing patients (routine care) at home	23,102	9.39	24,871	10.11	<0.001
No. of nursing patients (continued care) at health center	26,115	10.62	20,022	8.14	<0.001
No. of nursing patients (continued care) at home	7,970	3.24	6,225	2.53	<0.001
No. of GP[a] patients (routine care) at health center or by telephone	215,925	87.78	203,282	82.64	<0.001
No. of GP[a] patients (routine care) at home	22,656	9.21	17,034	6.92	<0.001
No. of GP[a] patients (continued care) at health center	43,085	17.51	36,746	14.94	<0.001
No. of GP[a] patients (continued care) at home	9,529	3.87	6,761	2.75	<0.001

[a]*General Practitioner.*

TABLE 6 | Number of visits and diagnostic test prescribed 6 months pre-lockdown and 6 months post-lockdown (Aragon, Spain. September 2019–November 2020).

	N	6 months before	6 months after	95%CI	p
		Mean (SD)			
No. of nursing visits (routine care) at health center or by telephone	125,990	4.51 (4.91)	3.80 (4.49)	0.69; 0.74	<0.001
No. of nursing visits (routine care) at home	12,472	6.64 (9.71)	6.22 (9.43)	0.26; 0.60	<0.001
No. of nursing visits (continued care) at health center	5,180	2.17 (3.17)	1.91 (2.82)	0.17; 0.34	<0.001
No. of nursing visits (continued care) at home	1,494	2.25 (3.31)	2.21 (3.98)	−0.17; 0.27	0.655
No. of GP[a] patients (routine care) at health center or by telephone	185,259	5.09 (4.16)	5.03 (4.61)	0.05; 0.09	<0.001
No. of GP[a] patients (routine care) at home	7,181	3.42 (3.63)	2.68 (2.88)	0.66; 0.82	<0.001
No. of GP[a] patients (continued care) at health center	11,868	1.79 (1.70)	1.83 (1.96)	−0.07; 0.00	0.079
No. of GP[a] patients (continued care) at home	1,640	1.73 (1.38)	1.63 (1.28)	0.02; 0.18	0.009
No. of visits to other professionals					
Physiotherapist	905	5.84 (6.16)	4.38 (4.96)	0.99; 1.93	<0.001
Midwife	400	1.98 (1.82)	2.39 (2.17)	−0.67; −0.14	0.003
Dental stomatologist	537	2.15 (1.72)	2.33 (1.77)	−0.38; 0.02	0.084
Social worker	855	2.53 (2.54)	2.88 (3.22)	−0.58; −0.14	0.002
No. of specialized care visits (first visit)	7,430	1.45 (0.84)	1.51 (0.88)	−0.08; −0.02	<0.001
No. of specialized care visits (successive visits)	61,878	2.61 (2.18)	2.53 (2.32)	0.06; 0.10	<0.001
No. of diagnostic test performed					
X-rays	34,541	1.13 (1.25)	0.96 (1.14)	0.15; 0.18	<0.001
Ultrasound	34,541	0.31 (0.55)	0.29 (0.53)	0.01; 0.02	<0.001
Resonance	34,541	0.12 (0.36)	0.13 (0.36)	−0.01; −0.00	0.002
CAT scans	34,541	0.31 (0.62)	0.32 (0.63)	−0.02; −0.01	<0.001
Blood count	43,387	0.31 (0.54)	0.23 (0.49)	0.07; 0.08	<0.001
Biochemistry	43,387	1.01 (0.66)	0.93 (0.67)	0.07; 0.09	<0.001
Microbiology	43,387	0.22 (0.62)	0.28 (0.69)	−0.07; −0.06	<0.001
Immunology	43,387	0.14 (0.39)	0.12 (0.36)	0.02; 0.02	<0.001
Coagulation test	43,387	0.03 (0.19)	0.04 (0.22)	−0.01; −0.01	<0.001
Urine test	43,387	0.35 (0.60)	0.31 (0.58)	0.03; 0.05	<0.001
No. of visits to emergency service	10,302	1.89 (1.24)	1.59 (1.15)	0.08; 0.13	<0.001
No. of hospital admissions	15,199	1.27 (0.67)	0.26 (0.67)	0.99; 1.03	<0.001
No. of days of hospital stay	2,725	15.35 (66.33)	14.91 (65.19)	−0.31; 1.20	0.249
No. of ICU[b] admissions	5	1 (0.00)	1 (0.00)		[c]
No. of days of ICU[b] stay	5	101.40 (87.67)	100.20 (89.33)	−2.13; 4.53	0.317[d]

[a]General Practitioner.
[b]Intensive Care Unit.
[c]The correlation and t cannot be calculated because the standard error of the difference is 0.
[d]Wilcoxon rank test.

outset of the pandemic, some papers suggested that treatment with antihypertensive drugs which act on the renin–angiotensin–aldosterone system might be a risk factor, in terms of severity, for hospitalized patients with COVID-19 infection [49]. Despite the fact that some scientific societies subsequently contradicted this [50], use of these drugs may have been slightly reduced.

Six months after the end of lockdown, PC services continue to receive fewer patients with hypertension than they did in the previous 6 months. Only those patients who received a home visit by their nurse (routine care) experienced an increase in the following 6 months. Fear of becoming infected and a possible worse prognosis, or the collateral effects of lockdown on the health status of older patients with hypertension may have hindered or prevented them from visiting the health center [51].

Similarly, 6 months after the end of strict lockdown, the number of visits to healthcare services (primary and specialized care) and the performance of diagnostic tests on patients with hypertension, have still not reached pre-pandemic levels. These results are consistent with those published by the WHO in its survey of national capacity for the prevention and control of non-transmissible diseases, in which 53% of the countries surveyed reported total or partial interruptions in hypertension-management services as a consequence of the pandemic [52].

With reference to the number of visits to other health center professionals, other studies [53, 54], suggest a decrease in midwife visits during lockdown what it meant a decrease in gynecological cancer diagnosis. This delay might have led to an increase in the number of visit during the following months, which would explain the results of our study. The social and economic impact of the health crisis would account for the increase in visits to PC social services [55]. Lastly, the observed increase in initial visits to specialized care might entail an increase in the number of patients on waiting lists. This could delay the diagnosis of some diseases and favor the development of complications.

As regards the increase in observed mortality in the second 6 months of the study period, the interruption in healthcare services for cardiovascular diseases during the pandemic could have delayed referral, diagnosis, and treatment of these diseases, thus contributing to the excess deaths [56].

Strengths and Limitations

Our study has some limitations. First, its large sample size means that small variations in these parameters may prove statistically significant.

Second, it is not known whether measurement of BP was exclusively made during nursing visits or whether, in contrast, it was combined with arterial self-measured blood pressure (SMBP) monitoring, something that would allow for a more accurate diagnosis to be made.

Thirdly, we only know the number of patients without a diagnosis of COVID-19, which is different from the number of patients without the disease (real non – infected). Moreover, in the case of some clinical variables, there are very few records. To be able to access these, a GP must validate the data. What this means in the context of this study is that we only had access to measurements which had been validated by GPs.

Furthermore, our study did not include self-reported data on the lifestyles (physical activity, eating habits, tobacco and alcohol consumption, etc.) followed by the population with hypertension during the months of lockdown. Hence, undertaking studies which included qualitative data and information on lifestyles would make it possible to better ascertain the effect of lockdown on the maintenance of daily routines and control of hypertension.

Lastly, it would be of interest to ascertain the trend in the clinical parameters of this disease over a longer period of time (i.e., 12 months after the end of strict lockdown).

Conclusion

This study contributes, from a longitudinal standpoint, to knowledge of the consequences of lockdown on a sample of patients with AHT but without a diagnosis of COVID-19 infection, by simultaneously considering clinical, pharmacological, and health-resource utilization variables.

The results of our study suggest that the COVID-19 pandemic has hindered access to routine care by patients with chronic diseases such as hypertension. However, the cancellation of medical visits and tests, coupled with changes in lifestyles induced by the pandemic, has not substantially compromised the health and quality of life of these patients.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Aragón Clinical Research Ethics Committee. (protocol code P 120/175, date of approval 13 May 2020). Written informed consent from the participants or their legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Conceptualization, BO-B and RM; formal analysis, SC-V, AC, BO-B, and AL-C; writing—original draft preparation, AL-C; writing—review and editing, BO-B, AC, JP-C and RM; supervision, BO-B, AC and RM. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Manuscrito 3: Analysis of Clinical Parameters, Drug Consumption and Use of Health Resources in a Southern European Population with Alcohol Abuse Disorder during COVID-19. Pandemic.

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Article

Analysis of Clinical Parameters, Drug Consumption and Use of Health Resources in a Southern European Population with Alcohol Abuse Disorder during COVID-19 Pandemic

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Abstract: The disruption in healthcare attention to people with alcohol dependence, along with psychological decompensation as a consequence of lockdown derived from the COVID-19 pandemic could have a negative impact on people who suffer from alcohol abuse disorder. Observational real world data pre-post study included 9966 men aged >16 years registered as having the diagnosis of alcohol abuse disorder in the electronic medical records (EMR) of the Aragon Regional Health Service (Spain). Clinical (Glutamate-oxaloacetate-GOT-, Glutamate pyruvate -GPT-, creatinine, glomerular filtration, systolic blood pressure -SBP-, diastolic blood pressure -DBP-, total cholesterol, LDL, HDL, triglycerides, and body mass index -BMI-), pharmacological (dose per inhabitant per day, DHD, of drugs used in addictive disorders, benzodiazepines and antidepressants) and health resource use variables (primary and specialized care) were considered. A Student's *t*-test for matched samples was performed to analyze the changes in clinical variables between alcohol abuse disorder patients with and without COVID-19. Only creatinine and LDL showed a significant but clinically irrelevant change six months after the end of the strict lockdown. The total number of DHDs for all drugs included in the study (except for benzodiazepines), decreased. In the same way, the use of health services by these patients also decreased. The impact of COVID-19 among this group of patients has been moderate. The reorganization of health and social services after the declaration of the state of alarm in our country made possible the maintenance of care for this vulnerable population.

Keywords: COVID-19; alcohol use disorder; lockdown; primary care; lifestyle; health resources

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1. Introduction

The COVID-19 outbreak caused an unprecedented public health crisis around the world [1]. The declaration of the coronavirus disease as a pandemic in March 2020, and its dramatic development thereafter, exposed the world population [2], especially at the beginning of the pandemic, to stressful situations [3]. In an effort to contain the spread of this new SARS-CoV-2 virus, the governments of many countries established restrictive measures based on limiting mobility. In the case of Spain, the government declared a state of national emergency on 15 March 2020, forcing citizens to confine themselves to their homes until 3 May [4]. These measures, which were required to slow the spread of the virus, seem to have had a significant impact on the physical and mental health of the population [5].

Although many studies have shown an increase in the levels of stress, anxiety and depression during the months of lockdown among the general population [6–11], few studies have evaluated the effect of this pandemic and the consequent lockdown on alcohol consumption patterns, despite the fact that the consumption of this substance could have been used to reduce the intensity of negative feelings caused by home lockdown [12].

It is estimated that in the world there are 237 million men and 46 million women who suffer from alcohol use disorder. In 2016, the harmful use of this substance caused more than 3 million deaths worldwide (three-quarters of these, in men), representing 5% of the global burden of disease [13]. Globally, that same year, alcohol consumption was the seventh highest risk factor for premature death and disability, and was the main risk factor among the population aged 15 to 49 years [14]. Among young men in this age group, alcohol abuse is also the leading cause of disability in our country [15].

Studies on the impact of the pandemic and lockdown on the consumption patterns of this substance in the general population show variability in their results. Some studies report a decrease in consumption during the months of lockdown [16,17], while other studies report an increase in consumption [18,19]. Those who increased their alcohol intake during lockdown experienced higher levels of stress, anxiety or depression than those who maintained their habitual consumption or reduced it [16,18,20,21]; likewise, this increase was associated more frequently with individuals who declared themselves addicted to alcohol before the pandemic [17]. Some studies suggested that the psychological decompensation resulting from lockdown away from a socio-affective network could cause an increase in alcohol consumption and in the number of relapses among those who had alcohol consumption disorders before the pandemic [22–24].

Before the pandemic, primary care (PC) services attended to most of the demands related to alcohol problems, therefore, a significant number of visits in these centers were motivated by this problem and by the pathologies related to alcohol consumption [15]. The pandemic, especially at the beginning, forced individuals to modify the functions of the PC teams, among which were the detection and early diagnosis of alcohol abuse disorder, the performance of motivational interventions and the referral to specialized treatment centers.

Changes in daily routines and the interruptions of care services for people with alcohol abuse disorder could have a particularly negative impact on the health status of this group [13,22]. Without a structured routine of non-alcohol related activities and without behavioral therapies, people with alcohol abuse disorders could more easily succumb to drinking during lockdown [22].

This increase in alcohol consumption during the pandemic could in turn worsen their health. Enough evidence has shown the existence of a dose-dependent effect between chronic alcohol consumption and viral infections (hepatitis C, HIV); thus, people with alcohol abuse disorders could have a higher risk of contracting COVID-19 [25]. Among this group, consumption of other substances (tobacco and other drugs) [26,27] and comorbidity with chronic (cancer, cardiovascular disease, liver disease, pancreatitis or diabetes) [28] and psychiatric pathologies (depression, disorder of generalized anxiety or bipolar disorder) is frequent [29], which could make them especially susceptible to a worse prognosis of infection [30].

Despite the fact that various studies have analyzed the impact of the pandemic and lockdown on the population with alcohol dependence during the peak of the pandemic, fewer articles have studied the impact of both in the following months after the end of the lockdown. The aim of this study is to analyze the changes in the clinical parameters, the consumption of drugs for the treatment of this addiction and the use of health resources between the six months before the start of the lockdown and the six months after its end in men diagnosed with alcohol abuse disorder in an autonomous community in northern Spain; we also aim to compare the variations in clinical parameters between patients with alcohol dependence not infected and those who were infected by COVID-19.

2. Materials and Methods

2.1. Design and Study Population

Observational real world data were collected pre-post study of men over 16 years of age in the Autonomous Community of Aragon (Spain), diagnosed with alcohol abuse disorder in their electronic medical records (EMR) according to the criteria of the International Classification of Primary Care (ICPC-2): code P15 [31]. This disorder is characterized by the loss of control over drinking, cause in the individual the compulsion to drink alcohol continuously or periodically in order to experience psychic effects or avoid the discomfort caused by its absence [32].

From the EMR, information was collected for each individual in the six months prior to the start of the lockdown (14 September 2019–15 March 2020) and in the six months after its end (3 May 2020–11 April 2020). The records collected during the months of strict lockdown were not considered because these were very scarce.

Finally, to find out which clinical parameters might be present more frequently in individuals with and without the infection we also investigated the differences in clinical parameters in the six months prior to the start of lockdown and in the six months after its ends, among individuals with a diagnosis of alcohol abuse who did not contract COVID-19 during the period of study and those who contracted the infection.

2.2. Data Sources

This study is based on data from the electronic medical records of the PC services of Aragon.

The implementation of EMR was completed throughout the Aragon health system in 2011. This record, shared by all the professionals that are part of the health system, contains the data generated throughout the care process (PC and hospital care) by the patients covered under the National Health System.

2.3. Variables

The sociodemographic variables included in this study were: sex, age, pharmaceutical service and basic health area. The number of deaths among the population under study for each of the measurement periods was also collected; as well as chronic comorbidities with prevalences greater than 5% [33] (arrhythmias, heart failure, ischemic heart disease, hypertension, dyslipidemia, obesity, overweight, disease in veins and arteries, cerebrovascular disease, diabetes, chronic bronchitis, COPD, asthma, disease kidney, hypo and hyperthyroidism anemia, neoplasia, hearing loss, cataracts, glaucoma, osteoarthritis, osteoporosis, dorsopathy, smoking, insomnia, chronic anxiety and depression, attempted suicide, and dementia).

Regarding the clinical and analytical parameters related to chronic alcohol consumption, the following were included: glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), blood creatinine, glomerular filtration, systolic (SBP) and diastolic blood pressure (DBP), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and body mass index (BMI).

Changes in pharmacological treatment were assessed through variations in the total number of defined daily doses per 1000 inhabitants per day (DHD) dispensed in the pharmacy. DHDs were calculated from the defined daily dose (DDD) stipulated by the World Health Organization (WHO), according to the following formula:

$$\mathrm{DHD} = \frac{\text{Registered consumption of the active ingredient} * 1000 \text{ inhabitants}}{\text{StandardDDD} * \text{nº inhabitants/period} * 365 \text{ days}} \quad (1)$$

Taking into account the anatomical, therapeutic, chemical (ATC) classification system, the codes of the drugs of choice for the treatment of this pathology were analyzed according to the Spanish Society of Family and Community Medicine (Sociedad Española de Medicina

de Familia y Comunitaria—semFYC) [34]: N07 (drugs used in additive disorders), N05 (benzodiazepines) and N06 (antidepressants).

Lastly, the use of health resources by these patients was assessed with the use of PC services (number of ordinary or continuous care visits at the health center or at home by the nurse or the general practitioner, and number of visits to other professionals in the health center) and with the use of hospital services (number of visits in outpatient care, number of diagnostic tests performed, number of visits to the emergency service, and number of hospitalizations) for each of the periods.

2.4. Statistical Analysis

The sample size allowed the use of parametric methods [35]. In order to know the sociodemographic characteristics and the most frequent chronic comorbidities among the study population, a descriptive analysis was carried out using frequencies, means and standard deviation.

For the clinical variables, the mean and standard deviation (SD) of each parameter at each of the study moments was calculated. If for the same individual there was more than one measurement for the same parameter, the mean and interquartile range (IQR) were calculated. To compare the differences in means in the clinical parameters between the previous measurement and the measurement at six months, the Student's *t*-test for paired samples was used.

After carrying out the Levene tests of homogeneity of variances, the Student's *t*-test (for equal or unequal variances) was used to compare the changes in clinical parameters between alcohol abuse disorder patients infected with COVID-19 and with those who did not contract the infection. For those variables with a fewer number of observations than 100, a Wilcoxon rank test was used.

Differences in drug consumption were assessed through the DHDs dispensed in the pharmacy to the study population in each of the periods. To determine the variations in the use of healthcare resources, the Student's *t*-test for paired samples was also used.

A statistical analysis was carried out using IBM SPSS Statistic 21 (IBM Corporation, New York, NY, USA) and R version 4.0.5. (R Foundation for Statistical Computing, Vienna, Austria).

2.5. Ethical Considerations

This work was carried out under the principles of the Declaration of Helsinki and complies with the ethical standards of the Aragón Clinical Research Ethics Committee (study protocol PI20–175).

The Aragonese Health Service provided the medical records of the patients included in the study. The treatment, communication and transfer of these personal data was adjusted to the provisions of Regulation (EU) 2016/679 of the European Parliament and Organic Law on Protection of Personal Data and guarantee of digital rights March 2018.

3. Results

Six months before the start of the lockdown, 9576 men over 16 years of age in Aragon had a diagnosis of alcohol abuse in their EMR. 9184 (95.9%) did not become infected with COVID-19 during the study months; 392 (4.1%), however, presented with the infection during the same period of time. Of these, 39 cases were declared during the months of lockdown and 351 in the six months after its end. Regarding the number of deaths from other causes than COVID-19, three people died in the months prior to the declaration of the state of alarm, 41 during lockdown and 145 in the following six months.

The mean age of the sample was 56.4 (12.9). Almost two thirds (71.3%) had an income of less than EUR 18,000 per year and more than half (51%) lived in urban areas with more than 10,000 inhabitants. Among the male population with chronic alcohol consumption, the most frequent chronic comorbidities were: dyslipidemia (46.1%), followed by smoking (44.3%), hypertension (36.9%) and anxiety and depression (30.4%) [Table 1].

Table 1. Sociodemographic data and chronic comorbidities in alcohol abuse disorder patients from Aragon.

Age	**Mean (SD)**	**56.4 (12.9)**
		N (%)
Pharmaceutical service		
<18,000		6824 (71.3)
Between 18,000–100,000		2007 (21.0)
>100,000		19 (0.2)
Free pharmacy		696 (7.3)
Mutualist		26 (0.3)
Uninsured		4 (0.0)
Basic health area		
Urban		5279 (55.1)
Rural		4297 (44.9)
Chronic comorbidities (Yes %)		
Somatic comorbidities		7820 (81.7)
Arrhythmias		519 (5.4)
Heart failure		195 (2.0)
Ischemic heart disease		532 (5.6)
Hypertension		3534 (36.9)
Dyslipidemia		4418 (46.1)
Obesity		1327 (13.9)
Overweight		160 (1.7)
Disease in veins/arteries		505 (5.3)
Cerebrovascular disease		464 (4.8)
Diabetes		1584 (16.5)
Chronic bronchitis		182 (1.9)
COPD		1009 (10.5)
Asthma		356 (3.7)
Chronic kidney disease		337 (3.5)
Hypothyroidism		350 (3.7)
Hyperthyroidism		117 (1.2)
Anemia		947 (9.9)
Neoplasia		2015 (21.0)
Hearing loss		763 (8.0)
Cataracts		714 (7.5)
Glaucoma		406 (4.2)
Osteoarthritis		419 (4.4)
Osteoporosis		110 (1.1)
Dorsopathy		2197 (22.9)
Psychological comorbidities		6231 (65.1)
Smoking		4241 (44.3)
Insomnia		1377 (14.4)
Anxiety and depression		2910 (30.4)
Autolytic attempt		149 (1.6)
Dementia		140 (1.5)

Standard deviation (SD); Chronic obstructive pulmonary disease (COPD).

The variations in the clinical parameters of these patients when comparing the baseline measurement with the measurement in the following six months can be observed in Table 2. Only the subtle worsening observed in blood creatinine [$p = 0.027$ (95% CI: −0.06–−0.00)] and the slight improvement in LDL cholesterol [$p = 0.043$ (95% CI: 0.25–16.06)] presented statistically significant differences.

Table 2. Changes in the clinical parameters of alcohol abuse disorder patients before and after lockdown.

		Six Months before	Six Months after	Difference between Pre—Follow Up	
	N	Mean (SD)		95% CI	*p*
GOT	87	33.5 (36.3)	29.7 (15.7)	−3.81; 11.31	0.327
GPT	94	29.5 (30.3)	27.6 (17.2)	−4.53; 8.31	0.561
Blood creatinine	110	0.9 (0.3)	1.0 (0.3)	−0.06; −0.00	0.027
Glomerular filtration	110	85.9 (20.9)	84.1 (21.4)	−0.08; 3.72	0.060
Systolic blood pressure	941	135.9 (15.8)	135.7 (16.5)	−0.83; 1.16	0.749
Diastolic blood pressure	941	78.0 (10.1)	77.9 (10.4)	−0.51; 0.70	0.752
Total cholesterol	109	204.5 (53.4)	198.3 (50.3)	−2.56; 14.93	0.164
LDL	92	119.9 (48.2)	111.7 (41.5)	0.25; 16.06	0.043
HDL	100	55.2 (19.4)	54.8 (19.0)	−2.16; 2.99	0.748
Triglycerides	102	148.3 (122.1)	151.2 (89.2)	−21.73; 15.91	0.760
BMI	347	30.3 (5.4)	30.2 (5.5)	−0.05; 0.27	0.179

Glutamate—oxaloacetate (GOT); Glutamate pyruvate (GPT); Low density lipoprotein (LDL); High density lipoprotein (HDL); Body mass index (BMI); Standard deviation (SD); Confidence interval (CI).

Table 3 shows the changes in drug use patterns among the population with this disorder. For all drugs used in the treatment of alcohol dependence, the total number of DHDs experienced a decrease in the six months following the end of lockdown. The same trend is shown in the total number of DHDs of antidepressants, with the exception of sertraline. In contrast, the total number of DHDs of benzodiazepines (diazepam, lorazepam, alprazolam, triazolam, lormetazepam, midazolam and loprazolam) was increased compared to the six months prior to the start of the lockdown.

Table 3. Number of DHDs six months before and six months after lockdown.

	Six Months before	Six Months after
Drugs used in addictive disorders		
Varenicline	4.22	2.87
Disulfiram	0.73	0.71
Acamprosate	0.001	0.001
Nalmefene	0.46	0.44
Naltrexone	0.17	0.14
Benzodiazepines		
Anxiolytics		
Diazepam	13.24	13.47
Potassium clorazepate	2.23	2.16
Lorazepam	61.97	68.91
Bromazepam	0.75	0.74
Clobazam	0.03	0.02
Ketazolam	0.24	0.24
Alprazolam	142.48	152.26
Hypnotics and sedatives		
Flurazepam	0.14	0.14
Triazolam	2.74	2.83
Lormetazepam	209.92	215.45
Midazolam	0.25	0.28
Brotizolam	1.77	0.73
Quazepam	0.01	0.01
Loprazolam	0.74	0.78

Table 3. *Cont.*

	Six Months before	Six Months after
Antidepressants		
Non-selective monoamine reuptake inhibitors		
Imipramine	0.001	0.001
Clomipramine	0.09	0.08
Amitriptyline	0.11	0.10
Nortriptyline	0.003	0.002
Doxepin	0.00	0.00
Maprotiline	0.01	0.01
Selective serotonin reuptake inhibitors		
Fluoxetine	2.71	2.36
Citalopram	0.62	0.59
Paroxetine	2.81	2.80
Sertraline	1.37	1.41
Fluvoxamine	0.01	0.01
Escitalopram	17.15	16.65

Daily human dose (DHD).

Variations in the use of health resources by patients diagnosed with alcohol abuse can be seen in Table 4. In the six months after the end of the lockdown, the number of visits to the nurse at the health center, whether under ordinary [$p < 0.001$ (95% CI: 0.21–0.69)] or continued care [$p = 0.005$ (95% CI: 0.17–0.97)] experienced a statistically significant decrease. In contrast, the number of visits to the general practitioner at the health center for ordinary care [$p < 0.001$ (95% CI: −0.53;−0.23)] and the number of visits to social work services [$p = 0.013$ (95% CI: −3.14;−0.39)] showed a statistically significant increase in relation to the six months prior to the start of lockdown.

Regarding the performance of diagnostic tests on these patients, the number of X-rays, hemograms, biochemical, immunological and urine tests were reduced. In contrast, the number of resonances and microbiology tests increased [$p < 0.005$].

The number of visits to hospital care services (number of visits to accident and emergency services and number of hospitalizations) by patients diagnosed with alcohol abuse also shows a decrease which is only statistically significant for the number of hospitalizations [$p < 0.001$ (95% CI: 0.88–1.04)].

The comparison of the clinical parameters between patients with alcohol use disorder infected with COVID-19 and those not infected can be seen in detail in Table 5. Patients infected by COVID-19 presented higher BMI values than those who did not contract the infection. This difference was significant both for the six months prior to the start of lockdown [$p = 0.010$ (95% CI: −3.07; −0.42)] and for the six months after its completion [$p = 0.001$ (95% CI: −6.02;1.52)]. For the rest of the variables, no statistically significant differences were found.

Table 4. Number of visits and diagnostic tests prescribed six months before and six months after lockdown.

		Six Months before	Six Months after		
	N	Mean (SD)		95% CI	*p*
No. of nursing visits (ordinary care) at health centre or by telephone	2738	4.72 (6.35)	4.27 (5.87)	0.21; 0.69	<0.001
No. of nursing visits (ordinary care) at home	135	6.10 (9.99)	6.63 (13.37)	−2.11; 1.04	0.505
No. of nursing visits (continuous care) at health centre	261	2.58 (3.49)	2.01 (2.08)	0.17; 0.97	0.005
No. of nursing visits (continuous care) at home	33	3.06 (7.31)	2.67 (6.60)	−0.50; 0.01	0.165 [a]
No. of general practitioner visits (ordinary care) at health centre or by telephone	5799	5.19 (5.04)	5.57 (5.69)	−0.53; −0.23	<0.001
No. of general practitioner visit (ordinary care) at home	82	3.13 (2.98)	2.78 (2.50)	−0.53;0.01	0.345 [a]
No. of general practitioner visits (continuous care) al health centre	523	2.03 (1.96)	2.12 (2.45)	−0.31; 0.12	0.395
No. of general practitioner visits (continuous care) at home	38	1.68 (0.93)	1.45 (1.06)	−0.49; 0.02	0.230 [a]
No. of visits to other professionals					
Social worker	56	2.70 (2.68)	4.46 (4.64)	0.01; 2.50	0.016 [a]
No. of visits to specialised care (first consultation)	264	1.51 (0.94)	1.54 (1.00)	−0.19; 0.14	0.787
No. of visits to specialised care (successive consultations)	1812	2.72 (2.33)	2.71 (2.66)	−0.12; 0.13	0.925
No. of diagnostic test performed					
X-rays	1335	1.23 (1.46)	1.07 (1.44)	0.07; 0.25	0.001
Ultrasound	1335	0.36 (0.61)	0.32 (0.55)	−0.00; 0.07	0.079
Resonance	1335	0.12 (0.36)	0.15 (0.41)	−0.06; −0.00	0.044
CT scans	1335	0.46 (0.78)	0.51 (0.78)	−0.09; 0.01	0.101
Digestive test	1335	0.01 (0.13)	0.01 (0.15)	−0.01; 0.01	0.777
Hemograms	1178	0.34 (0.56)	0.28 (0.51)	0.03; 0.10	0.001
Biochemistry	1178	1.04 (0.67)	0.85 (0.71)	0.14; 0.24	<0.001
Microbiology	1178	0.20 (0.62)	0.33 (0.74)	−0.17; −0.07	<0.001
Immunology test	1178	0.21 (0.45)	0.15 (0.40)	0.02; 0.08	<0.001
Coagulation	1178	0.03 (0.17)	0.04 (0.22)	−0.02; 0.00	0.123
Urine test	1178	0.31 (0.58)	0.24 (0.55)	0.03; 0.10	<0.001
No. of visits to A&E department	614	2.14 (2.51)	2.01 (2.29)	−0.04; 0.31	0.138
No. of hospital admission	666	1.37 (0.79)	0.41 (0.85)	0.88; 1.04	<0.001

Accident and emergency (A&E); Standard deviation (SD); Confidence interval (CI). [a] Wilcoxon signed- rank test.

Table 5. Changes in the clinical parameters of patients with alcohol use disorder with COVID-19 and without COVID-19 before lockdown and six months after.

	Six Months before						Six Months after					
	With COVID		Without COVID				With COVID		Without COVID			
	N	Mean (SD)	N	Mean (SD)	95% CI	*p*	N	Mean (SD)	N	Mean (SD)	95% CI	*p*
GOT	32	30.3 (11.9)	615	34.8 (36.9)	−8.31; 17.39	0.488	35	35.5 (23.6)	460	38.0 (48.5)	−13.75; 18.78	0.761
GPT	35	34.5 (26.2)	656	33.0 (28.5)	−11.19; 8.16	0.758	36	38.6 (41.9)	496	35.4 (41.0)	−17.09; 10.75	0.655
Blood creatinine	37	0.9 (0.2)	700	0.9 (0.2)	−0.08; 0.07	0.829	36	0.9 (0.3)	544	1.0 (0.3)	−0.07; 0.13	0.512
Glomerular filtration	37	91.9 (18.1)	700	90.1 (18.0)	−7.75; 4.19	0.558	36	88.6 (17.2)	544	86.7 (20.0)	−8.67; 4.71	0.562
SBP	128	135.1 (17.7)	2519	135.5 (16.7)	−2.52; 3.44	0.761	60	134.3 (20.7)	1343	135.7 (17.1)	−3.09; 5.86	0.543
DBP	128	78.3 (10.9)	2515	79.6 (10.8)	−0.55; 3.28	0.162	60	77.4 (13.9)	1343	79.2 (11.2)	−1.09; 4.75	0.220
BMI	70	31.5 (6.0)	1277	29.7 (5.4)	−3.07; −0.42	0.010	24	33.6 (6.1)	585	29.8 (5.5)	−6.02; 1.52	0.001

Glutamate—oxaloacetate (GOT); Glutamate pyruvate (GPT); Systolic blood pressure (SBP); Diastolic blood pressure (DBP); Body mass index (BMI); Standard deviation (SD); Confidence interval (CI).

4. Discussion

The results of our study do not show clinically relevant changes in the biological markers of this disease which would suggest the stable maintenance of alcohol consumption during the months of lockdown.

Other studies published in the population with alcohol use disorder also contradict the hypothesis of an increase in consumption during the health crisis when showing this maintenance [36], or even a decrease in the consumption [37,38] of this substance after the start of the sanitary measures established to stop the spread of the virus. However, some studies have reported an increase in alcohol consumption [24] and in the number of relapses during the months of lockdown [39,40] or having a higher risk of consumption those who experienced emotional distress, or lived alone at the onset of the pandemic [41]. Two studies carried out in our country [24] show opposite results as well. One of them analyzed the impact of COVID-19 in patients with alcohol use disorder collecting data during lockdown or immediately after the end of it. Its results showed results opposite to ours. However, our study considered the following six months, which could explain this opposite trend. The other study in Barcelona [36], which collected the data two months later to the end of lockdown, exposed a reduction in the frequency of alcohol use during lockdown. Nevertheless, this last study and others [36,37,39] only used self-reported

The maintenance of clinical parameters observed in our study could in part be explained by the continuous provision of care to these patients during and after lockdown. Some foundations in our community, such as the Zaragoza Solidarity Center—Proyecto Hombre (CSZ—PH), were recognized by the Ministry of Health of the Government of Aragon as essential services. This recognition allowed these services to remain open at all times, providing telematic or even face-to-face care to all patients and their families [42]. The same situation was found in other Spanish regions, where the maintenance of basic care for patients with alcohol use disorder seems to have cushioned the impact of COVID-19 by promoting abstinence and therefore protecting against possible relapses [43].

Regarding the variations in the consumption of drugs in the six months after the end of the lockdown, there are no notable differences in the total number of DHDs dispensed by the pharmacy in the drugs used for the treatment of dependencies or in the antidepressants. These slight variations would once again highlight the adequate management during the COVID-19 pandemic of the patient with alcohol abuse disorder [43] through telephonic consultations. On the other hand, the high rates of irritability, anxiety or somatization that several studies have reported [36,41] among this population during the months of lockdown could be behind the increase in the number of DHDs of some benzodiazepines (diazepam, lorazepam, alprazolam, triazolam, lormetazepam, midazolam and joprazolam).

The use of resources from the National Health System by patients with alcohol abuse disorder experienced a decrease compared to the six months prior to the start of lockdown. These results are in line with those published by the WHO in the survey on the impact of the pandemic on mental, neurological and substance use services [44], where 93% of the surveyed countries declared interruptions in these services. Telemedicine has been consolidated as one of the most frequent and effective alternatives to overcome these interruptions [43–45], and could explain the increase in the number of ordinary face-to-face or telephone visits to the general practitioners observed in our work. The increase, according to various reports published in our country [46,47], in the demand for social services in the months after the pandemic could explain the notable increase in the number of consultations to social work services.

Patients with substance abuse disorders usually present physical and mental comorbidities [28,29], which have been considered by some studies [48,49] as risk factors of greater severity of COVID-19 infection. The results of our work reflect a higher prevalence of obesity among patients with alcohol abuse disorder infected by COVID-19, which could contribute to a worse prognosis and evolution of the disease.

Regarding the excess of mortality by other causes observed in the six months after the end of lockdown, the emotional distress experienced [36,41] by this group during the

pandemic months, the possible decompensations from other chronic comorbidities [50,51], together with the consequent economic crisis generated by COVID-19, could have increased mortality and the number of suicides [52]. Previous studies [53] have placed alcohol dependence among the diagnostic groups with the highest risk of suicide, behind depression and schizophrenia.

Our study has several limitations. First of all, we do not have access to a quantified record of alcohol consumption in Standard Drinking Units, nor to some of the specific structured questionnaires used in PC such as the CAGE or the Alcohol Use Disorders Identification Test (AUDIT). The exclusive use of the EMR also prevented the collection of self-reported data on the lifestyles maintained during the months of the pandemic. Second, we do not know the phase in which patients with alcohol abuse are at (detoxification, cessation or rehabilitation), therefore our results should be interpreted with caution. Thirdly, we did not consider the cause of death of these patients or the records collected during the months of strict lockdown, because these were very scarce. Nonetheless, lockdown could have had a particularly negative impact on alcohol consumption, as shown in a study in our country that was previously mentioned. Finally, the number of records for each of the clinical variables included in this study was very limited, so the power to detect significant differences is likely to be small. Access to these data depends on their validation by the general practitioner, so we only had access to the data that were validated by the doctor. Furthermore, the number of statistical tests and calculated *p*-values in this article is large and therefore needs to be confirmed in further studies.

5. Conclusions

Our study contributes to the knowledge from a longitudinal perspective of the consequences of the COVID-19 pandemic in the clinical, pharmacological and health resources use parameters of a large sample of men diagnosed with alcohol abuse disorder.

Although unforeseen, the results of our study suggest that the impact of COVID-19 among this group has been moderate. The reorganization of health and social services after the declaration of the state of emergency in our country made it possible to maintain care for this vulnerable group.

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Manuscrito 4: Analysis of Drug and Health Resource Use Before and After COVID-19 Lockdown in a Population Undergoing Treatment for Depression or Anxiety.

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Analysis of Drug and Health Resource Use Before and After COVID-19 Lockdown in a Population Undergoing Treatment for Depression or Anxiety

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Introduction: The arrival of the COVID-19 pandemic modified the functions of Primary Care (PC) teams, which were forced to focus their resources on the diagnosis and treatment of SARS-CoV-2 infected patients. The disrupted healthcare of individuals with pre-existing mental disorders (depression or anxiety), as well as the psychological decompensation resulting from the lockdown caused by the COVID-19 pandemic, may have modified the use of drugs and health resources by these patients. The aim of this study is to determine the changes in these parameters, between the 6 months prior to the lockdown (09/14/2019 to 03/15/2020) and the 6 months following its end (05/03/2020 to 11/04/2020), in a population undergoing active treatment for depression or anxiety, according to the electronic clinical record.

Materials and Methods: Real world data observational study of 110,694 individuals aged >16 years suffering from active or undergoing treatment for depression or anxiety according to the electronic medical records of the Aragon Regional Health Service (Spain). Pharmacological variables [daily dose per inhabitant (DHD) dispensed by pharmacies of: anxiolytics, hypnotics/sedatives, and antidepressants] and variables related to the use of healthcare resources (number of primary and specialized healthcare visits) were considered. Student's *T*-tests for paired samples were performed to analyze differences between periods (pre–post). The level of significance was established at 5% ($p < 0.05$).

Results: The use of anxiolytic drugs increased as compared to its use over the 6 months prior to the lockdown. In contrast, the consumption of antidepressants was found to decrease. The use of health resources continued to be below pre-pandemic levels, 6 months post-lockdown end.

Conclusion: Changes in the use of health resources could have a negative impact on the parameters of these diseases. The increase in drug use, especially benzodiazepines, may suggest a worsening of the symptoms during the lockdown and in the subsequent months. It is a worrying sign, which points to the growth of this public health problem and the need for its prevention.

Keywords: COVID-19, depression, anxiety, quarantine, lifestyle, primary health care

INTRODUCTION

In March of 2020, the World Health Organization (WHO) declared the COVID-19 pandemic (World Health Organization (WHO), 2020a). Since then, the global population has been exposed to an endless number of stressful events. The huge threat presented by this new virus has forced numerous governments to implement restrictive measures that included limited mobility and at-home confinement. With the continued rise in infections and deaths, Spain's government declared a national state of alarm on 15 March 2020, placing the population in an unprecedented lockdown (Gobierno de España, 2020). These restrictive measures were useful in decreasing the incidence of cases, but they had a major impact on the physical and psychological wellbeing of the population (Ramírez-Ortiz et al., 2020; Valdés-Florido et al., 2020); especially for those who suffer from pre-existing mental disorders (Sheridan Rains et al., 2021).

Despite the high global morbidity caused by these disorders, mental health continues to be one of the most neglected areas of healthcare. Many of these disorders are treated in Primary Healthcare (World Health Organization (WHO), 2018), where the prevalence of psychiatric morbidity ranges between 25 and 30% (García-Toro et al., 2012) and where one out of every four patient appointments is due to these disorders (Gobierno de Canarias, 2008).

The collapse of Primary Care (PC) services at the onset of the COVID-19 pandemic may have interrupted the continuous healthcare services of these patients (World Health Organization (WHO), 2012; Kozloff et al., 2020; United Nations, 2020); and similarly, the fear of infection may have lowered the demand at healthcare centers (World Health Organization (WHO), 2020b), causing the anticipated psychopathological imbalances and an increased a posteriori demand (World Health Organization (WHO), 2012; Kozloff et al., 2020).

Social and physical distancing measures may have also had an especially negative impact on individuals suffering from mental disorders (Kozloff et al., 2020). Maintaining daily routines and social relationships is essential for the proper handling of these disorders (Druss, 2020; Kozloff et al., 2020; Sheridan Rains et al., 2021). Therefore, the interruption of these routines during the lockdown months may have exacerbated their symptoms (Fernández-Aranda et al., 2020; Zhou et al., 2020; Sheridan Rains et al., 2021). and might have favor the acquisition of unhealthy habits, which may, in turn, might have influence the physical health of these patients. In them are frequent comorbidities with other physical and also psychiatric pathologies (Firth et al., 2019).

Despite the considerable changes in daily routines and the potential decline in healthcare services provided to these patients during this crucial lockdown period, few studies have considered the impact of the COVID-19 pandemic and lockdown on the population suffering from pre-existing mental disorders (Vindegaard and Benros, 2020; Sheridan Rains et al., 2021). The few studies that have been carried out on this topic have tended to assess the short-term impact of this situation (during the peak of the pandemic) (Fernández-Aranda et al., 2020; Hao et al., 2020; Liu et al., 2020) using self-completion questionnaires (Vindegaard and Benros, 2020). The use of drugs as anxiolytics and anti-depressants as well as the consumption of health care resources are quantifiable data that can reveal behavioral change (feelings of sadness or anxiety, anhedonia, sleep disturbances, irritability, frustration, etc.) in his population. These indicators could be an indirect means of revealing the variation in psychological suffering of the population. The objective of this study is to determine and to analyze these changes, between the 6 months prior to the lockdown and the 6 months following its end, in a population undergoing active treatment for depression or anxiety, according to the electronic clinical record (ECR).

MATERIALS AND METHODS

Design and Study Population

A real world data observational study of a population of northern Spain (Aragon) over the age of 16, undergoing active treatment for depression or anxiety, according to the ECR.

Patients having registered episodes of depression or anxiety have been included [codes F30–F39 and F41 of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)], as well as those who, during the study period, had been dispensed some of the active ingredients used to treat these two disorders, according to the Spanish Society of Family and Community Medicine (semFYC) (Sociedad Española de Medicina de Familia y Comunitaria [semFYC], 2020a,b). According to the anatomical, therapeutic, and chemical classification (ATC), the following analyzed codes were considered: N05B (anxiolytic drugs), N05C (hypnotics and sedatives), and N06A (antidepressants).

For each individual, information was obtained from their ECR during the two distinct time periods. The first measurement was taken from the records from the 6 months prior to the onset of the lockdown (09/14/2019 to 03/15/2020) and the second was taken from the records from the 6 months following the end of the lockdown (05/03/2020 to 11/04/2020).

The ECR is extensively consolidated in Spain and Aragon, where it was fully implemented in 2011. The data contained in it are generated throughout the healthcare process (hospital and PC) for patients seen by the National Healthcare System (90% coverage). This information is unified and available for all healthcare professionals in the system.

Variables

Sex, age, pharmaceutical provision, and basic rural or urban health area (with more than 10,000 inhabitants), were the sociodemographic variables included in this study. For each of the measurement periods, the number of deaths in the study population was also considered; also chronic comorbidities with prevalences of over 5% were considered (Calderón-Larrañaga et al., 2017) [arrhythmias, heart failure, ischemic cardiopathy, dyslipidemia, obesity, excess weight, vein and artery disease, cerebrovascular disease, diabetes, chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease, hypo and hyperthyroidism, tobacco use, alcoholism, insomnia, attempted suicide, anemia, neoplasia, dementia, deafness, cataracts, glaucoma, arthrosis, osteoporosis, and back pain].

Changes in drug consumption patterns have been assessed via the variation in daily dose per inhabitant (DHD) dispensed by pharmacies. Based on the defined daily dose (DDD) stipulated by the WHO, DHDs were calculated according to the formula shown below:

$$DHD = \frac{Registered\ consumption\ of\ the\ active\ ingredient \times 1,000\ inhabitants}{Standard\ DDD \times no.inhabitants/period \times 365\ days} \quad (1)$$

To calculate this unit of measurement, firstly we considered as denominator the population undergoing active treatment for depression or anxiety. After that, we considered as denominator the total population of Aragon in the middle of each period.

Use of healthcare resources by these patients during the two study periods was assessed according to the use of PC services (number of nursing or general practitioner visits at the healthcare center or number of at-home healthcare visits and number of visits to other healthcare center professionals: physiotherapists, midwives, odontostomatologists, and social workers) and of hospital services [number of specialized care visits, number of diagnostic tests performed, number of visits to urgent care services, hospitalizations, and admission to intensive care units (ICU) and the duration of these stays].

Statistical Analysis

The large sample size permits the use of parametric analysis methods (Lubin et al., 2005). Frequencies, means, and standard variations were used for the descriptive analysis of the study variables.

To determine variations in drug consumption, the DHD for each period and their annual equivalents were calculated. To compare the differences in the use of healthcare resources between the base measurement and the measurement taken 6 months following the lockdown, the paired Student's T-test was used. For those variables with fewer number of observations than 100, Wilcoxon rank test was used. The level of significance was established at 5% ($p < 0.05$).

Statistical analysis was carried out using IBM SPSS Statistic 21 and R version 4.0.5.

Ethical Considerations

The protocol followed for this study was approved by the Clinical Research Ethics Committee of Aragon (PI20–175). The procedures carried out for the creation of this work complied with the ethical standards of the previously mentioned committee and with the 1975 Declaration of Helsinki.

The processing, notification, and transfer of personal data were carried out in accordance with Regulation (EU) 2016/679 of the European Parliament and Organic Law 03/2018 on the Protection of Personal Data and the guarantee of digital rights.

RESULTS

Prior to the onset of the lockdown in Aragon, according to the ECR, 110,694 individuals over the age of 16 were undergoing active treatment for depression or anxiety. Of these, 5,104 (4.61%) were positive for COVID-19 infection during the study period. As for the number of deaths, 1,804 individuals passed away during this period: 4 during the 6 months prior to the onset of the lockdown, 242 during the at-home lockdown months, and 1,558 during the subsequent 6 months.

The sample, having a mean age of 61.7 years (16.9), consisted mainly of women (74.4%). Over 70% had an annual income of less than 18,000 euros (70.3%), and over 50% resided in urban areas (53.4%). Regarding to the presence of comorbidities, dyslipidemia (45.9%), hypertension (40.5%), back pain (35.9%), neoplasia (29.5%), and insomnia (20.0%) were the most frequent chronic conditions found in the study population (**Table 1**).

Table 2 shows the variations in the consumption of drugs for the treatment of depression and anxiety among the population undergoing active treatment for these disorders and among general population. With respect to the pharmacological treatment of anxiety, in both groups there were a notable increase in the number of DHD of Alprazolam, Lormetazepam, and Lorazepam during the 6 months following the end of the lockdown. Other drugs, such as Triazolam or Brotizolam also experienced an increase in use among the population with depression and anxiety and among the general population, although to a lesser degree. With reference to anti-depressants, the number of DHD of both non-selective monoamine oxidase-inhibitors (MAO) and selective serotonin reuptake inhibitors (SSRIs), decreased as compared to the 6 months prior to the onset of the lockdown in both populations groups.

As seen in **Table 3**, the number of ordinary and continuous PC nursing or general practitioner visits at the healthcare center or at-home visits were reduced during the 6 months after the end of the lockdown. Only the number of visits to the PC general practitioner at the healthcare center or by telephone increased during this same period [$p < 0.001$ (95% CI: −0.23 to −0.16)]. Similarly, the number of visits to other professionals at the healthcare center, such as midwives [$p = 0.003$ (95% CI: −0.72 to

TABLE 1 | Sociodemographic date and chronic comorbidities in patients suffering from anxiety or depression in Aragon.

	N (%)
Sex	
Men	28,294 (25.6)
Women	82,400 (74.4)
Age	
Mean (SD)	61.7 (16.9)
Pharmaceutical service	
<18,000	77,779 (70.3)
Between 18,000–100,000	26,514 (24.0)
>100,000	391 (0.4)
Free pharmacy	5,505 (5.0)
Mutualist	474 (0.4)
Uninsured	31 (0.0)
Basic health area	
Urban	59,161 (53.4)
Rural	51,533 (46.6)
Chronic comorbidities (yes %)	
Arrhythmias	7,828 (7.1)
Heart failure	3,343 (3.0)
Ischemic heart disease	5,495 (5.0)
Hypertension	44,884 (40.5)
Dyslipidemia	50,792 (45.9)
Obesity	15,621 (14.1)
Overweight	2,432 (2.2)
Disease in veins/arteries	3,091 (2.8)
Cerebrovascular disease	6,613 (6.0)
Diabetes	14,295 (12.9)
Chronic bronchitis	1,592 (1.4)
COPD	4,556 (4.1)
Asthma	9,398 (8.5)
Chronic kidney disease	7,403 (6.7)
Hypothyroidism	16,011 (14.5)
Hyperthyroidism	6,652 (6.0)
Smoking	20,648 (18.7)
Alcoholism	2,013 (1.8)
Insomnia	22,105 (20.0)
Autolytic attempt	1,075 (1.0)
Anemia	20,372 (18.4)
Neoplasia	32,657 (29.5)
Dementia	4,034 (3.6)
Hearing loss	9,911 (9.0)
Cataracts	14,107 (12.7)
Glaucoma	8,500 (7.7)
Osteoarthritis	14,001 (12.6)
Osteoporosis	16,862 (15.3)
Back pain	39,788 (35.9)

SD, standard deviation; COPD, chronic obstructive pulmonary disease.

TABLE 2 | Number of DHD 6 months before and 6 months after lockdown.

	DHD (patients suffering from anxiety or depression)		DHD (general population)	
	Six months before	Six months after	Six months before	Six months after
Anxiolytics				
Diazepam	14.22	14.19	1.18	1.18
Potassium clorazepate	3.00	2.98	0.25	0.25
Lorazepam	196.74	198.38	16.38	16.50
Bromazepam	3.30	3.26	0.27	0.27
Clobazam	0.16	0.16	0.01	0.01
Ketazolam	0.96	0.95	0.08	0.08
Alprazolam	305.61	316.80	25.44	26.35
Pinazepam	0.004	0.004	0.00	0.00
Bentazepam	0.005	0.000	0.00	0.00
Hypnotics and sedatives				
Flurazepam	0.20	0.20	0.02	0.02
Triazolam	2.35	2.48	0.19	0.21
Lormetazepam	452.00	459.21	37.63	38.19
Midazolam	0.26	0.28	0.02	0.02
Brotizolam	5.18	5.96	0.43	0.50
Quazepam	0.02	0.03	0.00	0.00
Loprazolam	4.15	3.90	0.34	0.32
Antidepressants				
Non-selective monoamine reuptake inhibitors				
Imipramine	0.01	0.01	0.00	0.00
Clomipramine	0.19	0.18	0.02	0.01
Trimipramine	0.00	0.00	0.00	0.00
Amitriptyline	0.50	0.49	0.04	0.04
Nortriptyline	0.04	0.03	0.00	0.00
Doxepin	0.00	0.00	0.00	0.00
Maprotiline	0.02	0.01	0.00	0.00
Selective serotonin reuptake inhibitors				
Fluoxetine	9.78	9.78	0.81	0.81
Citalopram	3.31	3.13	0.27	0.26
Paroxetine	12.98	12.49	1.08	1.04
Sertraline	5.40	5.39	0.45	0.45
Fluvoxamine	0.07	0.07	0.00	0.00
Escitalopram	60.82	58.45	5.06	4.86

−0.14)], dentists [$p = 0.033$ (95% CI: −0.47 to −0.02)], and social workers [$p = 0.001$ (95% CI: −0.67 to −0.17)] increased; unlike the number of visits to physiotherapists, which experienced a notable decline [$p < 0.001$ (95% CI: 1.27 to 2.45)].

Regarding to the number of visits to specialists, the number of initial visits to these services increased as compared to the previous 6 months [$p = 0.003$ (95% CI: −0.10 to −0.2)]. On the other hand, the number of follow-up visits to these same services decreased [$p < 0.001$ (95% CI: 0.03 to 0.08)].

Diagnostic imaging (X-rays and ultrasounds) and laboratory testing (blood counts, bio-chemical analyses, and immunological tests) experienced a statistically significant decrease ($p \leq 0.001$). There was also a statistically significant increase found in resonance and microbiological testing ($p < 0.05$).

Finally, visits to hospital services (number of visits to urgent care and number of hospitalizations), also decreased during the study period ($p < 0.001$).

TABLE 3 | Number of visits and diagnostic tests prescribed 6 months before and 6 months after lockdown.

		Mean (SD)		95% CI	P
	N	Six months before	Six months after		
Number of nursing visits (ordinary care) at health center or by telephone	45,426	3.91 (4.50)	3.56 (4.17)	0.31; 0.39	< 0.001
Number of nursing visits (ordinary care) at home	4,674	5.98 (8.47)	5.70 (8.48)	0.03; 0.53	0.025
Number of nursing visits (continuous care) at health center	3,727	2.20 (3.21)	1.89 (2.77)	0.23; 0.39	< 0.001
Number of nursing visits (continuous care) at home	615	2.21 (2.90)	2.19 (4.63)	−0.37; 0.42	0.903
Number of general practitioner visits (ordinary care) at health center or by telephone	92,640	5.96 (5.10)	6.18 (5.69)	−0.23; −0.16	< 0.001
Number of general practitioner visit (ordinary care) at home	3,290	3.56 (3.82)	2.80 (3.19)	0.64; 0.89	< 0.001
Number of general practitioner visits (continuous care) at health center	9,358	2.06 (2.38)	2.07 (2.48)	−0.06; 0.04	0.715
Number of general practitioner visits (continuous care) at home	743	1.80 (1.44)	1.66 (1.34)	0.02; 0.26	0.022
Number of visits to other professionals					
Physiotherapist	678	6.30 (6.95)	4.44 (4.68)	1.27; 2.45	< 0.001
Midwife	584	2.35 (2.18)	2.79 (2.86)	−0.72; −0.14	0.003
Dentist	383	2.09 (1.67)	2.34 (1.77)	−0.47; −0.02	0.033
Social worker	653	2.63 (2.52)	3.06 (3.14)	−0.67; −0.17	0.001
Number of visits to specialized care (first consultation)	3,883	1.47 (0.85)	1.53 (0.92)	−0.10; −0.2	0.003
Number of visits to specialized care (successive consultations)	29,264	2.72 (2.32)	2.66 (2.41)	0.03; 0.08	< 0.001
Number of diagnostic tests performed					
X-rays	20,114	1.12 (1.23)	0.98 (1.19)	0.11; 0.16	< 0.001
Ultrasounds	20,114	0.30 (0.54)	0.28 (0.52)	0.01; 0.03	< 0.001
Resonances	20,114	0.14 (0.39)	0.15 (0.39)	−0.02; −0.01	0.010
CT scans	20,114	0.25 (0.57)	0.25 (0.57)	−0.01; 0.00	0.178
Digestive tests	20,114	0.01 (0.11)	0.01 (0.10)	−0.00; 0.00	0.921
Hemograms	22,451	0.30 (0.54)	0.26 (0.52)	0.03; 0.05	< 0.001
Biochemistry	22,451	1.01 (0.69)	0.90 (0.74)	0.10; 0.12	< 0.001
Microbiology	22,451	0.28 (0.67)	0.38 (0.79)	−0.11; −0.09	< 0.001
Immunology tests	22,451	0.11 (0.35)	0.10 (0.34)	0.00; 0.01	0.001
Coagulation	22,451	0.03 (0.19)	0.04 (0.20)	−0.01; −0.00	0.005
Urine tests	22,451	0.32 (0.59)	0.25 (0.56)	0.05; 0.07	< 0.001
Number of visits to A&E department	7,238	1.89 (1.67)	1.75 (1.49)	0.10; 0.18	< 0.001
Number of hospital admissions	6,413	1.27 (0.67)	0.28 (0.71)	0.96; 1.00	< 0.001
Number of days of hospital stays	1,230	16.66 (37.60)	17.11 (35.80)	−1.73; 0.83	0.493
Number of ICU admissions	5	1.00 (0.00)	1.00 (0.00)		*
Number of days of ICU stays	5	108.80 (73.24)	100.80 (81.12)	−40.00; 0.01	0.317[a]

*The correlation and t cannot be calculated because the standard error of the differences is 0. A&E, accident and emergency; ICU, intensive care unit; SD, standard deviation; 95% CI, confidence interval. [a]Wilcoxon signed-rank test.

DISCUSSION

The results of our study reveal variations in the total number of DHD dispensed in pharmacies for the pharmacological groups included in this study: N05B (anxiolytic drugs), N05C (hypnotics and sedatives), and N06A (antidepressants).

Regarding the increase observed in the total number of DHD of anxiolytic drugs (Alprazolam, Lormetazepam, and Lorazepam, mainly) during the 6 months following the onset of the lockdown; only one previous study, conducted in France on patients with depression, revealed similar results (Martinelli et al., 2021). Larger number of studies have analyzed the impact of the COVID-19 pandemic on the symptoms of patients having a past history of anxiety or depression. Individuals with prior mental illnesses appear to have had a higher risk or reporting increased levels of stress, anxiety, depression, impulsivity, anger, insomnias, or suicidal thoughts as compared to the general population (Hao et al., 2020; Liu et al., 2020). The increase in consumption of anxiolytic drugs shown in our study may be explained by the worsening of these symptoms (Martinelli et al., 2021). According to the Spanish Agency for Medicines and Medicinal Devices (AEMPS), at the end of 2019, the DHD of these drugs was 55.51. During the first quarter of 2020, it increased to 57.19, and by the fourth quarter of 2020, the consumption level peaked at 58.69 DHD (Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), 2021). Spain, one of the hardest-hit countries during the first wave of the COVID-19 pandemic (Kontis et al., 2020), was already (before the healthcare crisis) ranked third amongst the European OECD (Organization for Economic Co-operation and Development) countries in terms of consumption of anxiolytic drugs, especially by women (Simó, 2018).

With respect to the minor decline in the number of DHD for anti-depressants, similar results were found in a

study carried out in Portugal (Estrela et al., 2021). According to another study conducted in Aragon (Mestre, 2021), the follow-up period used for our study (6 months following the end of the lockdown) may be insufficient for the detection of changes in the consumption of these drugs. Immediately following the onset of the pandemic and throughout 2020, this study did not report any substantial changes in the prescribing of anti-depressants. As of 2021, however, an increased consumption became evident. This may be due to the continued pandemic situation.

The use of primary level care by these patients also declined during the months following the end of the lockdown. Previously published works (Firth et al., 2019) found interruptions in the care given to these patients as well as a redistribution of resources in response to the high number of positive COVID-19 cases. The increase observed in the number of PC visits to the general practitioner at the healthcare center or by telephone may be explained by the introduction of telemedicine, as a more effective alternative to in-person visits. Mental health is one of the specialties that best adapts to this tool, given that physical examination is not essential (Vieta et al., 2020).

The social and economic impact of the pandemic on the most vulnerable groups *a priori*, may be a cause of the increased social services demands (Grupo Estatal de Intervención en Emergencias Sociales, 2020). As for the increased number of visits to midwifes, although some studies (Ivanuš et al., 2021) suggest a decrease in the number of cervical cytology test during lockdown. The postponement of these visits to the midwife during the lockdown months might have led to an increased number of visits during the months following the end of this confinement period. In the same way, other studies (Davenport et al., 2020; Domínguez-Mejías et al., 2021) reveal an increase in symptoms of anxiety and depression amongst pregnant women during the pandemic months, which might have increased the number of these visits. Similarly might have occurred with the visits to the dentist. Postponing minor treatments may have led to larger problems (Elster and Parsi, 2021).

Finally, the increased number of initial visits to specialists may be a result of the declining physical health of these patients. Some studies (Van Rheenen et al., 2020) have revealed an increase in high-risk behaviors (alcohol consumption) during the pandemic months amongst individuals with previous mental illness; who usually have a higher number of comorbidities (obesity, diabetes, and cardiovascular illnesses) as compared to the general population (Firth et al., 2019), as well as higher prevalences of tobacco use (Prochaska et al., 2017).

The progressive increase in deaths is noteworthy. This increase, which may be the subject of future studies, may be related to the major impact of the first wave of the pandemic on Spain and its social and economic consequences. According to a recently published study (COVID-19 Mental Disorders Collaborators, 2021) in the most harshly hit countries (by the pandemic), an increased prevalence of depression and anxiety is anticipated. Both of these disorders and, even more so, the comorbidity between the two, are considered to be major risk factors in suicidal behavior (Moitra et al., 2021). The excess of mortality observed in our study during the 6 months following the end of the lockdown period may be explained in part by this fact. Statistics on suicide published in Spain in 2020 revealed an increase of 7.4% as compared to the prior year, a historical maximum (Fundación Española para la prevención del suicidio, 2021).

Any study should be interpreted with caution. Our choice was to analyze the changes in behavior over a short period, between 6 months before and 6 months after lockdown, by collating the modification of the use of the care system and of anti-depressant and anxiety drugs. Starting from a postula: these increases reflect not only the increase in psychological suffering in these patients but also, they may be a proxy for the increase in prevalences of depression in general population.

Although the sample size was large, the mean age of the sample was high (61.7 years).The duration of the study may not be long enough to see variations in the severity of depression. Depression is a disease that sets in gradually. While anxiety is subject to greater variability. But the significant increase in the use of anxiolytics is a warning sign. Studies should be continued to confirm or not the increase in the prevalence of depression, possibly expected thereafter.

Our source of information was a registry: the ECR. But this is not enough to provide objective information on the impact of the pandemic on the mental health of patients. To ensure the diagnosis of depression, the use of validated scales [Goldberg Anxiety and Depression Scale (GADS), Hamilton Anxiety Rating Scale, Beck Anxiety Inventory, etc.] will be necessary. In addition, it would be interesting to organize a qualitative research to complement this analysis. A cohort study using diagnostic tools to perform the sampling would be very useful in answering this question: are we on the cusp of an increase in depression in the general population due to the pandemic and which ones are the measures to deal with it?

Finally, the number of statistical tests and calculated *p*-values in this article is large and therefore needs to be confirmed in further studies.

CONCLUSION

This study offers contributions, from a long-term perspective, with regard to the knowledge of the repercussions of lockdown measures on the use of drugs and health care resources, in a sample of patients undergoing active treatment for anxiety and/or depression, according to the ECR.

The COVID-19 response should consider the mental health of the general population and should be especially cautious when considering more vulnerable groups, such as those with a past clinical history of depression or anxiety. Today, more than ever, it is necessary to invest in mental health services in an attempt to halt the anticipated growth of these disorders. Today, more than ever, it is necessary to invest in research and support measures for mental health services, to halt the anticipated growth of these disorders and the suffering in the population.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: the data generated during the course of the project may be requested from the senior researcher of the project, in aggregate form. Requests to access these datasets should be directed to BO-B.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Clinical Research Ethics Committee of Aragon (PI-20/175). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

BO-B: conceptualization. SC-V, AC, BO-B, and AL-C: formal analysis. AL-C: writing—original draft preparation. AC, PN, BO-B, and SC-V: writing—review and editing. AC and BO-B: supervision. All authors have read and agreed to the published version of the manuscript.

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Manuscrito 5: Evolution of Anxiety and Depression in Men during the First Six Month of the COVID-19 Pandemic and Factors Associated with Worsening of Mental Health: Retrospective Longitudinal Study.

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Original Research

Evolution of Anxiety and Depression in Men during the First Six Months of the COVID-19 Pandemic and Factors Associated with Worsening of Mental Health: Retrospective Longitudinal Study

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Abstract

Background: The Coronavirus disease (COVID-19) pandemic has had a huge impact on the psychological wellbeing of the population, however, few studies have analysed the psychological consequences for the most vulnerable groups, particularly those suffering from depression and anxiety, and specifically in men. The objective of this study is to analyse the changes in a population of men undergoing active treatment for depression or anxiety and factors associated with these changes. **Methods**: Retrospective, longitudinal and observational study of a population of 28,294 men in northern Spain. The study variables were sociodemographic variables, chronic comorbidities, COVID-19 infection, anxiolytic and antidepressant drug consumption, and use of healthcare resources. These variables were collected from the Primary Health Care electronic records for the two distinct periods (6 months before and 6 months following the end of the lockdown). To compare drug patterns and the use of healthcare resources a paired Student's *T*-test was used. To analyse associated factors related to a deterioration of mental disorders, a multivariate logistic regression was performed. **Results**: In relation to changes in drug patterns, 40% of men saw an increase in at least one Defined Daily Dose (DDD) of their prescribed drugs during the 6 months following lockdown and the number of appointments at health centres and home visits significantly decreased. Factors associated with a deterioration of mental disorders are being under 60 years old, having an income of less than 18,000 euros/year and suffering from more than one comorbidity. **Conclusions**: The pandemic had a significant impact on men with a previous diagnosis of depression and/or anxiety.

Keywords: depression; anxiety; men; COVID-19 pandemic; anxiolytic; antidepressant; drug consumption; use of healthcare resources

1. Introduction

Depression is considered the principal cause of disability worldwide, with anxiety being the sixth most prevalent cause. Both these conditions, especially depression, contribute to the overall global morbidity and mortality burden, and generate high levels of disability as well as economic and social costs [1]. By 2030, depression is expected to be the leading cause of morbidity in the world [2–5]. The prevalence of depression in Spain is 13% over one's lifetime and 4% per year [6]. From the healthcare system perspective, approximately 25–35% of all primary health care (PHC) patients suffer from psychiatric disorders, and over 80% of these patients suffer from depression or anxiety disorders [7]. It is well known that General Practitioners (GPs) only refer approximately 5–10% of psychiatric patients diagnosed in primary care settings to mental health services [8]. Therefore, these mental health disorders are managed chiefly at the PHC level.

It is a common belief that the probability of experiencing a depressive or anxious episode increases when certain genetic [9,10], demographic and psychosocial factors [11–14], as well as environmental factors [15–17] are present, among which the size of an individual's residence is considered [18,19]. Gender is prominent among these factors, with women having typically double the risk of developing severe depression than men [20–24]. Consequently, few studies have been conducted on the diagnosis, evolution and treatment of depression specifically in men [25,26]. Other frequently studied sociodemographic factors related to depression are: old age [27–31]; having a lower cultural and educational level [32–34]; experiencing a lack of relationships and social support [35–38]; and having a lower socioeconomic level [35,39,40]. Another analysed risk factor is the comorbidity of depression with other physical and psychiatric diseases [41,42].

As a result of the COVID-19 pandemic, which has devastated the entire world, the global population has been exposed to an endless number of stressful events such as restriction of social activities, limited mobility and/or lockdowns. These restrictive measures have been useful in reducing the spread of the virus, but they have had a huge impact on the physical and psychological wellbeing of the population [43]. Numerous studies have analysed the psychological consequences of the pandemic and lockdown on the mental health of the general population. Several meta-analyses concluded that the COVID-19 pandemic has increased mental health issues among the global population, mainly the prevalence of depression, anxiety and sleep disorders [44–47]. Factors associated with experiencing these symptoms are being female, a healthcare worker, suffering from a non-infectious chronic disease, contracting COVID-19 disease or having a high risk of doing so, having lower socioeconomic status, as well as being socially isolated.

However, few studies have analysed the psychological consequences of the pandemic for the most vulnerable groups, particularly those suffering from pre-existing mental disorders [48]. The lockdown, social and physical distancing measures and difficulty in maintaining daily routines during the pandemic may also have had an acutely negative impact on people with mental health disorders [48–52]. Furthermore, the collapse of PHC services at the onset of the pandemic and during each subsequent wave may have interrupted these patients' ongoing healthcare [49,53], causing a deterioration of their mental disorder and an imbalance in health service usage.

Given the lack of research on the consequences of the pandemic for those suffering from pre-existing mental disorders, especially in the case of men, the objective of this study is to determine and analyse the changes between 6 months prior to lockdown and 6 months after it was lifted in a population of men undergoing active treatment for depression or anxiety. We will also examine factors associated with these changes, looking at patients' electronic clinical history (ECH), held by PHC services. The use of this data from PHC records allows us to quantify the use of drugs such as anxiolytics and anti-depressants as well as how patients accessed healthcare resources, which may indicate a change in their condition.

The alternative hypotheses for this study are the following:

H1: Men with a previous diagnosis of depression and/or anxiety, who had undergone active treatment for these mental disorders at least six months before the beginning of the COVID-19 pandemic, experienced a worsening of their mental health status during the six first months of the pandemic.

H2: Men with a previous diagnosis of depression and/or anxiety, who had undergone active treatment for these mental disorders at least six months before the beginning of the COVID-19 pandemic, experienced a decrease in the number of consultations with health professionals during the six first months of the pandemic.

H3: There are associated factors between the worsening of mental health in men and having a previous diagnosis of depression and/or anxiety when these individuals had undergone active treatment for these mental disorders at least six months before the beginning of the COVID-19 pandemic.

2. Materials and Methods

This is a retrospective, longitudinal and observational study of a population of men in northern Spain (Aragon) over the age of 16, undergoing active treatment for depression and/or anxiety, according to their ECH.

Aragon is an autonomous community (one of Spain's 17 main administrative and political divisions) with a population of 1,328,753. Its territory takes in 47,719 square kilometres, and it has a population density of 28.20 people per square kilometre. It has an ageing population which is concentrated in rural areas, with the main cities having a younger population structure. The capital city of the region (Zaragoza) accounts for half of the population, and rural nuclei (with less than 2000 residents) account for 86% of municipalities, but only 16.8% of the overall population [54].

2.1 Sample and Sample Size

The sample consisted entirely of men with open electronic medical records held by health centres in the Autonomous Community of Aragon, with a diagnosis of depression and/or anxiety, who had undergone active treatment for these mental disorders (antidepressants and anxiolytic medication), prescribed by their GP at least 6 months before the declaration of the state of emergency in Spain (i.e., on or before 14/09/2019). Accordingly, the inclusion criteria are: men over 16 years of age, who have experienced episodes of depression and/or anxiety (codes F30-F39 and F41 of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)), and who, during the study period, were prescribed some of the active ingredients used to treat these two disorders. According to the Anatomical, Therapeutic, and Chemical Classification (ATC), the following codes were included: N05B (anxiolytic drugs), N05C (hypnotics and sedatives), and N06A (antidepressants).

Records containing inconsistencies in the database were excluded from the study. The total sample that met inclusion criteria consisted of 28,294 men.

Due to the universal nature of the healthcare system and the absence of other PHC providers, the data obtained in the study is considered to be representative of practically 100% of the population under study.

2.2 Study Variables

Data on sociodemographic variables, chronic comorbidities, COVID-19 infection, drug consumption, and use of healthcare resources were collected from the PHC records for the two distinct periods. The first measurement was taken from the records from the 6 months before the onset of the strict lockdown (14/09/2019 to 15/03/2020) and the second was taken from the records from the 6 months following the end of this lockdown during the first wave (03/05/2020 to 04/11/2020).

- Sociodemographic variables that are associated with the etiopathogenesis of depression and could be collected through the PHC record were: age, data on prescription charges which allowed us to determine peoples' income (less than 18,000 euros/year, 18,000 to 100,000 euros/year, over 100,000 euros/year, free prescriptions and uninsured), and residence in a rural or urban area (the latter is defined as having over 10,000 inhabitants).

- Chronic comorbidities; data on the following conditions were collected: arrhythmias, heart failure, ischemic cardiopathy, dyslipidaemia, obesity, excess weight, vein and artery disease, cerebrovascular disease, diabetes, chronic bronchitis, chronic obstructive pulmonary disease (COPD), asthma, chronic kidney disease, hypo and hyperthyroidism, tobacco addiction, alcoholism, insomnia, attempted suicide, anaemia, neoplasia, dementia, deafness, cataracts, glaucoma, arthrosis, osteoporosis, and back pain. These comorbidities present a prevalence of over 5% among the general population [55], and the data were collected at points six months before the start of lockdown, and six and twelve months after the end of the lockdown.

- Infection with COVID-19 during the study period, recorded as yes/no.

- Changes in drug consumption patterns have been assessed via the variation in defined daily dose (DDD) dispensed under medical prescription by pharmacies. These changes in drug consumption were coded negatively when there was an increase in the DDD of the active ingredient. The pharmacological treatments in the data have been grouped according to therapeutic group (ATC classification) [56] as: N05B (anxiolytic drugs), N05C (hypnotics and sedatives), and N06A (antidepressants). These Benzodiazepines are all first-instance medications for treating these disorders according to the Spanish Society of Family and Community Medicine [57]. They are listed as follows: (a) anxiolytics: diazepam, potassium clorazepate, lorazepam, bromazepam, clobazam, ketazolam, alprazolam, pinazepam, Bentazepam; (b) hypnotics and sedatives: flurazepam, triazolam, lormetazepam, midazolam, brotizolam, quazepam, loprazolam and (c) antidepressants: (ci) non-selective monoamine (MAO) reuptake inhibitors: imipramine, clomipramine, trimipramine, amitriptyline, nortriptyline, doxepin, maprotiline; (cii) selective serotonin reuptake inhibitors (SSRIs): fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram.

- The patients' use of healthcare resources was assessed through looking at how they used PHC services (number of ordinary or ongoing care visits to the health centre or home visits by the nurse or GP, and number of visits to a social worker at a health centre. Use of hospital services was also examined (number of specialised care visits, number of visits to accident and emergency (A&E) services, hospitalisations, admission to intensive care units (ICU) and the duration of these stays) for each of the periods in question.

2.3 Statistical Analysis

The sample size allowed for the use of parametric methods [58]. Firstly, a descriptive analysis of the study variables was carried out using frequencies, means and standard deviation (SD).

To determine variations in drug consumption, the difference in DDD for each period was calculated using a paired Student's *T*-test. For those variables observed in less than 100 cases, the Wilcoxon rank test was used. To compare the differences in the use of healthcare resources between the baseline measurement and the measurement taken 6 months following the end of lockdown, the same statistics were used.

To analyse associated factors related to the possible deterioration of mental disorders, changes in drug consumption patterns assessed via the increases in defined daily dose (DDD) were analysed as a dependent variable in a multivariate logistic regression. This indicator could be an indirect means of revealing the variation in this population's psychological suffering. The independent variables were age (under 40, 40 to 60, and over 60), income bracket (determined via prescription charges), residence in a rural or urban area, chronic comorbidities (grouped into those not presenting comorbidities or other chronic diseases, and those presenting 2 or more chronic diseases), and COVID-19 infection.

Statistical analysis was carried out using IBM SPSS Statistic 21 [59] and R 4.0.5. [60] on a PC with 16 MB of RAM.

3. Results

On 14/09/2019, there were 110,694 patients in Aragon with a diagnosis of depression and/or anxiety who were being actively treated for these mental disorders with antidepressants and anxiolytic medication, prescribed by their GP. Of these, 28,294 were men, 25.56% of the total.

Table 1 represents the sample according to the variables under study. The participants' mean age is 58.76 years old (SD 16.79). Among them, 60.6% had an annual income of less than 18,000 euros, and 53.9% resided in urban areas. In terms of comorbidities, dyslipidaemia (45.1%), hypertension (39.4%), back pain (29.4%), neoplasia (25.4%), and tobacco addiction (23.9%) were the

most frequently found chronic conditions among the study population. Only 4.4% of the participants suffered from a COVID-19 infection.

Table 1. Sociodemographic data, chronic comorbidities and COVID-19 infection in patients suffering from anxiety or depression in Aragon at least 6 months prior to the pandemic outbreak.

	n = 28294
Age, M (SD)	58.76 (16.79)
Income bracket (based on prescription charge data)	
<18000, n (%)	17152 (60.6)
18000–100000, n (%)	10076 (34.4)
>100000, n (%)	181 (0.6)
Free prescriptions, n (%)	1238 (4.4)
Uninsured, n (%)	8 (0.0)
Place of residence	
Urban, n (%)	15248 (53.9)
Rural, n (%)	13046 (46.1)
COVID-19 infection	
Yes, n (%)	1241 (4.4)
Chronic comorbidities	
Arrhythmias, yes n (%)	2239 (7.9)
Heart failure, yes n (%)	784 (2.8)
Ischemic heart disease, yes n (%)	2515 (8.9)
Hypertension, yes n (%)	11139 (39.4)
Dyslipidaemia, yes n (%)	12762 (45.1)
Obesity, yes n (%)	3234 (11.4)
Overweight, yes n (%)	451 (1.6)
Vein and artery disease, yes n (%)	1220 (4.3)
Cerebrovascular disease, yes n (%)	1985 (7.0)
Diabetes, yes n (%)	4296 (15.2)
Chronic bronchitis, yes n (%)	498 (1.8)
COPD, yes n (%)	2127 (7.5)
Asthma, yes n (%)	1698 (6.0)
Chronic kidney disease, yes n (%)	1737 (6.1)
Hypothyroidism, yes n (%)	1529 (5.4)
Hyperthyroidism, yes n (%)	649 (2.3)
Tobacco addiction, yes n (%)	6760 (23.9)
Alcoholism, yes n (%)	1294 (4.6)
Insomnia, yes n (%)	5764 (20.4)
Autolytic attempt, yes n (%)	332 (1.2)
Anaemia, yes n (%)	3105 (11.0)
Neoplasia, yes n (%)	7177 (25.4)
Dementia, yes n (%)	770 (2.7)
Hearing loss, yes n (%)	2575 (9.1)
Cataracts, yes n (%)	2764 (9.8)
Glaucoma, yes n (%)	1892 (6.7)
Osteoarthritis, yes n (%)	1827 (6.5)
Osteoporosis, yes n (%)	545 (1.9)
Back pain, yes n (%)	8330 (29.4)

Note: COPD, Chronic obstructive pulmonary disease.

As for new diagnoses of psychiatric comorbidity in this population in the 6 months prior to the lockdown, there were 253 (0.9%) new diagnoses of tobacco addiction, 50 (0.2%) of alcoholism, 402 (1.4%) of insomnia and 39 (0.1%) of attempted suicide. However, in the 6-month period following the lockdown being implemented, there were 66 (0.2%) new diagnoses of tobacco addiction, 41 (0.1%) of alcoholism, 194 (0.7%) of insomnia, and 23 (0.1%) suicide attempts.

When considering pharmaceutical treatments, the active ingredients most often prescribed to men with depression and/or anxiety are anxiolytics (lorazepam, diazepam, alprazolam) hypnotics and sedatives (lormetazepam) and antidepressants (escitalopram, paroxetine, sertraline, fluoxetine, and amitriptyline). In relation to changes in drug patterns, as shown in detail in Table 2, it is relevant to highlight that 11,038 men (40%) saw an increase in at least one DDD of their prescribed drugs during the 6 months following lockdown. Looking at the active ingredients, 15% of the men that took diazepam saw an increase in DDD during the six months after lockdown ended, as did 11.1% of those who took alprazolam, 12% of those who took lormetazepam, 14% of those who took amitriptyline, 16.9% of those who took fluoxetine, 11.3% of those who took sertraline, 9.5% of those who took escitalopram, and 8.2% of those who took paroxetine.

As seen in Table 3, the number of ordinary and continuous PHC nursing appointments at health centres and the number of ordinary care GP home visits significantly decreased during the six months after the end of the lockdown. The number of PHC appointments attended for ongoing and ordinary care, as well as appointments with specialists, did not show significant differences. Finally, visits to hospital (no. of visits to urgent care and no. of hospitalisations), also decreased during the study period ($p < 0.001$).

In terms of factors associated with a deterioration of mental disorders, considering men that see an increase or decrease in their prescribed DDD as an indicator of heightened psychological suffering, a multivariable logistic regression was performed, the results of which are displayed in Table 4. Being under 60 years old, having an income of less than 18,000 euros/year and suffering from more than one comorbidity are associated with an increase in the DDD of anxiolytic drugs (N05B), hypnotics and sedatives (N05C), and/or antidepressants (N06A).

4. Discussion

This study analyses a sample consisting of patients that had been diagnosed with depression and/or anxiety who were being actively treated for these mental disorders with antidepressants and anxiolytic medication prescribed by their GP, at least six months before the lockdown. Of these patients, 25.56% were men, which means that there were 3 women for every man with depression in Aragon. This percentage has remained stable over the last ten years,

Table 2. Number and percentage of men taking each active ingredient with a stable, reduced or increased DDD.

Active ingredient	N (%)	Stable or reduced DDD N (%)	Increased DDD N (%)
Benzodiazepines			
Anxiolytics			
Diazepam	4656 (16.4)	3947 (84.8)	709 (15)
Potassium clorazepate	1434 (5.1)	1271 (88.6)	163 (11.4)
Lorazepam	11157 (39.4)	10612 (91.8)	945 (8.2)
Bromazepam	161 (0.6)	141 (87.6)	20 (12.4)
Clobazam	52 (0.2)	49 (94.2)	3 (5.8)
Ketazolam	499 (1.7)	449 (90)	50 (10)
Alprazolam	3903 (13.8)	3470 (88.9)	433 (11.1)
Pinazepam	2 (0.0)	2 (100)	0 (0)
Bentazepam	550 (1.9)	506 (92)	44 (8)
Hypnotics and sedatives			
Flurazepam	119 (0.4)	102 (85.7)	17 (14.3)
Triazolam	13 (0.0)	0 (0)	13 (100)
Lormetazepam	3973 (14.0)	3496 (88)	477 (12)
Midazolam	161 (0.6)	141 (87.6)	20 (12.4)
Brotizolam	16 (0.0)	0 (0)	16 (100)
Quazepam	4 (0.0)	3 (75)	1 (25)
Loprazolam	52 (0.2)	46 (88.5)	6 (11.5)
Antidepressants			
Non-selective monoamine reuptake inhibitors			
Imipramine	19 (0.0)	11 (57.9)	8 (42.1)
Clomipramine	426 (1.5)	387 (90.8)	39 (9.2)
Amitriptyline	993 (3.5)	854 (86)	139 (14)
Nortriptyline	52 (0.2)	40 (76.9)	12 (23.1)
Doxepin	6 (0.0)	5 (83.3)	1(16.7)
Maprotiline	8 (0.0)	2 (25)	6 (75)
Selective serotonin reuptake inhibitors			
Fluoxetine	1377 (4.8)	1144 (83.1)	233 (16.9)
Citalopram	780 (2.7)	732 (93.8)	48 (6.2)
Paroxetine	2757 (9.7)	2531 (91.8)	226 (8.2)
Sertraline	2525 (8.9)	2239 (88.7)	286 (11.3)
Fluvoxamine	99 (0.3)	82 (82.8)	17 (17.2)
Escitalopram	5383 (19.0)	4873 (90.5)	510 (9.5)

which can be seen when comparing these data to other studies using data from PHC clinical records in Aragon [61].

Epidemiological studies suggest that there are considerable differences between men and women in terms of the prevalence and presentation of depression. Women are more than twice as likely to be diagnosed with depression and may also report more atypical and anxiety-like symptoms than men [62,63]. Several studies support the argument that these epidemiological differences are related to psychological, neurochemical, anatomical, hormonal, genetic, and personality-related factors [26,63], but also to the nature of the roles that men and women perform [36].

Furthermore, the sample for this study presents high comorbidity with other chronic conditions, which is consistent with other studies. In fact, just as comorbidity with other chronic conditions is high (64.9–71.0%) (diabetes, hypertension, cardiovascular diseases and cancer, among others) [64–66], so is comorbidity with other psychiatric diseases (40–66%) [67]. A noteworthy result is that in the 6 months after lockdown ended there were fewer new diagnoses of psychiatric comorbidities in comparison with the 6 months prior to lockdown. Except for attempted suicide, these results have to be considered with caution, given that the decrease in the use of health services may have led to an underdiagnosis bias. In the case of attempted suicides, 39 (0.1%) men with diagnoses of depression and anxiety had attempted suicide in the six months prior to lockdown, while this number dropped to 23 in the subsequent 6 months. According to recently published studies [68,69], in the countries hit worst by the pandemic, an increased prevalence of depression and anxiety was anticipated, and several questionnaire-based studies of the general population have shown this to have been the case [70]. Both of these disorders and, even more so, comorbidity between the two, are considered to be major risk factors in suicidal behaviour [71]. Suicide data published in Spain in 2020 showed an increase of 7.4% on the previous year [72], but this increase has not been reflected among men diagnosed with depres-

Table 3. Number of consultations with health professionals in the six months prior to lockdown, and the six months after it ended.

		Six months prior	Six months after		
	N	Mean (SD)		95% CI	*p*
No. of nursing appointments at health centre or by telephone (ordinary care)	10676	4.15 (5.12)	3.83 (4.96)	0.22; 0.41	<0.001
No. of nursing home visits (ordinary care)	922	6.02 (8.19)	5.95 (8.29)	–0.45; 0.58	0.811
No. of nursing appointments at health centre (ongoing care)	980	2.51 (4.55)	2.14 (4.20)	0.19; 0.54	<0.001
No. of nursing home visits (ongoing care)	163	2.35 (2.88)	2.58 (5.83)	–1.18; 0.71	0.628
No. of GP appointments at health centre or by telephone (ordinary care)	22595	5.87 (5.26)	5.86 (5.70)	–0.06; 0.08	0.818
No. of GP home visits (ordinary care)	628	3.39 (3.36)	3.02 (4.04)	0.08; 0.66	0.012
No. of GP appointments at health centre (ongoing care)	2282	2.17 (3.23)	2.08 (2.88)	–0.01; 0.19	0.060
No. of GP home visits (ongoing care)	197	1.99 (1.73)	1.79 (1.48)	–0.06; 0.46	0.143
No. of visits to PHC social worker	185	2.50 (2.13)	2.72 (2.98)	–0.67; 0.13	0.188
No. of visits for specialised care (first consultation)	955	1.50 (0.87)	1.54 (0.90)	–0.11; 0.04	0.384
No. of visits for specialised care (successive consultations)	7261	2.70 (2.27)	2.68 (2.48)	–0.03; 0.07	0.492
No. of visits to A&E department	1946	2.03 (2.11)	1.82 (1.77)	0.12; 0.29	<0.001
No. of hospital admissions	1948	1.32 (0.74)	0.35 (0.80)	0.92; 1.01	<0.001
No. of days spent in hospital	463	17.28 (39.42)	19.02 (36.38)	–4.15; 0.68	0.159
No. of ICU admissions	2	1.00 (0.00)	1.00 (0.00)		*
No. of days spent in ICU	2	82.5 (6.36)	82.5 (6.36)		*

Note: CI, Confidence Interval; ICU, Intensive Care Unit; PHC, Primary Health Care; A&E department, Accident and Emergency department.
* The correlation and t cannot be calculated because the standard error of the difference is 0.

Table 4. Multivariable logistic regression of factors associated with a deterioration of depression and anxiety.

	B	Exp (B) Odds ratio	95% Confidence Interval for Exp (B)	*p*-value
Intercept	–0.487			<0.001
Aged under 40 years	0.266	1.241	1.206; 1.413	<0.001
Aged 40 to 60 years	0.216	1.241	1.177; 1.308	<0.001
Aged over 60 years		Ref		.
Income <18,000 euros/year	0.062	1.064	1.011; 1.120	0.017
Income >18,000 euros/year		Ref		.
One comorbidity	–0.112	0.094	0.820; 0.975	0.011
Two or more comorbidities		Ref		.
Residence in urban area	–0.021	0.979	0.933; 1.028	0.394
Residence in rural area		Ref		.
No COVID-19 infection	–0.064	0.938	0.835; 1.054	0.282
COVID-19 infection		Ref		.

sion and/or anxiety before the pandemic began.

According to the results of the study, the hypotheses for this study have been verified. Men with a previous diagnosis of depression and/or anxiety, who had undergone active treatment for these mental disorders at least six months before the beginning of the COVID-19 pandemic, experienced a worsening of their mental health status and experienced a decrease in the number of consultations with health professionals during the six first months of the pandemic. It is relevant to highlight that 40% of the participants saw an increase in at least one of the DDD of their prescribed drugs during the 6 months after lockdown ended. We chose to analyse changes in the status of depression and anxiety in men over a 14-month period (from 6 months prior to until 6 months after the end of lockdown, i.e., from 14/09/2019 to 04/11/2020) by collating changes in the use of healthcare system resources and consumption of anti-depressant and anxiety drugs, starting with the hypothesis that increases in use or consumption may reflect an increase in psychological suffering in these patients. However, 60% of the patients saw their DDD remain stable or decrease. These data may be related to the natural evolution and treatment of depression and anxiety, but may also indicate the abandonment of treatment. According to a study conducted by Serna *et al.* [73], 78% of patients who take antidepressants abandon treatment within 6 months, with men being more likely than women to do so. The National Institute for Health and Care Excellence (NICE) guide recommends continuing treatment with antidepressant drugs for at least 6 months after remission of the episode [74]. The mainte-

nance dose should be the same as that which obtained the improvement, as it has been observed that those patients who have their dose reduced have higher rates of relapse than those who continue with the same dose. The cessation of antidepressant treatment should be done by reducing the dose gradually, usually over a period of 4 weeks [75]. Given that the total monitoring period of this study is approximately 14 months, maintenance or even reduction of medication can be considered as an indication that clinical practice guidelines are have been followed [75], depending on the evolution of the patient's condition.

The fact that 40% of the participants saw an increase in at least one of the DDDs of their prescribed drugs during the 6 months after the lockdown ended, cannot be related to a progressive increase in prescription, as the diagnosis was made almost 8 months prior. Therefore, these data confirm an increase in psychological discomfort during the first wave. Some previous studies show a higher psychological effects of the pandemic and the lockdown (fear, anxiety, sadness, sleep quality) in people with previous mental illness compare with the general population [50,76–78]. This could explain the increse of the consumption of anxiolytic drugs and antidepressants not only among the general population [44,47,69,79] but also among vulnerable people such as patients with depression and anxiety [48–52]. The restrictions of the pandemic forced to modify clinical practice. In Spain and other countries [78] care for patients with these pathologies was diminished. Togheter, the fear of contagion, that among this group was higher according to some studies [50,77] could also explain the decrease in the number of PC and hospital care visits observed in our study.

Related to the third hypothesis, there are associated factors between the worsening of mental health in men and having a previous diagnosis of depression and/or anxiety when these individuals had undergone active treatment for these mental disorders at least six months before the beginning of the COVID-19 pandemic. Among the factors associated with an increase in the DDD are being younger (of working age), having an income of less than 18,000 euros/year and suffering from more than one comorbidity. These results are consistent with the social and economic impact the pandemic has had and evince devastating psychological distress among people from poorer socioeconomic groups. The relationship between depression, anxiety, the economic crisis and unemployment has been well-established in the literature [16,33,35,61,64,80–85]. On the other hand, people suffering from comorbidities during the first wave were more likely to have their DDD increased for their anxiety and depression medication, since these comorbidities are risk factors for developing a serious COVID-19 episode [86–88]. This may explain the higher incidence of anxiety and depression.

Our study has some significant strengths, mainly its PHC context, the healthcare setting where most depression and anxiety episodes are managed and treated, as well as its ecological nature. Furthermore, while most studies have analysed the psychological consequences of the pandemic and lockdown on the mental health of the general population, our study attempts to shed light on the evolution of men with pre-existing mental disorders (depression and anxiety) who had been undergoing active treatment during the six months of the pandemic. As a result, our paper aims to fill a current gap that exists regarding knowledge about the psychological consequences of the pandemic for the most vulnerable groups, such as those suffering from pre-existing mental disorders. On the other hand, it also has its limitations. For example, the duration of the study may not be long enough to detect variations in the severity of depression. Depression is a disease that develops gradually, whereas anxiety is more variable. But the variations in the patterns of anxiolytic and antidepressant consumption which are not explained by the natural course of the disease are a warning sign. Studies should be carried out to corroborate or refute our findings. Our source of information was clinical records: the ECH. But this is not sufficient to provide objective information on the impact of the pandemic on patients' mental health. In addition, to confirm the diagnosis of depression, the use of validated scales would be necessary. A cohort study using diagnostic tools to perform sampling would be extremely useful in answering the question regarding the impact of the COVID-19 pandemic on the mental health of the population. Finally, the last limitation is that, despite the study including men in Aragón (Spain) who had received a diagnosis for depression and anxiety by their GP and who had undergone active treatment for these mental disorders at least six months before the beginning of the COVID-19 pandemic, the sample is representative of an ageing population and, therefore, presents a large number of comorbid chronic diseases.

5. Conclusions

In summary, after the strict lockdown during the first wave of COVID-19, the pandemic had a significant impact on men with a previous diagnosis of depression and/or anxiety. Of these men, 40% had their prescription for medication to treat these mental disorders increased, demonstrating increased psychological suffering. Their use of healthcare resources also decreased. The presence of comorbidities and a greater vulnerability to economic instability are factors related to this deterioration.

Abbreviations

A&E, Accident and emergency; ATC, Anatomical, Therapeutic, and Chemical Classification; COPD, chronic obstructive pulmonary disease; ECH, Electronic clinical history; DDD, Defined daily dose; GPs, General Practitioners; ICU, Intensive care unit; PHC, (MAO) non-selective monoamine;PHC, Primary Health Care; SSRI, selective serotonin reuptake inhibitors; SD, Standard deviation.

Author Contributions

Conceptualization, BO-B and AL-C; formal analysis, SC-V, AC-F, BO-B and AL-C; writing—original draft preparation, BO-B and AL-C; writing—review and editing, AA-L, BO-B, AL-C, SC-V and AC-F; supervision, BO-B, AL-C and AA-L. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

The authors declare that all procedures contributing to this work comply with the ethical standards of the Aragon Clinical Research Ethics Committee (part of the Department of Health of the Government of Aragon, Spain) and with the Helsinki Declaration of 1975, as revised in 2008. The Aragon Clinical Research Ethics Committee approved the Study Protocol (PI20-175).

Data on the prevalence of depression were obtained from clinical records, provided in a anonymised format by the Aragon Health Service. The processing, notification, and transfer of personal data were carried out in accordance with Regulation (EU) 2016/679 of the European Parliament and Spanish Organic Law 03/2018 on the Protection of Personal Data and the guarantee of digital rights.

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Conflict of Interest

The authors declare no conflict of interest.

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DISCUSIÓN

5.1 Variaciones en los parámetros clínicos:

Los resultados obtenidos en la línea de investigación de esta Tesis Doctoral muestran, seis meses después de la finalización del confinamiento estricto domiciliario, pequeñas variaciones en los parámetros clínicos de los pacientes con patologías crónicas. En lo referente a la valoración de los trastornos físicos (diabetes mellitus e hipertensión arterial) se observó una sutil mejoría en algunos parámetros analíticos (colesterol total, LDL y HDL) y antropométricos (peso e IMC), y un ligero empeoramiento en los valores de TAS y TAD (particularmente entre las mujeres) y en los marcadores de función renal. Aunque estadísticamente significativas ($p < 0,05$), estas diferencias observadas fueron pequeñas y carecen de relevancia clínica.

Estudios previos[136-144] sobre las consecuencias de la pandemia en el control analítico de estas afecciones crónicas, han mostrado variabilidad en sus resultados. Algunos trabajos, han reportado empeoramiento del control glucémico entre pacientes con diabetes mellitus tipo 2[136,137], y valores más altos de presión arterial sistólica y diastólica a corto y largo plazo (primeros 8 meses de la pandemia) entre pacientes hipertensos[138,139]. Otros manuscritos han expuesto, sin embargo, un efecto nulo de la pandemia sobre los parámetros clínicos de ambos trastornos[140-142] o incluso, mejoras significativas en el control glucémico (principalmente en pacientes con diabetes mellitus tipo 1) y en las cifras de presión arterial[136,143,144]. En cuanto a la proporción de pacientes que mantuvo niveles en rango para estos parámetros o que incluso experimentó alguna mejoría, más del 80% de los pacientes hipertensos en la C. A. de Aragón, mantuvo o mejoró sus cifras de TAS en los seis meses posteriores al fin del confinamiento y, más del 90% sus cifras de TAD. Estos resultados sugieren, que la mayoría de pacientes con patologías crónicas que antes de la pandemia acudían con regularidad a sus controles en los CAP, permanecieron estables durante y después del confinamiento, no experimentando un deterioro repentino[103].

Las pequeñas diferencias observadas en nuestra investigación podrían estar motivadas por el mayor impacto psicológico de la pandemia sobre los pacientes con condiciones físicas crónicas[87], quienes, según algunos estudios[11,145], presentaban ya antes de la crisis sanitaria mayores prevalencias de comorbilidades psiquiátricas que la población general.

La fuerte correlación demostrada por algunos metaanálisis entre las enfermedades crónicas preexistentes y peores resultados de salud a causa de la infección por COVID-19 (diabetes mellitus [Odds ratio [OR] 2,61; IC95% 1,93 – 3,52] e hipertensión arterial [OR 2,84; IC95% 2,22 – 3,63])[61], podría haber incrementado los niveles de estrés percibido entre estos

pacientes[85]. Asimismo, las medidas de distanciamiento impuestas para frenar la curva de contagios podrían haber provocado aislamiento social y soledad[87], los cuales han sido asociados con interrupciones en los patrones de sueño y descanso[146]. El aumento del estrés y de las alteraciones del ritmo circadiano de sueño-vigilia durante la pandemia, podrían explicar el incremento en las mediciones de tensión arterial que se observó en nuestro estudio[147,148]. El hallazgo del mayor incremento de los valores de presión arterial entre las mujeres ha sido también reportado por otro trabajo[147], haciendo patente el mayor impacto de estas y otras pandemias entre las mujeres[81,147].

Por otra parte, el conocimiento de los pacientes sobre la influencia de su patología en el pronóstico de la infección podría haber supuesto, no solo un mayor cumplimiento de las medidas restrictivas para evitar el contagio (utilización de mascarilla, lavado de manos, aislamiento social, etc.)[52,149], sino también, un mejor manejo de su enfermedad y la realización de cambios positivos en el autocuidado[150-153]. Algunos estudios[150], han evidenciado un mayor control de los niveles de glucosa en sangre entre los pacientes diabéticos durante los meses de la pandemia, además de la adopción de patrones alimentarios más saludables (mayor consumo de frutas y verduras, menor consumo de carnes procesadas y de bebidas azucaradas)[151-153] y de un aumento de la actividad física[150,151]. La sutil mejoría que mostraron los resultados en algunos parámetros analíticos (colesterol total, LDL y HDL) y antropométricos (peso e IMC) podría estar, en parte, explicada por estos últimos hechos.

Respecto a las variaciones en los parámetros clínicos de los pacientes con trastorno por abuso crónico de alcohol, no se encontraron cambios significativos en los marcadores biológicos. Estos resultados van en la misma línea que los de otro estudio realizado también en nuestro país[154], en el que no se evidenciaron cambios en la frecuencia de consumo de alcohol antes y después del confinamiento. El mantenimiento de la atención básica a estos pacientes a través de consultas telemáticas como alternativa eficaz a las visitas presenciales, podría estar detrás del escaso impacto de la pandemia en los parámetros clínicos de esta patología[155]. No obstante, un incremento moderado en el consumo de alcohol podría no verse reflejado en el examen analítico. Según el National Institute on Alcohol Abuse and Alcoholism[156], se precisa un aumento de la ingesta prolongada en el tiempo (varias semanas) para poder observar variaciones en los biomarcadores indirectos de consumo de alcohol (GOT, GPT). A pesar de no haber observado cambios clínicos significativos, algunos estudios[154,155] ponen en evidencia resultados adversos en la salud mental de los pacientes con trastorno por abuso crónico de alcohol durante la pandemia. De igual manera, múltiples manuscritos[86,157,158] apuntan a un deterioro de los síntomas entre los pacientes con trastornos de ansiedad y/o depresión durante el mismo

periodo. Tal y como se comentó en el apartado de metodología, la no disponibilidad de la información obtenida en las entrevistas clínicas de los pacientes con estos trastornos, ni de las escalas validadas utilizadas en APS para evaluar las variaciones en los niveles de ansiedad y depresión, impidió valorar el efecto psicológico de la pandemia entre estos pacientes. A pesar de ello, las variaciones encontradas en el número de DDD y DHD de los fármacos utilizados para el tratamiento de estas enfermedades, hacen sospechar un mayor impacto negativo de la pandemia entre los pacientes con problemas mentales preexistentes.

5.2 Cambios en la dispensación de medicamentos:

Un requisito importante para el buen control de las enfermedades crónicas es la continuidad de la medicación[159]. En Aragón, desde 2013 la prescripción de fármacos en APS se realiza a través de sistemas electrónicos[160]. La crisis sanitaria originada por el coronavirus, obligó a las CC. AA. a modificar estos sistemas, facilitando la renovación de las recetas electrónicas por vía telefónica. Además, en todo el estado español, se flexibilizaron los plazos de renovación de medicamentos, para que los pacientes polimedicados pudieran retirar el mayor número de tratamientos en una única visita a la farmacia comunitaria. Las escasas variaciones encontradas en el número de DDD y DHD dispensadas en farmacia en los seis meses posteriores al fin del confinamiento, podrían estar motivadas por la instauración de estas nuevas medidas que, sin la necesidad de desplazamiento al centro de salud, aseguraron el acceso continuo a los medicamentos[161].

Resultados similares fueron informados por varios estudios realizados en Europa y Asia[102,162,163]. Uno de ellos[163], con un enfoque afín al nuestro, pero con un diseño transnacional (incluyó 8 regiones europeas entre ellas, Cataluña), también evidenció que la dispensación de medicamentos para las enfermedades crónicas más comunes se vio poco afectada por la pandemia. No obstante, los pacientes crónicos podrían haber presentado dificultades para conseguir sus tratamientos. Según los resultados del cuestionario online desarrollado en nuestro país durante la segunda ola de la pandemia por la Plataforma de Organizaciones de Pacientes (POP)[164], el 25% de la población con patologías crónicas encontró problemas para acceder a sus tratamientos farmacológicos.

A pesar de ello, no se encontraron cambios de gran magnitud en el número de DDD y DHD dispensadas en farmacia en los seis meses posteriores al fin del confinamiento, a excepción de los siguientes grupos terapéuticos:

- Metformina (A10BA02): pese a las escasas variaciones e incluso a las ligeras mejorías observadas en algunos parámetros clínicos y antropométricos de los pacientes con diabetes mellitus, esta biguanida experimentó un aumento en el número de DHD dispensadas en farmacia durante los seis meses posteriores a la finalización del confinamiento. El mejor manejo de la enfermedad por parte de estos pacientes al conocer el papel que su patología tenía en la gravedad de los síntomas de COVID-19[150-153], pudo favorecer igualmente la adherencia al tratamiento[150]. Una mayor toma de la medicación antidiabética respecto a la etapa pre pandémica, pudo observase en otro estudio llevado a cabo en las Islas Canarias sobre una muestra de pacientes con diabetes mellitus tipo 2[165]. Resultados opuestos han sido también mostrados por otros trabajos [166,167], indicando un efecto negativo de la pandemia por COVID-19 en el cumplimiento del tratamiento crónico de la diabetes mellitus. Estos trabajos[166,167], fueron sin embargo realizados en países con ingresos medios-altos según las estimaciones del Banco Mundial[168,169] (Turquía y México - donde la accesibilidad a la medicación pudo ser menor) y, en muestras con una edad media entre 15 y 23 años inferior a la de nuestro estudio.

- Enalapril (CO9AA02) y Ramipril (CO9AA05): a pesar del ligero incremento en los valores de tensión arterial observado en nuestro estudio, en los seis meses siguientes al fin del confinamiento estos dos principios activos, ampliamente utilizados en el tratamiento antihipertensivo, experimentaron un descenso en el número de DHD. Durante los primeros meses de la pandemia, se publicaron algunos informes[170,171] que sugerían mayor riesgo de infección y de síntomas más graves de la enfermedad de COVID-19 entre quienes se encontraban en tratamiento con inhibidores de la enzima convertidora de angiotensina (IECAS). Aunque algunas sociedades científicas[172,173] recomendaron continuar con el tratamiento habitual al no demostrarse un aumento del riesgo de infección[174], ni de la severidad de la enfermedad[175] o de la mortalidad[175,176], algunos pacientes podrían haber dejado de tomar su medicación[172].

- Alprazolam (N05BA12), Lorazepam (N05BA06) y Lormetazepam (N05CD06): el incremento observado en el número de DDD y DHD dispensadas para estos grupos farmacológicos, sugiere mayores niveles de malestar psicológico durante el confinamiento domiciliario y los meses posteriores, entre las personas con trastorno mental preexistente (abuso crónico de alcohol, ansiedad y/o depresión). Otros trabajos[86,157,158], ya han indicado un mayor impacto de la pandemia en la salud mental

de estos colectivos en comparación con la población general, la cual también ha experimentado un incremento en el consumo de psicofármacos desde el inicio de la pandemia[177-179]. El crecimiento en el número de DHD entre la población general también puede observarse en nuestro estudio. Aunque estas variaciones sean de menor magnitud que las encontradas entre los pacientes con tratamiento activo para los trastornos de ansiedad y depresión, este aumento en el número de dispensaciones es particularmente preocupante en nuestro país, especialmente entre las mujeres. Antes de la pandemia (2015), España se situaba un 37% por encima del consumo medio de hipnóticos y sedantes y, multiplicaba casi por 2,5 el consumo medio europeo de ansiolíticos[180]. Tal y como apuntaban las estimaciones publicadas por Santomauro DF et al[181], los países más afectados durante la primera ola de la pandemia podrían haber experimentado una mayor exacerbación de los determinantes de mala salud. Este hecho podría haber contribuido a convertir a nuestro país, según el informe de la Junta Internacional de Fiscalización de Estupefacientes (JIFE), en el líder mundial de consumo lícito de ansiolíticos, hipnóticos y sedantes en 2021[182].

- Escitalopram (N06AB10), Paroxetina (N06AB05) y Fluoxetina (N06AB03): estos inhibidores selectivos de la recaptación de la serotonina (ISRS) experimentaron un descenso en el número de DDD y DHD dispensadas en los seis meses posteriores al fin del confinamiento. La misma tendencia fue reportada en algunos trabajos desarrollados en Canadá[183], Portugal[184] y España[185] donde la prescripción y/o dispensación de fármacos antidepresivos también experimentó un descenso temporal estadísticamente significativo tras el inicio de la pandemia. Estas caídas, pueden estar relacionadas con el aumento de los síntomas depresivos entre los pacientes con mayor carga de trastornos de salud mental. A pesar de que el deterioro de los síntomas podría sugerir el incremento o ajuste en las dosis de estos fármacos, en los individuos con mayor sintomatología depresiva dicho empeoramiento podría haber supuesto la interrupción del tratamiento. Estudios previos[186] sugieren que tener un régimen de medicación más complejo se asocia con una menor adherencia al tratamiento.

5.3 Diferencias en la utilización de recursos sanitarios:

Seis meses después del final del confinamiento, en Aragón, gran parte de los servicios sanitarios de APS y de atención especializada, no han recuperado los niveles de prestación de atención pre pandémicos. Esto sugiere, tal y como indican numerosos informes realizados por diversos organismos[97,187,188] que, durante los primeros meses de la pandemia, la atención a los pacientes con patologías crónicas se vio en mayor o menor medida interrumpida, pospuesta o cancelada.

Entre estas afecciones crónicas, la diabetes mellitus (38%), la EPOC (9%) y la hipertensión arterial (8%) se han descrito como las condiciones cuya atención y cuidado han sido interrumpidas en mayor magnitud durante la pandemia[99-101]. Los trastornos crónicos abordados en esta tesis en los objetivos 1 y 2 (diabetes mellitus e hipertensión arterial), han mostrado una reducción en el número de visitas a enfermería (a demanda, programada y urgente) en el CAP y a domicilio, en los meses siguientes al fin del confinamiento. Otros estudios han evidenciado también el efecto negativo de la crisis sanitaria en la atención enfermera a los pacientes crónicos, al observarse reducciones en indicadores de calidad como el screening del pie diabético[101] o el control ambulatorio de la tensión arterial[189]. En cuanto a las visitas al médico de familia (MF), para ambos trastornos (diabetes mellitus e hipertensión arterial) se observó también un descenso en el número de visitas. La misma tendencia fue mostrada por otros autores[190,191], que observaron importantes reducciones en los procedimientos diagnósticos y terapéuticos de estas condiciones durante el año 2020, en comparación con el año anterior. Contrariamente, destaca el aumento en el número de visitas al médico de atención continuada (MAC) en el centro de salud, observado especialmente en los pacientes con diabetes mellitus. Este problema de salud se presenta frecuentemente asociado a hipertensión arterial[32,192] y a otras enfermedades[192], multiplicando la coexistencia de las patologías, el riesgo de complicaciones macro o microvasculares[193]. Entre los pacientes con diabetes mellitus más vulnerables (mayor edad, pluripatológicos, polimedicados, en terapia con insulina), la telemedicina como alternativa a las visitas presenciales pudo no ser tan eficaz, presentando este colectivo un mayor riesgo de deterioro[194]. Del mismo modo, los cambios antagónicos respecto al envejecimiento saludable que trajo consigo la pandemia[195] (reducción de la movilidad, de las relaciones sociales, etc.) podrían haber catalizado el agravamiento o la aparición de complicaciones entre este grupo de pacientes más frágiles.

Tal y como se expuso con anterioridad, otro de los colectivos más afectados negativamente por la pandemia y su confinamiento, podría estar formado por las personas con algún trastorno

mental subyacente[86,157,158]. En nuestro trabajo, este hecho se pondría de manifiesto a través de las variaciones en la dispensación de algunos fármacos utilizados en el tratamiento de estas afecciones (Alprazolam, Lorazepam y Lormetazepam), y también, en la mayor utilización de los recursos médicos por parte de estos pacientes. En los seis meses siguientes al fin del confinamiento, en todos los trastornos psíquicos analizados (abuso crónico de alcohol y ansiedad y/o depresión) se observó un incremento en el número de consultas al MF en el centro de salud. Estos resultados, concuerdan con los mostrados por otros estudios cualitativos[196,197] que también informan de un mayor número de visitas al MF tras el confinamiento entre los pacientes con trastornos mentales preexistentes (generalmente en modalidad no presencial).

A pesar de las interrupciones en los servicios esenciales de salud, y de la posible persistencia de las mismas, incluso 12 meses después del inicio de la crisis sanitaria[198], nuestros resultados mostraron (para algunos de los procesos analizados) un incremento en los meses posteriores al fin del confinamiento en el número de visitas a otros profesionales del CAP: matrona y odontología. Los retrasos generados por la caída (durante marzo y mayo de 2020) en el número de exámenes citológicos de cérvix, en el diagnóstico de otros cánceres ginecológicos, así como en la atención y detección de problemas de la mujer en el climaterio[199-201], podrían haber aumentado la demanda en los meses siguientes. Esto mismo podría haber ocurrido con la atención a la salud bucodental. Al inicio de la pandemia se vio prácticamente suspendida, no solo por incluirse en la categoría de “no esencial”, sino también por el riesgo de infección al que se exponían los odontólogos[202].

Finalmente, de manera unánime, en todas las patologías analizadas se observó una mayor tendencia a visitar la consulta del trabajador/a social. La falta de recursos fruto de la paralización de la actividad económica no esencial al inicio de la pandemia o, el retraso en el pago de los ERTE (expediente de regulación temporal de empleo), pudo aumentar el número de nuevos demandantes de ayuda. De la misma forma, el deterioro o la ruptura del tejido social que cuidaba a las personas mayores (especialmente a aquellas que vivían solas antes de la pandemia), podría también haber precipitado la intervención de los servicios sociales sobre estos colectivos vulnerables[203,204].

Análogamente, el número de derivaciones al especialista (primera visita) mostró una tendencia ascendente tras el fin del confinamiento en alguno de los procesos analizados (hipertensión arterial y ansiedad y/o depresión). En el caso de la hipertensión arterial, su elevada prevalencia entre los mayores de 65 años (por encima del 60% en nuestra C. A.)[205] y la coexistencia de esta patología con múltiples enfermedades[206], podría haber aumentado el riesgo

de eventos adversos ante la falta de atención durante la primera ola de la pandemia. De este modo, la reducción en los estándares de atención a los pacientes con HTA más vulnerables (mayor edad, pluripatológicos, polimedicados), pudo haber determinado un aumento en la tasa de complicaciones[207], lo que conllevó un mayor número de derivaciones a las consultas de atención especializada (que lentamente fueron reanudando su actividad). En cuanto al incremento observado entre los pacientes con ansiedad y/o depresión, el impacto de la pandemia podría haber tenido repercusiones negativas no solo a nivel psicológico, sino también biológico. Las medidas de distanciamiento social impuestas podrían haber trastocado las rutinas diarias y las relaciones sociales de estos pacientes[208], empeorando su sintomatología psiquiátrica[158,209] e influyendo esto en el manejo clínico de sus comorbilidades físicas[210]. Estas comorbilidades podrían asimismo determinar el riesgo de empeoramiento de la propia patología psiquiátrica. Nuestros resultados sugieren que entre los hombres con ansiedad y/o depresión, la presencia de más de una comorbilidad, la edad por debajo de los 60 años y los ingresos inferiores a 18.000€/año se asociaron con un mayor riesgo de deterioro psicológico durante la pandemia.

Este incremento en el número de derivaciones al especialista ha podido tener consecuencias importantes en los sistemas de gestión de listas de espera. Según los datos del Ministerio de Sanidad, Aragón ocupó en diciembre de 2020 el peor puesto del ranking nacional con un tiempo medio de espera de 147 días para ser visto por el especialista[211]. Este aumento en los tiempos de respuesta asistencial pudo implicar un retraso en el diagnóstico y en el inicio de los tratamientos. Durante los primeros meses de la pandemia, los nuevos diagnósticos de enfermedades crónicas como la hipertensión arterial, la diabetes mellitus, la cardiopatía isquémica, el cáncer, la ansiedad o la depresión se redujeron considerablemente[27,212,213]. En el mismo periodo de tiempo, las pruebas de detección (de laboratorio y de imagen) de estos trastornos también se vieron reducidas, como bien muestran los resultados de nuestro trabajo y de otros estudios[198,214]. El infra diagnóstico de estas y otras patologías pudo aumentar el número de pacientes diagnosticados en fases más avanzadas de la enfermedad, suponiendo esto un retraso en el inicio de las terapias y a su vez, un mayor número de complicaciones o una peor calidad de vida. Desafortunadamente, para algunas patologías el retraso en el diagnóstico y tratamiento pudo afectar gravemente al pronóstico de supervivencia[215].

5.4 Mortalidad en los meses posteriores al fin del confinamiento:

Según estimaciones de la OMS, entre 13 y 16 millones de muertes fueron, durante 2020 y 2021, atribuibles al impacto directo e indirecto de la pandemia de COVID-19 en todo el mundo[216].

En 2020, se produjeron en nuestro país 493.776 fallecimientos. Ese año, España alcanzó un récord histórico en el número de defunciones, con un 17,9% más de muertes que el año anterior. Este exceso de mortalidad se debió en parte a las muertes relacionadas directamente con la pandemia (respecto al año anterior, los fallecimientos debidos a enfermedades infecciosas aumentaron un 1.220,4%). Según los datos del Instituto Nacional de Estadística (INE)[217], más de 70.000 decesos estuvieron relacionados con la COVID-19. En alrededor de 60.300 se demostró la existencia del virus como causante, mientras que en casi 14.500 muertes, el fallecimiento se asoció con la infección pero el virus no pudo ser identificado. Este incremento en la mortalidad se relacionó también con otras causas de muerte diferentes a la COVID-19 (las muertes a causa de enfermedades del sistema circulatorio aumentaron un 2,8% respecto al 2019). Aunque el análisis de la mortalidad no se estableció como uno de los objetivos de esta Tesis Doctoral, en todos los manuscritos se observó un incremento en la tasa bruta de mortalidad por otras causas en el periodo posterior al fin del confinamiento (del 3 de mayo al 4 de noviembre de 2020).

Este incremento observado en la mortalidad por causas distintas a la COVID-19, podría explicarse, en el caso de la diabetes mellitus y la hipertensión arterial, por el particular incremento que experimentaron estas causas de muerte respecto al 2019. Según el INE, las enfermedades hipertensivas y la diabetes mellitus fueron las causas de muerte que más aumentaron en 2020 (un 20,4% y un 17,1% respectivamente)[217].

El impacto de la pandemia en los sistemas de salud podría explicar parte del exceso de mortalidad observado por otras causas distintas a la infección. La sobrecarga de los servicios sanitarios junto con el miedo a asistir a los CAP por temor al contagio pudo impedir en algunos casos la prevención y el tratamiento adecuado de estos procesos o, incluso el acceso a los servicios sanitarios[216]. Algunos estudios también han sugerido que los pacientes crónicos más vulnerables (personas de mayor edad con comorbilidades), podrían haber experimentado un mayor temor a la exposición del COVID-19[218], y por lo tanto una mayor necesidad de practicar el distanciamiento físico[219]. La soledad y el aislamiento social, podrían haber afectado la salud y bienestar de estos pacientes más frágiles, puesto que se ha demostrado que ambas están

asociadas con un mayor riesgo de problemas de salud (depresión, deterioro cognitivo, demencia) y un mayor riesgo de muerte[219].

De esta manera, la pandemia por COVID-19 ha contribuido a elevar la mortalidad por enfermedades crónicas y a su vez, las enfermedades crónicas han contribuido a aumentar la mortalidad por COVID-19[220]. Como ya se mencionó en la introducción, la mayoría de las muertes por coronavirus, se produjeron en personas de edad avanzada con problemas de salud subyacentes como la hipertensión arterial, la diabetes mellitus tipo 2, la cardiopatía isquémica o la EPOC[221,222]. Según el INE, en nuestro país, la principal comorbilidad de las personas fallecidas por COVID-19 fue la hipertensión arterial (presente en el 12,8% de los fallecidos con el virus, y en el 20,3% de los fallecidos con sospecha de la infección)[217].

En los que respecta a las muertes por causas externas (accidentes, caídas, agresiones, ahogamientos, etc.), en 2020 se produjeron 16.000 fallecimientos en España. El suicidio continuó siendo la primera causa de muerte no natural con 3.941 fallecidos, una media de 11 personas al día. Estas cifras suponen un aumento de 270 defunciones respecto a 2019 (un 7,4% más), convirtiendo al 2020 en el año con más suicidios en la historia de España desde que se tienen registros[217,223]. Entre los pacientes con trastorno por abuso crónico de alcohol, ansiedad y/o depresión, parte del incremento de la mortalidad observado podría estar justificado por el incremento en el número de muertes por suicidio. Algunos autores[224,225] sugieren que hasta en el 90% de los casos de suicidio, existe un trastorno psiquiátrico subyacente. La ansiedad, la depresión y el trastorno por abuso de alcohol son, por este orden, los trastornos mentales con mayores prevalencias en el mundo; siendo también alguno de estos, los grupos diagnósticos que presentan mayor riesgo de suicidio (depresión [RR = 19,9], esquizofrenia [RR = 12,6] y dependencia del alcohol [RR = 9,8])[225]. Los efectos psicológicos de la pandemia y del distanciamiento entre los pacientes con las patologías anteriormente mencionadas, podrían haber exacerbado los factores de riesgo de suicidio[226]. Del mismo modo, tras el fin del confinamiento, pero todavía en situación de pandemia, los pacientes con trastornos depresivos mostraron una disminución en el número de DDD y DHD de algunos ISRS. Según apuntan algunos estudios[227], es posible que el tratamiento con estos fármacos reduzca el riesgo de comportamiento suicida en adultos; por lo que la reducción o el abandono de los mismos, podría también haber contribuido al incremento del número de fallecimientos por esta causa.

5.5 La Atención Primaria de Salud tras la pandemia:

Seis meses después de la finalización del confinamiento, la sobrecarga asistencial tras las primeras oleadas de la pandemia junto con el agotamiento de los profesionales sanitarios y otros problemas organizativos, siguieron limitando en la C. A. de Aragón el control y seguimiento de los pacientes crónicos desde APS.

A pesar de estas interrupciones en la atención a la cronicidad, los resultados de nuestros estudios sugieren que una parte importante de los pacientes con diagnóstico de diabetes mellitus e hipertensión arterial, no experimentaron deterioro clínico, ni cambios analíticos y farmacológicos importantes entre mayo y noviembre de 2020. Entre los pacientes crónicos con mayor complejidad clínica y entre aquellos con problemas de salud mental preexistentes (trastorno por abuso crónico de alcohol, ansiedad y/o depresión), el impacto de la pandemia pudo ser sin embargo mayor. Al inicio de la pandemia, la necesidad de atención a las personas infectadas por el virus desplazó el control y seguimiento de los pacientes con patologías no COVID más vulnerables, generando una situación de "desprotección"[228]; la cual seis meses después del final del confinamiento, tuvo un impacto en la morbilidad y en la mortalidad por enfermedades crónicas.

¿Qué implicación podría tener para los sistemas de salud y, particularmente para la APS, dicho impacto en la cronicidad?

Durante los meses siguientes al fin del confinamiento domiciliario, los centros asistenciales de APS, exhaustos tras la primera ola, continuaron centrando gran parte de sus recursos en la atención a los pacientes con infección activa[229]. Igualmente, la prolongación de la pandemia en el tiempo continuó generando (aunque probablemente en menor magnitud) un retraso en la atención preventiva, diagnóstica y terapéutica de los pacientes no COVID[198,228], hecho que pudo haber perpetuado o incluso acrecentado el impacto negativo en la morbilidad de los pacientes más frágiles[230]. Además, durante este mismo periodo comenzó a surgir una nueva categoría de pacientes crónicos: los afectados por secuelas persistentes tras la infección por coronavirus. Estos pacientes, podrían representar hasta al 10-15% de los afectados por la enfermedad[231], y se caracterizan por padecer una amplia variedad de problemas crónicos de salud hasta 12 semanas después de la infección[232]. El abordaje individualizado de estos nuevos pacientes recayó también sobre los equipos de APS, quienes desde entonces realizan la evaluación y seguimiento de los mismos[233] y gestionan su derivación a atención especializada para un manejo multidisciplinar[231]. Adicionalmente, según los resultados de un estudio publicado por Al-Aly Z et al[234], los servicios de APS podrían estar enfrentándose en paralelo a

una mayor tendencia a la cronicidad a edades más tempranas entre aquellos pacientes que hubiesen pasado la infección[235].

De esta manera, la COVID-19 ha supuesto y supone una emergencia de salud crónica agudizada en una sociedad envejecida como la nuestra[220]. Ya antes de la crisis sanitaria del coronavirus, este fenómeno demográfico y las proyecciones para los próximos años (en 2065 se prevé que el 29% de la población española tenga 65 y más años[236]), planteaban un importante desafío social y de salud pública en nuestro país y en otras regiones de Europa[237]. El proceso de envejecimiento y su asociación a múltiples trastornos crónicos junto con el impacto de la pandemia en las enfermedades no transmisibles, podrían aumentar no solo la utilización de los servicios sociales, sino también de los servicios sanitarios, especialmente los de APS, donde se lleva a cabo una atención longitudinal de estos trastornos[237, 238].

Bajo estas premisas, se hace necesario modificar la gestión y organización de los sistemas sanitarios y más concretamente el abordaje de los pacientes crónicos. A la fecha de culminación de estas Tesis Doctoral, esta necesidad de modificación sigue vigente. En 2019, con anterioridad a la crisis sanitaria del coronavirus, la OMS amplió el Plan de Acción Mundial para la prevención y control de las enfermedades no transmisibles 2013-2020 hasta el año 2030, con la finalidad de alcanzar una reducción de un tercio en la mortalidad prematura por estas causas[8]. Tanto en el Plan de Acción Mundial de la OMS[7] como en el documento del Ministerio de Sanidad del Gobierno de España sobre la Estrategia para el Abordaje de la Cronicidad en el SNS[41], el fortalecimiento de los equipos de Atención Primaria y la reorganización de la atención se establecen como algunas de las intervenciones organizativas prioritarias para la mejora de la prevención y control de las enfermedades crónicas. Para que la APS alcance el liderazgo que le corresponde, debe avanzar hacia una atención más estratificada que clasifique a los pacientes en función de la carga de enfermedad, las desigualdades en salud y las necesidades sociosanitarias[239]. Para la implementación de esta estrategia en la C. A. de Aragón, el departamento de sanidad puso en marcha en 2017 el proyecto de atención al Paciente Crónico Complejo (PCC)[240]. Teniendo en cuenta la situación de salud de los individuos, la utilización que estos hacen de los servicios sanitarios, el consumo farmacéutico y otras variables de ajuste, a través de herramientas de estratificación de Grupos de Morbilidad Ajustados (GMA) se identificó a los pacientes con mayor complejidad. Su identificación, permitía que fuesen atendidos de la manera más adecuada, minimizando así el riesgo de descompensaciones y la aparición de eventos adversos. Este proyecto, que se estableció teniendo como eje operativo la APS en coordinación con las unidades de atención a enfermos crónicos complejos (UCC) establecidas

en los hospitales generales de la comunidad[240], se vio interrumpido tras el inicio de la pandemia cuando estás UCC fueron reconvertidas para atender a otro tipo de pacientes[241].

Nuestros resultados ponen también de manifiesto las consecuencias directas e indirectas de la pandemia sobre el bienestar psicológico de uno de los colectivos más vulnerables: las personas con enfermedad mental preexistente. Urge potenciar la atención a la salud mental en los servicios de APS, tanto para el mejor manejo de las personas con trastornos psicopatológicos ya establecidos, como para evitar que el sufrimiento psicosocial postpandemia se cronifique[242]. Uno de los principales problemas de la salud mental en nuestro país, es la precariedad de recursos dentro del ámbito sociosanitario público[243]. Según el Plan de Atención Primaria y Comunitaria de Aragón 2022-2023[244], solamente 20 psicólogos clínicos desempeñan su trabajo en APS en nuestra C. A. En el Servicio Aragonés de Salud hay 5,7 profesionales de la psicología clínica por cada 100.000 habitantes. Estas cifras son similares a las nacionales (con 5,6 profesionales por cada 100.000 habitantes), pero están todavía lejos de las de otros países europeos que tienen de media ocho, diez e incluso doce profesionales por cada 100.000 habitantes[245]. El número insuficiente de profesionales podría fomentar la medicalización de estos problemas como primera alternativa de tratamiento[245], contribuyendo ello al aumento de las elevadas cifras de consumo de ansiolíticos, hipnóticos y sedantes en nuestro país. La inversión en salud mental es especialmente necesaria tras la pandemia en un país tan castigado como el nuestro y, en el que antes de la crisis sanitaria, apenas el 5% del gasto total sanitario se destinaba a la prevención y tratamiento de estos trastornos[246].

Por todo esto, es imprescindible aumentar el porcentaje del Producto Interior Bruto (PIB) que se asigna a la APS. A pesar de que en los últimos años el gasto sanitario público en Aragón se ha incrementado, la mayor inversión se ha realizado en los servicios hospitalarios (65,8% de gasto en 2019)[244]. En APS el porcentaje de gasto ha sido mucho menor (13,2%)[244], casi 12 puntos por debajo de las recomendaciones de la OMS[247].

Otro aspecto relevante, lo constituye el hecho de que las enfermedades crónicas estén influidas por determinantes de salud relacionados con los estilos de vida (inactividad física, dieta poco saludable, tabaquismo, consumo nocivo de alcohol) y con otras condiciones sociales, culturales o ambientales (condición de vida, trabajo, nivel de educación o ingresos) que se distribuyen de manera desigual entre la población y explican la mayor parte de las inequidades en salud[41,239]. Para resolver estas inequidades en salud, es indispensable favorecer las condiciones de vida de las poblaciones y disminuir la desigualdad social[247]. Dada la influencia de estos determinantes en la salud, se debe trabajar en un enfoque holístico y multisectorial que

considere la participación de más agentes en la construcción de políticas públicas de salud. El enfoque de "Salud en todas las políticas", aboga por la formulación de políticas (tanto en el ámbito de la salud como fuera de él), que tengan sistemáticamente en cuenta las implicaciones de dichas decisiones en la salud de la población[237]. Y desde esta perspectiva, la APS tiene un papel fundamental en la lucha contra las inequidades[239]. Dentro del sistema sanitario, es posible priorizar programas y estrategias de salud destinados a favorecer a los colectivos más vulnerables, los cuales solo resultarán efectivos si los propios pacientes se implican en el cuidado de su salud[247].

El primer nivel asistencial ha sido, en coordinación con los equipos de Salud Pública, el centro de atención de la crisis pandémica. La COVID-19 nos ha presentado no solo la oportunidad para repensar el futuro de la APS, donde la telemedicina y la consulta digital deberían normalizarse, sino también la importancia de controlar las enfermedades crónicas como requisito previo fundamental para contener mejor futuras enfermedades infecciosas emergentes. Ante esta realidad, urge reforzar ambos servicios. Solo así, se conseguirá un mayor y mejor control de las enfermedades no transmisibles y por consiguiente, una reducción del impacto de futuras pandemias en el estado de salud de la población[248].

5.6 Limitaciones y fortalezas:

Los resultados de esta investigación presentan algunas limitaciones. En primer lugar, aunque nuestros estudios consideraron exclusivamente a pacientes con patologías crónicas sin infección documentada de SARS-CoV-2, la escasez de pruebas diagnósticas durante la primera ola de la pandemia podría haber facilitado la inclusión de pacientes con patologías crónicas que sí pasaron la enfermedad (pacientes sin diagnósticos *versus* pacientes sin enfermedad). Bajo esta condición que no se ha podido controlar, supondríamos que aquellas personas que han pasado la enfermedad lo han hecho de una forma clínica, sin formalizarse ningún diagnóstico de infección por coronavirus en la historia clínica. En segundo lugar, a pesar de que la infección viral podía tener un importante impacto negativo en los pacientes con enfermedades pulmonares crónicas (asma, EPOC, etc.), estas patologías respiratorias no fueron consideradas por la falta de registros clínicos en los meses posteriores al fin del confinamiento. Durante la fase pandémica, las pruebas de exploración de la función respiratoria realizadas rutinariamente en los CAP (espirometrías) se paralizaron, ya que los aerosoles emitidos durante su realización podrían favorecer la diseminación del virus. Por otro lado, la escasez de mediciones registradas durante los meses de confinamiento domiciliario estricto (del 16/03/2020 al 02/05/2020), impidieron

valorar el efecto de las medidas restrictivas impuestas para frenar la propagación del virus en la salud de estos pacientes. En esa misma línea, para alguna de las variables clínicas consideradas el número de observaciones fue también reducido, ya que para poder acceder a estos registros el MF debía previamente validar dichos datos. Así pues, solo tuvimos acceso a aquellas mediciones que habían sido validadas por el MF.

En cuanto a las fuentes de información, como ya se comentó previamente, todos los datos relativos a los pacientes objeto de estudio, están basados en datos clínico-administrativos provenientes de las HCE de Atención Primaria. Especialmente en el caso de los pacientes con trastornos psicopatológicos ya establecidos (trastorno por abuso crónico de alcohol, ansiedad y/o depresión), no fue posible el acceso a los registros cuantificados del consumo de alcohol en Unidades de Bebida Estándar (UBE), ni a los resultados de cuestionarios estructurados específicos utilizados en APS (Alcohol Use Disorder Identification Test –AUDIT–, Escala de Depresión y Ansiedad de Goldberg, Escala de Depresión Geriátrica de Yesavage, Escala de Ansiedad de Hamilton o, Inventario de Ansiedad de Beck). Esta limitación, impidió realizar una evaluación más completa del impacto de la pandemia en la salud mental de los pacientes con estas patologías.

A pesar de las altas prevalencias de trastornos metabólicos entre las personas con enfermedades mentales, en los objetivos 4 y 5 no se analizaron otros parámetros analíticos (glucemia, HbA1c, colesterol total, LDL, HDL, IMC, etc.). A parte del deterioro psicológico observado, la presencia de variaciones en estos indicadores podría haber sugerido también el deterioro de la salud física entre estos pacientes. En lo que respecta a las comorbilidades físicas, a pesar de que los perfiles clínicos de los pacientes con diabetes mellitus tipo 1 y 2 son bastante diferentes, éstos fueron considerados conjuntamente. Por otra parte, entre los pacientes con hipertensión arterial, no se pudo establecer si las mediciones de las cifras de tensión se realizaron exclusivamente en la consulta de enfermería o, si por el contrario, los pacientes comunicaron los valores a su enfermera tras realizar en su domicilio la automedición de la misma. Adicionalmente, en ninguno de los trabajos se incluyó información aportada por los propios pacientes sobre la modificación de las rutinas y estilos de vida (dieta, actividad física, consumo de tabaco o alcohol), ni tampoco de la percepción subjetiva del impacto de la pandemia en el estado de salud.

Respecto al consumo de medicamentos, tal y como se describió previamente, se consideró únicamente el número de unidades dispensadas en farmacia. A pesar de que el número de unidades dispensadas proporciona información más fiable acerca del consumo que

el número de unidades prescritas, se debe tener presente que no todo fármaco dispensado es necesariamente consumido. Respecto a la utilización de recursos sanitarios, en el número de visitas a enfermería o medicina en el CAP no se pudo hacer distinciones según la tipología de consulta (presencial o telemática). Por ello, no se consiguió valorar la magnitud del cambio en la modalidad de atención a los pacientes con trastornos crónicos durante los primeros meses de pandemia.

Por otra parte, a pesar del exceso de mortalidad por otras causas distintas a la infección por coronavirus observado en todos nuestros resultados, desconocemos la condición de salud que causó estos fallecimientos. Disponer de este dato, hubiese permitido conocer las causas de muerte vinculadas indirectamente con la COVID-19 que experimentaron un mayor incremento. De hecho, con posterioridad al periodo de análisis de esta Tesis Doctoral, en verano de 2021 y especialmente en 2022 (entre junio y agosto), se evidenció un exceso de defunciones por todas las causas[249].

La no presentación de los resultados desagregados por sexos (excepto para el manuscrito 4) es otra limitación, ya que este es un determinante social que influye no solamente en el estado de salud, sino también en los comportamientos de salud y en el uso de los servicios sanitarios.

Para acabar, el periodo de estudio (seis meses tras el fin del confinamiento) podría haber resultado insuficiente para observar variaciones en el estado de salud de los pacientes con patologías crónicas. Las sucesivas olas de la pandemia junto con las nuevas variantes del virus (alpha, beta, gamma, delta, omicrón), podrían haber tenido un efecto acumulativo sobre un sistema sanitario cada vez más debilitado. Finalmente, con un tamaño muestral tan grande pudimos encontrar variaciones que, aun siendo reales y significativas, fueron tan pequeñas que carecían de interés desde el punto de vista clínico.

En cuanto a las fortalezas, esta Tesis Doctoral contribuye al conocimiento de las repercusiones de la pandemia de COVID-19 sobre algunas enfermedades crónicas que se manejan desde APS considerando conjuntamente variables clínicas, farmacológicas y de utilización de recursos. Las evidencias generadas proporcionan un mayor conocimiento sobre las consecuencias de la pandemia sobre poblaciones con patologías crónicas subyacentes, lo cual puede contribuir al aumento y mejora de la planificación y gestión de recursos ante futuras pandemias. Una de las principales virtudes de nuestro trabajo, es la disponibilidad de una gran base de datos poblacional. Destacar también el uso de datos clínico-administrativos provenientes de las HCE de Atención Primaria. La utilización de datos del mundo real o RWD, en

el contexto de un SNS con cobertura universal, permitió no solo incluir en el análisis a una gran cantidad de individuos, sino también arrojar conclusiones más exhaustivas y fiables que las derivadas únicamente de estudios basados en encuestas, al evitar el sesgo de recuerdo característico de los datos auto informados. Asimismo, su disponibilidad supuso un coste más reducido. Por último, esta Tesis Doctoral está basada en un proyecto financiado en convocatoria pública competitiva, específica para COVID-19, del Departamento de Ciencia, Universidad y Sociedad del Conocimiento, lo que le otorga un mayor soporte metodológico y de calidad. Sus resultados han sido ya transferidos a la gestión sanitaria.

5.7 Líneas de investigación futuras:

Está línea de investigación sobre el efecto de la pandemia en la cronicidad y la evolución de la misma, requiere de una continuidad que evalúe los cambios en los parámetros clínicos, farmacológicos y de utilización de recursos sanitarios durante un periodo de tiempo más extenso (12 meses tras el fin del confinamiento). De igual manera, sería de gran interés presentar estos resultados desagregados por sexo, para valorar así la tendencia y magnitud de los cambios en el tiempo y las diferencias entre hombres y mujeres. Como se comentó anteriormente, la situación pandémica se prolongó durante meses dejando varias oleadas de contagios, hecho que sin duda ha aumentado progresivamente la extenuación del sistema sanitario y especialmente de la APS. Análogamente, estudios que analicen el exceso de mortalidad por otras causas no relacionadas con la infección son necesarios para comprender en detalle este fenómeno, el cual podría ser estudiado aplicando la metodología de series de tiempo interrumpido (ITS) a través de métodos estadísticos de regresión segmentada. Por otro lado, la utilización de sistemas de información geográfica (SIG), nos permitiría representar a través de mapas las zonas básicas de salud más afectadas e identificar clusters geográficos.

Por último, la realización de estudios con un enfoque cualitativo permitiría comprender mejor las repercusiones de la pandemia por COVID-19 en las personas con estas y otras patologías crónicas, al proporcionar percepciones subjetiva de los propios pacientes acerca del impacto de la crisis sanitaria en el control de su enfermedad.

CONCLUSIONES

1. Seis meses después de la finalización del confinamiento estricto domiciliario, los pacientes con diabetes mellitus e hipertensión arterial, mostraron pequeñas variaciones en los parámetros clínicos. Algunos datos analíticos (colesterol total, LDL y HDL) y antropométricos (peso e IMC) mostraron una sutil mejoría, mientras que las cifras de TAS y TAD experimentaron un ligero empeoramiento (particularmente entre las mujeres). Estas variaciones mostraron significación estadística, pero fueron tan pequeñas que carecen de relevancia clínica.
2. En el mismo periodo, los pacientes crónicos con trastorno por abuso crónico de alcohol no experimentaron cambios significativos en los marcadores biológicos de esta enfermedad.
3. Entre mayo y noviembre de 2020, la gran mayoría de grupos farmacológicos incluidos en los cuatro trastornos crónicos abordados en esta Tesis Doctoral, mostraron variaciones de pequeña magnitud en el número de DDD y DHD dispensadas en farmacias.
4. Algunos grupos farmacológicos experimentaron variaciones de mayor magnitud. La Metformina (A10BA02) mostró un aumento significativo en el número de DHD en los 6 meses siguientes. Para el mismo periodo de tiempo, Enalapril (CO9AA02) y Ramipril (CO9AA05) experimentaron una reducción significativa en el número de dispensaciones.
5. Respecto a los fármacos para el tratamiento de los trastornos psíquicos, algunas benzodiacepinas (Alprazolam (N05BA12), Lorazepam (N05BA06) y Lormetazepam (N05CD06)) incrementaron el número de dispensaciones en los meses siguientes al fin del confinamiento. ISRS como Escitalopram (N06AB10), Paroxetina (N06AB05) y Fluoxetina (N06AB03) experimentaron un descenso.
6. Durante los primeros meses de la pandemia, la atención a los pacientes con patologías crónicas en Aragón se vio interrumpida, no habiendo recuperado gran parte de los servicios sanitarios (consultas a enfermería, realización de pruebas diagnósticas, atención hospitalaria, etc.) de la C. A. los niveles de atención pre pandémicos a finales del año 2020.
7. Otros servicios sanitarios, especialmente las consultas a medicina de familia y a atención médica continuada se vieron incrementadas en los meses siguientes al fin del confinamiento entre los pacientes con trastornos crónicos psíquicos (abuso crónico de alcohol y ansiedad y/o depresión) y físicos (diabetes mellitus).

8. En todos los objetivos se evidenció un incremento en el número de visitas a la consulta del trabajador/a social. Este hecho, pondría de manifiesto el impacto social de la crisis sanitaria del coronavirus en nuestra comunidad.
9. El número de derivaciones al especialista (primera visita), mostró una tendencia ascendente tras el fin del confinamiento en alguno de los trastornos físicos (hipertensión arterial) y psicológicos (ansiedad y/o depresión) analizados. Dicho incremento, podría haber tenido consecuencias importantes en los sistemas de gestión de listas de espera, así como en la mortalidad no COVID.
10. En todos los trastornos crónicos incluidos en este trabajo de investigación, se observó un incremento en la tasa bruta de mortalidad por otras causas en el periodo posterior al fin del confinamiento (del 3 de mayo al 4 de noviembre de 2020). La COVID-19 podría haber tenido un alto impacto en la mortalidad con origen no COVID entre los pacientes crónicos de la C. A. de Aragón.

CONCLUSIONS

1. Six months after the end of strict lockdown, patients with diabetes mellitus and arterial hypertension showed small variations in clinical parameters. Some analytical (total cholesterol and LDL) and anthropometric (weight and BMI) data showed a subtle improvement, while the SBP and DBP values experienced a slight worsening (particularly among women). These variations showed statistical significance but were so small that they lack clinical relevance.
2. In the same period, chronic patients with chronic alcohol use disorder did not experience significant changes in the biological markers of this disease.
3. Between May and November 2020, the vast majority of pharmacological groups included in the four chronic disorders addressed in this Doctoral Thesis, showed small-magnitude variations in the number of DDD and DHD dispensed in pharmacies.
4. Some pharmacological groups experienced larger variations. Metformin (A10BA02) showed a significant increase in the number of DHD in the following 6 months. For the same period Enalapril (CO9AA02) and Ramipril (CO9AA05) experienced a significant reduction in the number of dispensations.
5. Regarding drugs for the treatment of chronic mental), some benzodiazepines (such as Alprazolam (N05BA12), Lorazepam (N05BA06) and Lormetazepam (N05CD06)) increased the number of dispensed DHD in the months following the end of lockdown. SSRIs such as Escitalopram (N06AB10), Paroxetine (N06AB05) and Fluoxetine (N06AB03) experienced a decline.
6. During the first months of the pandemic, care for patients with chronic pathologies in Aragon was interrupted. Most of the health services (nursing consultations, diagnostic tests, hospital care, etc.) had not recovered pre-pandemic levels of care at the end of 2020.
7. Other health services, especially general practitioner visits and continued medical care consultations increased among patients with chronic mental disorders (chronic alcohol abuse and anxiety and/or depression) and with physical disorders (diabetes mellitus) in the months following the end of lockdown.
8. In all the objectives an increase in the number of visits to the social worker's office was observed. This fact would highlight the social impact of the coronavirus health crisis in our community.
9. The number of referrals to the specialist (first visit) also showed an upward trend after the end of lockdown in some of the physical (arterial hypertension) and psychological

(anxiety and/or depression) disorders analyzed. This increase could have had important consequences on the waiting list management systems, as well as on non-COVID mortality.

10. In all chronic disorders included in this research work, an increase in the crude mortality rate from other causes was observed in the period after the end of lockdown (from May 3 to November 4, 2020). COVID-19 could have had a high impact on mortality of non-COVID origin among chronic patients in the Autonomous Region of Aragon.

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ANEXOS

Anexo 1. DDD y DHD.

Siguiendo las recomendaciones de la OMS, en esta Tesis Doctoral, la dispensación de los medicamentos ha sido expresada a través de las Dosis Diarias Definidas (DDD) y de las DDD por 1.000 Habitantes y Día (DHD).

La Dosis Diaria Definida (DDD) es una unidad técnica de medida que se corresponde con la dosis media diaria de mantenimiento de un medicamento en adultos, cuando se usa rutinariamente para su indicación principal. La OMS, en el portal web: https://www.whocc.no/atc_ddd_index/ presenta para cada principio activo y vía de administración las dosis medias diarias de mantenimiento (Ejemplo: Paracetamol 3.000 mg). No obstante, el número de DDD puede variar según la dosis prescrita o según en número de unidades por envase (Ejemplo: Paracetamol 650 mg en envase de 20 comprimidos, Paracetamol 1.000 mg en envase de 30 comprimidos). Por ello, aunque las DDD fijadas por la OMS (DDD_{OMS}) son aceptadas internacionalmente, ha de tenerse en cuenta que la dosis diaria que realmente se prescribe a cada paciente en cada situación clínica puede variar respecto a la dosis fijada por la OMS.

El cálculo del número de DDD de un medicamento, se obtiene dividiendo la cantidad total de principio activo dispensado entre la DDD del principio activo[126,127].

$$\text{DDD} = \frac{\text{nº envases} * \text{nº ff env} * \text{contenido ff}}{\text{DDD OMS}}$$

nº envases: número de envases dispensados.
nº ff env: número de formas farmacéuticas por envase.
Contenido ff: contenido en principio activo por forma farmacéutica.

Por ejemplo, en un determinado país se dispensaron 1.150.000 envases de 20 comprimidos de 1.000 mg de Paracetamol. Teniendo en cuenta que la DDD de Paracetamol (N02BE01) por vía oral es de 3.000 mg, el número de DDD dispensados de Paracetamol oral para ese año fue de:

$$\text{DDD} = \frac{1.150.000 * 20 * 1.000}{3.000} = 7.666.666$$

En ese año, se dispensaron 7.666.666 DDD de Paracetamol oral.

En general, el número de DDD consumidas en un área geográfica se expresa por 1.000 habitantes y por día. La DDD por 1.000 Habitantes y Día (DHD), es otra unidad de medida estandarizada del consumo de medicamentos. Las DHD pretenden proporcionar una estimación de la cantidad de fármaco que consume una población en un periodo temporal. Su cálculo se obtiene a través de la siguiente fórmula:[126,127]

$$\text{DHD} = \frac{(\text{nº envases} * \text{nº ff env} * \text{contenido ff}) * 1.000 \text{ habitantes}}{\text{DDD OMS} * \text{nº habitantes de la población a estudio} * 365 \text{ días}}$$

nº envases: número de envases dispensados.
nº ff env: número de formas farmacéuticas por envase.
Contenido ff: contenido en principio activo por forma farmacéutica.

Siguiendo el ejemplo anterior, supongamos que durante un año se han vendido 1.150.00 envases de 20 comprimidos de 1.000 mg de Paracetamol en un país con una población de 477.000 habitantes. Si la DDD de Paracetamol oral es 3.000 mg:

$$\text{DHD} = \frac{(150.000 * 20 * 1.000) * 1.000}{3.000 * 477.000 * 365} = 44.03$$

Cada día de dicho año un promedio de 44 de cada 1.000 habitantes fueron tratadas con una DDD del medicamento.

Anexo 2. Aprobación Comité Ético de Investigación Clínica de Aragón.

GOBIERNO DE ARAGON
Departamento de Sanidad

Informe Dictamen Favorable

C.P. - C.I. PI20/175

13 de mayo de 2020

Dña. María González Hinjos, Secretaria del CEIC Aragón (CEICA)

CERTIFICA

1º. Que el CEIC Aragón (CEICA) en su reunión del día 13/05/2020, Acta Nº 11/2020 ha evaluado la propuesta del investigador referida al estudio:

Título: ANÁLISIS DE LAS REPERCUSIONES DE LAS MEDIDAS DE CONFINAMIENTO EN LAS ENFERMEDADES CRÓNICAS QUE SE MANEJAN DESDE ATENCIÓN PRIMARIA DE SALUD

Investigadora Principal: Bárbara Oliván Blázquez, Universidad de Zaragoza

Versión protocolo: v2, 08/05/2020

2º. Considera que

- El proyecto se plantea siguiendo los requisitos de la Ley 14/2007, de 3 de julio, de Investigación Biomédica y su realización es pertinente.
- Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y están justificados los riesgos y molestias previsibles para el sujeto.
- Es adecuada la utilización y la obtención de los datos.
- El alcance de las compensaciones económicas previstas no interfiere con el respeto a los postulados éticos.
- La capacidad de los Investigadores y los medios disponibles son apropiados para llevar a cabo el estudio.

3º. Por lo que este CEIC emite **DICTAMEN FAVORABLE a la realización del estudio.**

Lo que firmo en Zaragoza

GONZALEZ HINJOS MARIA - DNI 03857456B

Firmado digitalmente por GONZALEZ HINJOS MARIA - DNI 03857456B
Fecha: 2020.05.15 11:28:57 +02'00'

María González Hinjos
Secretaria del CEIC Aragón (CEICA)

Tel. 976 71 5836 Fax. 976 71 55 54 Correo electrónico mgonzalezh.ceic@aragon.es

Para Alejandro: gracias por hacer que todo sea más sencillo y, sobre todo, más divertido.