UNIVERSITAT DE BARCELONA

Identification of risk factors for poor prognosis and impact of different therapeutic strategies in a cohort of hospitalised patients with COVID-19

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IDENTIFICATION OF RISK FACTORS FOR POOR PROGNOSIS AND IMPACT OF DIFFERENT THERAPEUTIC STRATEGIES IN A COHORT OF HOSPITALISED PATIENTS WITH COVID-19

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I.

Abbreviations

ACE-2: Angiotensin-converting enzyme 2

ALAT: Alanine aminotransferase

ARDS: Acute respiratory distress syndrome

ASAT: Aspartate aminotransferase

AUC: Area under the curve

CART: Chimeric antigen receptor T cell

CCDC: Chinese Centre for Disease Control and Prevention

CD: Cluster of differentiation

CDC: Centre for Disease Control and Prevention

CI: Confidence interval

CM: Convoluted membrane

COPD: Chronic obstructive pulmonary disease

COVID-19: Coronavirus disease 2019

CRP: C-reactive protein

CRS: Cytokine release syndrome

CT: Threshold cycle

CXCL10: C-X-C motif chemokine ligand 10

DAMPS: Disease associated molecular patterns

DNA: Deoxynucleic acid

ECDC: European Centre for Disease Prevention and Control

ECMO: Extracorporeal membrane oxygenation

EHR: Electronic health records

FDA: Food and Drug Administration

FiO2: Fraction of inspired oxygen

FSE: Ribosomal frameshifting element

gRNA: Genomic ribonucleic acid

HCoV: Human coronavirus

HR: Hazard ratio

IBM: International Business Machines Corporation

ICU: Intensive care unit

IFN-γ: Interferon gamma

IL: Interleukin

IP-10: Interferon induced protein 10

IQR: Interquartile range

LDH: Lactate dehydrogenase

MERS-CoV: Middle east respiratory syndrome related coronavirus

MIP: Macrophage inflammatory protein

OIE: World Organization for Animal Health

OR: Odds ratio

ORF: Open reading frame

PaO2: Arterial oxygen partial pressure

PCR: Polimerase chain reaction

R0: Basic reproduction number

RBD: Receptor binding domain

RdRp: RNA dependent RNA polymerase

RNA: Ribonucleic acid

ROC: Receiver operating characteristic

rRT-PCR: Real-time reverse transcription polymerase chain reaction

RT-PCR: Reverse transcription polymerase chain reaction

SARS: Severe acute respiratory syndrome

SARS-CoV: Severe acute respiratory syndrome coronavirus

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SD: Standard deviation

sgRNA: Sub-genomic ribonucleic acid

SILD: Sistema de lectura i dispensació de dades (System for reading and dispensing data)

SpO2: Oxygen saturation by pulse oximeter

SPSS: Statistical Package for the Social Sciences

TMPRSS2: Transmembrane protease serine 2

TNF: Tumoral necrosis factor

TRS: Transcription regulatory sequence

UK: United Kingdom

USA: United States of America

VAP: Ventilator-associated pneumonia

VAT: Ventilator-associated tracheobronchitis

VEGF: Vascular endothelial growth factor

VOC: Variants of concern

WHO: World Health Organization

II.

SCIENTIFIC PRODUCTION

This doctoral thesis is based on the compendium of the following original articles published in indexed journals and a short report as complementary scientific production.

1. **Meira F**, Albiach L, Carbonell C, Martín-Oterino J, Martín-Ordiales M, Linares L, Macaya I, Agüero D, Ambrosioni J, Bodro M, Cardozo C, Chumbita M, de la Mora L, García-Pouton N, Garcia-Vidal C, González-Cordón A, Hernández-Meneses M, Inciarte A, Laguno M, Leal L, Morata L, Puerta-Alcalde P, Rico V, Letona L, Cózar-Llistó A, Dueñas G, Solá M, Torres B, Rojas J, Moreno A, Moreno-García E, Torres M, Martínez JA, Soriano A, García F. Experience with the use of siltuximab in patients with SARS-CoV-2 infection. *Rev Esp Quimioter* 2021; **34**: 337–341
   Impact Factor: 2.515 (3rd quartile).

2. **Meira F**, Moreno-Garcia E, Linares L, Macaya I, Tomé A, Hernandez-Meneses M, Albiach L, Morata L, Letona L, Bodro M, Cozar-Llisto A, Cardozo C, Chumbita M, Pitart C, Ambrosioni J, Rico V, Puerta-Alcalde P, Garcia-Pouton N, Marco F, Garcia-Vidal C, Soriano A, Martínez JA. Impact of Inflammatory Response Modifiers on the Incidence of Hospital-Acquired Infections in Patients with COVID-19. *Infect Dis Ther* 2021; **10**: 1407–1418.
   Impact Factor: 6.119 (1st quartile).

3. Garcia-Vidal C*, **Meira F***, Cózar-Llistó A, Dueñas G, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, Cardozo C, Hernandez-Meneses M, Alonso-Navarro R, Rico V, Agüero D, Bodro M, Morata L, Jordan C, Lopera C, Ambrosioni J, Segui F, Grafia N, Castro P, García F, Mensa J, Martínez JA, Sanjuan G, Soriano A and COVID-19 researcher group. Real-life use of remdesivir in hospitalized patients with COVID-19. *Rev Esp Quimioter* 2021; **34**: 136–140.
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   Impact Factor: 0.09 (4^{th} quartile).

5. Garcia-Vidal C, Cozar-Llisto A, **Meira F**, Duenas G, Puerta-Alcalde P, Cilloniz C, Garcia-Pouton N, Chumbita M, Cardozo C, Hernandez M, Rico V, Bodro M, Morata L, Castro P, Almuedo-Riera A, García F, Mensa J, Martínez JA, Sanjuan, Torres A, Nicolas JM, Soriano A, COVID-19-researcher group Trends in mortality of hospitalised COVID-19 patients: A single centre observational cohort study from Spain. *Lancet Reg Health Eur* 2021; **3**: 100041.
   Impact Factor: N/A (quartile N/A) *(data unavailable, new journal)*

III.

ABSTRACT IN SPANISH

IDENTIFICACION DE FACTORES DE RIESGO DE MAL PRONOSTICO E IMPACTO DE DIFERENTES ESTRATEGIAS TERAPEUTICAS EN UNA COHORTE DE PACIENTES HOSPITALIZADOS POR COVID-19

Introdución En diciembre de 2019 se identificó una enfermedad emergente en Wuhan, China, de la cual se sabía muy poco en el momento: el riesgo de transmisión y las manifestaciones clínicas no estaban claras. En una de las primeras cartas a la población sobre este asunto, el ECDC del 9 de enero de 2020 describió la necesidad de precaución y comunicó que, con la información presentada, existía un pequeño riesgo de evolución pandémica. Esto refleja lo difícil que es predecir la evolución y su potencial propagación cuando surge un virus completamente nuevo. La enfermedad recibió el nombre de COVID-19 (Coronavirus diseases-19) debido a la identificación de un nuevo coronavirus como agente infeccioso, y antes de finales de enero de 2020 la Organización Mundial de la Salud declaró una emergencia de salud pública internacional. Al final del primer año de la pandemia (enero de 2021) había más de 103 millones de casos confirmados con más de 2 millones de muertes, en mayo de 2021 había más de 167 millones de casos confirmados y más de 3,4 millones de muertes, y en septiembre de 2022 esas cifras eran de más de 600 millones de casos confirmados y más de 6 millones de muertes.

El SARS-CoV-2 es un virus ARN de sentido positivo con un gran ARN lineal único de aproximadamente 30.000 bases. El genoma contiene 15 genes que codifican 27 proteínas: 4 proteínas estructurales, la nucleocápside (N), la envoltura (E), las proteínas de membrana (M) y de espiga (S), y una gran poliproteína que escinde en 16 proteínas no estructurales, entre ellas la ARN polimerasa dependiente de ARN y la exorribonucleasa, que son esenciales para la replicación viral y la lectura de prueba evitando mutaciones. La proteína S se une al receptor ACE2 presente en las células epiteliales de las vías respiratorias, los neumocitos tipos 1 y 2, los enterocitos, el endotelio cardíaco y vascular, el epitelio tubular renal y los hepatocitos. La rápida replicación en el epitelio pulmonar inferior desencadena una intensa activación del sistema inmunitario que conduce al síndrome de dificultad respiratoria aguda (SDRA).

Durante el periodo de estudio, en nuestra región predominaron las variantes Wuhan, seguida de las variantes alfa y delta. Aunque la tasa de mutación de los coronavirus es baja, el número masivo de infecciones en todo el mundo explica la aparición de variantes con modificaciones en la proteína espiga que aumentan la afinidad por el receptor ACE2, lo que conlleva una mayor transmisibilidad y hace que una nueva variante se pueda convertir en predominante en pocas semanas. Un ejemplo es la mutación en el aminoácido 681 de la proteína pico, asociada a la alta transmisibilidad de la variante Delta.

La presentación clínica de COVID-19 varía desde casos asintomáticos o leves con fiebre autolimitada, dolor de cabeza, tos, astenia, faringitis, diarrea hasta enfermedades graves caracterizadas por insuficiencia respiratoria. Desde los primeros estudios, se describió a la población anciana, mayor de 65 años, como los pacientes con más riesgo de desarrollar peores desenlaces, así como la presencia de comorbilidades como hipertensión, obesidad o inmunodepresión.

Al inicio de esta recopilación de datos no existía ningún tratamiento o antivírico específico aprobado para el SARS-CoV-2. Teniendo esto en cuenta, iniciamos esta tesis para mejorar el manejo clínico de esos pacientes.

Hipótesis El uso de inhibidores de interleukina-6 pueden impactar la progresión de COVID-19 para enfermedad severa; Estos y otros tratamientos modificadores de la respuesta inmune pueden interferir en el riesgo de infecciones adquiridas en el hospital; El tratamiento con remdesivir puede alterar el pronóstico de los pacientes ingresados por COVID-19; La población con más de 80 años puede tener fatores de riesgo específicos relacionados con peor pronóstico; Durante el primer año de la pandemia ha habido un cambio en las manifestaciones clínicas, tratamientos y desenlaces de los pacientes ingresados con COVID-19.

Objetivos Esta tesis tiene como principal objetivo proporcionar a la comunidad científica conocimientos sobre las manifestaciones clínicas y características de los pacientes hospitalizados con COVID-19 y el impacto de los primeros tratamientos implementados durante el primer año de la pandemia. Analizar y describir el papel de las distintas estrategias contra el virus y la reacción inflamatoria, sobre todo en poblaciones de alto riesgo como los ancianos. Además, describir cómo la aplicación

de las distintas estrategias puede repercutir en la tasa de mortalidad durante los primeros meses de la pandemia.

Métodos Se realizaron estudios retrospectivos sobre la cohorte de pacientes ingresados con COVID-19 en el Hospital Clínic de Barcelona. Los datos se obtuvieron por extracción automática de la historia clínica electrónica del paciente mediante el uso de un sistema inteligente de extracción de datos (SILD) y manualmente a partir de la revisión de historias clínicas e introduciendo la información en una base de datos diseñada en REDCap específicamente para recoger pacientes con COVID-19, den el periodo de febrero de 2020 hasta febrero de 2021. El análisis estadístico se realizó mediante el programa IBM SPSS Statistics 22.0.

Resultados En base a las hipótesis y objetivos presentados, se han realizado 5 estudios descritos a continuación. En lo que se refiere al primer estudio, ya desde los inicios de la pandemia, se hizo evidente que la interleucina-6 (IL-6) desempeñaba un papel importante en el síndrome de liberación de citoquinas asociado al COVID-19, por lo que la inhibición de esta citoquina se propuso como una alternativa potencial para la neumonía grave debida al SARS-CoV-2. En la primera descripción sobre tocilizumab, un anticuerpo monoclonal dirigido contra el receptor de IL-6, se incluyeron 21 pacientes que ingresaron en un hospital en China, en pocos días los pacientes mejoraron notablemente, y ninguno falleció. El objetivo principal del primer estudio de esta tesis fue describir las características y el resultado clínico de los primeros 31 pacientes de dos hospitales con infección por SARS-CoV-2 que recibieron tratamiento con siltuximab, un anticuerpo monoclonal que inhibe directamente la IL-6.

Asimismo, varios estudios observacionales comparativos sugirieron que, en pacientes con enfermedad pulmonar por SARS-CoV-2 grave, el tocilizumab podía disminuir la necesidad de ventilación mecánica y mejorar la supervivencia. Además, un ensayo clínico aleatorizado demostró que la dexametasona reducía la mortalidad en pacientes que requerían asistencia respiratoria. El objetivo del segundo estudio fue investigar la posible influencia de la administración de modificadores de la respuesta inflamatoria, incluidos los biológicos anti-IL-6 y los corticosteroides, sobre la incidencia de infecciones hospitalarias en pacientes ingresados con COVID-19.

Inicialmente, los pacientes con COVID-19 recibieron unicamente tratamiento de soporte para aliviar los síntomas, así como antivirales según los datos in vitro que mostraban actividad. El 1 de mayo de 2020, remdesivir recibió la autorización de uso de emergencia de la Food and Drug Administration (FDA) para pacientes hospitalizados con COVID-19 y fue aprobado oficialmente el 22 de octubre de 2020. El objetivo del tercer estudio fue informar sobre nuestra experiencia con el uso de remdesivir entre julio y septiembre de 2020.

Numerosos estudios encontraron que la edad avanzada se asociaba con un mayor riesgo de enfermedad grave, complicaciones y mortalidad de COVID-19. A pesar de que los pacientes de más de 80 años tenían características clínicas y factores de riesgo distintos, en particular múltiples comorbilidades y polifarmacia, había poca información sobre esta población específica. En el cuarto estudio nos propusimos describir y comparar las características clínicas, las complicaciones, el tratamiento y los resultados en pacientes muy ancianos con COVID-19 durante las tres primeras olas de la pandemia en España.

El brote de COVID-19 llegó a España a finales de febrero de 2020 y supuso un gran reto tanto para los profesionales sanitarios como para los sistemas de salud, con una elevada morbilidad y mortalidad. Sin embargo, nuestros conocimientos sobre la COVID-19 mejoraron y rápidamente se dispuso de nuevas terapias antivirales y antiinflamatorias. Aún faltaban estudios clínicos que describieran los cambios a lo largo de los meses en las características y el tratamiento de los pacientes con COVID-19 y su impacto en las tendencias de mortalidad en la vida real. El quinto estudio pretendió aportar información sobre este aspecto con datos sobre las características de los pacientes, los tratamientos y su impacto en la mortalidad de los pacientes hospitalizados por COVID-19 describiendo la evolución durante el primer año de pandemia.

Conclusiones Con los estudios hemos podido concluir que: siltuximab administrado en los primeros 10 días de síntomas en pacientes con elevación en los niveles de proteína C reactiva (PCR) fue una alternativa bien tolerada al tratamiento con tocilizumab. La exposición aguda de pacientes con COVID-19 ingresados a tratamientos con moduladores de la respuesta inmune como inhibidores de la IL-6 o corticosteroides no pareció interferir en el riesgo de adquirir infecciones nosocomiales. El uso de remdesivir en pacientes ingresados se asoció a baja

mortalidad con un perfil de seguridad aceptable. Los pacientes con más de 80 años con elevada frecuencia respiratoria, niveles altos de LDH y PCR tuvieran mayor riesgo de ingreso a la UCI. Finalmente, hemos descrito una mortalidad ha 30 días en los pacientes con COVID-19 ingresados inferior en comparación con la mortalidad global de otras series y una reducción progresiva de la mortalidad con las modificaciones de manejo clínico durante el curso de la pandemia.

Comprender cómo se presentó y trató la enfermedad al principio puede servir como herramienta de aprendizaje para entender mejor la experiencia real de enfrentarse a una pandemia de virus emergente y puede ayudar a la comunidad científica a identificar estrategias positivas y negativas para prevenir futuros errores.

1.

INTRODUCTION

Declaration of COVID-19 pandemic

In December of 2019 an emergent disease was identified in Wuhan, China.(1) Little was known at that time: the transmission risk and clinical manifestations were not clear.(2) The world was alarmed in an unexpected way, causing different information to circulate. In one of the first letters to the population regarding this issue, the ECDC on January 9th, 2020, described the need for caution and communicated that, with the presented information, there was a small risk for a pandemic evolution.(3) This reflects how difficult is to predict the evolution and its potential spreading when a completely new virus emerges. Indeed, reports of new cases outside China were reported at the beginning of 2020.(4) The disease received the name of COVID-19 (**Co**rona**vi**rus **d**iseases-19) due to the identification of a new coronavirus as the infective agent, and before the end of January 2020 the World Health Organization declared an international public health emergency.(5)

Heterogeneous outcomes and different clinical manifestations were described, with patients presenting from no symptoms to mild or even very serious clinical manifestations.(5) In march of 2020, the CCDC (Chinese Center for Disease Control and Prevention) described COVID-19 as a disease with similar clinical presentation of SARS (severe acute respiratory syndrome), a different diseases caused by other coronaviruses, but with a global mortality of 2.3%, inferior than the global mortality rate of SARS (9.5%) or Middle East respiratory syndrome (MERS) (34.4%).(6) A different article from the World Health Organization Collaborating Centre for Infectious Diseases Epidemiology and Control from the University of Hong Kong affirmed that this mortality rate of 2,3% could be underestimated since the mortality of hospitalized patients could reach 14%.(7) Moreover, hospitals and facilities around the world faced an unparalleled number of new hospital-admissions, with many patients requiring admission at ICU (intensive care unit) and, in some regions, without enough available beds for the patients that needed one.(8)

Scientific information was starting to be published in many places with alarming death rates and two studies described alarming data on mortality. Richardson et al.(9) reported an overall mortality of 21% in a New York City cohort of 2634 patients who died or were discharged and a mortality rate higher than 75% in intubated patients. Zhou et al reported 28.2% mortality in a cohort of 191 hospitalized patients in Wuhan, China and the 32 intubated patients presented a mortality of 96.9%.(10)

Despite the fact that the world was not prepared for what was happening, the scientific community had already notified government and public leaders that the world was at risk for a new pandemic and the possibility that this future pandemic would possibly be a zoonosis caused by a new coronavirus.(11)

A zoonosis is defined as a disease or infection, which is naturally transmissible between animals and humans and according to the World Organisation for Animal Health (previously Office International des Epizooties), 75% of emerging infectious diseases in humans are zoonotic.(12) Some examples include: influenza (flu), MERS, SARS, Rift Valley fever, Ebola, rabies, brucellosis, and leptospirosis.(13) The reservoir is the animal that carries the viruses without developing the diseases, in case of SARS-CoV-2, such as bats. The contact of reservoirs with other mammals can transmit the virus and cause disease on these other mammals. Later on, due to the proximity of the sick mammals with humans (easily to occur in places such as live markets) the virus can gain the ability to survive and cause infection.(14)

The epicentre of the COVID-19 epidemic was finally traced to a market located in the North of the river that crossed Wuhan, China more precisely at the place where there were live animals present in the area. The genetic sequence of the coronavirus founded in those animals match the sequence of the coronavirus circulating.(15)

Characteristics of SARS-CoV-2

The SARS-CoV-2 virus belongs to the family *Coronaviridae (International Committee on Taxonomy of Viruses)*, subfamily *Orthocoronavirinae,* subdivided into 4 genera. The *Alphacoronaviruses* genus includes the human coronaviruses (HCoVs) HCoV-229E and HCoV-N63L, both are associated with mild respiratory infections. The virus SARS-CoV-2 was included in the *Betacoronaviruses* genus, along with SARS-CoV (severe acute respiratory syndrome coronavirus), MERS-CoV (Middle East respiratory syndrome coronavirus) two highly pathogenic virus and the other HCoVs: HCoV-HKU1 and HCoV-OC43 both associated with mild respiratory infections. The other two genera are the *Gammacoronavirus* and *Deltacoronavirus* and do not affect humans.(16)

The SARS-CoV-2 is a positive sense RNA virus with a large single linear RNA of aproximately 30.000 bases. The genome contains 15 genes encoding 27 proteins: 4 structural proteins, the nucleocapsid (N), the envelope (E), the membrane (M) and spike

(S) proteins, and a large polyprotein that cleaves in 16 non-structural proteins (nsp) including the RNA-dependent RNA polymerase and the exoribonuclease that are essential for viral replication and proof-reading avoiding mutations.(16,17) In comparison with the other coronavirus genome SARS-CoV-2 has a more similar composition to the SARS-CoV than with the MERS-CoV genome.(18)

Epidemiology, mechanisms of transmission and emergence of variants

At the end of the first year of the pandemic (January 2021) there were more than 103 million confirmed cases with over 2 million deaths, in May 2021 there were over 167 million confirmed cases and over 3,4 million deaths, and in September 2022 those numbers were of over 600 million confirmed cases, and over 6 million deaths.(19)

The basic reproduction number (R_0) can be used to evaluate the potential spread or decline of a disease: A R_0 less than 1 means the ongoing infection causes less than 1 new infection per infected patient (suggesting that the number of cases will decline with time and may disappear); a R_0 equal to 1, suggests small risk for an epidemic; a R_0 greater than 1, suggests cases could grow exponentially and cause an epidemic or even a pandemic.(20)

Different basic reproduction number (R_0) was estimated in the beginning, the value was described to be between 2.2(21), 2.5 (5) or 2.79 (22), a higher value in comparison with another coronavirus such as SARS-CoV (1.7-1.9) (18) or MERS (<1).(23) In comparison, in the previous 2009 pandemic of influenza H1N1 the R_0 estimated was 2.4.(24)

One of the factors associated with the higher spread of COVID-19 was that the peak of viral replication rate happened just before the beginning of symptoms, which impaired the optimal instauration of preventions measures.(25) In a comparison, MERS and SARS-CoV have characteristics that difficult communitarian transmission. For SARS-CoV, the time of higher viral replication rate was described as happening 10 days after the beginning of symptoms, and for MERS-CoV, the virus infection led to more severe clinical manifestation associated with hospitalization or death.(18)

The mechanism of virus transmission was unclear, and it was understood that the transmission could occur by direct contact or by spreading respiratory droplets.(26,27) Finally SARS-CoV-2 transmission was accepted as mainly airborne.(28)

From the beginning of the pandemic until now different variants of SARS-CoV 2 were described.(29) When important mutations are found they are classified as Variants of Concern (VOC) they are: Alpha (UK, September 2020), Beta (South Africa, September 2020), Gamma (Brazil, December 2020), Delta (India, December 2020) and Omicron variant (South Africa and Botswana, November 2021).(30)

During the study period, Wuhan followed by alpha and delta variants predominated in our region. Although the mutation rate of coronavirus is low, the massive number of infections around the world explains the emergence of variants with modifications in the spike protein that increase the affinity for the ACE2 receptor, leading to a higher transmissibility (higher R_0) and becoming predominant in few weeks. One example is the mutation at the 681 amino acid of the spike protein, associated with the high transmissibility of Delta variant, as the mutation facilitated the cleavage of the viral spike subunit S2 aiding the entry of the virus into the cells.(31)

Pathophysiology

Host entry: SARS-CoV-2 uses similar mechanisms as SARS-CoV, both viruses have high affinity to the angiotensin-converting enzyme 2 (ACE-2) at the cell-membrane. ACE-2 is present in different organ tissues such as the inferior respiratory tract, heart, kidney, brain, gastrointestinal tract, and others.(32) Other possible cell-receptors for SARS-CoV-2 are under investigation, in cell cultures, such as heparan sulfate (HS), to determinate their role in the virus infection.(16)

Cell entry: SARS-CoV-2 virus spike (S) protein is composed of two domains, S1 and S2. At S1 is where the receptor-binding domain (RBD) is located, responsible for the union with the ACE-2 receptor, and the S2 is responsible for the fusion of the virus and the cell membrane. After the binding of S1, a cleavage of the S2 domain is performed by cell-surface proteases such as transmembrane protease serine 2 (TMPRSS2) which allows it to enter the cell. As an alternative process, the virus can enter by endocytosis and the fusion process is dependent of the S cleavage performed by endosomal or lysosomal proteases cathepsins (cathepsin L). As consequence of the membrane fusion, the virus genome separates from the N protein, both are released in the cell's cytoplasm and the process of virus translation starts.(16)

Translation: The viral genome was characterized as having at the 5'terminal position, two overlapped ORFs (open-reading frames), ORF1a and ORF1b. The viral translation of the ORF1ab is possible due to a ribosomal frameshifting element (FSE).(33) It is triggered by a slippery sequence followed by an RNA pseudoknot structure that causes the ribosome to bypass the stop-codon at the end of ORF1a and performed a continuous translation of ORF1ab.(33) This element is a unique characteristic of the coronavirus and is different in only one nucleotide in the SARS-CoV-2 and SARS-CoV.(34) The translation of only of the ORF1a portion, originates the polyprotein 1a (pp1a) that encodes nsp1-11 and the continuous translation of ORF1ab will generate the pp1ab. Regarding the translation of ORF1ab, the translation of the ORF1a portion will encode the nsp1-10, without including the nsp11, and translation of the ORF1b portion will encod nsp12-16.(33)

Other ORFs, are translated from subgenomic RNAs. The ORFs located at the 3' position, encodes for the 4 viral structural proteins (N, E, M, S) and the remaining ORF (such as ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8 and ORF9b) encodes for different accessory proteins.(35)

Some nsp functions had already been described.(36) The nsp1-11 will act principally in the modulation of immune response (e.g., nsp1 involved in type IFN inhibition) and as cofactor in the process of replication and transcription. The nsp3 and nsp 5 were described as responsible for polypeptide cleavage (nsp3- papain-like proteinase (PLpro); nsp5- 3C-like proteinase (3CLpro).(36) Nsp6 function was associated with doble membrane vesicles (DMV) formation; nsp7-8, co-factors that act as primases along with nsp12, RNA-dependent RNA polymerase (RdRp), to form the Viral replication and Transcription complex along with viral nsp9 as single-strand binding protein; nsp13 as RNA helicase, a proofreading exonuclease (nsp14), other cofactors (nsp10), and capping enzymes (nsp16).(33)

Viral replication: the viral replication process takes place in convoluted-membrane (CM) structures originating from the Golgi complex. At electron microscopy those structures are described as double membrane vesicles.(37) The transcription process can happen as a continuous process forming a new negative single strain genomic RNA (gRNA) or as a non-continuous process, forming a subgenomic RNA (sgRNA or sgmRNAs). After the replication-transcription process they are again transformed into positive genomic ssRNA and subgenomic RNA. The regulation of the transcription

process is mediated by transcription-regulatory sequences (TRS) within the viral genome.(37)

The subgenomic RNA (sgRNAs o sgmRNAs) encodes the structural and accessory proteins of the virus. Structure proteins are essential for the assemblement of the new virion and the accessory proteins will take part in the regulation of the cell's immune response facilitating the survivor of the infected cell against host defence.(33)

The virus S protein binds to the ACE2 receptor present in epithelial cells of the respiratory tract cell, the pneumocytes types 1 and 2, enterocytes, cardiac and vascular endothelium, renal tubular epithelium, and hepatocytes.(38)

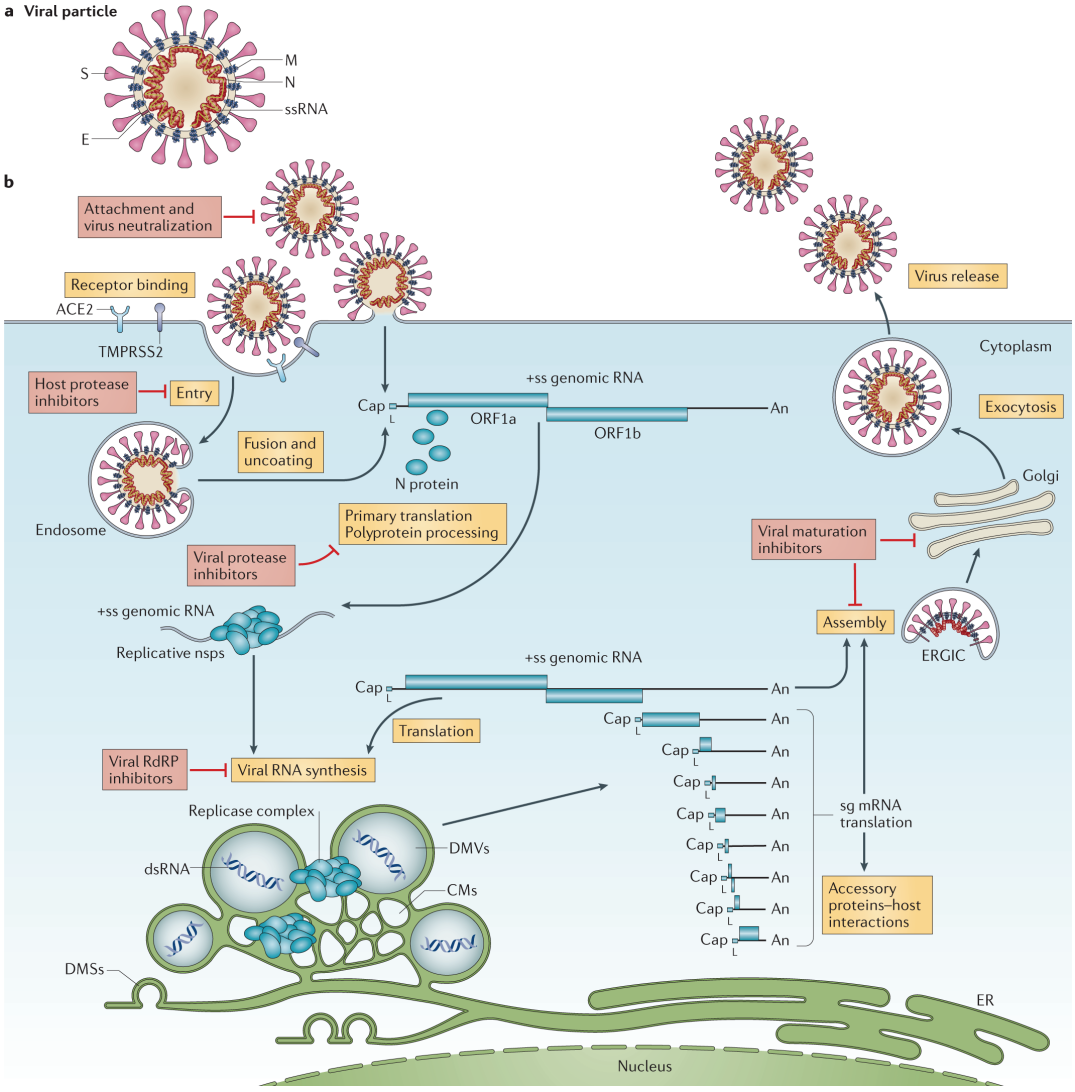

Figure 1. Representation of the life cycle of SARS-CoV-2. Source: (37)

The suggested down-regulation of receptors ACE2(39) and the rapid replication in the lower pulmonary epithelium trigger an intense activation of immune response(40) and have been described as possible causes to acute respiratory distress syndrome (ARDS), a clinical syndrome composed by the presence of bilateral infiltrates and hypoxemia illustrated by a decreased ratio of arterial PO2 to inhaled FiO2.(41)

The viral infection can also cause an endothelial dysfunction resulting in an excess of thrombin production and reduction of the fibrinolysis process, causing an hypercoagulation state that is intensified by hypoxia leading to a prothrombotic state.(42)

As a result of viral infection, pathogen-associated molecular patterns (PAMPS) are recognized by the host pattern recognitions receptors (PRRs) activating the innate immunity cells (first line of defence against the virus), characterized by having the type-I interferon system an important part of the innate response.(36) The viral antagonism of the innate immune response is essential for viral survival and successful replication.(43)

The presence of double-strand RNA (dsRNA) is recognized in the cytoplasm by receptors such as retinoic acid-inducible gene I (RIG-I) and melanoma differentiation gene 5 (MDA5) or in the endosome by toll-like receptors (TLRs). These receptors interact with mitochondrial antiviral signalling proteins (MAVS) responsible for recruit kinases that will activate interferon regulatory factors 3/7(IRF3/7) that translocate to the nucleus and activate the expression of IFNα/β, that induce expression of IFN-stimulated genes (ISGs). The expression of ISGs happens via the singling pathways of Janus activated kinase (Jak), signal and activator of transcription (STAT1). It was demonstrated that cells infected with SARS-CoV-2 had insignificant expression of IFN-β and ISG during the early moments of the infections, only being activated later resulting in an altered type-I IFN response. The authors described that ORF6, nsp1, nsp 12 and nsp13 and M are the main viral proteins involved in the inhibited IFN production.(43)

When the innate immune system fails to eliminate the virus, the adaptive immune system is recruited. This broad activation of the immune system initially takes place at the alveolar macrophages and endothelial cells. In contact with PAMPS, the cells start to secrete proinflammatory cytokines and chemokines, including: interleukin1-beta (IL-1β), interleukin6 (IL-6), interferon gamma (IFN-γ), (produced by the T-cells recruited), interferon induced protein10 (IP-10 o CXCL10), tumoral necrosis factor (TNF),

macrophage inflammatory protein 1-alfa y 1-beta (MIP-1α y MIP-1β) and vascular endothelial growth factor (VEGF).(44)

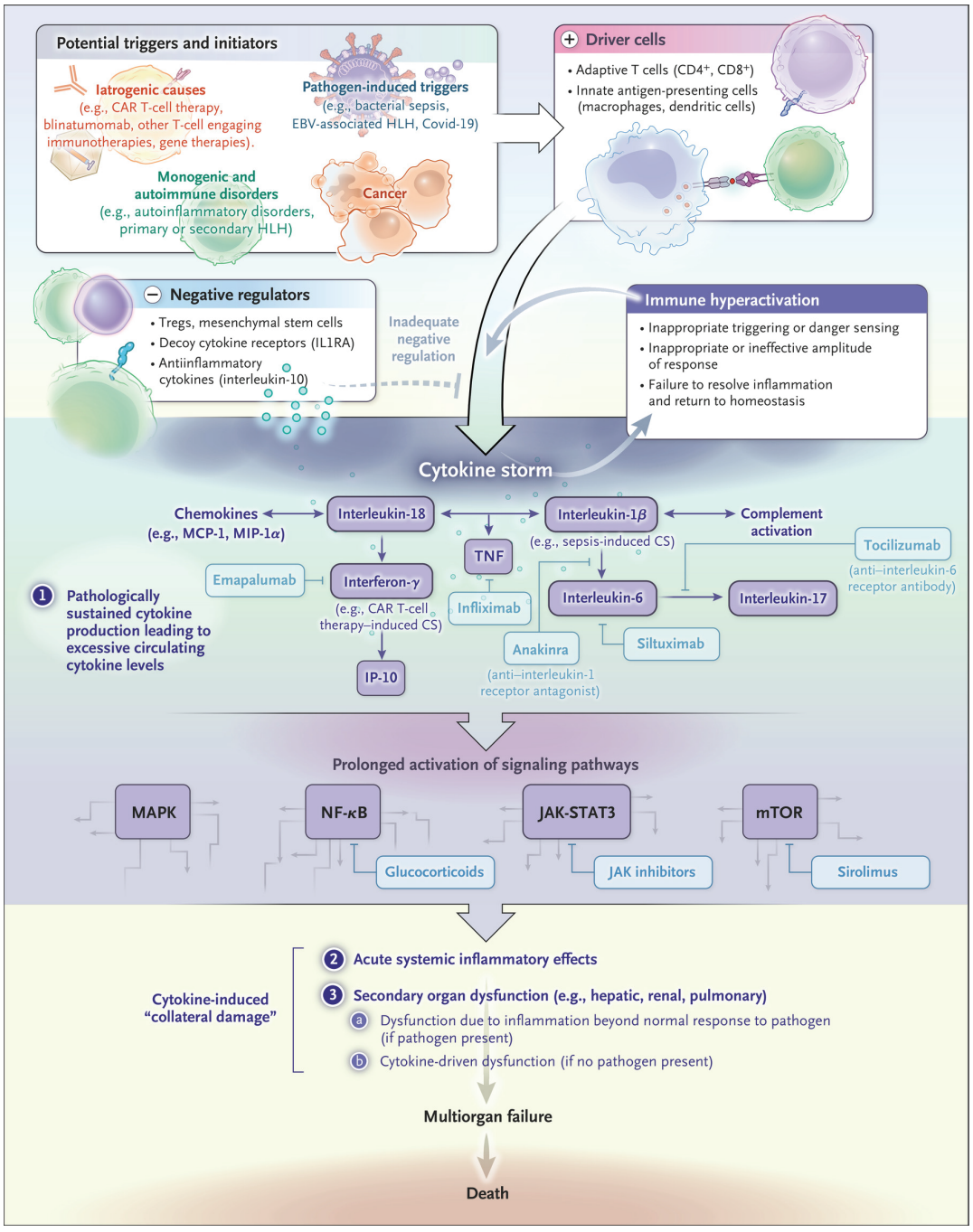

Figure 2. Schematics of the pathophysiology of the cytokine storm caused by SARS-CoV-2. Source: (44)

The alteration of these cytokines and chemokines can be reflected in alteration of laboratory parameters such as increased values of C-reactive protein (C-RP) and D-

dimer.(44) As a consequence of these cytokines and chemokines secretion, monocytes macrophages and neutrophils are recruited by the lung, activating higher secretion of inflammatory cytokines, leading to a so called *cytokine storm* that causes an inflammatory state leading to fever, hypoxia, accumulation of fluids in the lung and lung injury, and also an increase in vascular permeability and leakage.(44)

The SARS-CoV-2 infection also causes a delay in activation of dendritic cells, resulting in impaired T-cell response.(45) In a Chinese report from the beginning of the pandemic, of 201 patients, lymphopenia and reduced CD3 and CD4 T-cell counts were described as commonly seen in analytical parameters.(46) Later on, a review of T-cell relationship with COVID-19 confirmed that decrease in T-cells CD4 and CD8 and B-cells has been reported in patients with COVID-19.(47) There is an ongoing discussion on whether the impaired function of T-cells or the hyperactivation followed by an exhaustion of the T-cell response is the main factor for the abnormal function of T-cells.(47)

Clinical Manifestations

In the beginning of the pandemic, the clinical manifestations of COVID-19 were compared with other coronaviruses diseases, and it was described as more similar to the clinical presentation of SARS, in the account of the cases of ARDS described, than to MERS presentations, usually characterized by renal damage and even more serious disease, commonly leading to multiple organ failure.(18)

The clinical presentations of COVID-19 varies from asymptomatic or mild cases with self-limiting fever, headache, cough, asthenia, pharyngitis and diarrhoea, to moderate cases, requiring hospitalization with pulmonary involvement (20% of cases in the beginning of the pandemic) (1,2,7) or to severe disease characterized by respiratory failure and thrombotic manifestations, or even cases with chronic or persistent symptoms.(48) The report of the first year of the pandemic described that symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days.(38) A more recent metanalysis found a pooled incubation period of 6.57 days.(49)

In different studies, patients who required hospitalization, frequently presented high fever with altered laboratory values such as lymphopenia, increased lactate dehydrogenase values (LDH) and elevated C reactive protein values.(50,51) A particular presentation of dyspnoea was described in some patients that presented with signs of hypoxia such as

low values of blood oxygen saturation but no respiratory distress, a phenomenon of "happy hypoxia", when there is still no increased airway resistance thus not promoting at the respiratory centre a sense of alteration of breathing.(52) The arterial hypoxemia in those cases could be a consequence of different factors, such as intrapulmonary shunting, when there is a perfusion of non-aerated lung tissue due to lung oedema or alveolar collapse; a dysregulated pulmonary vasoconstriction, due to ACE downregulation, impaired lung diffusion, due to dead cells and fibrin that forms a hyalin membrane and formation of intravascular microthrombi as consequence of endothelial injury.(52) Patients with pneumonia usually presented a chest X-ray with a peripheral interstitial lung infiltrate usually in the bases and the involvement of both lungs were common. In the CT scan the patterns of glass infiltrates associated or not with consolidations or the "crazy-paving" pattern (an enlargement of the interlobular septum) were commonly described.(53) Some patients could even present pulmonary embolism, as result of the inflammatory and prothrombotic injuries.(42) In those cases, high D-dimer values were commonly described.(54)

Since the first studies, the elderly population, age over 65, was described as the patients with more risk to develop worst outcomes.(9,46,55) The presence of comorbidities such as hypertension and obesity were also associated with more severe cases.(44,48) Immunosuppressive patients were also described as having more severe disease and to present with persistent viral replication. (56) The severity of the disease in those patients has been described as a consequence of the hyperactivated immunity or as consequence of a failure in resolving the inflammatory state, as a result of a persistent viral replication.(56) Several scores and tools were developed since the start of the pandemic to help predict outcomes based on patient characteristics (age sex comorbidities, clinical state, laboratory and imaging results.) and to help identify treatments and managements according to different clinical manifestations.(57)

Diagnosis

Diagnosis of SARS-CoV-2 has been made by the detection of the virus by real-time reverse transcription polymerase chain reaction (RT-PCR), using E gene or RdRp as primers.(58) Since the viral RNA can still be detected by RT-PCR long after clinical recovery, what could cause unnecessary prolongation of isolation measures, the detection

of sub genomic RNA is also under study as it could better identify replication-competent viruses.(59)

The detection of virus antigens by lateral flow immunochromatography was the second most used diagnostic tool (detection of proteins S, M, or N), with a described specificity of 97-99% and sensibility of 80%, in the first year of the pandemic, when performed during the first 5 to 7 days of symptoms onset.(60)

Clinical management and prognosis

At the beginning of this data collection there was no specific antiviral treatment approved for SARS-CoV-2.(61) With this in mind, we started this thesis to improve the clinical management for those patients. We analysed the role of different strategies against the virus and the inflammatory reaction, particularly in high-risk populations, such as the elderly and finally we described how the implementation of different strategies impacted the mortality rate within the first months of the pandemic.

Treatments

The recommended treatment for mild and self-limited cases in March 2020 for patients without comorbidities was just symptomatic treatment associated with orientation on isolation measures to prevent community transmission.(62)

Patients with moderate or more serious cases were hospitalized to receive supportive treatment that included oxygen supplementations, fluid management and other necessary treatments such as antithrombotic prophylaxis or antibiotic in cases of secondary bacterial coinfection. (63)

Antiviral treatment

For those patients, different antiviral treatments started to be studied. During the period of this thesis data collection the treatments used in Spain included: hydroxychloroquine, azithromycin, Lopinavir-Ritonavir and remdesivir. In addition to other treatment strategies such as interferon treatments and treatment with convalescent plasma.

Hydroxychloroquine is a chloroquine derivative that alters the pH of endosome and lysosome, necessary for the fusion between virus and host cells. At the beginning of the pandemic the Chinese included this treatment in guidelines after reporting a better outcome in Chinese clinical trials conducted in more than 100 patients treated with hydroxychloroquine had a better outcome.(64) In a French open label non-randomised clinical trial with 36 patients treated with hydroxychloroquine in which, depending on their clinical presentation azithromycin was added, the authors described that the treatment was efficient in clearing nasopharyngeal carriage of SARS-CoV-2 in only 3 to 6 days, in most patients. The authors described a significant difference observed between hydroxychloroquine-treated patients and controls and highlighted at the results section the importance that those results were published quickly given the urgent need for an effective drug against SARS-CoV-2 at that moment of pandemic context.(65) Later the ORCHID trial, a randomised clinical trial with 479 hospitalized adults with respiratory symptoms of COVID-19, followed from April to June 2020 with the primary endpoint of clinical improvement at day 14 described that there was no significantly difference in patients randomised to receive hydroxychloroquine compared with placebo (adjusted odds ratio, 1.02) and the consultation did not support the use of hydroxychloroquine for treatment of COVID-19.(66)

Lopinavir-ritonavir is a type 1 aspartate protease inhibitor of the Human immunodeficiency virus (HIV) and was one of the first empirical treatment used for SARS-COV-2, since it had been previously described as having in vitro inhibitory activity against SARS-CoV.(67) Against MERS-COV some case reports have suggested that the combination of lopinavir–ritonavir with ribavirin and interferon alfa resulted in virologic clearance and survival.(68)

In 2020 The LOTUS China a randomised, controlled, open-label trial, was conducted in 199 patients hospitalized with COVID-19. Of note, the authors described that the viral RNA loads over time did not differ between the lopinavir–ritonavir recipients and those receiving standard support treatment. The conclusion of the study was that lopinavir–ritonavir treatment added to standard supportive care was not associated with clinical improvement or mortality in seriously ill patients with COVID-19 different from that associated with standard care alone.(69)

Ivermectin is approved for use in humans to treat onchocerciasis, lymphatic filariasis, strongyloidiasis and scabies in several countries. It was studied as a therapeutic option for viral infections, with data showing some in vitro activity against a broad range of viruses, including HIV, dengue, influenza, and Zika virus, likely through inhibition of importin a/b1-mediated nuclear import of viral proteins. (70,71)

The interest of use of ivermectin for treating COVID-19 started with the results of a preclinical in vitro study that found that bathing SARS-CoV-2–infected Vero-hSLAM cells with 5-μM ivermectin led to an approximately 5000-fold reduction in viral RNA.(72) A retrospective study conducted in four hospitals in South Florida (The ICON study) that included two hundred eighty patients, 173 treated with ivermectin and 107 without ivermectin, described in Univariate analysis a lower mortality in the ivermectin group (15.0% vs 25.2%; OR, 0.52; 95% CI, 0.29-0.96; P= .03).(73) These findings were not confirmed in clinical trials conducted latter such as the EPIC trial in Colombia that included a total of 476 adult patients with mild disease and symptoms for 7 days or fewer (at home or hospitalized) enrolled between July 15 and November 30, 2020.They followed up through December 21, 2020 and concluded that among adults with mild COVID-19, a 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms.(74) Finally in 2023 a higher-dose randomised clinical trial including 1206 participants concluded that treatment with ivermectin for 6 days compared with placebo did not improve time to recovery.(75)

Remdesivir is a nucleoside analogue, a class of small-molecule antivirals which can directly inhibit viral transcription and replication by targeting the viral RNA-dependent RNA polymerase. remdesivir has in vitro activity documented against different viruses, among them SARS-Cov-1 and MERS-CoV.(76) As for in vivo, there is evidence of safety, from compassionate use experience, for its use to treat patients with Ebola virus infection.(77) In COVID-19 infections, remdesivir, that is administered as pro drug, acts interfering with the virus RNA dependent RNA polymerase, when converted to its active form.(78)

During the pandemic different trials were conducted to assess the benefits of remdesivir as treatment for COVID-19 patients. Wang et al.(79) published the results of a

randomised clinical trial conducted in 10 hospitals in China. In this trial, patients were stratified according to the need of oxygen support in two groups: one group included patients with no oxygen support or oxygen support with nasal duct or mask; and other group that included patient with high-flow, non-invasive ventilation, invasive ventilation oxygen support, or extracorporeal membrane oxygenation. They included 158 patients in the group of remdesivir and 78 in the group of placebo treatment. The study failed to achieve an improvement at the primary endpoint of time to clinical improvement within 28 days after randomisation. Although not statistically significant, in the group of patients treated within 10 days of symptom onset, in the ITT population, those receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo (median 18·0 days [IQR 12·0–28·0] vs 23·0 days [15·0–28·0]; HR 1·52 [0·95–2·43]. The 28-day mortality percentage was similar between the two groups (22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group). The was not a statistical significance in decreasing of viral load in both groups, even after stratified by interval from symptoms onset to start of study treatment. (79)

Another important study was the ATCC-1 (Adaptive Covid-19 Clinical trial),(78) that Included a total of 1062 randomised patients (541 assigned to remdesivir and 521 to placebo). Patients went stratification according to disease severity (severe disease were considered: requiring supplemental oxygen or presenting oxygen saturation as measured by pulse oximetry of 94% or lower- while breathing ambient air- or presence of tachypnoea (respiratory rate ≥24 breaths per minute). The median recovery time was of 10 days in remdesivir treated patients, and 15 days among patients treated with placebo (rate ratio for recovery, 1.29; 95% Confidence Interval (CI),1.12 to 1.49; P<0.001). Regarding mortality, statistical significance was not achieved, the rate for mortality by day 29 was 11.4% with remdesivir and 15.2% with placebo (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Finally, the study concluded that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalised with COVID-19 with evidence of lower respiratory tract infection.(78)

A different study from Spinner et al (80)was conducted from March 2020 to April 2020, at 105 hospitals in different countries (United States, Europe, and Asia) only with patients with moderate COVID-19 pneumonia (patients with any radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air). The authors found that patients randomised to remdesivir treatment for up to 5 days had significantly higher odds

of achieving the endpoint of better clinical status distribution on day 11, than those receiving standard care (odds ratio, 1.65; 95% CI,1.09-2.48; P=0.02). Of note the authors described a low mortality overall, less than 2%, by day 28 with only 9 deaths (2 (1%) in the 5-day remdesivir group, 3 (2%) in the 10-day remdesivir group, and 4 (2%) in the standard care group very different from the mortality rates published by other investigators. (80)

Another result published in 2020 was the remdesivir WHO SOLIDARITY that included 5451 patients. In this publication, there was not a statistical significance in mortality in patients treated with remdesivir versus control (rate ratio 0.95, 95%CI 0,81-1,111) but the results reveal a potential for an important decrease in mortality. (81)

The WHO Solidarity repurposed antiviral trial was an important study regarding COVID-19 antiviral administration. It was conducted in 405 hospitals in 30 countries. Patients hospitalised with COVID-19 were randomised to receive one of the trial drug regimens and its control (drug available but patient assigned to the same care without that drug) and stratified by age and need for mechanical ventilation at randomisation. The intention-to-treat primary endpoint was in-hospital mortality in the four pairwise comparisons of each trial drug. A total of 11,330 patients were randomised: 2750 to receive remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to no trial drug. The hydroxychloroquine, lopinavir, and interferon regimens were discontinued for futility on, respectively, June, July, and October of 2020. No differences in mortality were described. (81) Finally, a systematic review that included evidence from 8 randomised clinical trials, that yielded a total of 10480 individual patient data, the authors described the results of remdesivir treatment for hospitalised patients with COVID-19. In the study the authors described the subgroups where remdesivir treatment could be associated with better outcomes. The meta-analysis concluded that remdesivir reduced 28-day mortality rate in hospitalised patients, that required no oxygen supplementation or that needed low-flow oxygen supplementation at baseline (mortality 9.1% in the remdesivir group vs. 11.2% at no-remdesivir group; aOR 0.80, 95% CI 0.70-0.93). The authors could not reach a statistically significant conclusion regarding patients that needed higher than low-flow oxygen supplementation when treated with remdesivir.(82)

These results finally lead the US Food and Drug Administration (FDA) to grant emergency use authorization of remdesivir for patients with severe COVID-19 (83) and

the European Medicines Agency (EMA) to grant conditional marketing authorization to remdesivir for treatment of COVID-19 inpatients 12 years of age or older with pneumonia who require supplemental oxygen.(84)

Later, a study including 562 patients that evaluated early administration of remdesivir for 3 days among non-hospitalised patients, with at least one risk factor for COVID-19 disease progression, that included 562 patients concluded that patients treated with remdesivir had an 87% lower risk of COVID-19-related hospitalisation or death than the placebo treated patients.(85)

Other antivirals

Favipravir is a nucleotide analogue that selectively inhibits the viral RNA dependent RNA polymerase or causes lethal mutagenesis upon incorporation into the virus RNA. It was approved for treatment of novel influenza virus in China in 2020 with the advantage of being available as an oral formulation, that facilitates earlier administration, before hospitalisation. It was studied in a randomised, open-label, multicentre, phase 3 trial that included RT-PCR confirmed COVID-19 patients with mild-to-moderate symptoms (including asymptomatic).(86) The inclusion period was from May to July, 2020. A total of 150 patients were randomised to favipiravir (n = 75) or control (n = 75). The median time to clinical cure was 3 days in the favipiravir group and 5 days in the control arm and the authors concluded that a significant improvement in time to clinical cure suggests that favipiravir may be beneficial. On the other side, adverse events were observed in 36% of favipiravir and 8% of control patients, although the authors reaffirm that no event lead to drug discontinuation or dose change and that the majority of adverse events were mild to moderate, being the most commonly observed events asymptomatic transient increases in uric acid and liver enzymes.(86)

Nirmatrelvir + Ritonavir (Paxlovid) is another oral antiviral treatment. It is an inhibitor of the protease that acts against the Mpro viral proteins, responsible for the cleavage of 2 polyproteins. In vitro, it is active against all human infectious coronavirus.(87) It is used in association with ritonavir to increase nirmatrelvir concentration to reach therapeutic level. The need to use ritonavir is a disadvantage since ritonavir interactions with other treatments are common and must be monitored. Regarding COVID-19 studies, the EPIC-

HR clinical trial conducted in non-hospitalised patients described a reduction for hospitalisation or death of 88% in patients, treated with nirmatrelvir-ritonavir versus placebo.(88)

In a more recent scenario, an observational, retrospective study conducted with data from the electronic medical records of the Clalit Health Services (CHS) in Israel from January 2022 to March 2022 (Omicron variants), described that in 65 years or older patients, hospitalisations and death due to COVID-19 were significantly lower in patients that received nirmatrelvir, and also described that benefit was not seen for younger adults. (89)

Molnupiravir is a prodrug of the beta-D-N4-hydroxycytidine (NHC), a ribonucleoside with wide antiviral activity against RNAs viruses. After administration, NHC circulates systemically, then suffers intracellular phosphorylation to be converted into NHC triphosphate. This molecule is finally incorporated in the viral RNA by the viral RNA polymerase leading to deadly mutations for the virus. However, the risk associated with this augmented mutagenic activity led the FDA to request the company to closely monitor the appearance of virus mutations in treated patients. (90)

The MOVe-OUt trial in COVID-19 included 1433 non hospitalised patients with 5 or less days of symptoms and with at least one risk factor for severe COVID-19 (age >60 years-old; active cancer; chronic kidney disease; chronic obstructive pulmonary disease; obesity, defined by a body-mass index greater than 30; serious heart conditions such as heart failure, coronary artery disease, or cardiomyopathies; or diabetes mellitus). The authors described that the percentage of participants who were hospitalised or died through day 29 was lower in the molnupiravir group than in the placebo group 6.8% [48 of 709] vs. 9.7% [68 of 699]. (90)

Other strategies to fight the virus

Convalescent plasma: As no antivirals were available another strategy that underwent investigation is the use of convalescent plasma treatment. Convalescent plasma works as a source of antiviral neutralising antibodies. In one study high-titter COVID-19 convalescent plasma administered in the beginning of hospitalisation reduced the incidence of death from COVID-19 by 50%. (91)

However, data have not shown a consistent benefit in hospitalised patients. (92) In the PLACID clinical trial conducted in 39 hospitals in India, with 400 patients with COVID-19 , the authors described a progression to severe disease (PaO2/FiO2 <100) or all-cause mortality at 28 days after enrolment in 44 (19%) patients treated with convalescent plasma and in 41 (18%)participants in the control arm (risk difference 0.008 (95% confidence interval: 0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54) concluding that convalescent plasma was not associated with a reduction in progression to severe COVID-19 or all-cause mortality.(93)

Still treatment with convalescent plasma is under study since it can be used as an alternative outpatient treatment, especially in comparison with treatments that are frequently nor available for low or middle income countries.(94) A more recent multicentre double-blind, randomised, controlled trial, conducted between June, 2020 and October 2021, evaluated the efficacy and safety of early outpatient treatment with convalescent plasma, in comparison with control plasma.(95) The study included symptomatic patients (until 9 days from symptoms start) with positive tests for SARS-CoV-2 regardless of their risk factors for disease progression or vaccination status. A total of 1181 patients received a transfusion. The primary outcome was COVID-19–related hospitalisation within 28 days after transfusion occurred in 17 of 592 participants treated with convalescent plasma (2.9%) and 37 of 589 patients treated with control plasma (6.3%) (absolute risk reduction, 3.4 percentage points; 95% confidence interval, 1.0 to 5.8; *p* 0.005). The authors concluded that treatment with convalescent plasma (administered until 9 days after the onset of symptoms) reduced the risk of disease progression leading to hospitalisation.(95)

Monoclonal antibodies: Monoclonal antibodies (mAbs) against the virus act mainly by interaction with to the receptor binding domain and can neutralize the virus. They were studied in different moments of the disease: as pre-exposures prophylaxis; post exposition prophylaxis, as early treatments or late treatments of the infection.(96,97) With the evolution of COVID-19 pandemic, different virus strains were known and the dominant variant, circulating in society changed over time.(30) Since the monoclonal antibodies are direct to the specific parts of the virus, mainly the spike protein, mutations on those domains that are the characteristic of the different variants made some of the monoclonal antibodies less effective.(98)

In the clinical trial conducted with the use of bamlanivimab+etesevimab, in an outpatient's scenario showed a decrease in COVID-19 related hospitalisation or death from any cause.(96) In February of 2021 bamlanivimab+etesevimab, was approved by the Food and Drug Administration (FDA) for post-exposure prophylaxis. (99)

Sotrovimab, trial results showed that risk of hospitalisation or death was reduced in 85% when compared to placebo.(97) The treatment was approved by the FDA in May 2021 since it was active against the Delta variants of the virus and has become less active after the arrival of the Omicron variants and is no longer indicated. (100)

Immunomodulatory treatments

Since the first wave of COVID-19 severe clinical presentations were related to intense inflammatory response presenting with hypoxia and multiple lung consolidations and even ARDS. (101,102) It is important to understand in which moment of the infection the use of treatments with effects on the inflammatory states are most beneficial since those treatments can have a negative effects (contributing to persistence of the virus) or a positive effects (an adequate control of the hyperactive immune response) on the infection.(44) Other complications of blocking the immune response could also be a higher incidence of secondary infections and even a worsening in the patients outcome.(101)

Corticosteroids

At the beginning of the pandemics the use of corticosteroids as treatment for COVID-19 was not a recommended approach by the World Health Organization, based on previous experience publications.(103) A study published in intensive care medicine, 2011 by Martin-Loeches et al.(104) described that the early use of corticosteroid therapy on these patients increased the risk of VAP although it did not show an increased risk of death. The first studies published in China did not describe a benefit in patients treated with corticosteroids.(103)

Nevertheless, new trials in COVID-19 would change that knowledge. The more important one, the RECOVERY trial (102) an open-label, randomised clinical trial finally described that the use of dexamethasone therapy was associated with a decreased 28-day mortality in patients that required non-invasive supplemental oxygen (23,3 vs. 26.2%; rate ratio

0.82, 95%CI 0.72-0.94) and mechanical ventilation (29.3% vs. 41,4% in placebo, rate ratio 0.64, 95%, CI0,51-0,81). On the other hand no significant effect was demonstrated in patients that did not need oxygen support. This trial guided the recommendation of current COVID-19 treatment with 6mg/Kg of Dexamethasone for 5-10 days for COVID-19 patients that need oxygen support. (102)

Another randomised, placebo-controlled trial, the METCOVID trial (105) conducted from April to June 2020 in Manaus-Brazil with hospitalised COVID-19 concluded differently. In this trial patients were randomised to corticosteroid treatment, intravenous Methylprednisolone (MP) 0.5 mg/kg or placebo (saline solution) twice daily for 5 days. A total of 393 patients were analysed as mITT (modified intention to treat), 194 assigned to MP and 199 to placebo, 81,3% of the patients had infection with SARS-CoV-2 confirmed by RT-PCR. The study showed no statistical difference between both groups regarding the primary outcome of 28-day mortality (76/199 (38.2%) in the placebo group versus 72/194 (37.1%) in the MP group (P =0.629)). In the results section, authors suggest that the high mortality rates described could be associated with the local site and highlight that the different results in comparison with the RECOVERY trial could be a reflection that, when adjusted by equivalence corticosteroid dose, the daily total dose used in METCOVID was higher and also that the patients in the RECOVERY trial were treated for more time (approximately 10 days).(105) This is in line with a recent trial showing that higher corticosteroid dose is associated with worse outcome in hospitalised patients with COVID-19 and hypoxia who required either no oxygen or low-flow oxygen.(106)

Furthermore, the CODEX trial, a randomised multicentre clinical trial, also conducted in Brazil,(107) included patients with COVID-19 and moderate or severe ARDS, treated in 41 intensive care units (ICUs). The study enrolled 299 patients in either dexamethasone versus standard care, and described that patients randomised to the dexamethasone group had a mean 6.6 ventilator-free days (95% CI, 5.0-8.2) during the first 28 days vs 4.0 ventilator-free (days alive and free of mechanical ventilation) days (95% CI, 2.9-5.4) in the standard care group (difference, 2.26; 95% CI, 0.2-4.38;P = .04) and that at 7 days, patients in the dexamethasone group had a mean SOFA score of 6.1 (95% CI, 5.5-6.7) vs 7.5 (95% CI, 6.9-8.1) in the standard care group (difference, -1.16; 95%CI, -1.94 to -0.38;p=0.004). The authors concluded that intravenous dexamethasone plus standard care compared with standard care alone resulted in a statistically significant increase in the

number of ventilator-free days over 28 days. There was no significant difference in the prespecified secondary outcomes of all-cause mortality at 28 days.(107)

Finally, a WHO prospective meta-analysis of clinical trials that englobed 7 randomised trials that included 1703 critically ill patients described that the administration of systemic corticosteroids, compared with usual-care or placebo, was associated with lower 28-day all-cause mortality (summary odds ratio, 0.66).(108)

Other Immunomodulatory treatments

As previously mentioned, since the inflammation response was an intense characteristic of severe COVID-19, different strategies were studied such as Anakinra, (inhibitors of interleukin 1- IL-1), monoclonal antibodies anti interleukin-6 (IL-6) such as tocilizumab or siltuximab, or inhibitors of janus kinase (JAK1/JAK2) such as baricitinib. (61)

Tocilizumab is an anti-interleukin-6 (IL-6) receptor monoclonal antibody, approved as treatment for different inflammatory diseases was evaluated in the EMPACTA trial (Evaluating Minority Patients with Actemra), (109) a global, phase 3 clinical trial. The authors included 389 patients hospitalised and with COVID-19 pneumonia that did not require mechanical ventilation and compared standard care plus one or two doses of either tocilizumab (8 mg per kilogram of body weight intravenously) versus placebo regarding the need for mechanical ventilation or death by day 28. According to the results described, tocilizumab reduced the risk of progression to the composite outcome of mechanical ventilation or death (hazard ratio, 0.56; 95% CI,0.33 to 0.97; P= 0.04), but it did not improve survival.(109) On the other hand the COVACTA, also a randomised clinical trial that included 294 in the tocilizumab group and 144 in the placebo group did not find a significantly better clinical status or a lower mortality by day 28 in tocilizumab versus placebo group. The mortality described by the authors was 19.7% in the tocilizumab group and 19.4% in the placebo group (weighted difference, 0.3 percentage points; 95% CI, –7.6 to 8.2; nominal P=0.94). The populations from the 2 trials were different since the COVACTA trial included patients that were also requiring mechanical ventilation.(110)

Siltuximab is an anti-IL-6 inhibitor that binds to soluble IL-6 preventing the binding of IL-6 to both soluble and membrane IL-6 receptor, inactivating IL-6 induced signalling. The drug is currently approved for the treatment of Castleman disease.(111) In a prospective, observational study performed in Italy with COVID-19 patients that require oxygen support, the author described that those patients treated with siltuximab (as compassionate use) had improved survival and ventilatory outcomes. There were no severe adverse events of note, and authors suggested more information was necessary to understand the role of siltuximab in the treatment of COVID-19. (112)

Anakinra is a recombinant human IL-1 receptor antagonist, approved for the treatment of patients with rheumatoid arthritis, gouty arthritis, and other rare auto-inflammatory syndromes. In the open-label, phase 2 SAVE study, the authors describe a 70% decrease in the relative risk of progression to severe respiratory failure and a significant reduction in 28-day mortality with anakinra treatment compared to standard of care.(113) The following phase 3 study, SAVE-MORE ,concluded that early treatment (within the first 10 days of symptoms) with anakinra guided by inflammatory biomarkers levels in patients hospitalised with moderate and severe COVID-19 significantly reduced 28 day mortality and shorter hospital stay. (114)

A different randomised open label trial was performed in France (CORIMUNO-ANA-1)(115) that included 116 patients with mild-to-moderate COVID-19 pneumonia, requiring at least 3 L/min of oxygen by mask or nasal cannula but without ventilation assistance, and a C-reactive protein serum values greater than 25 mg/L, not requiring admission to the intensive care unit at hospitalisation. The study was stopped early after the results of interim analysis due to futility, and the authors described that Anakinra did not improve outcomes of need for non-invasive or mechanical ventilation or death by day 28 in patients with mild-to-moderate COVID-19 pneumonia. In the discussion, the authors highlight that the negative results of the trial could be related to the dose of Anakinra used or that the hyperinflammatory status of those COVID-19 patients could not be related to an excess of IL-1 signalling, and instead could be a result of combination of different proinflammatory cytokines.(115)

Baricitinib is a Janus kinase inhibitor (JAK 1 and 2) which interferes with the signalling of cytokines such as interleukin-2, interleukin-6, interleukin-10, interferon-γ, and granulocyte–macrophage colony-stimulating factor. It also acts against SARS-CoV-2

through the impairment of AP2-associated protein kinase 1(AAK1) that prevents SARS-CoV-2 cellular entry.(116)

A randomised clinical trial (ACTT-2) that included 1033 patients evaluated treatment with remdesivir plus placebo versus remdesivir plus baricitinib in patients with COVID-19. Patients in the baricitinib group recovered a median of 1 day faster than patients in the remdesivir and placebo group (median, 7 days vs. 8 days; rate ratio for recovery, 1.16; 95% confidence interval [CI], 1.01 to 1.32; P= 0.03 by log-rank test stratified according to actual baseline severity). The authors concluded that treatment with baricitinib in association with remdesivir was superior to remdesivir alone in reducing recovery time and accelerating clinical status improvement in patients who received high-flow oxygen or non-invasive ventilation.(117) In a different study published by Wolfe et al. (ACTT-4) the authors compared baricitib plus remdesivir administration versus dexamethasone plus remdesivir treatment, with placebo treatment in both arms, in hospitalised patients that needed oxygen supplementation, not including invasive mechanical ventilation. A total of 1010 patient, mostly from the U.S.A. were enrolled in the trial. The authors did not find a statistically significant difference between the two treatment regimens regarding progression to invasive mechanical ventilation or 29-days mortality rates. However, the dexamethasone arm did present a higher number of SAEs (risk difference 7·7% [1·8–13·4]; p=0·012). This was the first article to compare dexamethasone versus other type of immunomodulatory treatment for COVID-19 patients. (118)

To compare the differences within those different type of immunomodulatory treatments, Karampitsakos et al. published a non-inferiority trial to compare tocilizumab to baricitinib treatment, in patients with severe COVID-19 (PaO2/FiO2 ratio <200). The study, performed in Greece, included a total of 250 patient randomised to receive baricitinib (125 patients) or tocilizumab (126 patients), both receiving standard of care therapy for COVID-19. The primary outcome of progression to invasive mechanical ventilation or 28-day death rate was 39,2% in the arm treated with baricitinib and 44,4% in the arm treated with tocilizumab. The authors concluded that baricitinib treatment was non-inferior to tocilizumab treatment in patients with severe COVID-19. (119)

Anticoagulant therapy

The cases of thrombosis and pulmonary embolism associated with COVID-19 were not uncommon, raising the necessity to understand the role of anticoagulant therapy for those patients.(120) In 2020, a Chinese study with 499 patient, included 99 patients treated with heparin, and concluded that anticoagulant therapy, mainly with low molecular weight heparin appeared to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria (<4) or with markedly elevated D-dimer.(42)

In a study that included 2219 non critically ill patients the authors compared treatment with therapeutic-dose anticoagulation with usual care thromboprophylaxis in respect of need for use of cardiovascular or respiratory organ support. The authors found that the probability that therapeutic-dose anticoagulation increased organ support-free days as compared with usual-care thromboprophylaxis was 98.6% (adjusted odds ratio, 1.27; 95% credible interval, 1.03 to 1.58). Authors concluded that in noncritically ill patients with COVID-19, an initial strategy of therapeutic-dose anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis.(121) Regarding the critically ill COVID-19 patients, the initial strategy of therapeutic-dose anticoagulation with heparin did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than did usual-care pharmacologic thromboprophylaxis.(122)

Vaccines

Finally in December of 2021 the first vaccination was started. Now according to WHO data as of 5 March 2023, a total of 13,228,728,467 vaccine doses have been administered.(19)

Preface to the investigation

At the beginning of the pandemic, the different clinical and therapeutic scenarios described below led us to investigate and publish the results that compile this thesis.

Experience with the use of siltuximab in patients with SARS-CoV-2 infection

Interleukin-6 (IL-6) plays an important role in the cytokine release syndrome; therefore, the inhibition of this cytokine has been proposed as a potential alternative for severe pneumonia due to SARS-CoV-2.(123) The first description included 21 patients that were admitted in a Chinese hospital and received tocilizumab, a recombinant humanized anti-human IL-6 receptor monoclonal antibody. In few days, symptoms improved remarkably, in 75.0% of patients lowering of their oxygen intake was possible and no patient died. Currently, there is experience with tocilizumab in randomised trials.(124,125) No one of these studies have demonstrated a reduction in the mortality rate among those receiving the anti-IL-6 therapy but they were not powered enough to detect differences in mortality and at least in one of them there was a significant reduction in the intensive care unit (ICU) admission among those receiving tocilizumab.(109) Siltuximab is a chimeric monoclonal antibody that binds to and neutralizes the effect of IL-6 (112) instead of blocking the IL-6 receptor. A study from Italy evaluated siltuximab in 30 patients that were matched to 30 control patients using the propensity score analysis of baseline covariates. The 30-day mortality rate was significantly lower in the siltuximab-treated than the matched-control cohort patients (HR 0·462, 95% CI 0·221– 0·965); p=0·0399). Sixteen siltuximab-treated patients were discharged from hospital, four remained on mechanical ventilation, and 10 patients died.(112)

Impact of inflammatory response modifiers on the incidence of hospital-acquired infections in patients with COVID-19

A number of comparative observational studies have suggested that in patients with severe or worsening SARS-CoV-2 pulmonary disease, tocilizumab, a monoclonal antibody directed against the IL-6 receptor, may decrease the need for mechanical ventilation and improve survival.(109,126) Moreover, in our clinical setting, a

personalized treatment with selective IL-6 and/or IL-1 blockade based on the individual patterns of inflammatory markers was associated with better survival.(127) In addition, a randomised clinical trial has proved that dexamethasone reduces mortality in patients requiring respiratory support.(102) Among other inhibitors of specific cytokines or more general inflammatory pathways, anakinra may be effective in patients with severe pneumonia and a hyperinflammatory state,(115,128,129) and baricitinib in combination with remdesivir improved the clinical status of patients with COVID-19, particularly those receiving high-flux oxygen or non-invasive ventilation.(117)

Although the first concern that inflammatory response modifiers could worsen the prognosis of COVID-19 by increasing viral replication or persistence has been mitigated by clinical experience, the possibility that they may still increase the rate of hospital-acquired infection has not been completely discarded.(130–134)

Real-life use of remdesivir in hospitalized patients with COVID-19

Initially, patients with COVID-19 received supportive care to relieve symptoms as well as antivirals according to in vitro data showing activity. However, these drugs failed to prove efficacy.(135) On May 1st, 2020, remdesivir received Food and Drug Administration (FDA) emergency use authorization for hospitalized patients with COVID-19 and was officially approved on October 22nd, 2020. Initial clinical trials using a control arm demonstrated the superiority of remdesivir in terms of clinical status improvement at day 28 (78) or at day 11 (80); however, initial clinical trials performed in China (79) and a recent report from the Solidarity trial (81) did not prove that remdesivir had no benefit.(136,137) Different outcomes and the potential influence of when remdesivir was administered after symptom onset could explain the apparently controversial results in the aforementioned trials.(138)

COVID-19 in patients aged 80 years and over during the peaks of the first three pandemic waves at a Spanish tertiary hospital

Since the beginning of the pandemic, Spain has been hit by five waves of COVID-19. Age was widely used as a prioritizing criterion for ICU admission, which has been one of the most controversial aspects of the pandemic thus far.(139) Numerous studies have

found older age to be associated with higher risk of severe illness, complications, and mortality in COVID-19.(140) Despite that patients aged ≥80 years have distinct clinical features and risk factors, notably multiple comorbidities and polypharmacy, there is little information on this specific population.(141)

Trends in mortality of hospitalized COVID-19 patients: A single center observational cohort study from Spain

The outbreak of coronavirus disease 2019 (COVID-19) reached Spain by the end of February and has been a major challenge for both health care professionals and health systems, with high morbidity and mortality.(10,55,142–144)However, our understanding of COVID-19 has rapidly improved. Antiviral treatment options have been better defined and the use of anti-inflammatory therapies and personalised approaches has shown to improve outcomes.(78,102,127) Yet, there is a lack of clinical studies describing changes over months in COVID-19 patients' characteristics and management and their impact on mortality trends in real-life. Such descriptions of mortality rates in current patients with COVID- 19 are mandatory, should we aim to place into perspective results obtained from different studies, including trials, that have been carried out during different moments of the pandemic. Further, knowledge of current mortality rates and patient characteristics may serve as references for establishing quality of care.

Need for the investigation

The COVID-19 pandemic, caused by the emergent virus SARS-CoV-2 had affected a great part of worldwide human populations, had presented with different clinical manifestations in different groups of patients with different age, sex or underlying conditions, leading to an intense public health impact.

Patients who end up hospitalised with COVID-19 could evolve to a serious disease or even death and treatment strategies are not completely established. Although there is more information and there are vaccines there is still much to learn.

This thesis has as its main objective to provide the scientific community with knowledge regarding the clinical manifestations and characteristics of hospitalised patients with

COVID-19 and the impact of the first treatments strategies in this group of patients during the first year of the pandemic.

Comprehending how the disease was presented and treated at the beginning might serve as a learning tool to better understand the real experience of facing an emergent virus pandemic and might help the scientific community identify positive and negative strategies to prevent future mistakes.

2.

HYPOTHESES

1. The use of an interleukin-6 early blocker such as siltuximab could avoid the progression of COVID-19 to severe disease.

2. The use of inflammatory response modifiers such as anti-interleukin 6 (IL-6) treatments and/or corticosteroids as treatment for hospitalised patients with COVID-19 might have, as consequence, an increase of hospital acquired infections in these patients.

3. The use of remdesivir as an antiviral can influence the outcomes in patients hospitalised with COVID-19

4. There are specific risk factors within the elderly population (>80 years) that can be related to worst outcomes when hospitalised due to COVID-19.

5. Different aspects regarding patients' clinical manifestations, treatments and outcomes are changing during the course of COVID-19 Pandemic.

3.

OBJECTIVES

1. To describe the clinical characteristics and diseases evolution in SARS-CoV-2 infected patients that received siltuximab according to local protocol.

2. To evaluate the influence of receiving treatment with inflammatory response modifiers in the incidence of hospital acquired infections in patients with COVID-19.

3. To communicate our experience with use of remdesivir as treatment for COVID-19 patients since it became available as a compassionate use in Spain for this indication.

4. To evaluate the clinical characteristics and outcomes of elderly (>80 years) patients with COVID-19 across the first year of the pandemic in Spain.

5. To describe the changes we had in our real-life experience during the first year of the pandemic and try to identify risk factors associated with worse outcomes.

4.

MATERIALS, METHODS, AND RESULTS

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Experience with the use of siltuximab in patients with SARS-CoV-2 infection

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ABSTRACT

Objectives. The study aims to describe characteristics and clinical outcome of patients with SARS-CoV-2 infection that received siltuximab according to a protocol that aimed to early block the activity of IL-6 to avoid the progression of the inflammatory flare.

Patients and methods. Retrospective review of the first 31 patients with SARS-CoV-2 treated with siltuximab, in Hospital Clinic of Barcelona or Hospital Universitario Salamanca, from March to April 2020 with positive polymerase-chain reaction (PCR) from a nasopharyngeal swab.

Results. The cohort included 31 cases that received siltuximab with a median (IQR) age of 62 (56-71) and 71% were males. The most frequent comorbidity was hypertension (48%). The median dose of siltuximab was 800 mg ranging between 785 and 900 mg. 7 patients received siltuximab as a salvage therapy after one dose of tocilizumab. At the end of the study, a total of 26 (83.9) patients had been discharged alive and the mortality rate was 16.1% but only 1 out of 24 that received siltuximab as a first line option (4%).

Conclusions. Siltuximab is a well-tolerated alternative to tocilizumab when administered as a first line option in patients with COVID-19 pneumonia within the first 10 days from symptoms onset and high C-reactive protein.

Keywords: IL-6; siltuximab; COVID-19 mortality.

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Experiencia con el uso de siltuximab en pacientes con infección por SARS-CoV-2

RESUMEN

Objetivo. Nuestro estudio tiene como objetivo describir las características clínicas y evolución de los pacientes infectados por SARS-CoV-2 tratados con siltuximab, de acuerdo con el protocolo local, con objetivo de bloquear precozmente la actividad de la Interleukina-6 evitando la progresión de la cascada inflamatoria.

Pacientes y métodos. Estudio retrospectivo de los primeros 31 pacientes con COVID-19 tratados con siltuximab en el Hospital Clínic de Barcelona y en el Hospital Universitario de Salamanca, en el periodo de marzo a abril, que tenían una PCR en frotis nasal positiva para SARS-CoV-2.

Resultados. Fueron incluidos 31 pacientes tratados con siltuximab, con una mediana (RIC) de edad de 62 años (56-71) y una prevalencia de varones del 71%. La comorbilidad más frecuente fue la hipertensión arterial (48%). La mediana de dosis administrada de siltuximab fue 800 mg con un rango de 785 mg a 900 mg. Siete pacientes recibieron siltuximab como terapia de rescate después de una dosis de tocilizumab. Al final del estudio, un total de 26 (83.9) pacientes recibieron alta hospitalaria vivos. La tasa de mortalidad fue de 16.1%, sin embargo, solo 1 de los 24 pacientes que recibieron siltuximab como primera línea de tratamiento falleció (4%).

Conclusiones. Siltuximab es una alternativa bien tolerada al uso de tocilizumab como primera línea de tratamiento para pacientes con neumonía por COVID-19 dentro de los primeros 10 días de síntomas y con proteína C-reactiva elevada.

Palabras clave: IL-6; siltuximab; COVID-19, mortalidad.

INTRODUCTION

Infection by Coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan and rapidly spread around the world. SARS-CoV-2 is characterized by a high viral replication during the first days associated to a range of clinical manifestations from asymptomatic or mild to classical symptoms including fever, bad general status, myalgia, and cough. More than 80% of the infected patients have a self-limited infection but 15-20% develop a severe pneumonia and require hospital admission. In contrast to other respiratory virus bacterial co-infection is not a major cause of hospitalization, but it is characterized by a progressive respiratory failure, and bilateral infiltrates in the X-ray that resembles an adult distress respiratory syndrome (ARDS) [1]. This clinical pattern associated with severe lymphopenia and high C-reactive protein (CRP) and other raised inflammatory parameters suggests that this corresponds with the cytokine release syndrome (CRS) [2].

Interleukin-6 (IL-6) plays an important role in CRS, therefore, the inhibition of this cytokine has been proposed as potential alternative for severe pneumonia due to SARS-CoV-2 [3]. The first description included 21 patients that were admitted in a Chinese hospital and received tocilizumab, a recombinant humanized anti-human IL-6 receptor monoclonal antibody. In few days, symptoms improved remarkably, in 75.0% of patients lowering of their oxygen intake was possible and no patient died. Currently, there is experience with tocilizumab in randomized trials [4,5]. No one of these studies have demonstrated a reduction in the mortality rate among those receiving the anti-IL-6 therapy but they were not powered enough to detect differences in mortality and at least in one of them there was a significant reduction in the intensive care unit (ICU) admission among those receiving tocilizumab [6]. Siltuximab is a chimeric monoclonal antibody that binds to and neutralizes the effect of IL-6 [7] instead of blocking the IL-6 receptor. A study from Italy evaluated siltuximab in 30 patients that were matched to 30 control patients using the propensity score analysis of baseline covariates. The 30-day mortality rate was significantly lower in the siltuximab-treated than the matched-control cohort patients (HR 0·462, 95% CI 0·221– 0·965); p=0·0399). Sixteen siltuximab-treated patients were discharged from hospital, four remained on mechanical ventilation, and 10 patients died. However, this article is included in a repository and it is not yet peer reviewed.

The main objective of the present article is to describe the characteristics and clinical outcome of the first 31 patients in two hospitals with a SARS-CoV-2 infection that received treatment with siltuximab according to a protocol that aimed to early block the activity of IL-6 to avoid the progression of the inflammatory flare.

PATIENTS AND METHODS

Both Hospitals ethical committees approved the study. The Institutional Ethics Committee of the Hospital Clinic of Barcelona approved the study and due to the nature of retrospective chart review, waived the need for inform consent from individual patients (HCB/2020/0273).

Patients admitted to Hospital Clinic of Barcelona or Hospital Universitario Salamanca, from March to April 2020 with a positive polymerase-chain reaction (PCR) from a nasopharyngeal swab or fulfilling the clinical diagnostic criteria for SARS-CoV-2 and treated with siltuximab were retrospectively reviewed.

The criteria for hospital admission were similar in both hospitals, including patients with respiratory symptoms and pneumonia (uni- or bilateral interstitial infiltrates) as indicated by the chest X-ray. For ARDS, the Berlin definition [8] was applied. When arterial blood oxygen pressure (PaO_2) was not available, the ratio between the percentage of oxygen saturation by fraction of oxygen inspired (SpO_2/FiO_2) ≤ 315 suggested ARDS in non-ventilated patients [9]. The antiviral treatment was initiated to all patients and consisted of lopinavir/ritonavir 400/100 mg twice a day for 7-14 days plus hydroxychloroquine 400 mg/12h on the first day, followed by 200 mg/12h for

Table 1 Baseline characteristics.

Study population	N (%)
N° of patients	31
Age, median (IQR), years	62 (56-71)
Male sex (%)	22 (71)
Median follow-up, days (IQR)	14 (9-20)
Comorbidities	
Hypertension	15 (48.4)
Dyslipidaemia	11 (35.5)
Cardiomyopathy	4 (12.9)
Chronic respiratory disease	4 (12.9)
Diabetes mellitus	3 (9.7)
Chronic kidney disease	4 (12.9)
Initial symptoms	
Fever	30 (96.8)
Cough	23 (74.2)
Dyspnoea	14 (45.2)
Median days from symptom onset until admission (IQR)	7 (5-10)
Median days from admission to siltuximab administration (IQR)	2 (1-4)
Siltuximab administration in the regular ward (%)	25 (80.6)
Siltuximab administration in the ICU (%)	6 (19.4)
ARDS at hospital admission (%)	12 (38.7)
In hospital complications	
Acute renal failure without dialysis	5 (16)
Thrombosis	2 (6.5)
ARDS during hospitalization	13 (41.9)
Nosocomial infections	7 (22.6)
Urinary tract infection	3 (9.7)
Catheter associated infection	3 (9.7)
Not identified	1 (3.2)
Clinical outcomes (%)	
ICU admission in global cohort	11 (35.5)
ICU admission in 25 patients receiving siltuximab at general ward	5 (16.1)
Mechanical ventilation	
Non-invasive	9 (29)
Invasive	6 (19.4)
ICU discharge (%)	9 (81.8)
In-hospital mortality (%)	5 (16.1)

ICU, intensive care unit. ADRS, acute distress respiratory syndrome.

the next 4 days. From 18th of March, azithromycin 500 mg the first day and 250 mg/24h for 4 additional days was added to the regimen. The indication of an IL-6 inhibitor was the presence of pneumonia and progressive respiratory failure defined as the need of increasing the FiO_2 and a CRP ≥ 7 mg/dL or ferritin ≥800 ng/mL or lymphocyte count < 800 cells/mm^3. The first line option was tocilizumab but during the pandemic period the availability was limited and the alternative we chose was siltuximab. The dose was 11 mg/kg and a second dose could be administered at the physician's discretion. Siltuximab, in the majority of the cases presented in this report, was the first-line option but in some of them it was administered 24-48h after the first dose of tocilizumab due to non-adequate response (salvage therapy). The outcomes of the present study include intensive care unit (ICU) admission (for those patients that received siltuximab at the general ward), need of mechanical ventilation, in-hospital mortality rate and other complications including pulmonary embolisms and nosocomial infections.

Categorical variables were described using the absolute number and percentage and continuous variables using the median and interquartile range (IQR). The analysis was performed in SPSS version 23 (SPSS Inc., Chicago, IL).

RESULTS

The cohort included 31 cases that received siltuximab with a median (IQR) age of 62 (56-71) and 71% were males. The most frequent comorbidities were hypertension (48%), dyslipidaemia (35.5%), cardiomyopathy (12.9%), chronic respiratory disease (12.9%), chronic kidney disease (12.9%), and diabetes (9.7%). The median days from symptoms onset to hospital admission were 7 ranging from 5 to 10 days. Fever was a presenting symptom in 96.8% of patients, 74% also reported dry cough and 45.2% reported dyspnoea at hospital admission (table 1). Twenty-five (80.6%) patients had ARDS, 12 at hospital admission and 13 during hospital admission. ARDS was mild in 13 (41.9%) patients, moderate in 11 (35.5%), and severe in 1 (3.2%). All patients had a positive PCR from a nasopharyngeal swab and unilateral or bilateral interstitial infiltrate in the chest-X ray. Main laboratory findings at hospital admission are shown in table 2.

The median dose was siltuximab was 800 mg ranging between 785 and 900 mg. All patients received as antiviral treatment lopinavir/ritonavir plus hydroxychloroquine. Azithromycin was administered for 26 (83.9%) patients and 5 patients received remdesivir. As for other interleukin inhibitors, 8 patients also received tocilizumab and 6 anakinra. Eighteen

Table 2 Laboratory findings at hospital admission.

Laboratory findings, Median (IQR)	N (%)
D-dimer (ng/mL)[a]	800 (425-1,025)
Lymphocytes count (cell/mm^3)	900 (700-1,100)
C-reactive protein (mg/dL)	9.78 (5.09-24.64)
Ferritin (ng/mL)[b]	1,772 (971-2,204)
Lactate dehydrogenase (U/L)	346 (287-427)

[a] Measured in 30 cases; [b] Measured in 19 cases

Table 3 Additional antiviral and anti-inflammatory treatments.

Treatments received (%)	N (%)
Hydroxychloroquine	31 (100)
Lopinavir/ritonavir	31 (100)
Azithromycin	26 (83.9)
Remdesivir	5 (16.1)
Interferon	1 (3.2)
Steroid therapy	18 (58.1)
Steroid therapy prior to siltuximab	11 (35.5)
Tocilizumab	8 (25.8)
Tocilizumab prior to siltuximab	7 (22.58)
Days from tocilizumab administration to siltuximab (IQR)	2 (1-3)
Anakinra	7 (22.6)
Anakinra after siltuximab administration	6 (19.4)

patients (58.1%) received steroid therapy, 11 before siltuximab, 6 after, and 1 the same day (table 3).

Of the 25 patients that received siltuximab at a regular ward, 5 (16%) required intensive care unit (ICU) admission while 6 patients received siltuximab already in the ICU. Out of these 11 patients that required ICU admission, 6 required invasive mechanical ventilation (table 1). At the moment of the last revision, 26 (83.9) patients had been discharged alive and the mortality rate was 16.1% (5 patients). The mortality rate among the 7 patients that received siltuximab as a salvage therapy after tocilizumab was 43% (3 out of 7). On the other hand, only one patient out of 24 that received siltuximab as a first line option died (4%). Other clinical complications during admission included: thrombosis in 2 patients (one had a pulmonary embolism), 5 presented acute renal failure without need for dialysis, and 7 (22.6%) developed nosocomial infections during hospital admission, 3 a urinary tract infection and 3 a catheter-related bacteraemia (table 1).

DISCUSSION

Monoclonal antibodies directed against key inflammatory cytokines represent a class of adjunctive therapies for SARS-CoV-2 infected patients. The rationale for their use is that the underlying pathophysiology of significant organ damage in the lungs is caused by a cytokine storm being IL-6 one of the key drivers. Therefore, monoclonal antibodies against IL-6 could theoretically improve clinical outcome. Many observational studies have demonstrated a potential efficacy of blocking the IL-6 pathway mainly using tocilizumab [10,11], in contrast, randomized trials have shown negative results in terms of reduction of mortality, but one has demonstrated a reduction in the risk of ICU admission [6]. Siltuximab was administrated to 31 patients with severe COVID-19 and the results when it is administered as a first line option are similar to those reported in our cohort using tocilizumab in the same indication [12]. As it would be expected, those patients that received siltuximab as a salvage therapy had a significantly worse outcome. Considering the mechanism of action of monoclonal antibodies, now it seems not reasonable to use it as a salvage therapy and when the patient is not responding to the IL-6 inhibition, probably these patients are not responding to IL-6 inhibition due to a different pathogenic mechanism that requires further investigation including co-bacterial infection, thrombosis or macrophage activation syndrome that require different treatment approaches.

In conclusion, siltuximab is a well-tolerated alternative to tocilizumab when administered as a first line option in patients with COVID-19 pneumonia within the first 10 days from symptoms onset and high C-reactive protein. In the future, it is necessary to better define the characteristics of patients that benefit from IL-6 inhibition as well as the precise timing of its administration.

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CONFLICTS OF INTEREST

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ORIGINAL RESEARCH

Impact of Inflammatory Response Modifiers on the Incidence of Hospital-Acquired Infections in Patients with COVID-19

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ABSTRACT

Introduction: The study aim was to assess the influence of inflammatory response modifiers, including anti-interleukin-6 (IL-6) biologics and corticosteroids, on the incidence of hospital-acquired infections in patients with coronavirus disease 2019 (COVID-19).

Methods: Case–control study performed at a university hospital from February 26 to May 26, 2020. Cases were defined as patients with COVID-19 who developed hospital-acquired infections. For each case, two controls were selected among patients without infections. Cases and controls were matched obeying three criteria in a hierarchical sequence: length of hospital stay up until the first infection; comorbidity; and need for Intensive care unit (ICU) admission. Conditional logistic regression analysis was used to estimate the association of exposures with being a case.

Results: A total of 71 cases and 142 controls were included. Independent predictors for acquiring a hospital infection were chronic liver disease [odds ratio (OR) 16.56, 95% CI 1.87–146.5, $p = 0.012$], morbid obesity (OR 6.11, 95% CI 1.06–35.4, $p = 0.043$), current or past smoking (OR 4.15, 95% CI 1.45–11.88, $p = 0.008$), exposure to hydroxychloroquine (OR 0.2, 95% CI 0.041–1, $p = 0.053$), and invasive mechanical ventilation (OR 61.5, 95% CI 11.08–341, $p \leq 0.0001$).

Conclusions: Inflammatory response modifiers had no influence on acquisition of nosocomial infections in admitted patients with COVID-19. Hospital-acquired infections primarily occurred in the critically ill and invasive mechanical ventilation was the main exposure conferring risk.

Keywords: COVID-19; Inflammatory response modifiers; Nosocomial infections; SARS-CoV-2

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Key Summary Points
In patients with COVID-19 that received inflammatory response modifiers, the most common infections were ventilator-associated respiratory tract infections (tracheobronchitis or pneumonia).
The majority of patients with COVID-19 treated with inflammatory response modifiers were in an intensive care unit when the first hospital infection was diagnosed.
In patients treated with inflammatory response modifiers, the main risk factors for acquiring a nosocomial infection were chronic liver disease, morbid obesity, current or past smoking, and invasive mechanical ventilation.
Inflammatory response modifiers had no influence on acquisition of nosocomial infections in admitted patients with COVID-19.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14610504.

INTRODUCTION

Severe coronavirus disease 2019 (COVID-19) is characterized by an exaggerated inflammatory response mediated by an excessive production of interleukin-6 (IL-6) and other pro-inflammatory cytokines [1]. The clinical success of several therapeutic approaches has served as a proof of concept for the involvement of this "cytokine storm" in the pathogenesis of respiratory deterioration and progression to ARDS (acute respiratory distress syndrome) in patients with COVID-19. A number of comparative observational studies have suggested that in patients with severe or worsening SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pulmonary disease, tocilizumab, a monoclonal antibody directed against the IL-6 receptor, may decrease the need for mechanical ventilation and improve survival [2, 3]. Moreover, in our clinical setting, a personalized treatment with selective IL-6 and/or IL-1 blockade based on the individual patterns of inflammatory markers was associated with better survival [4]. In addition, a randomized clinical trial has proved that dexamethasone reduces mortality in patients requiring respiratory support [5]. Among other inhibitors of specific cytokines or more general inflammatory pathways, anakinra may be effective in patients with severe pneumonia and a hyperinflammatory state [6–8], and baricitinib in combination with remdesivir improved the clinical status of patients with COVID-19, particularly those receiving high-flux oxygen or noninvasive ventilation [9].

Although the first concern that inflammatory response modifiers could worsen the prognosis of COVID-19 by increasing viral replication or persistence has been mitigated by clinical experience, the possibility that they may still increase the rate of hospital-acquired infection has not been completely discarded [10–14]. The aim of the present study was to investigate the possible influence of the administration of inflammatory response modifiers, including anti-IL-6 biologics and corticosteroids, on the incidence of hospital-acquired infections in admitted patients with COVID-19.

METHODS

This is a case–control study performed with data retrieved from a specifically created database during the COVID-19 epidemic at a 750-bed university hospital in Barcelona (Spain). The study period was between February 26 and May 26, 2020. Cases were defined as patients with COVID-19 acquiring an infection during their hospital stay. Diagnosis of COVID-19 was based on a positive RT-PCR in a nasopharyngeal

swab or lower respiratory secretions. For each case, two controls were selected among patients with COVID-19 who did not acquire any infection. Three matching criteria were used in a hierarchical sequence. All controls must have had a length of hospital stay at least equal to the time elapsed from admission to the date of the first nosocomial infection in cases (equal or higher time at risk). After fulfilling this requirement, they were matched, if feasible, for the presence of any comorbidity and lastly for the need for ICU admission. To proceed with the selection, patients and controls were listed in an ascending order of time at risk and then for each consecutive case; the two closest controls fulfilling the time at risk and then the other matching criteria were chosen.

Hospital-acquired infections were defined according to the Centers for Disease Control and Prevention (CDC) criteria [15]. For ventilator-associated tracheobronchitis (VAT), the definition proposed by Craven et al. was used [16]. Only microbiologically documented infections deserving directed antibiotic therapy at the attending physician's discretion were included. Exposures had to be present for at least 24 h before the onset of infection. According to the local protocol, tocilizumab was administered as two doses of 400–600 mg/12 h apart with the option for a third dose 24 h later if there was progression of respiratory failure; however, at some point during the epidemic, only a single dose of 400 mg could be used because of shortages. Siltuximab and sarilumab were administered as single doses of 11 mg/kg and 200 mg, respectively. Anakinra was given as 200 mg/12 h up to 5 days and baricitinib as 4 mg/day for 10 days. In regards to corticosteroids, the local protocol recommended methylprednisolone 1 mg/kg/day to a maximum of 250 mg/day for 3 days followed by 0.5 mg/kg for three additional days. However, other schedules like prednisone 1–2 mg/kg/day, dexamethasone 6 mg/kg/day, or hydroxycortisone 100–400 mg/day for 10 days were also used at the discretion of the attending physician. Some patients continued treatment with lower doses of prednisone for longer periods as therapy for organizing pneumonia.

Assessed variables included demographics (age and sex), comorbidities, ICU admission, invasive and non-invasive mechanical ventilation, use of any medication (lopinavir–ritonavir, hydroxychloroquine, azithromycin, interferon-β, tocilizumab, other anti-IL-6 agents, baricitinib, anakinra, corticosteroids, antibiotics, and vasopressors), site of infection, and involved microorganisms in infected patients. Unfortunately, exposure to intravenous and urinary catheters was not recorded.

The median and the first and third quartiles were the measures of central tendency and dispersion displayed in this study, respectively. For univariate analysis, comparisons of continuous variables were performed by using the *t* test or Mann–Whitney *U* test depending on whether a normal distribution could be assumed or not. Categorical variables were compared by the chi-squared test or Fisher exact test when necessary. In order to assess the independent association of clinical characteristics and exposures with being a case, multivariate analysis was performed by using a conditional logistic regression procedure. In multivariate analysis, only variables with a univariate p value < 0.2 were allowed to enter the model and further selection was done by a stepwise backward procedure with a p value to step in and out of the model of 0.05. Calculations were done by using version 22 of the SPSS statistical package.

Compliance with Ethics Guidelines

The Institutional Ethics Committee of the Hospital Clinic of Barcelona approved the study and, owing to the nature of retrospective chart review, waived the need for inform consent from individual patients (HCB/2020/0273).

RESULTS

During the study period, 109 hospital-acquired infections were diagnosed in 71 patients. A single infection developed in 41 (57.7%) patients, two in 22 (30.9%), and three in 8 (11.2%). The most common infection was ventilator-associated tracheobronchitis ($n = 33$, 30.2%) followed by urinary tract infection

(n = 29, 26.6%), catheter-related bloodstream infection (n = 24, 22%), ventilator-associated pneumonia (n = 15, 13.7%), and others (n = 8, 7.3%). Median days from hospital admission to administration of tocilizumab, anakinra, and corticosteroids were 2 (0–4), 4 (1.75–8.75), and 2 (0–5), respectively, without significant differences between cases and controls. In case patients, median times elapsed from the onset of tocilizumab, anakinra, and corticosteroids to infection were 10 days (7–19), 8 days (3.75–21.75), and 10 days (6.75–17.25), respectively. Sixty-three patients (88.7%) were in ICU when the first hospital infection was diagnosed. In these patients, median time to ICU admission was 0 days (0–2 days) and that from ICU admission to the first nosocomial infection was 10 days (7–19 days). Sixteen (22.5%) cases and 33 (23.2%) controls died in hospital (OR 0.96, 95% CI 0.48–1.89, p = 0.9). Table 1 shows the etiological microorganisms of the different hospital-acquired infections.

Among infected patients, the median number of infections was 1 (1–2) regardless of whether they received biologics or corticosteroids. The comparative frequencies of clinical characteristics and exposures in cases and controls with their corresponding measurements of association are shown in Table 2. Cases were more likely than controls to be older, to have been transferred from another hospital, to have a history of alcohol abuse, to have ARDS, and to have been exposed to interferon-β, multiple antibiotics, ICU, vasopressors, and invasive mechanical ventilation. Chronic liver disease (p = 0.068) and morbid obesity (p = 0.066) were numerically more frequent in cases than controls, while cases shown a non-significant trend to be less exposed to hydroxychloroquine (p = 0.079). The median time at risk was 11 days. As expected from the procedure used for the selection of controls, significantly more patients in this group have a time at risk longer than the median.

Multivariate analysis selected the following as the best predictors for acquiring a nosocomial infection: chronic liver disease (OR 16.56, 95% CI 1.87–146.5, p = 0.012), morbid obesity (OR 6.11, 95% CI 1.06–35.4, p = 0.043), current or past smoking (OR 4.15, 95% CI 1.45–11.88, p = 0.008), exposure to hydroxychloroquine (OR 0.2, 95% CI 0.041–1, p = 0.053), and invasive mechanical ventilation (OR 61.5, 95% CI 11.08–341, $p \leq 0.0001$).

In 19 (26.7%) cases, a fungal species was involved, *Candida* spp. in 16, *Aspergillus fumigatus* in two, and *Fusarium* spp. in one. Of these, eight were unequivocally invasive (six episodes of catheter-related candidemia and two probable ventilator-associated pneumonia (VAP) due to filamentous fungi). However, when compared with controls, no association was found between having a fungal infection and exposure to tocilizumab (OR 0.81, 95% CI 0.28–2.39, p = 0.71), to any anti-IL-6 biologic (OR 0.53, 95% CI 0.17–1.6, p = 0.26), to corticosteroids (OR 0.84, 95% CI 0.21–3.33, p = 0.81), to biologics or corticosteroids (OR 0.17, 95% CI 0.01–1.6, p = 0.12), or to biologics plus corticosteroids (OR 0.7, 95% CI 0.22–2.23, p = 0.55). Exposure to high dose of either tocilizumab (> 600 mg) or a very high dose of corticosteroids (≥ 200 mg of prednisone equivalent) was not significantly different in cases and controls (OR 1.42, 95% CI 0.45–4.5, p = 0.54 for high-dose tocilizumab; OR 0.34, 95% CI 0.93–1.28, p = 0.11 for high-dose corticosteroids).

DISCUSSION

The main result of the present study is that there is no evidence of any deleterious influence of inflammatory response modifiers on the incidence of hospital-acquired infection in admitted patients with SARS-CoV-2 infection. In our experience, nosocomial infections in patients with COVID-19 primarily occurred in the critically ill, and mechanical ventilation was the only significant exposure conferring risk.

Data comparing the incidence of nosocomial infections in patients with severe COVID-19 between those taking and not taking inflammatory response modifies are relatively scarce. Several comparative retrospective studies have described a higher rate of infections in patients receiving tocilizumab than in controls. Somers et al. [10] observed a significantly increased rate of superinfection in treated patients (54% vs

Table 1 Microorganisms involved in 109 episodes of hospital-acquired infections in 71 hospitalized patients with COVID-19

Microorganism	VAP	VAT	Catheter-related bacteremia	Urinary tract infection	Other
Gram-positives	1	4	15	5	6
Methicillin-susceptible *Staphylococcus aureus*	1	4	–	–	–
Methicillin-resistant *S. aureus*	–	–	–	–	–
Coagulase-negative staphylococci	–	–	10	–	–
Streptococcus anginosus	–	–	1	–	–
Enterococcus faecalis	–	–	3	4	1
Enterococcus faecium		–	1	1	
Clostridioides difficile	–	–	–	–	2
Gram-negatives	12	21	3	21	0
Escherichia coli	–	–	–	3	–
ESBL-producing *E. coli*	–	–	–	3	–
Klebsiella pneumoniae	–	2	1	–	–
ESBL-producing *K. pneumoniae*	1	–	–	2	–
Klebsiella oxytoca	1	–	–	–	–
Proteus mirabilis	–	–	–	1	–
Enterobacter cloacae	2	2	2	–	–
Klebsiella aerogenes	2	1	–	–	–
Citrobacter spp.	–	–	–	1	–
Serratia marcescens	1	3	–	–	–
Carbapenemase-producing *Enterobacterales*	–	–	–	1	–
Non-MDR *Pseudomonas aeruginosa*	3	4	–	10	–
MDR *P. aeruginosa*	1	2	–	–	–
Stenotrophomonas maltophilia	1	4	–	–	–
Burkholderia gladioli		2	–	–	–
Bordetella spp.		1	–	–	–
Fungi	2	4	6	7	2
Candida spp.		3	6	7	2
Aspergillus spp.	1	1	–	–	–

Table 1 continued

Microorganism	VAP	VAT	Catheter-related bacteremia	Urinary tract infection	Other
Fusarium spp.	1	–	–	–	–

VAP ventilator-associated pneumonia, *VAT* ventilator-associated tracheobronchitis, *ESBL* extended-spectrum beta-lactamase, *MDR* multidrug-resistant

26%; $p < 0.001$), mostly due to a higher incidence of VAP. However, no difference between groups with regards to the frequency of bloodstream infections or development of more than one infection was observed. Guaraldi et al. [11] also observed an increased rate of hospital-acquired infections in patients treated with tocilizumab versus those in the standard of care group (13% vs 4%, $p > 0.001$), including four cases of invasive aspergillosis in the tocilizumab group and none in the standard of care. Kimmig et al. [12] reported a higher incidence of bacterial infections in patients receiving tocilizumab (adjusted OR 2.76, 95% CI 1.11–7.2), with all fungal infections occurring in the actively treated group. Lewis et al. [13], in a propensity-matched cohort study, also found an increased adjusted rate of secondary infections (OR 4.18, 95% CI 2.72–6.52) due to a higher incidence of bloodstream infections, pneumonia, and urinary tract infections. Lastly, Pettit et al. [14] reported an increased rate of late-onset infections in patients receiving tocilizumab (23% vs 8%, $p = 0.013$). Conversely, a higher rate of infections in patients taking tocilizumab was not observed in 14 prospective studies, including eight randomized controlled trials [2, 3, 8, 17–22]. The reasons for these discrepancies are not clear, but it can be speculated that the survival benefit associated with tocilizumab in several retrospective studies [10, 11, 13] could actually have prolonged the time at risk in this population and therefore the likelihood of getting an infection.

Our data suggests that when time at risk and other general predisposing factors (presence of any comorbidity and need for ICU admission) are similar between infected and not infected patients, no evidence of an increased risk of infection associated with exposure to biologics can be found. This also agrees with the lack of evidence of a higher risk of infection associated with a short (1–3 doses) exposure to tocilizumab in severely immunosuppressed patients with chimeric antigen receptor (CART) T cell-mediated cytokine release syndrome [23].

Data regarding other interleukin blockers are still sparser. Although IL-1 inhibitors (anakinra), like IL-6 blockers, have been associated with an increased rate of usually mild to moderate infection in the long-term treated patients with rheumatoid arthritis, no such increase has been observed with short-course regimens used for the therapy of patients with COVID-19 [6, 8] or of those with gout or sepsis [24, 25]. Lastly, in regards to corticosteroids, it is of note that despite their downregulation effect on the synthesis of pro-inflammatory cytokines and on the function of virtually any cell involved in the sensing of or response to invading microorganisms [26], their role as a risk factor for superinfection following short-term exposure is probably negligible. Several randomized clinical trials have assessed the therapeutic role of corticosteroids on COVID-19, and none of them reported a significantly higher incidence of superinfections in actively treated patients [5, 27–30]. This agrees with many randomized clinical trials conducted to evaluate the effect of acute exposure to corticosteroids on patients with sepsis or ARDS. The summarized evidence from these trials indicates that there is no association of corticosteroids with superinfection, regardless of the type of drug or specific regimen [31–33].

The present study suggests a possible protective effect of hydroxychloroquine on the acquisition of hospital-acquired infections, although the variable was retained in the multivariate model with borderline significance.

Table 2 Comparative prevalence of evaluated clinical characteristics and exposures in cases and controls (univariate analysis)

Characteristic or exposure	Controls (n = 142) (%)	Cases (n = 71) (%)	OR (95% CI)[a]	p[a]
Age > 65	62 (43.7)	42 (59.2)	2 (1.08–3.67)	0.024
Male sex	101 (71.1)	48 (67.6)	1.16 (0.64–2.11)	0.61
Transfer from other hospital	15 (10.6)	15 (21.1)	2.19 (1.01–4.75)	0.046
Any comorbidity	129 (90.9)	65 (91.5)	1.44 (0.18–11.1)	0.72
Chronic pulmonary disease	26 (18)	15 (21.1)	1.18 (0.59–2.36)	0.63
Diabetes	28 (19.7)	12 (16.9)	0.82 (0.38–1.76)	0.61
Hypertension	76 (53.5)	39 (54.9)	1.06 (0.58–1.91)	0.84
Heart disease	32 (22.5)	15 (21.1)	0.91 (0.44–1.8)	0.8
Cerebrovascular disease	10 (7)	4 (5.6)	0.8 (0.25–2.55)	0.7
HIV infection	3 (2.1)	1 (1.4)	0.66 (0.06–6.4)	0.72
Chronic renal insufficiency	19 (13.4)	10 (14.1)	1.06 (0.46–2.4)	0.88
Chronic liver disease	5 (3.5)	7 (9.9)	3.17 (0.91–11)	0.068
Solid organ cancer	12 (8.5)	6 (8.5)	1 (0.35–2.82)	1
Haematological cancer	9 (6.3)	1 (1.4)	0.22 (0.02–1.7)	0.15
Solid organ transplantation	8 (5.6)	2 (2.8)	0.46 (0.09–2.34)	0.35
Autoimmune disease	2 (1.4)	3 (4.2)	3 (0.5–17.9)	0.23
Immunosuppressors	16 (11.3)	6 (8.5)	0.71 (0.26–1.95)	0.51
Morbid obesity	9 (6.3)	10 (14.1)	2.5 (0.93–6.67)	0.066
Past or current smoking	44 (31)	30 (42.2)	1.31 (0.9–1.83)	0.1
Alcohol abuse	3 (2.1)	7 (9.9)	6.3 (1.29–30.7)	0.023
Lymphocyte count < 700 cells/μL	70 (49.3)	40 (56.3)	1.32 (0.74–2.35)	0.33
Tocilizumab	85 (59.9)	36 (50.7)	0.67 (0.36–1.22)	0.19
High-dose tocilizumab	18 (12.7)	9 (12.7)	1 (0.4–2.29)	1
Siltuximab	5 (3.5)	5 (7)	2.19 (0.57–8.36)	0.24
Sarilumab	2 (1.4)	–	0.026 (0–5748)	0.56
Any anti-IL6	92 (64.8)	41 (57.7)	0.73 (0.4–1.33)	0.3
Anakinra (%)	38 (26.8)	14 (19.7)	0.68 (0.35–1.34)	0.27
Baricitinib	3 (0.42)	–	0.026 (0–601)	0.47
Corticosteroids	105 (73.9)	51 (71.8)	0.87 (0.41–1.8)	0.7
High-dose corticosteroids	49 (34.5)	16 (22.5)	0.53 (0.27–1.06)	0.07

Table 2 continued

Characteristic or exposure	Controls (n = 142) (%)	Cases (n = 71) (%)	OR (95% CI)[a]	p[a]
Lopinavir–ritonavir	130 (91.5)	64 (90.1)	0.82 (0.28–2.34)	0.71
Hydroxychloroquine	137 (96.5)	64 (90.1)	0.35 (0.1–1.12)	0.079
Remdesivir	12 (8.5)	5 (7)	0.82 (0.28–2.41)	0.72
Interferon-β	35 (24.6)	30 (42.3)	2.17 (1.19–3.9)	0.01
Azithromycin	119 (83.8)	53 (76.6)	0.59 (0.3–1.16)	0.12
Any other antibiotic	119 (83.8)	61 (85.9)	1.17 (0.53–2.57)	0.69
≥ 2 antibiotics	75 (52.8)	47 (66.2)	1.84 (0.98–3.45)	0.058
≥ 3 antibiotics	36 (25.4)	24 (33.8)	1.47 (0.8–2.72)	0.2
≥ 4 antibiotics	5 (3.5)	7 (9.9)	3.78 (0.95–15)	0.059
ICU	115 (81)	63 (88.7)	5.92 (1.21–28.8)	0.027
Vasopressors	48 (33.8)	51 (71.8)	6.63 (3.07–14.4)	< 0.0001
Invasive mechanical ventilation	39 (27.5)	56 (78.9)	16.1 (5.77–45.2)	< 0.0001
Non-invasive mechanical ventilation	22 (15.5)	6 (8.5)	0.48 (0.18–1.31)	0.15
ARDS	102 (71.8)	60 (84.5)	2.21 (1.03–4.74)	0.04
Statins	15 (10.6)	10 (14.1)	1.35 (0.59–3.06)	0.47
Days at risk ≥ 11 days	110 (77.5)	41 (57.7)	0.21 (0.08–0.5)	< 0.0001

[a] OR, 95% CI, and p values estimated by conditional logistic regression analysis

This finding is intriguing and difficult to explain. Hydroxychloroquine accumulates in the lysosomes and other cellular organelles and neutralizes their acidic pH. This property endows the drug with in vitro activity against many viruses, as well as bacteria and fungi located in the appropriate intracellular environment, where a synergistic effect with several antimicrobial agents may occur [34]. However, in the clinical setting, hydroxychloroquine combined with appropriate antibiotics has proved to be critically effective only for the treatment of Q fever and Whipple disease. Actually, after much initial discussion and several randomized clinical trials, hydroxychloroquine has proved to be ineffective for both prevention and treatment of COVID-19 [35]. We cannot discard that the association of less hydroxychloroquine exposure with acquisition of nosocomial infections observed in our study stemmed from a possible more severe condition of case patients.

The present study was intended to assess the possible influence of inflammation-response modifiers on the rate of hospital-acquired infections, not to evaluate the relative incidence of nosocomial infection in patients with SARS-CoV-2. Currently, there is no definitive answer to this issue, due mainly to a substantial lack of comparative data between patients with COVID-19 and appropriate controls without SARS-CoV-2 infection [36–40]. The available evidence suggests that patients with COVID-19 do not seem to be particularly prone to acquire nosocomial bacterial infections or invasive candidiasis. However, an increased incidence of

invasive aspergillosis among intubated patients with COVID-19 cannot be completely dismissed [41, 42].

Our study has the common drawbacks of being relatively small, unicentric, and observational. In addition, matching was not wholly successful, exposure to intravenous and urinary catheters was not documented, and the duration of exposure to inflammatory response modifiers was not systematically registered. Moreover, we limited follow-up to the length of hospital stay; hence late-onset infections possibly related to past exposure to biologics or corticosteroids, such as tuberculosis, were not assessed. A last concerning issue is the possibility of misclassification bias of true bacterial or fungal infections, particularly those of pulmonary location, by using common clinical or radiological surveillance criteria in a population already overwhelmed with basal and evolving radiological chest abnormalities and high inflammatory markers. We tried to retain diagnostic specificity by including the requirement of microbiological documentation and directed antibiotic therapy as additional criteria to ascertain cases and distinguish them from controls.

CONCLUSIONS

Acute exposure of patients with severe COVID-19 to inflammatory response modifiers, including IL-6 blockers and corticosteroids, does not seem to increase the risk of acquiring a nosocomial infection beyond that expected in unexposed patients with SARS-CoV-2 infection of similar severity.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Real-life use of remdesivir in hospitalized patients with COVID-19

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ABSTRACT

Objective. Controversial results on remdesivir efficacy have been reported. We aimed to report our real-life experience with the use of remdesivir from its availability in Spain.

Methods. We performed a descriptive study of all patients admitted for ≥48 hours with confirmed COVID-19 who received remdesivir between the 1st of July and the 30th of September 2020.

Results. A total of 123 patients out of 242 admitted with COVID-19 at our hospital (50.8%) received remdesivir. Median age was 58 years, 61% were males and 56.9 % received at least one anti-inflammatory treatment. No adverse events requiring remdesivir discontinuation were reported. The need of intensive care unit admission, mechanical ventilation and 30-days mortality were 19.5%, 7.3% and 4.1%, respectively.

Conclusion. In our real-life experience, the use of remdesivir in hospitalized patients with COVID-19 was associated with a low mortality rate and good safety profile.

Keywords: Antivirals; COVID-19; outcome; remdesivir.

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Uso en vida real de remdesivir en pacientes hospitalizados con COVID-19

RESUMEN

Objetivo. Se han comunicado resultados controvertidos sobre la eficacia de remdesivir. Nuestro objetivo es comunicar nuestra experiencia en vida real con el uso de remdesivir desde su disponibilidad en España.

Métodos. Realizamos un estudio descriptivo de todos los pacientes ingresados durante ≥48 horas con COVID-19 confirmado que recibieron remdesivir entre el 1 de julio y el 30 de septiembre de 2020.

Resultados. Un total de 123 pacientes de los 242 ingresados con COVID-19 en nuestro hospital (50,8%) recibieron remdesivir. La mediana de edad fue de 58 años, el 61% eran varones y el 56,9% recibieron al menos un tratamiento antiinflamatorio. No se registraron acontecimientos adversos que requirieran la interrupción del remdesivir. La necesidad de ingreso en la unidad de cuidados intensivos, la ventilación mecánica y la mortalidad a los 30 días fueron del 19,5%, el 7,3% y el 4,1%, respectivamente.

Conclusiones. En nuestra experiencia, el uso de remdesivir en pacientes hospitalizados con COVID-19 se asoció con una baja tasa de mortalidad y un buen perfil de seguridad.

Palabras clave: Antivirales; COVID-19; resultados; remdesivir

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) emerged at the end of 2019, causing a devasting pandemic and reported one million deaths [1]. Initially, patients with COVID-19 received supportive care to relieve symptoms as well as antivirals according to in vitro data showing activity. However, these drugs failed to prove efficacy [2,3]. On May 1st, 2020, remdesivir received Food and Drug Administration (FDA) emergency use authorization for hospitalized patients with COVID-19 and was officially approved on October 22nd, 2020. Initial clinical trials using a control arm demonstrated the superiority of remdesivir in terms of clinical status improvement at day 28 [4] or at day 11 [5]; however, initial clinical trials performed in China [6] and a recent report from the Solidarity trial [7] did not prove that remdesivir had no benefit [8,9]. Different outcomes and the potential influence of when remdesivir was administered after symptom onset could explain the apparently controversial results in the aforementioned trials [10].

We aim to report our experience using remdesivir from July to September 2020, since the drug was made available in Spain.

METHODS

Study design and patients. This observational cohort study was performed at Hospital Clinic in Barcelona (Spain), a 700-bed university center that provides care for an urban population of 500,000 adults. All patients admitted for ≥48 hours with COVID-19 who received remdesivir between July 1st and the September 30th, 2020, were included. All patients had a COVID-19 diagnosis confirmed by real-time reverse-transcription polymerase chain reaction (rRT-PCR) performed on nasopharyngeal throat swabs. The Institutional Ethics Committee of Hospital Clinic of Barcelona approved the study and due to the nature of the retrospective data review, waived the need for informed consent from individual patients (HCB/2020/0273).

During this period, remdesivir treatment had to be approved by the Spanish Ministry of Health and dispensed by the Spanish Agency of Drugs and Health Products. Indication for remdesivir fell under consideration of attending physicians in July; however, beginning August 1st, the Spanish Agency of Drugs and Health Products established common criteria for all institutions in Spain. Criteria to prescribe remdesivir included hospitalized patients with severe pneumonia due to SARS-CoV-2 documented by rRT-PCR, serology or antigen test, and all the following characteristics: 1) aged >12 years and >40 kg; 2) need of supplemental low-flow oxygen; 3) ≤7 days from symptom onset to remdesivir prescription; and 4) met at least two of these three criteria: respiratory rate ≥24 bpm, oxygen saturation at air ambient ≤94%, or PaO_2/FiO_2 <300 mmHg. Exclusion criteria included requirement of supplemental high-flow oxygen, mechanical ventilation, vasoactive drugs, extracorporeal membrane oxygenation (ECMO), or meeting criteria for multiorgan failure. Contraindications included aspartate amino transferase (ASAT) and alanine amino transferase (ALAT) ≥5 times the normal range values, glomerular filtration <30 mL/min, hemodialysis, or peritoneal dialysis.

Data collection. For all patients hospitalized with COVID-19, high-quality data concerning demographics (age, sex), epidemiology, comorbidities, laboratory tests, microbiological results, treatment and outcomes were collected directly from electronic health records (EHR) using an intelligent system (SILDv1.0 system, S34M®) as described elsewhere [11].

Statistical analysis. Qualitative variables are presented as percentages and quantitative variables as median and interquartile range (IQR).

RESULTS

We assessed 242 consecutive adults with COVID-19 at our hospital during the study period. Of these patients, 123 (50.8%) received remdesivir. The median age was 58 years (range 48-69) and 61% were male. Characteristics are detailed in Table 1. Remarkably, remdesivir was used in four patients with chronic kidney disease and in 24 immune-supressed patients (13 with solid neoplasm, 8 with a hematological disease and 3 with HIV infection). The median (IQR) days from symptom onset to remdesivir prescription was 7 (4-9).

Table 2 shows the treatment options and outcome. In the cohort, 56.9 % of patients received at least one anti-inflammatory treatment, being the most frequent dexamethasone (n=57) and/or tocilizumab (n=33). Remdesivir was administered at the same time with dexamethasone in 24 patients (24/57; 42%) and with tocilizumab in 19 (19/33; 57%). C-reactive protein median (IQR) values at dexamethasone and tocilizumab administration were 14.3 (13.6-17.4) mg/dL and 13.2 (7.8-16.1) mg/dL, respectively.

The median (IQR) baseline creatinine was 0.86 mg/dL (0.72-1.08); but 6 patients had a creatinine value of >1.5 mg/dL (1.52 to 1.75 mg/dL) when remdesivir was prescribed. All these patients were discharged with a creatinine value of <1.40 mg/dL (0.84 to 1.40 mg/dL). One patient, with an initial creatinine value of 1.39 mg/dL, was discharged with the value at 1.72 mg/dL. The median (IQR) values of ASAT and ALAT at baseline (before starting remdesivir) were 39 (24-64) U/L and 36 (23-61) U/L, respectively. The median values at hospital discharge were 33 (19-57) U/L and 60 (35-97) U/L, respectively. The median (IQR) lymphocyte counts at baseline and at hospital discharge were 1 (0.8-1.3) $x10^9$/L and 1.7 (1.2-2.2) $x10^9$/L, respectively. No adverse events requiring remdesivir discontinuation were reported.

Needs for intensive care unit (ICU) admission and mechanical ventilation was 19.5% and 7.3%, respectively. The 30-day mortality rate was 4.1% (5/123), and 8.3% (2/24) among patients that required ICU admission. All dead patients had ≥80 years and all concomitantly received any anti-inflammatory therapy. The 30-day mortality among patients receiving concomitantly remdesivir and dexamethasone was 16.7% and 5.3% with tocilizumab.

Table 1 Clinical characteristics of 123 consecutive adults treated with remdesivir for COVID-19.

Patient characteristics	
Median (IQR) age, in years	58 (48-69)
Age > 65 years (%)	41 (33.3%)
Sex male, n (%)	75 (61%)
Comorbidities (%)	
Hypertension	50 (40.7%)
Diabetes mellitus	27 (22%)
Chronic heart disease	19 (15.4%)
Chronic lung disease	24 (19.5%)
Chronic liver disease	6 (3%)
Chronic kidney disease	4 (3.3%)
Solid neoplasm	13 (10.6%)
Hematological disease	8 (6.5%)
HIV	3 (2.4%)
Median (IQR) days from symptom onset to hospital admission	6 (4-8)
Median (IQR) days from symptom onset to remdesivir	7 (4-9)
Vital signs at admission	
Median (IQR) temperature (ºC)	37 (36.5-38)
Median (IQR) respiratory rate (rpm)	20 (18-26)
Respiratory rate > 20 (%)	80 (65%)
Median (IQR) oxygen saturation (%)	94 (93-95)
Oxygen saturation < 94% (%)	48 (39%)
Median (IQR) cardiac rate (rpm)	91 (82-100)
Laboratory at admission, median (IQR)	
Ferritin (ng/mL)	495 (287-1096)
C-RP (mg/dL)	7.99 (4.69-14.47)
D-dimer (ng/mL)	500 (300-900)
LDH (U/L)	323 (265,75-376)
Lymphocyte count (x10^9/L)	1 (0.7-1.3)
Creatinine (mg/dL)	0.86 (0.72-1.08)
ASAT (U/L)	39 U/L (24-64)
ALAT (U/L)	36 U/L (23-61)

Table 2 Concomitant treatment and outcomes of 123 consecutive adults treated with remdesivir for COVID-19.

Treatment	
Other drugs with potential antiviral effect	
Lopinavir/ritonavir (%)	1 (0.8%)
Anti-inflammatory effect	
Tocilizumab (%)	33 (26.8%)
Anakinra (%)	7 (5.7%)
Methyl-prednisolone (%)	14 (11.4%)
Dexamethasone (%)	57 (46.3%)
Prednisone (%)	24 (19.5%)
Antibiotic treatment	
Ceftriaxone (%)	52 (42.8%)
Ceftaroline (%)	16 (13%)
Outcomes	
Median (IQR) of length of hospital stay	8 (6-12)
ICU admission (%)	24 (19.5%)
Need of mechanical ventilation (%)	9 (7.3%)
30-day mortality (%)	5 (4.1)

DISCUSSION

This is the first report to assess the efficacy and tolerability of remdesivir in a real-life cohort of patients with COVID-19, including those with cancer or hematological disease. Our results documented a low mortality rate (4.1%) in hospitalized patients receiving remdesivir for severe pneumonia due to SARS-CoV-2. This rate is in line with that reported in the ACTT-1 study that randomized patients to remdesivir or placebo [4]. Our patients mainly correspond to those in the ACTT-1 study with a baseline ordinal score of 5 (hospitalized patients requiring supplemental oxygen) who had a mortality rate of 3.8% in the remdesivir arm versus 12.3% in the control arm. The total number of patients in this study subgroup was 435 (232 and 203 in each arm), being the largest group. This is reasonable since this is the most common type of patients requiring hospital admission in the daily practice, therefore, our results enlarge the experience in this important subgroup.

The most severe patients required co-administration of an anti-inflammatory therapy, and as expected they had the highest mortality rate. Interestingly, the concomitant use of remdesivir and tocilizumab was associated with the lowest mortality rate in this group (5.3%), in line with the recent report showing better outcomes among patients receiving remdesivir plus baricitinib [12]. Both inmune-modulators inhibit specific pathways of inflammatory cascade instead of the broad-spectrum inhibition induced by steroids with potential harmful consequences [13].

The optimal timing for remdesivir treatment remains to be clarified. SARS-CoV-2 shedding from the respiratory tract peaks during the first 2-3 days from clinical symptom onset and rapidly decreases [14], consistent with a brief window of clinical benefit from antiviral drugs. In this scenario, prompt initiation of antiviral treatment may be the key point to improve outcomes of patients with COVID-19. Such approach has been documented in other respiratory virus such as the influenza, with the use of neuraminidase inhibitors [15]. In our cohort, remdesivir was administered earlier than in the ACTT-1

study (median of 7 vs. 9 days from symptom onset to remdesivir) [4]. Such early drug administration could explain the shorter length of hospital stay (8 vs. 12 days) and lower need of mechanical ventilation (7.3 vs. 12.9%). A prior trial [6] failed to demonstrate any benefits from remdesivir treatment in patients with COVID-19; however, the median days from symptom onset to remdesivir was 11 and, indeed, 37 of the 196 (19%) patients had undetectable viral RNA on nasopharyngeal and oropharyngeal swabs obtained at baseline. Considering all together, this data suggests that patients included in this study were in a late stage with low viral load and, therefore, the expected benefit of an antiviral in this population is mimimal.

The impact of remdesivir on reducing viral shedding has been reported in macaques [16]. Information about viral shedding in humans receiving remdesivir treatment is, however, lacking. Such information is important to define the duration of transmissibility and the potential consequences on the isolation measures.

Our cohort supports the good tolerability profile of remdesivir, presenting with no serious adverse events and, in particular, no alterations in liver enzymes. No patient required discontinuation of the drug.

The main limitation of this study was its retrospective nature and a possible underreporting of adverse events. However, we were able to closely monitor laboratory parameters to minimize this problem. However, the strength of our study is that the Spanish Ministry of Health perfectly defined the indication for remdesivir and our results support such current indication.

We conclude that the use of remdesivir in hospitalized patients with pneumonia due to SARS-CoV-2 is associated with a low mortality rate and has a good safety profile.

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CONFLICT OF INTERESTS

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Short Report PNEUMON

COVID-19 in patients aged 80 years and over during the peaks of the first three pandemic waves at a Spanish tertiary hospital

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ABSTRACT

INTRODUCTION COVID-19 disproportionately impacts patients aged ≥80 years, yet few studies have focused on this population. We aimed to investigate the clinical characteristics and outcomes of very elderly patients with COVID-19 across three consecutive waves in Spain.

METHODS We retrospectively evaluated very elderly patients admitted with COVID-19 to a university hospital in Barcelona, Spain, across the three first waves. Main outcomes were ICU admission and 30-day mortality.

RESULTS From March 2020 to February 2021, 3105 patients diagnosed with COVID-19 were admitted. Of these, 655 (21%) were very elderly patients, 50% were female and median age was 86 (83; 89) years. ICU admission and ICU-mortality rates were 11% and 42%, respectively; male sex, respiratory rate ≥25 breaths/min, LDH ≥337.5 U/L and C-reactive protein ≥11.5 mg/dL were significantly associated with ICU admission in the multivariable analysis. Overall, 30-day mortality was 34%. The ICU admission rate was significantly higher during the first wave compared to the third wave (16% vs 8%; p=0.009), whereas no significant differences in 30-day mortality were found between waves (p=0.107).

CONCLUSIONS We observed an increase in the percentage of very elderly patients admitted to the ICU during the three first pandemic peaks. ICU admission more likely occurs in very elderly male patients with higher respiratory rate, with elevate LDH and C-reactive protein. Overall, our 30-day mortality rate was lower compared to other series globally.

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INTRODUCTION

Since the beginning of the pandemic, Spain has been hit by five waves of COVID-19. Age was widely used as a prioritizing criterion for ICU admission, which has been one of the most controversial aspects of the pandemic thus far[1]. Numerous studies have found older age to be associated with higher risk of severe illness, complications, and mortality in COVID-19[2]. Despite that patients aged ≥80 years have distinct clinical features and risk factors, notably multiple comorbidities and polypharmacy[3], there is little information on this specific population.

We aimed to describe and compare the clinical characteristics, complications, therapy and outcomes in very elderly patients with COVID-19 during the first three waves of the pandemic in Spain.

METHODS

We retrospectively evaluated all consecutive very elderly patients admitted to Hospital Clinic, Barcelona (Spain). All patients admitted >48 h with a definite diagnosis of COVID-19 (either confirmed by RT-PCR or fulfilling clinical criteria in place) between March 2020 and February 2021 were included. The primary outcome was ICU mortality. Secondary outcomes included length of hospital stay, early mortality (within 5 days of admission), 30-day mortality and need for mechanical ventilation. We divided the study population into three groups for the analysis: first wave (March to June 2020), second wave (July to November 2020) and third wave (December 2020 to February 2021).

Categorical variables were compared between the three groups using the χ^2 test, while continuous variables with the Kruskal-Wallis test. In the event of a significant overall test, we conducted *post hoc* pairwise comparisons with Bonferroni correction. We examined the association of risk factors with ICU admission using logistic regression models. After bivariate analyses, we selected independent variables at a p<0.25. All the variables were put into a multivariable logistic regression analysis model. Final variable selection was performed using the backward stepwise selection method, except for period, which had to appear in the model. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the final model. The receiver

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operating characteristic (ROC) curve was used to assess the discriminatory ability of the model to distinguish ICU patients from ward patients and is expressed as the area under the ROC curve (AUC). The level of significance was set at 0.05 (two-tailed). All analyses were performed using IBM SPSS Statistics version 26.0 (Armonk, New York, USA).

RESULTS

From March 2020 to February 2021, 3105 patients diagnosed with COVID-19 were admitted. A total of 655 (21%) were very elderly patients and were included in our study [first wave 289/1447 (20%); second wave 145/765 (19%); third wave 221/893 (25%)], 50% were females, and median age was 86 (83; 89) years.

The median time from symptoms to COVID-19 diagnosis was 5 (2; 8) days. At least one comorbidity was present in 91% of patients, the most frequent of which were hypertension (74%) and chronic heart disease (53%) (Table 1).

Seventy-four (11%) patients were admitted to the ICU, 51% of whom during the first 48 h of hospital stay. Overall, 30-day mortality was 34%.

No significant differences were observed regarding age, sex, or time from onset of symptoms to COVID-19 diagnosis between patients in the three waves (Table 1). A significantly higher proportion of COPD patients were admitted during the second (17%) and third (14%) waves, than in the first wave (8%). No other significant differences were observed in other comorbidities between groups by wave (Table 1).

On admission, patients in the second and third waves more frequently presented tachypnea than patients in the first wave. Patients in the first wave presented the highest median levels of D-dimer. Overall, the use of drugs widely varied across waves, particularly in the case of hydroxychloroquine, lopinavir-ritonavir, azithromycin, and ceftriaxone (whose usage decreased with time), remdesivir and dexamethasone (increasingly used, Table 1).

ICU admission rates rose significantly, from 8% in the first wave to 16% in the third wave (p=0.009). Forty-eight (7%) patients received mechanical ventilation (5% non-invasive

Table 1. Demographics and clinical characteristics of COVID-19 patients hospitalized during the three waves

Characteristics	Total (n=655) Median (Q1; Q2) or n (%)	1st wave (n=289) Median (Q1; Q2) or n (%)	2nd wave (n=145) Median (Q1; Q2) or n (%)	3rd wave (n=221) Median (Q1; Q2) or n (%)	p
Age (years)	86 (83; 89)	86 (83; 89)	85 (82; 89)	86 (83; 89)	0.468
Sex (male)	327 (50)	134 (46)	73 (50)	120 (54)	0.205
Comorbidity	594 (91)	271 (94)	129 (89)	194 (88)	0.050
Chronic heart disease	348 (53)	155 (54)	76 (52)	117 (53)	0.969
Diabetes mellitus	180 (27)	83 (29)	34 (23)	63 (29)	0.467
Hematological disease	53 (8)	20 (7)	14 (10)	19 (9)	0.581
Chronic kidney disease	179 (27)	79 (27)	37 (26)	63 (29)	0.821
Chronic liver disease	32 (5)	13 (4)	7 (5)	12 (5)	0.889
Hypertension	485 (74)	218 (75)	102 (70)	165 (75)	0.505
Cancer	163 (25)	66 (23)	35 (24)	62 (28)	0.391
Solid organ transplantation	4 (1)	4 (1)	0 (0)	0 (0)	0.078
Chronic lung disease	205 (31)	83 (29)	51 (35)	71 (32)	0.372
Asthma	26 (4)	8 (3)	7 (5)	11 (5)	0.375
Bronchiectasis	38 (6)	10 (3)	11 (8)	17 (8)	0.075
COPD	81 (12)	24 (8)	25 (17)	32 (14)	**0.014**[ab]
Pulmonary hypertension	21 (3)	10 (3)	4 (3)	7 (3)	0.926
Symptoms onset to COVID-19 diagnosis (days)	5 (2; 8)	5 (2; 8)	5 (3; 8)	5 (2; 7)	0.653
Heart rate (beats/min)	89 (80; 101)	89 (80; 102)	89 (81; 101)	89 (80; 100)	0.877
Respiratory rate (breaths/min)	23 (20; 28)	21 (18; 28)	24 (20; 28)	24 (20; 28)	**0.001**[ab]
Oxygen saturation (%)	95 (94; 97)	95 (93; 97)	95.5 (94; 97)	95 (94; 97)	0.349
Diastolic blood pressure (mmHg)	70 (61; 78)	69 (60; 77)	70 (61.5; 80)	70 (62; 78)	0.634

Continued

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Table 1. Continued

Characteristics	Total (n=655) Median (Q1; Q2) or n (%)	1st wave (n=289) Median (Q1; Q2) or n (%)	2nd wave (n=145) Median (Q1; Q2) or n (%)	3rd wave (n=221) Median (Q1; Q2) or n (%)	p
Systolic blood pressure (mmHg)	127 (114; 144)	127 (114; 145)	128 (117.5; 146)	127 (112; 141)	0.578
Temperature (°C)	37.2 (36.6; 37.8)	37.2 (36.5; 37.8)	37.3 (36.7; 38)	37.1 (36.6; 37.8)	0.611
ALT (U/L)	21 (14; 33)	21 (13.5; 32)	19 (14; 34)	21 (13.5; 34)	0.877
AST (U/L)	34 (25; 51)	34 (23; 52.5)	32.5 (25; 48)	35 (26; 53)	0.386
Creatinine (mg/dL)	1.18 (0.89; 1.65)	1.10 (0.86; 1.62)	1.13 (0.87; 1.58)	1.25 (0.94; 1.83)	0.056
D-dimer (ng/mL)	1200 (700; 2950)	1400 (800; 4000)	1100 (600; 2400)	1200 (700; 2300)	**0.047**[c]
Ferritin (ng/mL)	443.5 (185; 1003)	464 (196; 1088)	436 (167; 871)	402.5 (208; 1086)	0.330
Glucose (mg/dL)	129 (105; 165)	123 (103; 163)	135 (106.5; 158.5)	133 (108; 178)	0.227
C-reactive protein (mg/dL)	9 (4; 16.7)	8.7 (4; 17.3)	8.6 (4.1; 16)	9.1 (3.8; 16.6)	0.718
Procalcitonin (ng/mL)	0.17 (0.08; 0.46)	0.18 (0.08; 0.45)	0.15 (0.09; 0.37)	0.19 (0.09; 0.53)	0.478
LDH (U/L)	309 (240; 402)	309 (237; 422)	318 (245; 391)	300 (235; 395)	0.827
Troponin (ng/L)	28.4 (14.5; 77.3)	26.5 (13.6; 76.5)	28.4 (16.4; 68.5)	34.6 (15.4; 111.4)	0.406
Leucocyte count ($\times 10^9$/L)	7.05 (5.24; 9.91)	7.12 (5.24; 10.03)	6.59 (5.08; 9.50)	7.18 (5.33; 9.71)	0.344
Platelet count ($\times 10^9$/L)	186 (141; 245)	188 (143; 250)	181 (148; 232)	186 (131; 243)	0.313
Lymphocyte count ($\times 10^9$/L)	0.90 (0.60; 1.20)	0.85 (0.60; 1.20)	0.90 (0.70; 1.20)	0.90 (0.60; 1.20)	0.463
Neutrophil-to-lymphocyte ratio	6.2 (3.7; 10.3)	6.3 (3.8; 10.9)	5.3 (3.4; 9.8)	6.4 (4; 9.9)	0.117
Noninvasive mechanical ventilation	33 (5)	8 (3)	9 (6)	16 (7)	0.056
Invasive mechanical ventilation	15 (2)	5 (2)	7 (5)	3 (1)	0.066
LOS (days)	8 (5; 14)	8 (4; 13)	9 (6; 14)	9 (5; 15)	**0.011**[ab]
ICU admission	74 (11)	22 (8)	16 (11)	36 (16)	**0.009**[b]
Hydroxychloroquine	220 (34)	220 (76)	0 (0)	0 (0)	**<0.001**[ab]
Lopinavir/ritonavir	157 (24)	157 (54)	0 (0)	0 (0)	**<0.001**[ab]
Azithromycin	257 (39)	224 (78)	15 (10)	18 (8)	**<0.001**[ab]
Ceftriaxone	349 (53)	170 (59)	74 (51)	105 (48)	**0.033**[b]
Remdesivir	70 (11)	4 (1)	33 (23)	33 (15)	**<0.001**[ab]
Corticosteroids	389 (59)	123 (43)	99 (68)	167 (76)	**<0.001**[ab]
Dexamethasone	223 (34)	5 (2)	76 (52)	142 (64)	**<0.001**[ab]
Methylprednisolone	206 (31)	105 (36)	34 (23)	67 (30)	**<0.001**[a]
Prednisone	112 (17)	49 (17)	23 (16)	40 (18)	0.166
ICU mortality[d]	31 (42)	12 (55)	4 (25)	15 (42)	0.190
Early mortality	99 (15)	64 (22)	12 (8)	23 (10)	**<0.001**[ab]
30-day mortality	223 (34)	111 (38)	43 (30)	69 (31)	0.107

COPD: chronic obstructive pulmonary disease. ICU: intensive care unit. LOS: length of hospital stay. Q1: first quartile. Q3: third quartile. LDH: lactate dehydrogenase. a p<0.05 for comparison between the groups of 1st wave and 2nd wave. b p<0.05 for comparison between the groups of 1st wave and 3rd wave. c p<0.05 for comparison between the groups of 2nd wave and 3rd wave. d 74 patients were used to calculate the percentages (22 patients in the 1st wave, 16 in the 2nd wave, and 36 in the 3rd wave).

and 2% invasive mechanical ventilation), with no differences between waves.

Early mortality was 15% (99), with a significant decrease, from 22% in the first wave to 10% in the third wave (p<0.001). ICU mortality was 42% (31), with no differences between waves. There were 223 (34%) patients who died at 30 days after admission, with no differences between waves. Male sex, respiratory rate ≥25 breaths/min, LDH ≥337.5 U/L and C-reactive protein ≥11.5 mg/dL were significantly associated with ICU admission in the multivariable analysis

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Table 2. Significant univariate logistic regression analysis for variables associated with ICU admission and independent predictors of ICU admission determined by multivariable logistic regression analysis[a]

Variable	Univariate[b]			Multivariable (n=279)[cd]			Multivariable (n=279)[ce]		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Period			0.028			0.080			0.076
First wave (Ref.)	1	-	-	1	-	-	1	-	-
Second wave	1.09	0.54–2.22	0.811	0.87	0.37–2.06	0.752	0.93	0.40–2.16	0.874
Third wave	2.12	1.16–3.88	0.015	2.03	0.93–4.44	0.076	2.08	0.98–4.43	0.058
Male sex	3.06	1.73–5.40	<0.001	2.41	1.19–4.88	0.014	2.30	1.16–4.53	0.017
Heart rate (+1 beats/min)[f]	1.01	1.00–1.03	0.052	-	-	-	-	-	-
Respiratory rate (+1 breaths/min)[f]	1.15	1.10–1.21	<0.001	1.13	1.07–1.20	<0.001	-	-	-
Respiratory rate ≥25 breaths/min[g]	5.60	3.17–9.89	<0.001	-	-	-	4.28	2.24–8.18	<0.001
Oxygen saturation (+1%)[f]	0.90	0.83–0.97	0.009	-	-	-	-	-	-
Diastolic blood pressure (+1 mmHg)[fh]	0.96	0.94–0.99	0.001	-	-	-	-	-	-
Systolic blood pressure (+1 mmHg)[f]	0.99	0.98–1.00	0.123	-	-	-	-	-	-
Temperature (+1°C)[f]	1.23	0.92–1.64	0.154	-	-	-	-	-	-
ALT (+1 U/L)[f]	1.01	1.00–1.02	0.059	-	-	-	-	-	-
AST (+1 U/L)[fh]	1.02	1.00–1.03	0.011	-	-	-	-	-	-
Creatinine (+1 mg/dL)[f]	1.15	0.92–1.44	0.208	-	-	-	-	-	-
Glucose (+1 mg/dL)[f]	1.01	1.00–1.01	0.001	-	-	-	-	-	-
LDH (+1 U/L)[f]	1.01	1.00–1.01	<0.001	1.01	1.00 – 1.01	0.001	-	-	-
LDH ≥337.5 U/L[g]	3.92	2.24–6.87	<0.001	-	-	-	2.41	1.22–4.76	0.011
C-reactive protein (+1 mg/dL)[f]	1.08	1.05–1.12	<0.001	1.06	1.01–1.10	0.010	-	-	-
C-reactive protein ≥11.5 mg/dL[g]	3.49	2.03–6.00	<0.001	-	-	-	2.38	1.22–4.67	0.011
Neutrophil-to-lymphocyte ratio (+1)[f]	1.07	1.03–1.12	<0.001	-	-	-	-	-	-

ALT: indicates alanine transaminase. AST: aspartate transaminase. CI: confidence interval. LDH: lactate dehydrogenase. OR: odds ratio. Data are shown as estimated ORs (95% CIs) of the explanatory variables in the ICU admission group. The OR represents the odds that the presence of ICU admission will occur given exposure of the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure; for continuous predictors, the OR represents the increase in odds of the outcome of interest with every one unit increase in the input variable. The p-value is based on the null hypothesis that all ORs relating to an explanatory variable equal unity (no effect). aPatients who were not admitted to ICU and with a DNR were excluded. bThe variables analyzed in the univariate analysis were sex, diabetes mellitus, chronic heart disease, chronic kidney disease, chronic liver disease, hypertension, COPD, heart rate, respiratory rate, oxygen saturation, diastolic blood pressure, systolic blood pressure, temperature, ALT, AST, creatinine, glucose, LDH, C-reactive protein, leucocytes, neutrophil-to-lymphocyte ratio, and platelets. cAdjusted for period of admission. dHosmer–Lemeshow goodness-of-fit test, p=0.684. Area under the ROC curve, AUC=0.82 (95% CI: 0.76–0.88). e Hosmer–Lemeshow goodness-of-fit test, p=0.086. Area under the ROC curve, AUC=0.80 (95% CI: 0.73–0.87). f '+1' indicates an increase by one unit. gCut-off obtained from ROC curve. hVariable excluded of multivariable analysis because of collinearity with another significant variable.

(Table 2). The AUC was 0.80 (95% CI: 0.73–0.87) for the predictive model.

DISCUSSION

In accordance with data from other regions[4,5], where elderly patients were reported to be the population most affected by COVID-19, the burden of COVID-19 in very elderly patients remained high throughout the three first waves in Spain. The proportion of patients with COPD increased between the first and third waves. Despite the reported overall relatively low incidence of COVID-19 in COPD patients (1.1–10%)[6,7], COPD patients have an increased risk of severe disease and poor outcomes[8]. Thus, the increase in COPD across waves may be explained because this population may have taken isolation measures more seriously and, consequently, reduced their rates of infection, provided that it was made clear from the early stages of the pandemic that SARS-CoV-2 severely affected the lungs. Also, the use of inhaled corticosteroids may

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offer a protective effect in these patients, as recently reported[9].

In our study, 91% of our patients presented at least one comorbidity, 15% of the patients died in the first 5 days after admission, and ICU mortality was 42%, which shows the disproportionate impact of COVID-19 on these patients; this increased impact has also been widely reported for the elderly population though not specifically in very elderly patients[10]. Early recognition of severe COVID-19 in very elderly patients may allow prompt complication management, thus improving outcomes or optimizing comfort in patients who are not candidates for aggressive therapeutic measures. During the pandemic peaks, we observed a significant increase in the use of remdesivir and corticosteroids, whereas hydroxycloroquine, lopinavir/ritonavir, and azythromycin were progressively abandoned, which is in line with the results of the main platform clinical trials on COVID-19 (i.e. WHO Solidarity trial[11], RECOVERY[12], REMAP-CAP[13]). Overall, 11% of very elderly patients were admitted to the ICU, with rates increasing between the first and third waves (8–16%), which are likely related to the availability of ICU beds. During the first wave, the Spanish health system, including ICUs, was largely overwhelmed and prioritization criteria that included advanced age or reduced functionality in nursery homes residents were implemented in many hospitals[1]. We found that male sex, respiratory rate, and C-reactive protein were associated to a higher likelihood of ICU admission, which has already been reported[5,6,10,14]. Meanwhile, 30-day mortality rates, although remarkably lower overall (34%) compared to other series worldwide (46–54%)[2,14,15], are strikingly high figures that highlight the vulnerability of very elderly patients to COVID-19 and therefore the relevance of preventive measures.

Strengths and limitations

The strengths of this study include the large sample size, the special focus on very elderly patients, and the information on three consecutive COVID-19 wave peaks. The study does, however, have some limitations that need to be addressed. The data were collected from a single academic teaching hospital in Spain; it may not be possible to extrapolate results to patients admitted to different hospitals or in other countries. Second, data on quality of life, frailty, and/or functional status were not recorded, which may have led to an underestimation of their potential predictive value.

CONCLUSIONS

We observed an increase in the percentage of very elderly patients admitted to the ICU during the three first pandemic peaks. ICU admission more likely occurs in very elderly male patients with higher respiratory rate, with elevated LDH and C-reactive protein. Overall, our 30-day mortality rate was lower compared to other series globally.

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CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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ETHICAL APPROVAL AND INFORMED CONSENT

The study was approved by the local Institutional Review Board (HCB/2020/0273). The need for written informed consent was waived due to the non-interventional design of the study.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

AUTHORS' CONTRIBUTIONS

CC, FM, GD and AS conceived the study. CC, FM, GD and JG executed the search and extracted data. FM, GD and AG performed the analysis of data, with inputs from CC, MC, PP, NC, VR, AT, CG and AS. All authors contributed to the interpretation of data. CC, FM, GD and AS wrote the initial draft of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version. AS and CC are guarantors for the study.

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Research paper

Trends in mortality of hospitalised COVID-19 patients: A single centre observational cohort study from Spain

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ABSTRACT

Background: We aimed to describe changes in characteristics and treatment strategies of hospitalised patients with COVID-19 and detail the mortality trend over time.
Methods: Observational cohort study of all consecutive patients admitted ≥ 48 h to Hospital Clínic of Barcelona for COVID-19 (1 March–30 September 2020).
Findings: A total of 1645 consecutive patients with COVID-19 were assessed over a 7-month period. Overall mortality (≤30 days) was 9.7% (159 patients), 7.7% in patients hospitalised in regular wards and 16.7 % in patients requiring ICU admission. Overall mortality decreased from 11.6% in the first month to 1.4% in the last month, reflecting a progressive, significant downward trend (p for trend <0.001). Patients' age changed over time, peaking in June. Most changes in the use of antivirals and anti-inflammatory treatments were documented. Age (OR 1.1, CI 1.1–1.12), chronic heart disease, (OR 1.7, CI 1.1–2.9), D-dimer>700 ng/mL (OR 2.3, CI 1.3–4.1), ferritin>489 ng/mL (OR 1.9; CI 1.5–3.2), C-RP>7 mg/dL (OR 2.6; CI 1.5–4.6), and shorter duration from symptom onset to hospital admission (OR 1.11; CI 1.04–1.17) were factors associated with 30-day mortality at hospital admission. Conversely, hospital admission in the last months (OR 0.80; CI 0.65–0.98) was significantly associated with lower mortality.
Interpretation: In-hospital mortality has decreased in patients with COVID-19 over the last, few months, even though main patient characteristics remain similar. Several changes made when managing patients may explain this decreasing trend. Our study provides current data on mortality of patients hospitalised with COVID-19 that might be useful in establishing quality of standard of care.
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RESUMEN

Contexto: Nuestro objetivo es describir los cambios en las características y las estrategias de tratamiento de los pacientes hospitalizados por COVID-19, y detallar la tendencia de la mortalidad en el tiempo.
Métodos: Estudio observacional de cohortes de todos los pacientes consecutivos, ingresados por COVID-19 durante más de 48 horas, en el Hospital Clínic de Barcelona (del 1 de marzo al 30 de septiembre de 2020).
Resultados: Un total de 1645 pacientes consecutivos fueron evaluados durante un período de 7 meses. La mortalidad global (≤30 días) fue del 9.7% (159 pacientes): 7.7% en pacientes hospitalizados en salas convencionales, y 16.7% en pacientes que requirieron ingreso en UCI. La mortalidad global disminuyó del 11.6% en el primer mes al 1.4% en el último mes evaluado, reflejando una progresiva y significativa tendencia a la baja (p para la tendencia <0.001). La edad de los pacientes ha cambiado con el tiempo, habiendo alcanzado su pico en junio. La mayoría de cambios en el uso de antivirales y antiinflamatorios se han documentado. La edad (OR 1.1; CI 1.1–1.12), cardiopatía crónica (OR 1.7; CI 1.1–2.9), dímero-D>700 ng/mL (OR 2.3; CI 1.3–4.1), ferritina>489 ng/mL (OR 1.9; CI 1.5–3.2), PCR>7 mg/dL (OR 2.6; CI 1.5–4.6), y una menor duración desde el inicio de síntomas a la hospitalización (OR 1.11; CI 1.04–1.17) fueron factores asociados a la mortalidad intrahospitalaria a 30 días. Por el contrario, el ingreso hospitalario previo en los últimos meses (OR 0.80; CI 0.65–0.98) se asoció significativamente a una menor mortalidad.
Discusión: La mortalidad intrahospitalaria ha disminuido en los pacientes con COVID-19 durante los últimos meses, incluso siendo similares las características de los pacientes. Algunos cambios realizados en el manejo de estos pacientes podrían explicar esta tendencia decreciente. Nuestro estudio aporta datos actualizados en la mortalidad de los pacientes hospitalizados con COVID-19, que podrían ser útiles de cara a establecer unos cuidados estándar de calidad.
Financiación: EIT Health, European Union's Horizon 2020 Research and Innovation Programme, EDRD. PPA [CM18/00132], NGP [FI19/00133] y CGV [FIS PI18/01061], han recibido becas del Ministerio de Sanidad y Consumo, ISCIII.

Research in context

Evidence before this study

We searched PubMed for articles that documented risk factors for ICU admission and mortality in patients with COVID-19, as well as treatment options. We used the search terms ("SARS-CoV-2" OR "COVID-19") AND ("death" OR "mortality" OR "ICU" OR "treatment" OR "management"), with no language or time restrictions. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become the primary cause of global mortality due to infectious diseases in the world. Overall mortality in cohorts of patients hospitalised with coronavirus disease 2019 (COVID-19) ranged from 28% to 39%. However, there is a lack of clinical studies describing changes over months in COVID-19 management and their impact on mortality trends in real-life patients with COVID-19.

Added value of this study

This is the first study to describe how in-hospital mortality in patients with COVID-19 has decreased over months, even though main patient characteristics remain similar.

Implications of all the available evidence

We detail several changes made when managing patients with COVID-19 that may explain the decreasing in-hospital mortality trend. Our study provides current data on mortality for patients hospitalised with COVID-19 that might prove useful in establishing quality of standard of care.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a leading cause of death due to infectious diseases. In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) occurred, reaching Spain by the end of February. This infection has been a major challenge for both health care professionals and health systems, with high morbidity and mortality [1–5].

However, our understanding of COVID-19 has rapidly improved. Antiviral treatment options have been better defined and the use of anti-inflammatory therapies and personalised approaches has shown to improve outcomes [6–8]. Yet, there is a lack of clinical studies describing changes over months in COVID-19 patients' characteristics and management and their impact on mortality trends in real-life. Such descriptions of mortality rates in current patients with COVID-19 are mandatory, should we aim to place into perspective results obtained from different studies, including trials, that have been carried out during different moments of the pandemic. Further, knowledge of current mortality rates and patient characteristics may serve as references for establishing quality of care.

Our study aimed to provide current data on updated mortality for patients hospitalised with COVID-19. The study also aimed to describe changes over time in characteristics and treatment strategies pertaining to patients with COVID-19 and define risk factors for mortality at hospital admission.

2. Methods

2.1. Study design and patients

This observational cohort study was performed at Hospital Clinic in Barcelona (Spain), a 700-bed university centre that provides broad and specialised medical, surgical, and intensive care for an urban population of 500,000 adults (>18 years old). All patients admitted for COVID-19 for ≥48 h between 1 March and 30 September 2020, were included. Clinical outcomes were monitored until 1 November 2020. All patients had a COVID-19 diagnosis confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) testing performed on nasopharyngeal throat swab specimens, and/or by fulfilling clinical diagnostic criteria provided during the pandemic peak for SARS-CoV-2 (March 2020 to May 2020). These criteria comprised the

presence of any of the following respiratory symptoms, including sore throat, congestion, cough, dyspnoea, new loss of taste and/or smell, as well as uni- or bilateral interstitial infiltrates in chest X-rays. Early mortality was defined as death within the first 5 days of admission. The Institutional Ethics Committee of Hospital Clinic of Barcelona approved the study and due to the nature of the retrospective data review, waived the need for informed consent from individual patients (HCB/2020/0273).

2.2. Data collection and outcomes

For all patients hospitalised with COVID-19, data concerning demographics (age, gender), epidemiology, comorbidities, laboratory tests, microbiological results, treatment, and outcomes were collected directly from electronic health records (EHR). An intelligent system was used to retrieve the high-quality data from EHRs (SILDv1.0 system, S34M®) as described elsewhere [9].

2.3. Statistical analysis

Data are presented as percentages and numbers, means with SDs, medians and interquartile ranges (IQRs), or proportions and 95% CIs. Accordingly, the chi-squared test for equal proportion, *t* test, and Mann–Whitney *U* test were used to examine differences. To reduce the variability and noise of random in day-by-day data, we divided the study duration into month-defined timespans, setting March 2020 as the reference period.

To assess factors related with 30-day mortality at hospital admission, a multivariate regression model (step-forward procedure) was constructed using all variables significantly associated with mortality in univariate analyses. These variables included age, month of hospital admission, chronic heart disease, diabetes mellitus, haematological diseases, chronic kidney disease, hypertension, solid cancer, chronic lung disease, a respiratory rate higher than 20, oxygen saturation < 94%, D-dimer levels higher than 700 ng/mL, a lymphocyte count lower than 0.7 (10^9/L), LDH levels higher than 330 U/L, ferritin levels higher than 489 ng/mL, C-RP higher than 7 mg/dL, and days from symptom onset. Cut-off values were selected after analysing medians for each variable in patients who died, compared with those who survived. Laboratory markers were obtained at COVID-19 diagnosis. A second multivariate analysis was also performed with analytics as a continuous value. Adequacy of the models were assessed with the Hosmer–Lemeshow goodness-of-fit test and the area under the receiver operating characteristic curve was used to measure the predictive ability of the model. Potential confounders were investigated. Significance was set at a *p*-value of <0.05. Statistical analyses were performed with Microsoft SPSS-PC+, version 23.0 (SPSS, Chicago, IL, USA).

2.4. Role of the funding source

No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

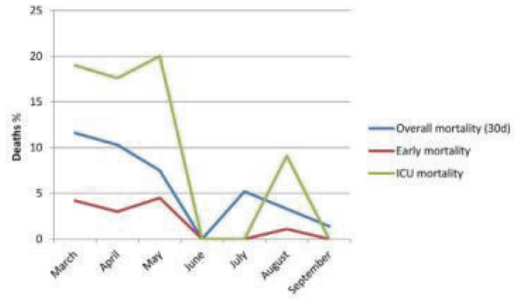

Fig. 1. Overall mortality trends for patients admitted with COVID-19 (distribution by months).

3. Results

3.1. Mortality trends

We assessed 1645 consecutive adults, 88.4% Caucasians, with COVID-19 at our hospital during the study period. Overall mortality (≤30 days) was 9.7% (159 patients), 7.7% in patients hospitalised in regular wards and 16.7 % in patients requiring ICU admission. Early mortality (5 days from admission) was 3.2% (53 patients). Furthermore, 60- and 90-day mortality were 10.8% (178 patients) and 11.4% (187 patients), respectively. Fig. 1 details the unadjusted overall mortality rates, with a reported 11.6% in the first month and 1.4% in the last month, and reflecting a progressive, significant downward trend (p for trend <0.001). Trends for ICU mortality (19.1% in the first month and 0% in the last month; *p* for trend 0.021) and early mortality (4.2% in the first month and 0% in the last month; *p* for trend 0.004) were also in decline. Table 1 details mortality by 10-year age intervals throughout the study period. Supplementary Tables 1 and 2 describe 60-day and 90-day mortality by age intervals.

3.2. Changes over time in patient characteristics and COVID-19 management

Table 2 details the main changes in epidemiologic characteristics throughout the study period. Mean age of patients changed significantly, peaking in June. Sex and comorbidity remained stable, as well as days from symptom onset to hospital admission. With respect to laboratory tests, ferritin and LDH levels gathered at admission were significantly higher in the final months whilst D-dimer levels were significantly higher within the first, few months of the pandemic. Further, lymphocyte count also significantly varied throughout the months, with the highest values recorded in June and July. Highest values registered for C-RP during hospital admission were in March and April. Regarding vital signs, variations in temperature were

Table 1
30-day mortality by 10-year age intervals throughout the study periods.

30-day mortality (%)	Period 1 March (*n*=810)	Period 2 April (*n*=504)	Period 3 May (*n*=67)	Period 4 June (*n*=22)	Period 5 July (*n*=77)	Period 6 August (*n*=91)	Period 7 September (*n*=74)	*p*
<40 y	1/90 (1%)	0/55 (0%)	0/9 (0%)	0/6 (0%)	0/14 (0%)	0/13 (0%)	0/7 (0%)	0•465
40–49 y	1/105 (1%)	0/62 (0%)	0/7 (0%)	0/0 (0%)	0/18 (0%)	0/12 (0%)	0/17 (0%)	0•474
50–59 y	6/155 (4%)	4/86 (5%)	0/7(0%)	0/4 (0%)	0/17(0%)	0/12(0%)	0/19(0%)	0•173
60–69 y	9/180 (5%)	8/90 (9%)	0/14 (0%)	0/2 (0%)	0/8 (0%)	0/25 (0%)	1/11 (9%)	0•482
70–79 y	38/186 (20%)	9/84 (11%)	2/10 (20%)	0/6 (0%)	1/11 (9%)	1/15 (7%)	0/11 (0%)	0•012
80–89 y	31/80 (39%)	22/94 (24%)	2/11 (18%)	0/3 (0%)	1/5 (20%)	2/12 (17%)	0/8 (0%)	0•005
>90 y	8/14 (57%)	9/33 (27%)	1/9 (11%)	0/1 (0%)	2/4 (50%)	0/2 (0%)	0/1 (0%)	0•133
All patients	94/810 (11•6%)	52/504 (10•3%)	5/67 (7•5%)	0/22 (0%)	4/77 (5•2%)	3/91 (3•3%)	1/74 (1•4%)	<0•001

Table 2
Changes in clinical characteristics of 1645 consecutive adults with COVID-19, divided by study periods.

	Period 1 March (*n*=810)	Period 2 April (*n*=504)	Period 3 May (*n*=67)	Period 4 June (*n*=22)	Period 5 July (*n*=77)	Period 6 August (*n*=91)	Period 7 September (*n*=74)	*p*
Patient characteristics								
Age-Median (IQR), in years	63 (51–74)	65 (53–81)	67 (53–84)	68 (33–79)	55 (45–72)	64•5 (50–72)	59 (45–72)	0•003
Age > 65 years (%)	48•5	52	55	57	32•5	50	32	0•018
Sex male, *n* (%)	60	54	49	48	58	53	61	0•404
Comorbidities (%)								
Hypertension	47	50	63	38	44	45	36•5	0•189
Diabetes mellitus	20	21	25	19	23	19	19	0•940
Chronic heart disease	24	3	46	33	18	26	19	0•775
Chronic lung disease	22	24	22	43	27	23	18	0•957
Chronic liver disease	6	5	6	0	5	3	1	0•076
Chronic kidney disease	12	14	24	9•5	8	12	7	0•340
Solid cancer	14	17	19	14	9	21	16	0•348
Haematological diseases	7	8	7•5	5	8	12	4	0•739
Solid organ transplantation	3	3	4•5	0	1	3	1	0•463
HIV	2	2	3	0	4	1	1	0•908
Symptom onset to hospital admission – Median (IQR), in days	7 (4–9)	7 (7–10)	7 (4•5–11)	7 (6–14)	6 (4–9)	5•5 (4–9)	7 (6–10)	0•502
Vital signs at admission; Median (IQR)								
Temperature – Median (°C)	37•3 (36•8–38•2)	36•9 (36•3–37•6)	36•8 (36•2–37•45)	37•2 (36•9–37,85)	37•2 (36•475–38•125)	37•35 (36•8–38•275)	36•75 (36•425–37•975)	<0•001
Respiratory rate – Median (rpm)	20 (18–24)	20 (18–24)	20 (18–26•5)	22 (18–31)	20•5 (18–26)	20 (19–25•5)	23 (20–27•5)	0•112
Respiratory rate > 20 (%)	55	59	43	37	62	61	66	0•106
Oxygen saturation[a] – Median	95 (93–96)	95 (94–97)	95 (93–98)	95 (92–95•5)	95 (94–96)	94 (92–96)	94•5 (92•25–96•75)	0•028
Oxygen saturation[a] < 94% (%)	43	32	30	32	27	40	39	0•102
Laboratory values at admission; Median (IQR)								
Ferritin (ng/mL)	643 (286–1279)	447 (246–1103)	184 (123–482)	296 (192•50–354)	474•50 320–1044)	808 (420•5–1361)	704 (289–1356•50)	<0•001
C-RP (mg/dL)	8,22 (3•92–14•10)	8•17 (4•02–15•45)	4•69 (2•29–12•44)	7•53 (4•48–13•41)	6•16 (4•00–12•86)	9•51 (5•965–16•875)	8•355 (3•375–13•820)	0•148
D-dimer (ng/mL)	800 (400–1300)	900 (500–1750)	1300 (650–4450)	600 (500–1000)	450 (375–925)	500 (300–1750)	600 (400–900)	<0•001
LDH (U/L)	327 (251•50–411•50)	297 (239–384)	255 (202–315)	246 (209–292)	323 (261–376)	322•5 (268–379)	295•5 (234–373•5)	<0•001
Procalcitonin (ng/mL)	0•12 (0•06–0•23)	0•11 (0•05–0•24)	0•17 (0•05–0•59)	0•03 (0•015–0•075)	0•085 (0•05–0•15)	0•135 (0•055–0•23)	0•08 (0•06–0•18)	0•156
Lymphocyte count	0•8 (0•6–1•2)	0•8 (0•6–1•1)	0•9 (0•7–1•6)	1•3 (0•95–1•5)	1•1 (0•8–1•4)	0•9 (0•5–1•3)	0•9 (0•7–1•1)	<0•001
C-RP at its highest during hospitalisation ≥ 15 (%)	43	37	31	42	33	34	33	0•008
C-RP at its highest during hospitalisation; median (IQR)	13 (7–20)	11 (6–19)	11 (4–17)	9•5 (3–20)	10 (5–19)	10 (6–17)	10 (5–18)	0•042

[a] These measurements were taken on room air at time of admission.

documented over time and no clear trend was observed. Oxygen saturation levels were at their poorest in the last, few months of the study.

Additionally, Table 3 details the main changes in treatments administered to patients throughout the study period. Antiviral approaches initially included hydroxychloroquine and lopinavir/ritonavir. However, use of such drugs decreased throughout the months and use of remdesivir became more prevalent. Time from symptom onset to remdesivir use decreased throughout the months. With respect to immunomodulatory approaches, some changes in corticosteroid use were documented, with dexamethasone progressively replacing methylprednisolone. The use of tocilizumab varied throughout the months, and the use of antibiotics significantly decreased. Supplementary table 3 details differences in treatments between ward and ICU patients.

A significant, declining trend was observed in patients either requiring ICU admission or who underwent invasive mechanical ventilation. ICU mortality, early mortality, and 30-day mortality significantly declined over time.

3.3. Factors associated with mortality at hospital admission

Independent factors associated with 30-day mortality at hospital admission were age (OR 1.1, CI 1.1–1.12), the presence of chronic heart disease (OR 1.7, CI 1.1–2.9), D-dimer levels higher than 700 ng/mL (OR 2.3, CI 1.3–4.1), ferritin levels higher than 489 ng/mL (OR 1.9; CI 1.5–3.2), C-RP higher than 7 mg/dL (OR 2.6; CI 1.5–4.6) and shorter duration from symptom onset to hospital admission (OR 1.11; CI 1.04–1.17). Conversely, hospital admission within the last, few months was significantly associated with lower mortality (OR 0.80; CI 0.65–0.98). The goodness-of-fit of the model was assessed with the Hosmer–Lemeshow test (p=0.791). The discriminatory power of the model, as evaluated by the area under the receiver operating characteristic curve, was 0.886 (95% CI, 0.86–0.92), demonstrating an excellent ability to predict 30-day mortality at hospital admission.

A second multivariate analysis including analytics as a continuous variable showed similar results. Independent risk factors associated with 30-day mortality at hospital admission were age (OR 1.1, CI 1.1–1.12); the presence of chronic kidney disease (OR 2.1, CI 1.2–3.7); LDH values (OR 1.01; CI 1.0–1.2); C-RP values (OR 1.1; CI 1.04–1.1) and shorter duration from symptom onset to hospital admission (OR 1.2; CI 1.1–1.2). Conversely, hospital admission within the last, few months was significantly associated with lower mortality (OR 0.81; CI 0.66–0.99). The goodness-of-fit of the model was assessed with the Hosmer–Lemeshow test (p=0.734). The discriminatory power of the model had an area under the receiver operating characteristic curve of 0.867 (95% CI, 0.838–0.896), demonstrating an excellent ability to predict 30-day mortality at hospital admission as well.

4. Discussion

This study is the first of its kind to include all consecutive patients with COVID-19 hospitalised for more than 48 hours and details a marked and decreased trend in 30-day mortality. Despite the fact that most countries have reported a decrease in mortality of patients with COVID, perhaps due to massive screening tests implemented to identify large numbers of patients with asymptomatic or mild infections and stop the pandemic [10], data concerning mortality rates in hospitalised patients are scarce. Three studies have reported a decreasing trend in mortality in patients with COVID-19. The first explored hospital mortality in 5121 patients from three academic hospitals in New York City, observing a decrease in mortality from 25.6% in March to 7.6% in August [11]. The second study reported a decreasing mortality amongst critically ill adults with COVID-19 from Emory Hospital in Atlanta, from 34.3% in March to 26.9% in July [12]. Finally, in a third study reporting mortality amongst 21,082 patients admitted to a high-dependency unit or ICU from March to June, rates decreased from 28.4% to 7.3% and 42% to 19.6%, respectively [13]. Our mortality rates significantly declined from the first wave period (March to May) to the second one. No significant differences were detected in the population aged <70 years, as the mortality rate in this group was low in both periods. In contrast, a significant reduction was observed in the subgroup of patients aged between 70–79 years and 80–89 years. In May 2020, Richardson et al. [14] reported the following mortality rates by age group: more than 63% in patients aged ≥ 90 years; 60% in patients aged 80–89 years; and 36% in patients aged 70–79 years. Our current mortality rates extremely differ. Between June and September 2020, only 7 of 79 (8.8%) patients older than 70 years who were admitted to our hospital died. However, it is important to consider differences in patient admission per month.

Potential explanations for the mortality declining in our institution include: 1) overall improvements in medical skills within these last several months; 2) better health care organisation and, as a result, avoidance of a system overload; 3) a change in patient characteristics; 4) the presence of viral variants with less pathogenicity; and/or 5) changes in treatment strategies.

The overload of patients and ICU capacity during the first wave of the pandemic could explain the high mortality rates reported worldwide; however, our institution was able to double the ICU capacity, which could partially explain the low mortality rate in our centre yet not its progressive, declining trend entirely. Similarly, no significant differences were observed in patient comorbidities, whilst the mean age of patients oscillated during the study period, peaking in June and slowly decreasing thereon. As age is one of the biggest driver of mortality in COVID-19 [14], this could be an explanation for the overall mortality rate. Yet, when we examined mortality by age groups, the reduction was observed in all strata. D-dimer and C-RP levels at onset were higher during the first, few months of the pandemic; however, several other factors with negative prognostic influence have been more frequently documented in recent admissions (e.g. higher levels of ferritin and/or LDH, and more cases of hypoxia at admission). Accordingly, it is difficult to confirm whether patient severity has changed during the study period. The spread of viral variants with less pathogenicity was described in Singapore [15]; however, since February 2020, the dominant virus variant in Europe has the G614 form of the Spike protein [16]. No data about the potential variation in the virulence of this variant has been described, although G614-bearing viruses have shown significantly higher infectious titres in vitro than D614 counterparts [16]. This phenomenon is, therefore, unlikely to explain variations in mortality.

We did observe major changes in treatment strategies that may explain the better outcomes. Our experience documented that the use of remdesivir substantially increased over time, and time from symptom onset to initial doses of remdesivir shortened. Other antivirals such as lopinavir/ritonavir or hydroxychloroquine have disappeared. Although some adverse events have been related with these drugs, namely cardiac events with hydroxychloroquine, we reviewed our experience and did not observe an increased mortality in this population (data not published).

Remdesivir has shown a reduction in mortality rate in the subgroup of patients with pneumonia and low-flow oxygen [7]. Along the same line, the impact of remdesivir on reducing viral shedding has been reported in macaques [17]; however, studies powered to assess the impact of such a finding on infection transmissibility and/or severe complications, such as coagulopathy or hyperinflammation, in infected humans are lacking. We observed a significant increase in the use of remdesivir during the second period. We cannot directly attribute changes in mortality rate to the increase in remdesivir use, as this is not a randomised study; however, mortality rate in our

Table 3
Changes in treatments and outcomes of 1645 consecutive adults with COVID-19, divided by study periods.

	Period 1 March (*n*=810)	Period 2 April (*n*=504)	Period 3 May (*n*=67)	Period 4 June (*n*=22)	Period 5 July (*n*=77)	Period 6 August (*n*=91)	Period 7 September (*n*=74)	*p*
Treatment								
Antiviral effect								
Remdesivir (%)	7	3	3	19	62	53	36•5	<0•001
Symptom onset to initiating treatment with remdesivir (median, IQR)	10 (7–12)	10 (6•5–12)		15 (8–19)	6•5 (4–9)	6 (4–8•5)	8 (7•5–9)	<0•001
Lopinavir/ritonavir (%)	92	69	42	9•5	1	0	0	<0•001
Hydroxychloroquine (%)	96	85	51	0	0	1	0	<0•001
Anti-inflammatory effect								
Any anti-inflammatory treatment (%)	56	57	43	33	57	48	50	0•069
Tocilizumab (%)	28•5	34	7•5	5	30	10	7	<0•001
Symptom onset to initiating treatment with tocilizumab (median, IQR)	10 (7–12)	9 (7–12)	13 (11–13)	–	9 (6–10)	8 (6–11)	13 (1–14)	0•127
C-RP median (IQR) at initiation of tocilizumab treatment	13 (8–20)	14 (9–20)	13 (7–20)	–	13 (8–18)	14 (8–20)	23 (15–27)	0•762
Any anti_IL-6*(%)	32	34	7•5	5	30	10	7	<0•001
Anakinra (%)	6	13•5	3	5	6•5	3	0	0•036
Methylprednisolone (%)	36	31	27	29	13	20	9•5	<0•001
Symptom onset to initiating treatment with methylprednisolone (median, IQR)	10 (7–14)	10 (6–13)	8 (4–12)	7 (7–7)	14 (7–18)	16 (5–24)	10 (4–19)	0•363
C-RP median (IQR) at initiation of methylprednisolone treatment	12 (7–19)	11 (6–18)	11 (5–14)	10 (0–22)	3 (1–5)	3 (1–6)	8 (4–12)	0•002
Dexamethasone (%)	6	5	3	5	38	31	31	<0•001
Symptom onset to initiating treatment with dexamethasone (median, IQR)	9 (6–13)	11•5 (7•5–13)	–	–	8 (5–10)	8 (5–10)	10 (8–13)	0•009
C-RP median (IQR) at initiation of dexamethasone treatment	14 (9–22)	13 (6–25)	–	–	11 (5–17)	14 (6–19)	12 (2–23)	0•521
Prednisone (%)	22	24	28	29	17	24	19	0•834
Oxygen therapy								
Any oxygen support (%)	28 (229/810)	42 (211/504)	42 (28/67)	36 (8/22)	40 (31/77)	37 (34/91)	32 (24/74)	0•027
Need of high flow oxygen (%)	3 (26/810)	2 (9/504)	0 (0/67)	9 (2/22)	3 (2/77)	7 (6/91)	3 (2/74)	0•370
Antibiotic treatment								
Ceftriaxone (%)	73	55	49	48	32•5	42	45	<0•001
Ceftaroline (%)	6	2	3	0	9	8	8	0•223
Outcomes								
Length of hospital stay; Median (IQR)	8 (5–14)	9 (6–14)	8 (5–12)	8 (4–10•5)	7 (5–10)	7 (5–11)	8 (5–12)	0•345
ICU admission (%)	24	20	22	24	12	24	15	0•048
Need of VM (%)	12	8	3	5	1	8	4	<0•001
ICU mortality (%)	19	18	20	0	0	9	0	0•023
Early mortality (%)	4	3	4•5	0	0	1	0	0•004
30-day mortality (%)	11•6	10•3	7•5	0	5•2	3•3	1•4	<0•001

hospitalised patients was <5% during the second period, in line with that reported in similar patients included in the ACTT-1 study [7].

Anti-inflammatory therapy has demonstrated a reduction in the mortality rate [8,18]. We therefore cannot attribute such reduction to a change in anti-inflammatory therapies; more details concerning the type of drug and moment of administration could be important, though. In an open-label, randomised trial comparing dexamethasone use vs. routine care in 2104 patients with a mean age of 67 years and 4321 patients, respectively, dexamethasone use resulted in lower 28-day mortality in those individuals receiving oxygen therapy. Most patients undergoing routine care did not receive any anti-inflammatory treatment. In the dexamethasone group, 28-day mortality was 22.9%, which is quite high when compared to our current rates. Trials assessing the utility of tocilizumab in patients with COVID-19 have not reported declining mortality [19–21], although some significant benefits have been observed. These trials are difficult to analyse due to factors such as the low number of patients included, especially when the routine care arm includes a high number of patients treated with other anti-inflammatory therapies; differences in baseline patient characteristics across groups, namely age; and a high number of patients who had been rescued with tocilizumab in the non-tocilizumab arm. It is worth mentioning that our study showed differences in ICU and non-ICU patients receiving anti-inflammatory and remdesivir treatment.

Improvements in general management of our cohort of patients hospitalised with COVID-19, including antiviral and anti-inflammatory therapies, are evident. The highest serum concentration of C-RP achieved during hospital admission and the need for ICU admission have also significantly decreased throughout the study period.

Risk factors for mortality at hospital admission have been previously described [3,14]. Our study is in agreement with results from these reports and provides two additional, important variables related with mortality: the impact of hospital admission during the first, few months of the pandemic and duration of symptom onset. In our study, those patients admitted with shorter duration of symptom onset independently had higher mortality. This fact may be related with a higher viral load in this population. Unfortunately, this variable was not available for the present analysis. Further studies evaluating the impact of this finding are warranted.

The strengths of this study include the high number of consecutive patients and compressive data collection. However, there are several limitations. First, the study was conducted in a single centre from Spain, where the public health system attends to all patients equally. This fact may make generalisation of our results difficult. Second, our data were collected directly from EHRs. Nonetheless, it is important to note that our hospital used an intelligent system to retrieve data from EHRs (SILDv1.0 system, S34M®). The data review process, which includes nine quality steps, ensures high quality of our data. Finally, since the end of March, we have implemented a programme that, under the supervision of infectious disease experts, comprises a computer-control centre for patients with COVID-19 that uses real-time data from EHRs to support attending physicians with different skill sets to provide quick, personalised medicine to our patients. The impact of this measure is difficult to assess, but as we have reported, has been related with better outcomes [6].

In conclusion, mortality in hospitalised patients with COVID-19 has decreased throughout these last several months, even though main patient characteristics remain similar except for age oscillating during the study period. Several changes made in patient management had been detailed, impacting a decreasing trend in 30-day mortality over various months, especially in elderly patients. Our study provides current data on mortality for patients hospitalised with COVID-19 that may be useful in establishing quality of standard of care.

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Declaration of Interests

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Supplementary materials

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5.

DISCUSSION

Infection by Coronavirus 2 (SARS-CoV-2) emerged in December 2019 in Wuhan and rapidly spread around the world. SARS-CoV-2 is characterized by a high viral replication during the first days associated to a range of clinical manifestations from asymptomatic or mild to classical symptoms including fever, bad general status, myalgia, and cough. More than 80% of the infected patients have a self-limited infection but 15-20% develop a severe pneumonia and require hospital admission. In contrast to other respiratory virus, bacterial co-infection is not a major cause of hospitalisation, but it is characterized by a progressive respiratory failure, and bilateral infiltrates in the X-ray that resembles an adult distress respiratory syndrome.(10) This clinical pattern associated with severe lymphopenia and high C-reactive protein and other raised inflammatory parameters suggests that this corresponds to the cytokine release syndrome.(145)

When a pandemic from a novel virus begins, the definition of best clinical management and treatment strategy can be a challenge. It is important to highlight that thanks to previous investigations, specially of other coronavirus, some of important virus characteristics were already started to be studied, and even some treatment that were studied for other viruses could be studied for the emergent pandemic. Of note, this thesis described mainly the first year of COVID-19 pandemic and it is remarkable how much things have changed since then.

Treatments that were used during the first months, with only the preclinical information on activity for coronavirus such as hydroxychloroquine, azithromycin, lopinavir-Ritonavir had already been confirmed in human clinical trials as non-effective treatments for COVID-19 and are no longer recommended.

COVID-19 is also characterized by an exaggerated inflammatory response mediated by an excessive production of interleukin-6 (IL-6) and other pro-inflammatory cytokines.(61) The clinical success of several therapeutic approaches has served as a proof of concept for the involvement of this cytokine storm in the pathogenesis of respiratory deterioration and progression to ARDS in patients with COVID-19. A number of comparative observational studies have suggested that in patients with severe or worsening SARS-CoV-2 pulmonary disease, tocilizumab, a monoclonal antibody directed against the IL-6 receptor, may decrease the need for mechanical ventilation and improve survival.(109,126)

During the course of the pandemic the use of anti-inflammatory treatments also changed. Strategies with anti-IL-6 inhibitors such as tocilizumab or siltuximab have had different results in clinical trials and currently the recommendation for its use should be individualized.(98)

In our article “Experience with the use of siltuximab in patients with SARS-CoV-2 infection” we discuss the role of monoclonal antibodies directed against key inflammatory cytokines as a class of adjunctive therapies for SARS-CoV-2 infected patients. The rationale for their use is that the underlying pathophysiology of significant organ damage in the lungs is caused by a cytokine storm, being IL-6 one of the key drivers. Therefore, monoclonal antibodies against IL-6 could theoretically improve clinical outcome. Many observational studies have demonstrated a potential efficacy of blocking the IL-6 pathway mainly using tocilizumab (146,147), in contrast, randomised trials have shown negative results in terms of reduction of mortality, but one has demonstrated a reduction in the risk of ICU admission.(109) Siltuximab was administrated to 31 patients with severe COVID-19 and the results when it was administered as a first line option were similar to those reported in our cohort using tocilizumab in the same indication.(148) As it would be expected, those patients that received siltuximab as a salvage therapy had a significantly worse outcome. Considering the mechanism of action of monoclonal antibodies, now it seems not reasonable to use it as a salvage therapy, and when the patient is not responding to the IL-6 inhibition, probably these patients are not responding to IL-6 inhibition due to a different pathogenic mechanism that requires further investigation, including co-bacterial infection, thrombosis or macrophage activation syndrome that require different treatment approaches.(149)

Later studies showed that the use of Baricitinib in combination with remdesivir had a positive result on patient outcome on a clinical trial, particularly those receiving high-flow oxygen or non-invasive ventilation.(117)

In addition, the role of corticosteroids use was finally defined. A randomised clinical trial has proved that dexamethasone reduces mortality in patients requiring respiratory support.(102) As a possible complication of these immunomodulatory treatments the incidence of secondary infections and co-infections related to COVID-19 started to be better understood, even with the description of an infection-related syndrome, the

COVID-19 Associated Pulmonary Aspergilloses (CAPA) with particular risk factors and manifestations.(150)

Regarding the risk of hospital acquired infection in our article “Impact of Inflammatory Response Modifiers on the Incidence of Hospital-Acquired Infections in Patients with COVID-19”, we found as the main result that there was no evidence of any deleterious influence of inflammatory response modifiers on the incidence of hospital-acquired infection in admitted patients with SARS-CoV-2 infection. In our experience, nosocomial infections in patients with COVID-19 primarily occurred in the critically ill, and mechanical ventilation was the only significant exposure conferring risk.(151)

Data comparing the incidence of nosocomial infections in patients with severe COVID-19 between those treated and not treated with inflammatory response modifiers are relatively scarce. Several comparative retrospective studies have described a higher rate of infections in patients receiving tocilizumab than in controls. Somers et al.(130) observed a significantly increased rate of superinfection in treated patients (54% vs 26%; $p < 0.001$), mostly due to a higher incidence of VAP. However, no differences between groups with regards to the frequency of bloodstream infections or development of more than one infection was observed. Guaraldi et al.(131) also observed an increased rate of hospital-acquired infections in patients treated with tocilizumab versus those in the standard of care group (13% vs 4%, $p < 0.001$), including four cases of invasive aspergillosis in the tocilizumab group and none in the standard of care. Kimmig et al. (132) reported a higher incidence of bacterial infections in patients receiving tocilizumab (adjusted OR 2.76, 95% CI 1.11–7.2), with all fungal infections occurring in the actively treated group. Lewis et al. (133), in a propensity-matched cohort study, also found an increased adjusted rate of secondary infections (OR 4.18, 95% CI 2.72–6.52) due to a higher incidence of bloodstream infections, pneumonia, and urinary tract infections. Lastly, Pettit et al. (134) reported an increased rate of late-onset infections in patients receiving tocilizumab (23% vs 8%, $p = 0.013$). Conversely, a higher rate of infections in patients taking tocilizumab was not observed in 14 prospective studies, including eight randomised controlled trials.(109,110,124,126,129,152–155) The reasons for these discrepancies are not clear, but it can be speculated that the survival benefit associated with tocilizumab in several retrospective studies (130,131,133) could actually have prolonged the time at risk in this population and therefore the likelihood of getting an infection.

Our data suggests that when time at risk and other general predisposing factors (presence of any comorbidity and need for ICU admission) are similar between infected and not infected patients, no evidence of an increased risk of infection associated with exposure to biologics can be found. This also agrees with the lack of evidence of a higher risk of infection associated with a short (1–3 doses) exposure to tocilizumab in severely immunosuppressed patients with chimeric antigen receptor (CART) T cell-mediated cytokine release syndrome.(156)

Data regarding other interleukin blockers are still sparse. Although IL-1 inhibitors (anakinra), like IL-6 blockers, have been associated with an increased rate of usually mild to moderate infection in the long-term treated patients with rheumatoid arthritis, no such increase has been observed with short-course regimens used for the therapy of patients with COVID-19 (115,129) or of those with gout or sepsis(157,158). Lastly, in regard to corticosteroids, it is of note that despite their downregulation effect on the synthesis of pro-inflammatory cytokines and on the function of virtually any cell involved in the sensing of or response to invading microorganisms(158), their role as a risk factor for superinfection following short-term exposure is probably negligible. Several randomised clinical trials have assessed the therapeutic role of corticosteroids on COVID-19, and none of them reported a significantly higher incidence of superinfections in actively treated patients.(102,105,107,159,160) This agrees with many randomised clinical trials conducted to evaluate the effect of acute exposure to corticosteroids on patients with sepsis or ARDS. The summarized evidence from these trials indicates that there is no association of corticosteroids with superinfection, regardless of the type of drug or specific regimen.(161–163)

The present study suggests a possible protective effect of hydroxychloroquine on the acquisition of hospital-acquired infections, although the variable was retained in the multivariate model with borderline significance. This finding is intriguing and difficult to explain. Hydroxychloroquine accumulates in the lysosomes and other cellular organelles and neutralizes their acidic pH. This property endows the drug with in vitro activity against many viruses, as well as bacteria and fungi located in the appropriate intracellular environment, where a synergistic effect with several antimicrobial agents may occur.(164) However, in the clinical setting, hydroxychloroquine combined with appropriate antibiotics has proved to be critically effective only for the treatment of Q

fever and Whipple disease. Actually, after much initial discussion and several randomised clinical trials, hydroxychloroquine has proved to be ineffective for both prevention and treatment of COVID-19.(165) We cannot discard that the association of less hydroxychloroquine exposure with acquisition of nosocomial infections observed in our study stemmed from a possible more severe condition of case patients.

The present study was intended to assess the possible influence of inflammation-response modifiers on the rate of hospital-acquired infections, not to evaluate the relative incidence of nosocomial infection in patients with SARS-CoV-2. Currently, there is no definitive answer to this issue, due mainly to a substantial lack of comparative data between patients with COVID-19 and appropriate controls without SARS-CoV-2 infection.(166–170) The available evidence suggests that patients with COVID-19 do not seem to be particularly prone to acquire nosocomial bacterial infections or invasive candidiasis. However, an increased incidence of invasive aspergillosis among intubated patients with COVID-19 cannot be completely dismissed.(150,171)

Our study has the common drawbacks of being relatively small, unicentric, and observational. In addition, matching was not wholly successful, exposure to intravenous and urinary catheters was not documented, and the duration of exposure to inflammatory response modifiers was not systematically registered. Moreover, we limited follow-up to the length of hospital stay; hence late-onset infections possibly related to past exposure to biologics or corticosteroids, such as tuberculosis, were not assessed. A last concerning issue is the possibility of misclassification bias of true bacterial or fungal infections, particularly those of pulmonary location, by using common clinical or radiological surveillance criteria in a population already overwhelmed with basal and evolving radiological chest abnormalities and high inflammatory markers. We tried to retain diagnostic specificity by including the requirement of microbiological documentation and directed antibiotic therapy as additional criteria to ascertain cases and distinguish them from controls.(151)

The antiviral treatments also advanced and new strategies not available during the first months of the pandemic started to be approved and some even lost their approval later on due to new evidences such as Molnupiravir or due to the emergence of resistant variants, in the case of mAbs.(30,83,90,100)

With respect to remdesivir, our article "Real-life use of remdesivir in hospitalised patients with COVID-19", was the first report to assess the efficacy and tolerability of remdesivir in a real-life cohort of patients with COVID-19, including those with cancer or haematological disease. Our results documented a low mortality rate (4.1%) in hospitalised patients receiving remdesivir for severe pneumonia due to SARS-CoV-2. This rate is in line with that reported in the ACTT-1 study that randomised patients to remdesivir or placebo.(78) Our patients mainly correspond to those in the ACTT-1 study with a baseline ordinal score of 5 (hospitalised patients requiring supplemental oxygen) who had a mortality rate of 3.8% in the remdesivir arm versus 12.3% in the control arm. The total number of patients in this study subgroup was 435 (232 and 203 in each arm), being the largest group. This is reasonable since this is the most common type of patients requiring hospital admission in the daily practice, therefore, our results enlarge the experience in this important subgroup.

The most severe patients required co-administration of an anti-inflammatory therapy, and as expected they had the highest mortality rate. Interestingly, the concomitant use of remdesivir and tocilizumab was associated with the lowest mortality rate in this group (5.3%), in line with the recent report showing better outcomes among patients receiving remdesivir plus baricitinib.(117) Both immune modulators inhibit specific pathways of the inflammatory cascade instead of the broad-spectrum inhibition induced by steroids with potential harmful consequences.(172)

The optimal timing for remdesivir treatment remains to be clarified. SARS-CoV-2 shedding from the respiratory tract peaks during the first 2-3 days from clinical symptom onset and rapidly decreases (173), consistent with a brief window of clinical benefit from antiviral drugs. In this scenario, prompt initiation of antiviral treatment may be the key point to improve outcomes of patients with COVID-19. Such approach has been documented in other respiratory virus such as the influenza, with the use of neuraminidase inhibitors.(174) In our cohort, remdesivir was administered earlier than in the ACTT-1 study (median of 7 vs. 9 days from symptom onset to remdesivir).(78) Such early drug administration could explain the shorter length of hospital stay (8 vs. 12 days) and lower need of mechanical ventilation (7.3 vs. 12.9%). A prior trial (79) failed to demonstrate any benefits from remdesivir treatment in patients with COVID-19; however, the median days from symptom onset to remdesivir was 11 and, indeed, 37 of the 196 (19%) patients

had undetectable viral RNA on nasopharyngeal and oropharyngeal swabs obtained at baseline. Considering all together, this data suggests that patients included in this study were in a late stage with low viral load and, therefore, the expected benefit of an antiviral in this population is minimal. The impact of remdesivir on reducing viral shedding has been reported in macaques.(175) Information about viral shedding in humans receiving remdesivir treatment is, however, lacking. Such information is important to define the duration of transmissibility and the potential consequences on the isolation measures.

Our cohort supports the good tolerability profile of remdesivir, presenting with no serious adverse events and, in particular, with no alterations in liver enzymes. No patient required discontinuation of the drug. The main limitation of this study was its retrospective nature and a possible underreporting of adverse events. However, we were able to closely monitor laboratory parameters to minimize this problem. However, the strength of our study is that the Spanish Ministry of Health perfectly defined the indication for remdesivir, and our results support such current indication.(176)

Even with treatment options available, the elderly population remains the one under a great risk for worst outcomes, although vaccination strategies really improved this scenario, they are still at higher risk of hospital admission.

In our article “COVID-19 in patients aged 80 years and over during the peaks of the first three pandemic waves at a Spanish tertiary hospital”, we reported, in accordance with data from other regions (50,177) that the elderly patients were reported to be the population most affected by COVID-19, the burden of COVID-19 in very elderly patients remained high throughout the three first waves in Spain. The proportion of patients with COPD increased between the first and third waves. Despite the reported overall relatively low incidence of COVID-19 in COPD patients (1.1–10%) (178,179) COPD patients have an increased risk of severe disease and poor outcomes.(180) Thus, the increase in COPD across waves may be explained because this population may have taken isolation measures more seriously and, consequently, reduced their rates of infection, provided that it was made clear from the early stages of the pandemic that SARS-CoV-2 severely affected the lungs. Also, the use of inhaled corticosteroids may offer a protective effect in these patients, as recently reported.(181)

In our study, 91% of our patients presented at least one comorbidity, 15% of the patients died in the first 5 days after admission, and ICU mortality was 42%, which shows the

disproportionate impact of COVID-19 on these patients; this increased impact has also been widely reported for the elderly population though not specifically in very elderly patients.(182) Early recognition of severe COVID-19 in very elderly patients may allow prompt complication management, thus improving outcomes or optimizing comfort in patients who are not candidates for aggressive therapeutic measures. During the pandemic peaks, we observed a significant increase in the use of remdesivir and corticosteroids, whereas hydroxychloroquine, lopinavir/ ritonavir, and azithromycin were progressively abandoned, which is in line with the results of the main platform clinical trials on COVID-19 (i.e. WHO Solidarity trial(81), RECOVERY(102), REMAP-CAP(159). Overall, 11% of very elderly patients were admitted to the ICU, with rates increasing between the first and third waves (8–16%), which are likely related to the availability of ICU beds. During the first wave, the Spanish health system, including ICUs, was largely overwhelmed and prioritization criteria that included advanced age or reduced functionality in nursery homes residents were implemented in many hospitals.(139) We found that male sex, respiratory rate, and C-reactive protein were associated to a higher likelihood of ICU admission, which has already been reported.(50,178,182) Meanwhile, 30-day mortality rates, although remarkably lower overall (34%) compared to other series worldwide (46–54%)(140,183) are strikingly high figures that highlight the vulnerability of very elderly patients to COVID-19 and therefore the relevance of preventive measures.

The strengths of this study include the large sample size, the special focus on very elderly patients, and the information on three consecutive COVID-19 wave peaks. The study does, however, have some limitations that need to be addressed. The data were collected from a single academic teaching hospital in Spain; it may not be possible to extrapolate results to patients admitted to different hospitals or in other countries. Second, data on quality of life, frailty, and/or functional status were not recorded, which may have led to an underestimation of their potential predictive value.(184)

Finally, the trends of mortality suffer an enormous change and could be described as the most important marker of how time and quality science production can impact a global pandemic evolution. Vaccination, the availability of approved antiviral treatments such as remdesivir, nirmatrelvir-ritonavir already included in reference guidelines, and even the change in the virus variant infection and virulence had contributed to now, in February 2023 the COVID-19 disease is in a completely different scenario than in 2020.

Our article “Trends in mortality of hospitalised COVID-19 patients: A single centre observational cohort study from Spain” was the first of its kind to include all consecutive patients with COVID-19 hospitalised for more than 48 hours and details a marked and decreased trend in 30-day mortality. Despite the fact that most countries have reported a decrease in mortality of patients with COVID-19, perhaps due to massive screening tests implemented to identify large numbers of patients with asymptomatic or mild infections and stop the pandemic (26), data concerning mortality rates in hospitalised patients are scarce. Three studies have reported a decreasing trend in mortality in patients with COVID-19. The first explored hospital mortality in 5121 patients from three academic hospitals in New York City, observing a decrease in mortality from 25.6% in March to 7.6% in August.(185) The second study reported a decreasing mortality amongst critically ill adults with COVID-19 from Emory Hospital in Atlanta, from 34.3% in March to 26.9% in July.(186) Finally, in a third study reporting mortality amongst 21082 patients admitted to a high-dependency unit (HDU) or ICU from March to June, rates decreased from 28.4% to 7.3% (HDU) and from 42% to 19.6% (ICU).(187)

Our mortality rates significantly declined from the first wave period (March to May) to the second one. No significant differences were detected in the population aged <70 years, as the mortality rate in this group was low in both periods. In contrast, a significant reduction was observed in the subgroup of patients aged between 70-79 years and 80-89 years.(188)

In May 2020, Richardson et al. (9) reported the following mortality rates by age group: more than 63% in patients aged 90 years; 60% in patients aged 80 89 years; and 36% in patients aged 70 79 years. Our current mortality rates extremely differ. Between June and September 2020, only 7 of 79 (8.8%) patients older than 70 years who were admitted to our hospital died. However, it is important to consider differences in patient admission per month. Potential explanations for the mortality declining in our institution include: 1) overall improvements in medical skills within these last several months; 2) better health care organisation and, as a result, avoidance of a system overload; 3) a change in patient characteristics; 4) the presence of viral variants with less pathogenicity; and/or 5) changes in treatment strategies.(188)

The overload of patients and ICU capacity during the first wave of the pandemic could explain the high mortality rates reported worldwide; however, our institution was able to

double the ICU capacity, which could partially explain the low mortality rate in our centre yet not its progressive, declining trend entirely. Similarly, no significant differences were observed in patient comorbidities, whilst the mean age of patients oscillated during the study period, peaking in June and slowly decreasing thereon. As age is one of the biggest drivers of mortality in COVID-19 (9), this could be an explanation for the overall mortality rate. Yet, when we examined mortality by age groups, the reduction was observed in all strata. D-dimer and C-RP levels at onset were higher during the first, few months of the pandemic; however, several other factors with negative prognostic influence have been more frequently documented in recent admissions (e.g. higher levels of ferritin and/or LDH, and more cases of hypoxia at admission). Accordingly, it is difficult to confirm whether patient severity has changed during the study period. The spread of viral variants with less pathogenicity was described in Singapore (189); however, since February 2020, the dominant virus variant in Europe has the G614 form of the Spike protein.(190) No data about the potential variation in the virulence of this variant has been described, although G614-bearing viruses have shown significantly higher infectious titres in vitro than D614 counterparts.(190) This phenomenon is, therefore, unlikely to explain variations in mortality. We did observe major changes in treatment strategies that may explain the better outcomes.

Our experience documented that the use of remdesivir substantially increased over time, and time from symptom onset to initial doses of remdesivir shortened. Remdesivir has shown a reduction in mortality rate in the subgroup of patients with pneumonia and low-flow oxygen.(78) Along the same line, the impact of remdesivir on reducing viral shedding has been reported in macaques;(175) however, studies powered to assess the impact of such a finding on infection transmissibility and/ or severe complications, such as coagulopathy or hyperinflammation, in infected humans are lacking. We observed a significant increase in the use of remdesivir during the second period. We cannot directly attribute changes in mortality rate to the increase in remdesivir use, as this is not a randomised study; however, mortality rate in our hospitalised patients was <5% during the second period, in line with that reported in similar patients included in the ACTT-1 study.(78)

Anti-inflammatory therapy has demonstrated a reduction in the mortality rate.(102,147) We therefore cannot attribute such reduction to a change in anti-inflammatory therapies;

more details concerning the type of drug and moment of administration could be important, though. In an open-label, randomised trial comparing dexamethasone use vs. routine care in 2104 patients with a mean age of 67 years and 4321 patients, respectively, dexamethasone use resulted in lower 28-day mortality in those individuals receiving oxygen therapy. Most patients undergoing routine care did not receive any anti-inflammatory treatment. In the dexamethasone group, 28-day mortality was 22.9%, which is quite high when compared to our current rates. Trials assessing the utility of tocilizumab in patients with COVID-19 have not reported declining mortality,(124,152,153) although some significant benefits have been observed. These trials are difficult to analyse due to factors such as the low number of patients included, especially when the routine care arm includes a high number of patients treated with other anti-inflammatory therapies; differences in baseline patient characteristics across groups, namely age; and a high number of patients who had been rescued with tocilizumab in the non-tocilizumab arm. It is worth mentioning that our study showed differences in ICU and non-ICU patients receiving anti-inflammatory and remdesivir treatment.(188)

Improvements in general management of our cohort of patients hospitalised with COVID-19, including antiviral and anti-inflammatory therapies, are evident. The highest serum concentration of C-RP achieved during hospital admission and the need for ICU admission have also significantly decreased throughout the study period.

Risk factors for mortality at hospital admission have been previously described.(9,142) Our study is in agreement with results from these reports and provides two additional important variables related with mortality: the impact of hospital admission during the first few months of the pandemic and duration of symptom onset. In our study, those patients admitted with shorter duration of symptom onset independently had higher mortality. This fact may be related with a higher viral load in this population. Unfortunately, this variable was not available for the present analysis. Further studies evaluating the impact of this finding are warranted.

The strengths of this study include the high number of consecutive patients and compressive data collection. However, there are several limitations. First, the study was conducted in a single centre from Spain, where the public health system attends to all patients equally. This fact may make generalisation of our results difficult. Second, our data were collected directly from EHRs. Nonetheless, it is important to note that our

hospital used an intelligent system to retrieve data from EHRs (SILDv1.0 system, S34M@). The data review process, which includes nine quality steps, ensures high quality of our data. Finally, since the end of March, we have implemented a programme that, under the supervision of infectious disease experts, comprises a computer control centre for patients with COVID-19 that uses real-time data from EHRs to support attending physicians with different skill sets to provide quick, personalised medicine to our patients. The impact of this measure is difficult to assess, but as we have reported, has been related with better outcomes.(127)

To conclude it is important to highlight that the work is not yet finished, there are still physio pathological mechanism of SARS-CoV-2 infections to be understood, clinical manifestation of COVID-19 to be better assessed, such as such as the persistent cases in immunocompromised patients or the long-COVID-19 symptoms that remains after a long period of time, to be better understood and investigated since no current approved treatment exists for those indications and finally there is still the present cases of COVID-19 infections in areas were neither vaccination or treatments are available for all the patients that need it.

We also must keep watching the continuous and normal virus evolution, new variants surveillance and never forget: The most important lesson is that investigation is the key to be able to anticipate events and be better prepare for when the next pandemic comes.

6.

CONCLUSIONS

1. Siltuximab is a well-tolerated alternative to tocilizumab when administered as a first line option in patients with COVID-19 pneumonia within the first 10 days from symptoms onset and high C-reactive protein.

2. In the future it is necessary to better define the characteristics of patients that benefit from IL-6 inhibition as well as the precise timing of its administration.

3. Acute exposure of patients with severe COVID-19 to inflammatory response modifiers, including IL-6 blockers and corticosteroids, does not seem to increase the risk of acquiring a nosocomial infection beyond that expected in unexposed patients with SARS-CoV-2 infection of similar severity.

4. The use of remdesivir in hospitalised patients with pneumonia due to SARS-CoV-2 is associated with a low mortality rate and has a good safety profile.

5. We observed an increase in the percentage of very elderly patients admitted to the ICU during the three first pandemic peaks.

6. ICU admission more likely occurs in very elderly male patients with higher respiratory rate, with elevated LDH and C-reactive protein.

7. Overall, our 30-day mortality rate was lower compared to other series globally.

8. Mortality in hospitalised patients with COVID-19 decreased throughout the study period, even though main patient characteristics remained similar except for age oscillating during the study period.

9. Several changes made in patient management had been detailed, impacting a decreasing trend in 30-day mortality over various months, especially in elderly patients. Our study provides current data on mortality for patients hospitalised with COVID-19 that may be useful in establishing quality of standard of care.

7.

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