Spanish Journal of Medicine

www.SpanishJMed.com

Volume 1, Issue 3, July-September 2021

eISSN: 2696-5631

EDITORIAL

Hospitalists and their roles in the COVID-2019 pandemic in the United States and beyond
C. Washburn, V. Gundareddy, and F. Kisuule

ORIGINAL ARTICLES

Prognostic and therapeutic stratification through the PROFUND scale in patients with heart failure and comorbidities: PROFUND-IC registry
B. Sánchez-Sauce, R. Iguarán-Bermúdez, J.L. García-Klepzig, S. Fernández, J. Barrado-Cuchillo, M. Villar-Martínez, P. Pérez-Mateo, L. López-García, F.J. Martín-Sánchez, E. Calvo-Manuel, J. Díez-Manglano, I. Vallejo-Maroto, M. Bernabeu-Wittel, Á. González-Franco, L.M. Beltrán-Romero, J.M. De-Miguel-Yanes, A. García-García, P. Llacer-Iborra, L. Manzano-Espinosa, J.M. Casas-Rojo, E. Andres, N. Lorenzo-Villalba, and M. Méndez-Bailón

REVIEW ARTICLES

Nationwide and international registries on scleroderma. Past, present, and future
M. Rubio-Rivas

Fighting the tragedy of nursing homes in the COVID-19 pandemic
M. Bernabeu-Wittel, L. Moreno-Gaviño, D. Nieto-Martín, C. Conde-Guzmán, M. Rincón-Gómez, P. Díaz-Jiménez, L. Giménez-Miranda, J. Ternero-Vega, S. Gutiérrez-Rivero, I. Vallejo-Maroto, R. Aparicio-Santos, C. Jiménez-Juan, and M. Ollero-Baturone

GUIDELINES AND CONSENSUS

Consensus 2021 for medical management of type 2 diabetes from the Diabetes, Obesity, and Nutrition Working Group of the Spanish Society of Internal Medicine
F.J. Carrasco-Sánchez, J.M. Fernández-Rodríguez, P.P. Casado-Escribano, J.P. Miramontes-González, R. Gómez-Huelgas, M.D. García-de-Lucas, J. Ena, and J. Carretero-Gómez

SEMI
SOCIEDAD ESPAÑOLA DE MEDICINA INTERNA
La visión global de la persona enferma

PERMANYER
www.permanyer.com

Spanish Journal of Medicine

EDITORIAL

Hospitalists and their roles in the COVID-2019 pandemic in the United States and beyond

*Catherine Washburn, Venkat Gundareddy, and Flora Kisuule**

Division of Hospital Medicine, Johns Hopkins Bayview Medical Center, Johns Hopkins School of Medicine, Baltimore, MD, USA

Introduction

In 2019, the virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread across the world causing coronavirus disease 2019 (COVID-19). On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic[1]. As hospitalizations increased, institutions around the world developed processes to address this need. Hospitalists were at the forefront of caring for COVID-19 patients, serving in multiple roles including: clinicians, operational disaster planners, researchers, innovators of COVID-19 care, and leaders of alternate care sites (ACS) for COVID-19 patients. We performed a literature review to understand the impact of hospitalists during the COVID-19 pandemic in the United States and abroad.

Background on hospital medicine

Hospital medicine is the fastest growing specialty in the United States with estimates of over 50,000[2] practitioners. Focusing on provision of comprehensive medical care to hospitalized patients, physicians who specialize in hospital medicine are known as hospitalists. Because they are close to the bedside, hospitalists expertly diagnose unusual conditions, anticipate problems, coordinate with consultants, and quickly recognize clinical crises. In addition, hospitalists teach, do research, and lead within their specialty and in hospital administration. Hospitalists promote patient safety and improve the efficiency and performance of hospitals and health systems.

An interesting aspect of the rapid expansion of hospital medicine is the growth of the field beyond the United States, shown by 20,000 North American Society of Hospital Medicine (SHM) members and an additional 126 international hospitalist members[3]. Although health care delivery, regulations and cultural norms across the world differ, there are striking similarities in the roles that hospitalists have played across the world in the fight against the COVID-19 pandemic.

Hospitalists as front-line clinicians

More than 122 million people have been infected with COVID-19 worldwide and 2.7 million have died[4]. The United States leads the world in the number of cases, nearly 30 million, and the number of deaths, over 500,000[5]. An estimated 20% of COVID-19 patients have severe disease requiring hospitalization and 6-17% of those require intensive care[6]. Dedicated units were developed in the United States and worldwide to centralize patient care and facilitate infection control. Strained health-care systems used creative staffing models to ensure adequate provider coverage. Hospitalists have provided direct patient care and anchored teams of redeployed clinicians unaccustomed

Correspondence:
*Flora Kisuule
E-mail: Fkisuul1@jhmi.edu

Date of reception: 27-03-2021
Date of acceptance: 07-06-2021
DOI: 10.24875/SJMED.21000011

Available online: 05-10-2021
Span J Med. 2021;1(3):132-135
www.spanishjmed.com

to hospital-based practice, mobilized in the face of surging COVID-19 numbers[7,8]. Hospitalists provided overnight coverage, trainee supervision, staffing of rapid response and cardiac arrest teams[8], and management of general medicine and intensive care patients, partnering with intensivists[9]. Quarantined hospitalists continued working from home, covering triage calls[10] or cross covering hospitalized patients, relieving the burden of hospitalists on site.

Spain ranks in the top ten countries in raw numbers of COVID-19 cases, 3.21 million, with approximately 73,000 deaths[5]. Hospital Clinico San Carolos, a 750-bed facility in Madrid, has 4 hospitalists who co-manage surgery patients. During the pandemic's first wave, this hospital doubled its bed capacity to 1400. Teams of medical and surgical specialists formed to care for COVID-19 patients. One hospitalist led a team of 16 doctors caring for 76-80 patients. In subsequent waves, these hospitalists engaged in direct patient care (Dr. Arantza Alvarez de Arcaya, Coordinadora de Medicine Hospitalista, personal communication, March 21, 2021).

Hospitalists in operational disaster planning

Hospital disaster response plans traditionally center on emergency departments. However, the COVID-19 pandemic has placed hospitalists front and center in hospital preparedness. They have around-the-clock in-house presence and expertise in admission triage, medical co-management, and coordination of complex medical care. Hospitalists are thus uniquely qualified to lead disaster preparedness efforts and have orchestrated complex and dynamic clinical operational plans in response to this pandemic[7,11]. Specifically, hospitalists have helped create biocontainment units for patients infected with SARS-CoV-2, developed staffing models to cover higher and fluctuating patient volumes, and developed frameworks for hospital operations in anticipation of a massive influx of acutely ill, medically complex, and highly contagious patients[7].

Hospitalists developing and providing leadership at alternate care sites

Models of COVID-19 peaks predicted hospital bed shortages worldwide and indeed many of these shortages were realized. Anticipating bed needs, governments around the world rushed into historically unprecedented interventions including the development of alternate care sites (ACSs). Convention halls, parking garages, abandoned industrial warehouses, and pavilions became overflow hospitals for COVID-19 patients in the United States, Canada, and Spain. Vancouver, in Canadian British Columbia, is home to a field hospital with 270 beds in its convention center, staffed in part, by hospitalists[12]. One of the longest running ACSs in the United States is the 250 bed Baltimore Convention Center Field Hospital (BCCFH), where the Chief Medical Officer (CMO), the associate CMO, and multiple medical directors are hospitalists[13]. These hospitalist leaders developed admission criteria and care processes to provide medical care on site until patients are ready for discharge[12], and BCCFH also offers COVID-19 testing, monoclonal antibody infusion, and vaccine administration. To date, the BCCFH has seen 1100 inpatients, administered 1500 antibody infusions, 34,000 vaccines, and 96,000 COVID-19 tests (Dr. Mindy Kantsiper, hospitalist and CMO, BCCFH, personal communication).

Hospitalists Innovating in COVID-19 care

The COVID-19 pandemic has brought opportunities for quality and patient safety initiatives. Hospitalists have led innovations in Point of Care Ultrasound (POCUS), tele-health, and extension of the virtual hospital model.

POCUS

Many hospitalists incorporate POCUS into their daily practice because it enhances their physical exam[14]. Recently clinicians have used POCUS imaging of the heart and lungs to support the diagnosis and progression of care of patients with COVID-19. The diagnostic accuracy of lung ultrasound has been reported to be similar to chest CT scans in patients with respiratory complaints[15]. Mathews et al. report that the American Society of Echocardiography has recommended the use of cardiac POCUS by frontline providers for detection or characterization of preexisting cardiovascular disease and early identification of worsening cardiac function associated with COVID-19[15,16]. Myriad cardiac complications have been described in this disease: acute coronary syndrome, myocarditis, arrhythmias, cardiomyopathy, and heart failure. POCUS can detect lower extremity deep vein thrombosis associated with the pro-inflammatory and hypercoagulable state of COVID-19 and facilitate placement of central and peripheral venous catheters.

Telemedicine

Telemedicine is not new but is increasingly recognized as an important tool in clinical care delivery[17-19]. Pre-pandemic telemedicine focused on mental health, primary care, and asynchronous store-and-forward applications[20]. During the COVID-19 pandemic, telehealth has been used both to progress the care of hospitalized patients[20] and to avoid transfers from rural hospitals to overwhelmed tertiary and quaternary care hospitals.

As states declared emergency status, financial and regulatory roadblocks to telehealth loosened, including limited reimbursement, HIPAA compliance, and interstate licensing restrictions. Guiterrez et al. adapted their Iowa tele-hospitalist program to link their tertiary care center with understaffed rural hospitals and to provide hospital-to-home telehealth for recently discharged patients[20]. In New York, Becker et al. created a tele-hospitalist service for COVID-19 patients on the general medical ward. They write: "*these hospitalists helped to coordinate care standardization, supervised clinical best practices, and communicated effectively with patient logistics and inpatient care teams. The combination of these tasks resulted in load balancing for our bedside internal medicine hospitalist teams.*"

Many hospitalist groups used inpatient tele-medicine to facilitate social distancing and limit provider exposure to infectious patients. Hospitalists took a history using HIPAA-compliant technology through the electronic health record, online platforms, iPads, or smartphones[8]. Hospitalists used technology to maintain their practice of connecting with their patients many times daily to address concerns.

Hospital at home

As SARS-CoV-2 spread, health systems became overwhelmed by COVID-19 cases. Staffing, supplies of equipment, and hospital and intensive care unit beds were insufficient, and quality of care suffered[21]. In response, Sitammagari et al. developed and deployed a virtual hospital program. This model provided proactive home monitoring and hospital level care through virtual observation and acute care units at home for eligible patients with COVID-19. At Atrium Health, the hospital at home extends the hospital medicine division. Hospitalists partner with nurses to provide intravenous fluids, antibiotics, respiratory treatments, and supplemental oxygen in this virtual acute care unit[21].

Hospitalists contributing to scholarship

When the WHO declared COVID-19 a pandemic, little was known about the virus and even less about its treatment. Front line hospitalists quickly turned their observations and experience into research that has contributed to the fund of knowledge in this novel disease. From pooled testing[22], ward adaptions[23], mortality[24], and outcomes of floor level COVID-19 cases[25], to glucocorticoid treatment[26,27] and non-invasive ventilation[28], hospitalists have innovated and published their findings. Hospitalists have also trained redeployed clinicians and developed the needed educational materials, including clinical guidelines, Electronic Health Record primers, and workflow tips.

Conclusion

Hospitalists add immense value to a hospital system in the areas of patient safety and quality, cost effective care, access and availability, patient satisfaction, leadership, and education[29]. Their 24/7 presence in the hospital means that they provide undivided attention to patient care. Hospitalists, therefore, have had a major role in the COVID-19 pandemic as front-line clinicians, leaders in developing operations to expand hospital physical and human resource capacity, and innovators at the leading edge of the development and evolution of care. This hospitalist impact is profound in the United States and beyond.

References

1. World Health Organization Director-general, Opening Remarks at the Media Briefing on COVID-19. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. [Last accessed on 2021 Mar 06].
2. Wachter RM, Goldman L. Zero to 50,000-The 20th anniversary of the hospitalist. N Engl J Med. 2016;375:1009-11.
3. Kisuule F, Howell E. Hospital medicine beyond the United States. Int J Gen Med. 2018;11:65-71.
4. World Health Organization. Coronavirus Disease (COVID-19) Dashboard. Geneva: World Health Organization; 2021 Available from: https://www.covid19.who.int. [Last accessed on 2021 Mar 21].
5. CDC Data Tracker. Available from: https://www.covid.cdc.gov/covid-data-tracker/#global-counts-rates. [Last accessed on 2021 Mar 21].
6. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese center for disease control and prevention. JAMA. 2020;323:1239-42.
7. Bowden K, Burnham E, Keniston A, Levin D, Limes J, Persoff J, et al. Harnessing the power of hospitalists in operational disaster planning: COVID-19. J Gen Intern Med. 2020;35:2732-7.
8. Jacobs L, Korcak J, Zetkulic M. Physician workforce response to the COVID-19 pandemic at an academic medical center. Disaster Med Public Health Prep. 2020;Oct 12:1-4.
9. Cutler T, Eisenberg N, Evans A. Inpatient management of COVID-19 pneumonia: a practical approach from the hospitalist perspective. J Gen Intern Med. 2020;Jun 4:1-4.
10. Yetmar Z, Issa M, Munawar S, Burton MC, Pureza V, Sohail MR, et al. Inpatient care of patients with COVID-19: a guide for hospitalists. Am J Med. 2020;133:1019-24.

11. Persoff J, Ornoff D, Little C. The role of hospital medicine in emergency preparedness: a framework for hospitalist leadership in disaster preparedness, response, and recovery. J Hosp Med. 2018;13:713-8.
12. Howelett K, Ontario BC. Quebec Begin Building Makeshift Hospitals in Preparation for Rise in COVID-19 Patients. Available from: https://www.theglobeandmail.com/canada/article-ontario-bc-quebec-begin-building-makeshift-hospitals-in. [Last accessed on 2021 Mar 03].
13. Chaudhary M, Howell E, Ficke J, Loffredo A, Wortman L, Benton GM, et al. Caring for patients at a COVID-19 field hospital. J Hosp Med. 2021;16:117-9.
14. Soni N, Schnobrich D, Mathews B, Tierney DM, Jensen TP, Dancel R, et al. Point-of-care ultrasound for hospitalists: a position statement of the society of hospital medicine. J Hosp Med. 2019;14:E1-6.
15. Mathews B, Koenig S, Kurian L, Galen B, Mints G, Liu G, et al. Clinical progress note: point-of-care ultrasound applications in COVID-19. J Hosp Med. 2020;15:353-5.
16. Johri AM, Galen B, Krikpatrick J, Lanspa M, Mulvagh S, Thamman R. ASE statement on point-of-care ultrasound (POCUS) during the 2019 novel coronoavirus pandemic. J Am Soc Echocardiogr. 2020;33:670-3.
17. Becker C, Lorman L, Gallapudi L, Nevins B, Scurlock C. Rapid implementation and adaptation of a telehospitalist service to coordinate and optimize care for COVID-19 patients. Telemed J E Health. 2021;27:388-96.
18. Moeckli J, Gutierrez J, Kaboli P. Perceived need and potential applications of a telehospitalist service in rural areas. Telemed J E Health. 2021;27:90-5.
19. Sanders RB, Simpson KN, Kazley AS, Giarrizzi GP. New hospital telemedicine services: potential market for a nighttime telehospitalist service. Telemed J E Health. 2014;20:902-8.
20. Gutierrez J, Kuperman E, Kaboli P. Using telehealth as a tool for rural hospitals in the COVID-19 pandemic response. J Rural Health. 2021;37:161-4.
21. Sitammagari K, Murphy S, Kowalkowski M, Chou SH, Sullivan M, Taylor S, et al. Insights from rapid deployment of a "Virtual Hospital" as standard care during the COVID-19 pandemic. Ann Intern Med. 2021;174:192-9.
22. Mastrianni D, Felivena R, Brooks T, McDermott B, Tan J, Vandell R, et al. Pooled testing for SARS-CoV-2 in hospitalized patients. J Hosp Med. 2020;15:538-9.
23. Auerbach A, O'Leary K, Greysen S, Harrison JD, Kripalani S, Ruhnke GW, et al. Hospital ward adaption during the Covid-19 pandemic: a national survey of academic medical centers. J Hosp Med. 2020;15:583-8.
24. Horwitz L, Jones S, Cerfolio R, Francois F, Greco J, Rudy B, et al. Trends in COVID-19 risk-adjusted mortality rates. J Hosp Med. 2021;16:90-2.
25. Nemer D, Wilner B, Burkle A, Aguilera J, Adewumi J, Gillombardo C, et al. Clinical characteristics and outcomes of non-ICU hospitalization for Covid-19 in a nonepicenter, centrally-monitored healthcare system. J Hosp Med. 2021;16:7-14.
26. Keller M, Kitsis E, Arora S, Chen JT, Agarwal S, Ross MJ, et al. Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with Covid-19. J Hosp Med. 2020;15:489-93.
27. Cui Z, Merritt Z, Assa A, Mustehsan H, Chung E, Liu S, et al. Early and significant reduction in C-reactive protein levels after corticosteroid therapy is associated with reduced mortality in patients with COVID-19. J Hosp Med. 2021;16:142-8.
28. Soares W III, Schoenfeld E, Visintainer P, Elia T, Medarametla V, Schoenfeld DA, et al. Safety assessment of a noninvasive respiratory protocol for adults with Covid-19. J Hosp Med. 2020;15:734-8.
29. Kisuule F, Howell E. Hospitalists and their impact on quality, patient safety, and satisfaction. Obstet Gynecol Clin North Am. 2015;42:433-46.

Spanish Journal of Medicine

ORIGINAL ARTICLE

Prognostic and therapeutic stratification through the PROFUND scale in patients with heart failure and comorbidities: PROFUND-IC registry

Beatriz Sánchez-Sauce[1], Rosario Iguarán-Bermúdez[2], José L. García-Klepzig[2], Santiago Fernández[2], Julia Barrado-Cuchillo[2], Miguel Villar-Martínez[2], Pablo Pérez-Mateo[2], Lidia López-García[3], Francisco J. Martín-Sánchez[4], Elpidio Calvo-Manuel[2], Jesús Díez-Manglano[5], Ignacio Vallejo-Maroto[6], Máximo Bernabeu-Wittel[7], Álvaro González-Franco[8], Luis Matías Beltrán-Romero[7], José M. De-Miguel-Yanes[9], Alejandra García-García[9], Pau Llacer-Iborra[10], Luis Manzano-Espinosa[10], José M. Casas-Rojo[11], Emmanuel Andres[12], Noel Lorenzo-Villalba[12], and Manuel Méndez-Bailón[2]*

[1]Department of Internal Medicine, Hospital Fundación de Alcorcón, Alcorcón; [2]Department of Internal Medicine; [3]Nursing School, and [4]Department of Emergency, Hospital Clínico San Carlos, Universidad Complutense de Madrid, Madrid; [5]Department of Internal Medicine, Hospital Royo Villanova, Zaragoza; [6]Department of Internal Medicine, Hospital San Juan de Dios del Aljarafe, Sevilla; [7]Department of Internal Medicine, Hospital Virgen del Rocío, Sevilla; [8]Department of Internal Medicine, Hospital Universitario Central de Asturias, Asturias; [9]Department of Internal Medicine, Hospital Gregorio Marañón, Madrid; [10]Department of Internal Medicine, Hospital Ramón y Cajal, Madrid; [11]Department of Internal Medicine, Hospital Infanta Cristina, Madrid. Spain; [12]Internal Medicine Service, Diabète et Maladies Métaboliques, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

Abstract

Introduction: The increase in life expectancy and the aging of the population are associated with an increase in the prevalence of chronic diseases. Comorbidities have an important impact on prognosis and functional capacity leading to a progressive deterioration of autonomy and quality of life and an increase in demand for medical care. Establishment of an accurate prognosis constitutes one of the primary objectives in healthcare. An accurate estimate of prognosis helps clinicians make diagnostic and therapeutic decisions, prevent iatrogenesis, and consider palliative care strategy as needed. It also allows the patient and family members to organize their preferences and priorities. **Objective:** To evaluate the PROFUND scale in patients with heart failure from a prognostic point of view. **Methods:** A multicenter cohort study including patients admitted for heart failure to internal medicine departments over a 6-month period will be carried out. Inclusion criteria are patients with a diagnosis of heart failure and at least two criteria of multipathological patients and NT-proBNP >1500 pg/ml upon admission. The PROFUND scale will be applied to all patients. Patients will be then stratified into four groups according to the PROFUND scale: low, moderate, moderate-high and high mortality risk. **Conclusion:** Our work is a prospective study that aims to apply the PROFUND scale to patients with heart failure in the hospital setting with the purpose of helping in decision-making with our patients, which could lead to improvements in the management of resources in our health system.

Key words: Heart failure. Comorbidity. Chronic disease.

Visual abstract available at https://spanishjmed.com/frame_esp.php?id=53

Correspondence:
*Beatriz Sánchez-Sauce
E-mail: beatrizsauce@gmail.com

Date of Reception: 08-06-2021
Date of Acceptance: 16-08-2021
DOI: 10.24875/SJMED.21000017

Available online: 05-10-2021
Span J Med. 2021;1(3):136-141
www.spanishjmed.com

Introduction

The prevalence and incidence of heart failure (HF) have been increasing in recent years as the population ages. The prevalence of HF is between 2 and 3%, reaching 10-20% in patients between 70 and 80 years[1-3]. This high prevalence creates an increase in the demand for health care, making HF the most important cause of admission to Spanish hospitals and representing 5% of all hospitalizations[2,3]. The frequency of hospital readmission for this disease ranges from 30% to 60% in the first 6 months following hospital discharge[4]. These patients show a different profile of comorbidity, which makes their care more complex. The comorbid conditions that are significantly increased include chronic renal failure, severe hematological disorders, malnutrition, psychiatric disorders, and pressure ulcers. These comorbidities could affect treatment and have an important prognostic impact leading to more hospital admissions, worsening quality of life, and increased mortality.

Most HF comorbidity registries tend to include conditions having a pathogenic relationship with HF and cardiovascular risk. Other conditions apparently unrelated to HF such as cognitive impairment, functional status, degenerative osteoarticular pathology, neoplastic processes, frailty, or socio-familial risk factors can directly influence the prognosis of these patients if they are not considered[5]. The RICA registry analyzed the prognostic value of baseline functional status, assessed by the Barthel index, showing a high prevalence of functional impairment in 55.9% of patients[6]. The pre-admission Barthel index was shown to be an independent predictor of short-term mortality.

It is in this context that the concept of pluripathology arises, identifying a population of patients with two or more chronic diseases with an equivalent degree of complexity. Pluripathology patients constitute a heterogeneous population with a series of easily identifiable common characteristics: greater complexity, clinical vulnerability, frailty, mortality, functional deterioration, polypharmacy, poorer health-related quality of life, and dependency[7,8].

The prevalence of pluripathology patients in hospital setting varies between 25% and 50%. HF is the most frequent defining category of pluripathology patients with a prevalence of 72-77%. In addition, there is a high prevalence among pluripathology patients of other cardiovascular comorbidities related to HF (ranging from 30% to 70%)[9]: arterial hypertension, diabetes, dyslipidemia, and atrial fibrillation.

In recent years, the PROFUND index, a specific tool for estimating the prognosis of mortality at 1 year in pluripathology patients, has been developed. This index was developed in a hospital-based multicenter cohort recruited in 36 Spanish hospitals. A total of 1632 patients were included and followed for 1 year and the index was subsequently derived and validated using standard methodology. This index stratifies 12-month mortality and is based on nine clinical, analytical, and socio-familial dimensions. The index stratifies pluripathology patients into four risk groups according to the score obtained, with mortality ranging from 12% to 14% in the lowest risk stratum to 61% to 68% in patients with 11 or more points[8,9]. However, this scale has not been evaluated in pluripathology patients with HF.

This study design aims to define the clinical characteristics of pluripathology patients with acute HF (AHF) and to prognostically stratify them using the PROFUND scale as well as to compare this stratification with other classic prognostic assessment scales in HF.

Methodology

Design, study population, variables, data collection and analysis, ethical aspects, and limitations of the study

Design and study population

This is a nationwide prospective multicenter cohort study from the HF study group and the Pluripathologic Patients and Advanced Age group of the Spanish Society of Internal Medicine. All patients > 18 years old admitted for HF as the main diagnosis in internal medicine services will be consecutively included over a period of 6 months-1 year. Inclusion and exclusion criteria are shown in table 1.

Table 1. Selection criteria for participating in the study

Inclusion criteria
– Patients admitted with a principal diagnosis of heart failure – Patients with NT-pro-brain natriuretic peptide (NT-proBNP) > 300 pg/mL on admission and/or on arrival at the emergency department
Exclusion criteria
– Signature of informed consent not obtained from either the patient or legal representative

Table 2. PROFUND scale variables

PROFUND scale	
Variable	**Points**
Age > 85 years	3
Clinical features	
– Active neoplasia	6
– Dementia	3
– NYHA functional class III-IV or mMRC 3-4	3
– Delirium during the last hospital admission	3
Hb < 10g/dL	3
Socio-familial features	
– Barthel index < 60	4
– Lack of caregiver or other than partner	2
– > 4 hospital admissions in the last 12 months	3

NYHA: New York Heart Failure Association Functional Classification. mMRC: modified Medical Research Council.

Table 3. Clinical categories for the identification of pluripathological patients

Clinical categories for the identification of pluripathological patients
CATEGORY A
A.1. Heart failure that in a clinically stable situation has been in NYHA II (symptoms with usual physical activity) A.2. Ischemic cardiomyopathy
CATEGORY B
B.1. Vasculitis and systemic autoimmune diseases B.2. Chronic kidney disease defined by glomerular filtration rate < 60 mL/m or proteinuria persisting for 3 months
CATEGORY C
C.1. Chronic respiratory disease that in a situation of clinical stability presented with Grade II dyspnea mMRC3 (dyspnea at usual pace in flat), FEV1
CATEGORY D
D.1. Chronic inflammatory bowel disease D.2. Chronic liver disease with signs of liver failure or portal hypertension
CATEGORY E
E.1. Stroke E.2. Neurological disease with permanent motor deficit limiting basic daily living activities (Barthel index < 60) E.3. Neurological disease with permanent cognitive impairment, at least moderate (Pfeiffer ≥ 5 or more errors)
CATEGORY F
F.1. Symptomatic peripheral arterial disease F.2. Diabetes mellitus with proliferative retinopathy or symptomatic neuropathy
CATEGORY G
G.1. Chronic anemia due to digestive losses or acquired hematologic disease G.2. Active solid or hematologic neoplasm that does not require treatment with curative intent
CATEGORY H
H.1. Chronic osteoarticular disease that causes by itself a limitation for basic daily living activities (Barthel index < 60)

FEV1: force expiratory volume.

Objectives

The main objective of the study is to stratify pluripathology patients with over a 6-12 month period in hospitals of the Spanish National Health System using the PROFUND scale (Table 2). Secondary objectives include: to evaluate the epidemiological and clinical characteristics of pluripathology patients with HF as the primary diagnosis and 30-day mortality, early hospital readmission (< 30 days), and 1-year mortality; and to evaluate the destination of care of pluripathology patients with AHF after discharge.

Data collection

Data from patients admitted for AHF to the internal medical department will be prospectively collected by researchers (medical and nursing personnel). The following parameters will be collected: date of birth, sex, toxic habits, arterial hypertension, dyslipidemia, diabetes mellitus, degree of ventricular dysfunction (LVEF), NYHA dyspnea functional class at baseline (2 weeks before admission), presence of pluripathology (defined by the presence of two or more chronic diseases of the clinical categories listed in Table 3), NT-proBNP levels, Cancer Antigen 125 (CA-125), presence of B lines on lung ultrasound, pleural effusion on chest X-rays or pulmonary echography, and inferior vena cava measurement by ultrasound. Data regarding the patient's HF history such as date of admission, date of readmission for HF, date of death, mortality due to cardiovascular and non-cardiovascular causes during follow-up, destination and treatment at discharge, will be collected.

Patients will be then stratified into four groups according to the PROFUND scale:

– Patients at low mortality risk (0-2 points): those in whom the probability of mortality at 1 year is < 14%
– Patients at moderate-low mortality risk (3-6 points): when the probability of mortality at 1 year is between 15 and 31%
– Patients at moderate-high mortality risk (7-10 points): when the probability of mortality at 1 year is between 32 and 50%
– Patients at high mortality risk (> 11 points): when the probability of mortality at 1 year is > 50%.

In addition, data about all-cause mortality and readmissions at 30 days, 6 months, and 1 year will be collected. Participants will be assessed by the following scales: PROFUND scale, which stratifies multipathological patients into four mortality risk groups at admission; MEESSI scale to evaluate 30-day mortality in patients with the diagnosis of AHF; Meta-analysis Global Group in Chronic HF (MAGGIC) scale for the prediction of survival at 1 and 3 years; and Barthel index which evaluates functional capacity.

Statistical analysis

The sample size was estimated assuming a confidence level of 95%, a precision of 5%, a loss rate of 10%, and a mortality rate at 12 months according to the data of the study on prognostic stratification and care approach for multipathologic patients of 13% for the low level, 26% for the low-intermediate level, 48% for the upper-intermediate level, and 64% for the high level. Based on these estimates, the expected number of patients would be 1,600, about 400 patients per risk group.

A separate analysis of in-hospital and out-of-hospital mortality will be performed.

The analysis will be performed using the SPSS program.

Ethical aspects

The project will be submitted to the Clinical Research Ethics Committee of each hospital. All investigators and personnel involved in the project are aware of, and will respect, local, and international regulations in the field of ethical considerations for human experimentation including the Helsinki declaration with its revisions, the Belmont report, and other related documents.

Data confidentiality will be maintained in accordance with the Data Protection Law (Organic Law 5/92 of October 29 on the regulation of the automated processing of personal data, BOE October 30, 1992, modified by Organic Law 15/1999, of December 13, on the Protection of Personal Data and Law 41/2002, of November 14).

All patients, in addition to being informed verbally in detail about the project, will give their Informed Consent in writing before being included in the study.

Discussion

Current status: rationale for a study of pluripathologic patients in AHF

Impact of pluripathology

Pluripathology has an important impact on the prognosis of patients in primary and hospital care settings. It is estimated that the annual mortality of patients with multiple pathologies in primary care is around 6%, while in hospitals it is around 20% during admission and 35% at 1 year. Mortality is significantly higher than in patients without multiple pathologies. Pluripathology also influences functional prognosis. These patients tend to deteriorate more during hospital admissions than non-pluripathological patients and most of them do not recover to their baseline functional state by the time of discharge. In addition, the group of patients with pluripathology presents a particular susceptibility and clinical fragility that leads to frequent demand for care due to exacerbations, worsening the patient's condition with a progressive deterioration of their autonomy and quality of life[9].

Need for prognostic stratification

HF is one of the main causes of death in the general population, but the prognosis varies widely depending on the patient. Quantification of the risk of these patients could improve and individualize the treatment, as well as help establish a therapeutic care plan. It is important for the patient and the family to understand the most accurate estimate of prognosis possible, leading to an appropriate choice of diagnostic, and therapeutic approaches and optimized planning of health care among HF patients[5,6].

For example, scales such as the MEESSI-AHF can be used to predict 30-day mortality in patients presenting to emergency departments with a diagnosis of AHF[10]. It can be very useful in estimating the prognosis of these patients and can help making clinical decisions such as whether to admit or discharge a patient based on the risk of dying in the next 30 days. The MEESSI-AHF score was obtained in 4,867 consecutive patients with AHF admitted

to Spanish emergency departments during 2009 and 2011 and was subsequently validated in 3,229 patients with AHF collected in 2014 (ST-elevation acute coronary syndrome patients were excluded from the study).

The MEESSI-AHF risk model includes 13 variables readily available in emergency departments. In some patients for whom troponin, NT-pro-brain natriuretic peptide, and/or baseline Barthel are unknown, the risk model can also be applied. Forty percent of patients classified as low risk (30-day mortality < 2%) should be considered potential candidates for discharge from the emergency department, without requiring admission, after an adequate response to initial treatment. The 10% of patients classified as very high risk (30-day mortality > 2%) may clearly benefit from hospital admission. The MEESSI-AHF risk scale may be found at the following link: http://meessi-ahf.risk.score-calculator-ica-semes.portalsemes.org.

However, the use of prognostic tools in this population is scarcely used. Among the scales related to cardiac dysfunction, the MAGGIC scale has shown the best accuracy. The MAGGIC scale is the result of the trial Meta-Analysis Global Group in Chronic HF (MAGGIC)[11]. The meta-analysis included 39,372 patients extracted from 30 studies (six randomized clinical trials and 24 observational registries), with a mean follow-up of 2.5 years (1.0-3.9) during which 40.2% of deaths occurred.

The risk predictor variables are age (for each 10-year increase), male sex, body mass index (for each 1 kg/m^2 increase above 30 kg/m^2), smoking, diabetes mellitus, NYHA functional Classes III and IV, left ventricular ejection fraction ≤ 40%, chronic obstructive pulmonary disease, HF diagnosed more than 18 months ago, and renal failure (for each 0.11 mg/dL increase above 3.97 mg/dL creatinine). The protective factors are systolic blood pressure (for each increase of 10 mmHg), NYHA I HF, and treatment with beta-blockers, angiotensin converting enzyme inhibitors, or angiotensin II receptor antagonist. When entering these values to establish the risk score, not all factors add 1 point of risk, but most add between 2 and 3 points, with a maximum of 15 points (those patients over 80 years of age and LVEF ≤ 40%). It is important to note that when several of the factors are individually combined, the risk is not simply added, but multiplied. Based on this risk scale, a probability of death at 1 year and at 3 years is generated, depending on the patient's characteristics. The MAGGIC scale is available on the internet (www.heartfailurerisk.org).

However, the reality is that most physicians do not use these scales in routine clinical practice. This is due to several reasons. First, we know that their accuracy at the individual level and in the short term is low; second, specific medical management according to patient risk has not been defined (with the exception of cardiac transplantation/ventricular assist devices); and finally, they do not usually include variables of significant importance in clinical practice such as comorbidity, frailty, functionality, or socio-affective type.

In patients with HF, comorbidities are often the cause of hospital readmission. In fact, in some series it has been observed that only one third or less of readmissions are due to HF *per se*[12]. This occurs more frequently in patients with HF with preserved ejection fraction, among whom mortality is often linked to non-cardiovascular diseases such as neoplasms, renal disease, or infections[13]. Taking into consideration the importance of comorbidities in morbidity and mortality of patients with HF, special attention has recently been drawn to the importance of a more global approach to HF patients rather than a restrictive assessment (i.e., by focusing exclusively on cardiac disease). This has led to the assessment of comorbidity acquiring greater prognostic importance in patients with HF.

The Charlson score is currently the most widely used instrument for prognostic assessment in patients with comorbidity[14]. It is a numerical summative scale, so that patients with higher scores are more likely to die at 12 months. Mortality by quartiles of the patients studied was as follows: score 0, 12%; score 1-2, 26%; score 3-4, 52%; and score > 5, 85%. The prognostic value of the Charlson score as an independent predictor of mortality or readmission at 1 year has also been confirmed in the RICA registry[15].

The PROFUND index[8,9] is a specific tool for estimating the 1-year mortality in multipathological patients. This index was developed in a multicenter hospital-based cohort recruited in 36 Spanish hospitals. A total of 1,632 patients were included and followed for 1 year and the index was subsequently derived and validated using standard methodology. This index stratifies mortality at 12 months and is based on nine clinical, analytical, and socio-familial dimensions. The index stratifies patients with multiple pathologies into four risk groups according to the score ranges obtained, with mortality ranging from 12% to 14% in the lowest risk stratum to 61% to 68% in those with 11 or more points. It has also shown to be useful in hospitalization areas outside internal medicine[16] (Cardiology Hospitalization Units) and in primary care[17] where the scoring ranges were recalibrated.

The use of prognostic indices will allow us to classify patients with HF into groups according to the estimated

risk of mortality, which is an important aid for improving health planning and decision making. Thus, we present this study with the aim of providing a tool, through the PROFUND scale, that stratifies patients with HF according to their prognosis, and thus guides decision-making and health planning for these patients.

Conclusion

Our work is a prospective study that aims to apply the PROFUND scale to patients with HF in the hospital setting with the purpose of helping in decision-making with our patients, which could lead to improvements in the management of resources in our health system.

Funding

This research was funded by Sociedad Española de Medicina Interna.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Cortina A, Reguero J, Segovia E, Lambert JL, Cortina R, Arias JC, et al. Prevalence of heart failure in Asturias (a region in the North of Spain). Am J Cardiol. 2001;87:1417-9.
2. Banegas JR, Rodríguez-Artalejo F, Guallar-Castillón P. Situación epidemiológica de la insuficiencia cardiaca en España. Rev Esp Cardiol Supl. 2006;6:4C-9C.
3. Fernández Gassó ML, Hernando-Arizaleta L, Palomar-Rodríguez JA, Soria-Arcos F, Pascual-Figal DA. Trends and characteristics of hospitalization for heart failure in a population setting from 2003 to 2013. Rev Esp Cardiol (Engl Ed). 2017;70:720-6.
4. Dharmarajan K. Comprehensive strategies to reduce readmissions in older patients with cardiovascular disease. Can J Cardiol. 2016; 32:1306-14.
5. Conde-Martel A, Hernández-Meneses M. Prevalencia y significado pronóstico de la comorbilidad en la insuficiencia cardiaca. Rev Clin Esp (Barc). 2016;216:222-8.
6. Formiga F, Chivite D, Conde A, Ruiz-Laiglesia F, Franco ÁG, Bocanegra CP, et al. Basal functional status predicts three-month mortality after a heart failure hospitalization in elderly patients-the prospective RICA study. Int J Cardiol. 2014;172:127-31.
7. García-Morillo JS, Bernabeu-Wittel M, Ollero-Baturone M, Aguilar-Guisad M, Ramírez-Duque N, de la Puente MA, et al. Incidencia y características clínicas de los pacientes con pluripatología ingresados en una unidad de medicina interna. Med Clin (Barc). 2005;125:5-9.
8. Bernabeu-Wittel M, Ollero-Baturone M, Moreno-Gaviño L, Barón-Franco B, Fuertes A, Murcia-Zaragoza J, et al. Development of a new predictive model for polypathological patients. The PROFUND index. Eur J Intern Med. 2011;22:311-7.
9. Bernabeu-Wittel M, Barón-Franco B, Nieto-Martín D, Moreno-Gaviño L, Ramírez-Duque N, Ollero-Baturone M. Estratificación pronóstica y abordaje asistencial de los pacientes pluripatológicos. Rev Clin Esp (Barc). 2017;217:410-9.
10. Miró Ò, Rossello X, Gil V, Martín-Sánchez FJ, Llorens P, Herrero-Puente P, et al. Predicting 30-day mortality for patients with acute heart failure in the emergency department: a cohort study. Ann Intern Med. 2017;167:698.
11. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34:1404-13.
12. Dunlay SM, Redfield MM, Weston SA, Therneau TM, Hall Long K, Shah ND, et al. Hospitalizations after heart failure diagnosis a community perspective. J Am Coll Cardiol. 2009;54:1695-702.
13. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol. 2012;59:998-1005.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.
15. Ruiz-Laiglesia FJ, Sanchez-Marteles M, Perez-Calvo JI, Formiga F, Bartolome-Satue JA, Armengou-Arxe A, et al. Comorbidity in heart failure. Results of the Spanish RICA registry. QJM. 2014;107:989-94.
16. López-Garrido MA, Martín-Portugués IA, Becerra-Muñoz VM, Orellana-Figueroa HN, Sánchez-Lora FJ, Morcillo-Hidalgo L, et al. Prevalencia de pluripatología y valor pronóstico del índice PROFUND en una unidad de hospitalización de Cardiología. Rev Clin Esp (Barc). 2017;217:87-94.
17. Colombo PB, Martín MD, de la Pisa BP, Lozano MJ, Camúñez MA, Wittel MB. Validación de un modelo pronóstico para pacientes pluripatológicos en atención primaria: estudio PROFUND en atención primaria. Aten Primaria. 2014;46 Suppl 3:41-8.

Spanish Journal of Medicine

REVIEW ARTICLE

Nationwide and international registries on scleroderma. Past, present, and future

*Manuel Rubio-Rivas**

Scleroderma and Sarcoidosis Section, Autoimmune Diseases Unit, Department of Internal Medicine, Hospital Universitario de Bellvitge-Instituto de Investigación Biomédica de Bellvitge (IDIBELL), Barcelona, Spain

Abstract

Systemic sclerosis (SSc) is a low-incidence autoimmune disease that requires collaborative work through national or international registries to advance scientifically. The present systematic review aims to be an update of all national and international registries to date. In total, 7 first-world countries have SSc registries. In addition, there are also 3 international SSc registries plus 2 other registries focused on SSc-related pulmonary arterial hypertension. These registries not only carry out clinical research but also allow the collection of serum, DNA and tissue samples, as well as collaborative work to carry out randomized clinical trials and collaboration with other registries not directly focused on SSc.

Key words: Scleroderma. Systemic sclerosis. Registry.

Introduction

Scleroderma or systemic sclerosis (SSc) is an autoimmune disease that can be considered a rare disease because of its incidence. As such, it makes it difficult to study in an isolated research center. Many years of follow-up and dedication are needed to be able to gather a sufficient number of patients to be able to undertake research work that will allow valid knowledge to be obtained and extrapolated to other populations. World leadership during the second half of the 20th century was held by large cohorts of a few centers such as the University of Pittsburgh[1], the Johns Hopkins Hospital in Baltimore[2], the University of Texas and Michigan[3], and the Royal Free Hospital in London[4] or provincial/state registries such as the South Australian Scleroderma Register[5]. All of them, but especially the first one in the 1980s, were the seeds of what later became known as national or international registries. Today it is mandatory in a disease of low incidence, and the autoimmune ones would enter there too, to work based on a registry of these characteristics. In 2011, an attempt was made to update the existing registries[6], but it is clear that a decade later, we need to update them and see where we are heading in SSc research through the registries.

This study aimed to conduct an updated review of the different national or international registries on SSc, focusing on their similarities and differences.

Methods

For the present study, a systematic review of national and international registries in SSc has been carried out. The search was performed by reviewing the Medline

Visual abstract available at https://spanishjmed.com/frame_esp.php?id=48

Correspondence:
*Manuel Rubio-Rivas
E-mail: mrubio@bellvitgehospital.cat

Date of reception: 04-01-2021
Date of acceptance: 05-04-2021
DOI: 10.24875/SJMED.M21000011

Available online: 05-10-2021
Span J Med. 2021;1(3):142-153
www.spanishjmed.com

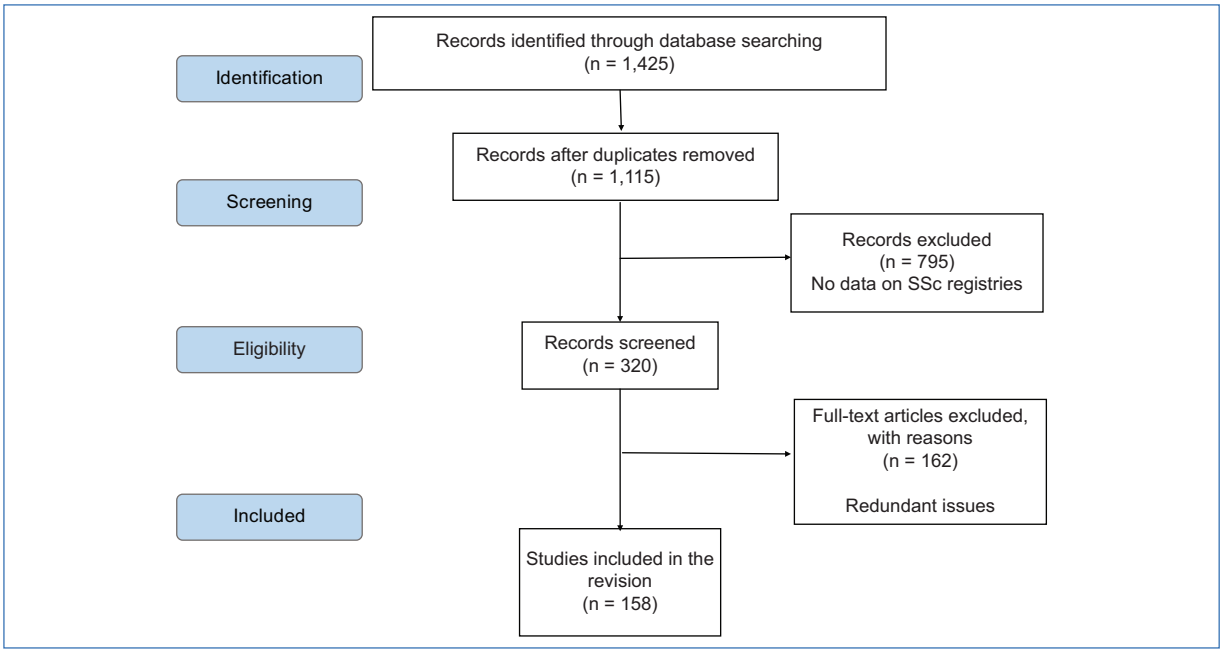

Figure 1. PRISMA 2009 flow diagram.

database following the terms ("Scleroderma, Systemic" [Mesh]) AND "Registries" [Mesh]). Besides, the medical bibliography of the medical coordinator of each of the registries was reviewed as well as a search following the name of the registry on PubMed and the webpage (when available) of the registry (Fig. 1). Not all registries present their data in the same way and at the same time. Thus, the data included in the supplementary tables are indicative and correspond in some cases to the paper of presentation of the registry and, in others, to one of the following papers (Suppl. Tables 1 and 2 and Figs. 2 and 3).

Results

Scleroderma registries

UK, 1995

The **UK Scleroderma Study Group (UKSSG)** is a working group of key centers that have a clinical and research interest in SSc and have worked collaboratively to promote research and clinical practice in SSc patients over the past 25 years. The group was established by Professor Dame Carol Black on the principle of inclusive participation. A national registry in the United Kingdom, initiated in 1995, includes details of 37 centers of SSc and contains data on > 2500 patients. It allows the collection of blood samples for DNA, serum, plasma, and skin biopsies. It also links to systematic databases maintained on pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD).

The UKSSG, mostly centered in the Royal Free Hospital in London, has enabled the study and development of management guidelines in renal[7] and gastrointestinal involvement[8] and in the management of digital ulcers (DU)[9]. It has also deepened the study and management of PAH and ILD[10-12]. It has also made advances in the treatment of diffuse forms of the disease[13,14] and the study of RNA pol III patients[15].

The head office is at the Royal Free Hospital in London and is headed by Dr. C. Denton.

Germany, 2003

The **German Network for Systemic Scleroderma (DNSS)** was founded in 2003 with a grant from the German Federal Ministry of Education and Research. There is an intense collaboration of different subspecialties, including dermatologists, rheumatologists, pulmonologists, and nephrologists. Like the other registries, it includes socio-demographic, clinical, laboratory, and follow-up data. DNSS maintains a centralized online patient registry that includes all SSc patient data on a standardized four-page DNSS questionnaire. The network also provides the infrastructure for collecting blood and tissue samples. It now gathers data from more than 3000 patients from over 40 centers.

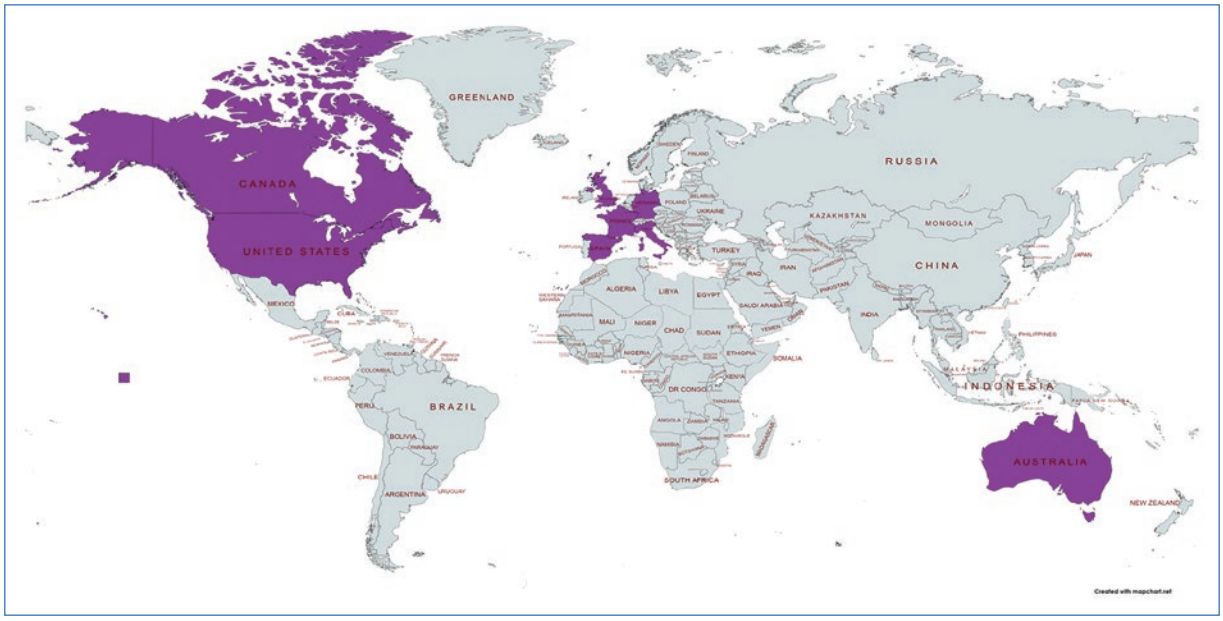

Figure 2. Map chart of the national systemic sclerosis registries.

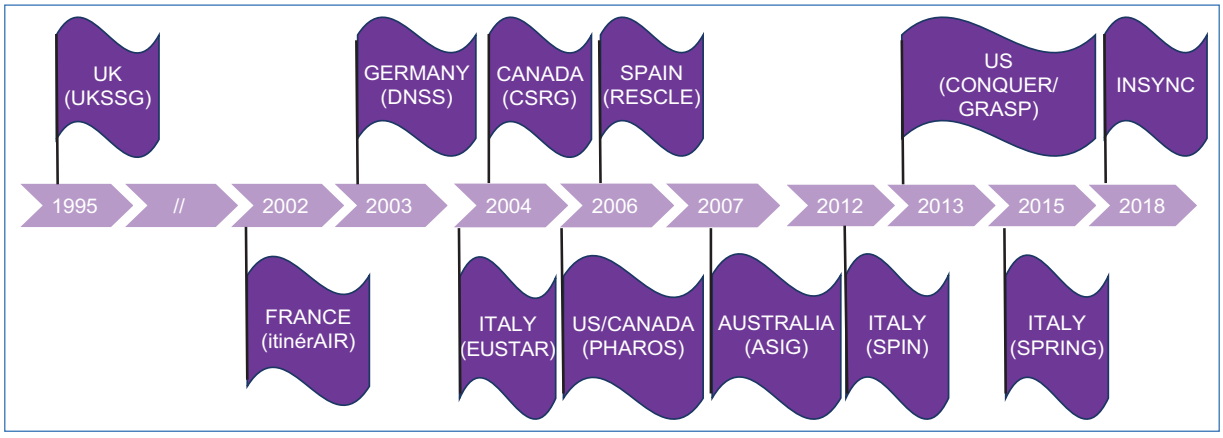

Figure 3. Timeline of the national systemic sclerosis registries over time.

The German registry has firstly served to characterize German patients with SSc[16]. It has provided advances in the correlation of cutaneous and visceral involvement as well as in the management of cutaneous vascular complications[17-20]. It has also served to immunologically characterize German patients on a national level[21]. It has also deepened the knowledge and prognostic evaluation of patients with overlap syndrome[22] and late-onset SSc[23] and the excessive use of corticosteroids and immunosuppressants in patients with SSc[24].

The Central Coordination Office was established at the Department of Dermatology and Venereology at the University of Cologne and acts as a data manager. It is directed by Dr. N. Hunzelmann.

EUSTAR, 2004

The **EULAR Scleroderma Trials and Research Group (EUSTAR)** was founded in 2004 at the University Hospital of Florence (Italy) with the support of a EULAR research grant under the chairmanship of

Marco Matucci. To promote awareness, understanding, and research into SSc and its care and treatment throughout Europe, the EUSTAR group was launched under the auspices of the EULAR standing committee on international clinical trials involving therapeutic trials (ESCISIT) and a prospective multicenter cohort of SSc was established. EUSTAR was initiated in 2003 and the SSc database was launched in 2004. It represents a multinational, prospective, and open SSc cohort. Participating centers enter the minimum essential data set (MEDS) with all consecutive consent patients who meet the ACR classification criteria for SSc. The MEDS was designed by consensus by EUSTAR members and covers demographics, disease duration, organ involvement, and laboratory data. Annual follow-up examinations are conducted. To improve long-term data analysis and follow-up of patients suitable for clinical and basic research trials, an online database (MEDS Online) was launched in June 2006[25]. Simultaneously, the MEDS was expanded with features such as right heart catheter measurements, medication, and a center-based biobank, which collects sera, tissue samples, and DNA material. To date, more than 11,000 patients from 234 centers are included in the study.

EUSTAR has been a constant source of recommendations in management, research, and biobanking strategies in SSc[26-30]. It has also contributed to the improvement of the clinical assessment of organic manifestations and the implementation of the modified Rodnan skin score and organic damage[31,32]. It has allowed the characterization of different geographical regions[33] and the study of differences between races[34]. It has made advances in the study of disability[35], cutaneous involvement[36,37], articular[38,39], vascular[40-42], cardiac[43], pulmonary,[44-47] and digestive involvement[48,49], also the identification of phenotypic clusters in SSc[50]. It has also made advances in the study of different subpopulations such as patients with young and late-onset SSc[51,52], early and very early SSc[53-55], also in those patients with antitopoisomerase I anti-bodies (ATA), anticentromere antibodies (ACA), anti-Ku, PM-Scl, RNA pol III antibodies, and in those antinuclear antibody (ANA) negative[56-60]. It has also contributed to the study of risk factors, including 2 prognostic scores[61-66]. It has finally conducted studies to assess the efficacy of tocilizumab, abatacept, rituximab, cyclophosphamide, and hydroxychloroquine in different subpopulations[67-71].

The current data center is located at the University Hospital of Zurich and is directed by Dr. O. Distler.

Canada, 2004

In 2003, a group of 17 rheumatologists from across Canada met and recognized the need to unite to better treat patients with SSc. The **Scleroderma Research Group of Canada (CSRG)** is a multicenter research cohort established in 2004. The CSRG has been made possible by grants from the Canadian Institutes for Health Research, private donations, Scleroderma Canada, all provincial scleroderma patient groups, the Scleroderma Healing Foundation, as well as several Canadian pharmaceutical companies. At present, the patient registry contains detailed longitudinal clinical data on over 1750 patients from 15 different sites, plus a biobank of samples.

The Canadian registry (CSRG) has been very prolific since its inception. It has focused on the study of quality of life[72], fatigue[73], frailty[74], pain[75], sleep disturbances[76], depression[77], malnutrition[78], work disability[79], self-reported physical health[80], oral health[81], SSc-associated cancer[82], sexual activity[83], the impact of socioeconomic status[84], and the cost of SSc[85]. It has also made advances in the immunological characterization of patients with SSc and its clinical implications, especially in those patients with antifibrillarin anti-bodies, ACA, Ro52, PM/Scl, TRIM 21, Th/To, Ku, and HMGCR[86-93], also those patients with negative ANA[94]. Knowledge of visceral gastrointestinal[95-97], pulmonary[98-100], renal[101], muscular[102], cutaneous[103], and vascular involvement[104] has also improved. It has also provided knowledge in aspects of the diagnosis of the disease[105] and in the assessment of organ damage[106]. It has also served to characterize a Native North American population with SSc[107]. Finally, it has furthered the study of a large subpopulation of patients with scleroderma sine scleroderma[108].

The head office is located at the Jewish General Hospital in Montreal and is headed by Dr. M. Baron and K. McKenna.

Spain, 2006

The **Spanish Registry of Scleroderma (RESCLE)** was created by the Autoimmune Systemic Disease Group (GEAS) of the Spanish Society of Internal Medicine in 2006 to compile a wide range of Spanish patients with SSc. At that time, there were 14 participating centers; today, there are 40 centers throughout the country. Thus, until 2006 the data were collected retrospectively and since 2006 (or the date of inclusion of a new center), it has been done prospectively. Epidemiological, clinical, laboratory, capillary, and immunological data covering

267 variables are included in the database. Annual follow-up examinations are conducted.

The Spanish scleroderma registry has not only characterized the Spanish population with SSc[109] but has also made advances in the characterization of liver involvement[110], vascular[111], ILD[112], and PAH[113], as well as the role of phosphodiesterase inhibitors and endothelin receptor antagonists as bi-therapies in the prognosis of PAH versus monotherapy[114]. The preventive role of these drugs in the development of PAH and the renal crisis has also been evaluated[115]. The registry has furthered the study of the immunological profile and, in particular, the study of serodiscordant patients with the cutaneous subtype[116,117]. It has also studied the subpopulation with early and very early SSc[118], as well as deepened into the causes of death and their change over time[119,120]. It has identified new risk factors and created a new long-term prognostic tool[121,122].

There is no registry-associated biobank to store evidence. To date, collects data from 2,238 patients. The central database coordinator and administrator is S&H Medical Science Service and medical coordination is directed by Dr. C.P. Simeón and V. Fonollosa from Vall d'Hebron University Hospital in Barcelona.

Australia, 2007

The **Steering Committee of the Scleroderma Interest Group of Australia (**Australian Scleroderma Interest Group [**ASIG])** met for the 1st time in November 2005 and in 2007 became a special interest group under the auspices of the Australian Rheumatology Association, a non-profit organization incorporated as a corporation in Australia. The ASIG is a multidisciplinary collaboration of rheumatologists, immunologists, cardiologists, and respiratory physicians from across Australia with a special interest in improving outcomes for patients with SSc and mixed connective tissue disease. In 2007, ASIG established the Australian Scleroderma Cohort Study (ASCS), using a web-based platform to detect the cardiac and pulmonary complications of these diseases as a service to patients with SSc and their rheumatologists. The main goal of the ASCS is to improve clinical care by increasing the rate of detection of SSc-related PAH and ILD to enable earlier identification of high-risk patients and the institution of timely treatment. Blood samples are collected and processed at most centers and transferred to Adelaide for storage in the ASIG blood biobank. All members of the ASIG are clinical rheumatologists. To date, over 1600 patients from 13 centers are included in the registry.

The ASIG registry has contributed to the field of PAH screening[123,124], GI involvement[125], overlap syndrome[126], quality of life[127], and activity impairment[128]. Furthermore, in the immunological characterization of patients, especially patients with anti-Ku, anti-RNA pol III, and anti-PM75-100[86,129-130], also the relation with occupational silica exposure[131].

The project coordinator and database administrator for ASIG were appointed in 2006 and is based in the Department of Rheumatology at St. Vincent's Hospital in Melbourne. It is directed by Dr. S. Proudmann and M. Nikpour.

Scleroderma Patient-centered Intervention Network (SPIN), 2012

The **SPIN,** an international collaboration of patient organizations, clinicians, and researchers, was recently organized and funded by the Canadian Institutes of Health Research. The long-term goals of SPIN are to develop, test, and disseminate accessible interventions to complement standard medical care and improve outcomes in SSc. The SPIN uses a novel research design, the Multiple Cohort Randomized clinical trial Design, to collect longitudinal data related to the problems experienced by people living with SSc and as a framework for the development, evaluation, and delivery of psychosocial and rehabilitation interventions. The first step toward the long-term objectives of the SPIN is the establishment of the SPIN Cohort[131]. It does not have an associated biobank. By 2020, more than 1700 patients have been recruited from 43 centers in Canada, the USA, UK, France, Spain, Mexico, and Australia.

The SPIN cohort has furthered the study of physical activity[132], physical and occupational therapy[133], hand function[134], and online self-care intervention in patients with SSc[135]. It has also made advances in the evaluation of mental health in the SSc population, recently also concerning COVID-19[136,137].

The SPIN is led by Dr. B. Thombs of the Jewish General Hospital and McGill University in Montreal, Canada.

The US, the CONQUER Registry, 2013

In 2011, the Prospective Registry of Early SSc (PRESS) was developed in the US in response to FDA and NIH calls for attention to Therapeutics for Rare and Neglected Diseases and developing tissue banks linked to clinical outcomes. PRESS researchers were contacted by the Scleroderma Research Foundation

(SRF) to build on their efforts. The overall goal of the SRF partnership with participating academic Scleroderma Centers is to accumulate the largest possible cohort of early-stage scleroderma patients. This highly collaborative effort, initially among 12 of the largest SSc centers in the United States, has been named **CONQUER** (an acronym for COllaborative, National QUality and Efficacy Registry for Tracking Disease Progression in SSc [scleroderma] Patients). The CONQUER Registry was developed in 2013. The SRF is a non-profit organization based in San Francisco. It is the nation's leading non-profit investor in medical research and its mission is to fund and facilitate the most promising and highest quality research aimed at improving therapies and ultimately curing scleroderma. The SRF has established strategic partnerships with several other sponsors who are providing financial and other support elements to ensure the success of the CONQUER Registry, in special Boehringer Ingelheim and Actelion laboratories. The Biorepository Center at The University of Texas Health Science Center at Houston will provide processing, storage, and management services for CONQUER Registry members, as it does for a variety of national research networks. The registry includes 12 SSc centers geographically distributed throughout the U.S., including California, Texas, Utah, Illinois, Michigan, Massachusetts, Maryland, New York, South Carolina, and Washington, D.C.

The CONQUER register has only published its initial set-up with baseline data from its longitudinal cohort[138].

The data center is based at the University of Utah, and the biospecimen repository is located at the University of Texas Health Science Center in Houston.

The US, the GRASP Registry, 2013

The **African American Scleroderma Genome Research Project (GRASP)** was established to improve our understanding of the clinical manifestations of SSc in African Americans and to conduct genomic analyses to identify key factors contributing to the occurrence and severity of their disease. To achieve these goals, a large cohort of African-American patients with SSc has been assembled and clinical data and DNA samples have been collected from all enrolled patients. The GRASP clinical database was established in 2013 and includes the sociodemographic and clinical characteristics of a U.S. cohort of exclusively African-American SSc patients enrolled retrospectively and prospectively over 30 years (1987-2016). African-American race was determined by patient self-identification. The GRASP consortium was supported by research funding from the SRF and the Intramural Research Programs of the National Human Genome Research Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The GRASP cohort currently consists of more than 1,200 extensively evaluated African-American SSc patients enrolled at 23 participating academic centers in the United States. This is the largest multicenter cohort of African American patients with SSc ever studied.

The GRASP cohort has published only its baseline data in which it characterizes the largest Afro-American SSc cohort described to date[139].

The data center is based at the Johns Hopkins University coordination site and is led by Dr. F. Wigley and F. Boin.

Italy, 2015

The **SPRING** is the last national registration to date. It was promoted by the Italian Society of Rheumatology in 2015. Study data were collected and managed using REDCap, electronic data capture tools hosted by SIR REDCap (Research Electronic Data Capture), which is a secure web-based application designed to support data capture for research studies. Patients were screened consecutively and enrolled at each participating center according to standardized study procedures. All patients were hierarchically classified into 4 different cohorts: (1) primary Raynaud's phenomenon (RP); (2) suspected secondary RP; (3) very early diagnosis of SSc (VEDOSS); (4) definitive SSc according to ACR/EULAR 2013 classification criteria for SSc. A biobank associated with the registry is not available to store evidence. To date, it includes more than 1700 patients from 38 centers.

Still, in its early days, the SPRING has served to characterize the Italian population with SSc[140].

The SPRING is led by Dr. C Ferri of the University of Modena and M Matucci of the University of Florence.

INSYNC, 2018

In 2018, the **International** SSc **Initiation Cohort (INSYNC)** pooled data from the ASCS, the cohort study of the Canadian Scleroderma Research Group (CSRG), the Leiden SSc cohort (Leiden CCIS cohort), Spain (the scleroderma cohort of the University Hospital 12 de Octubre in Madrid), and Sweden (the SSc cohort of the Rheumatology Unit of the Skane University Hospital, Lund). Here, data from national registries and cohorts from a single-center are combined. To date, INSYNC

includes sites in Canada, Australia, the Netherlands, Spain, Germany, Brazil, the United States, and Sweden. It should be noted that INSYNC relies entirely on the infrastructure of the CSRG for administrative and statistical support.

Still, in its early days, the INSYNC cohort has advanced the assessment of the health-related quality of life in patients with SSc[141].

It currently has more than 600 patients from 31 centers. It does not have a biobank.

Registries focused on SSc-related PAH

France, ItinérAIR-Sclérodermie, 2002

The **ItinérAIR-Sclérodermie Investigators Group** was established in 2002 to prospectively collect patients with SSc and group I PAH. The ItinérAIR-Sclérodermie registry includes data on 599 patients diagnosed with SSc. It has made advances in the diagnostic algorithm of PAH and its early detection[142]. It has also served to study the prevalence and incidence of PAH in a SSc population[143,144], as well as survival and risk factors for poor prognosis[145-147].

The registry is run by ACTELION PHARMACEUTICALS FRANCE, SAS and is headed by Dr. M. Humbert.

US/Canada, PHAROS, 2006

The **Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS)** Registry is a prospective multicenter study in compliance with the US Health Insurance Portability and Accountability Act (HIPAA) conducted at 19 US and Canadian sites. There were two patient populations enrolled in the registry: patients with SSc at risk for PAH and those with incident PAH. At-risk patient enrollment criteria were: (1) DLCO < 55% predicted with an FVC of > 70% predicted; (2) FVC/DLCO ratio > 1.6; or (3) estimated right ventricular systolic pressure > 40 mm Hg on ECG. At-risk patients underwent PAH screening annually or sooner if clinically indicated. Right heart catheterization (RHC) was performed for at-risk patients based on clinical indication during follow-up. Patients with incident PAH were diagnosed by RHC within 6 months of enrollment[148].

The PHAROS registry has allowed the study of risk factors in a subpopulation at risk of PAH and in a population already diagnosed with PAH[149-151]. It has also contributed to the hemodynamic study of these patients[152,153], the prognostic role of related antibodies, and biomarkers[154,155], the influence of ILD in these patients[156], and the response to oral therapy[157].

This is being coordinated by Dr. V. Steen at Georgetown University (Washington DC).

Discussion

The University of Pittsburgh Scleroderma Databank was the first SSc registry initiated in 1980. Although it has always functioned as a reference center in the US, it is still a single-center and, therefore, far from the objective of the present review. It is the prototype of all registries in SSc as it includes a comprehensive initial evaluation, standard SSc examination, laboratory studies, and yearly serum and DNA samples. Most importantly, it includes a comprehensive annual to biannual follow-up of patients. This databank now has > 4000 patients with > 30 years of follow-up data.

The path of clinical research in SSc has been through national registries. It has opened up possibilities unimaginable in the last century for most centers and has increased clinical knowledge of the disease. It has allowed better characterization of patients and improved knowledge of prognostic factors of the disease. We owe this luck firstly to the world reference center in Pittsburgh and its researchers and secondly to the researchers promoting the different registries in each of these countries mentioned above. In short, we are talking about 7 countries, not many, but they give a good account of what SSc is, at least in the first world (Suppl. Tables 1 and 2 and Figs. 2 and 3). Unfortunately, we do not have national registries in 3rd world countries or in developing or emerging countries. We do not have national data from Asia or Africa either. In general, national registries cover the entire spectrum of the disease, although the ASIG is mainly focused on pulmonary manifestations (PAH and ILD). In recent years, supranational initiatives have appeared, first with EUSTAR and later with SPIN and INSYNC. The case of the SPIN is special because it is specifically designed to perform randomized clinical trials, it opens a door to a different type of systematic collaboration between various working groups.

If the same disease has already benefited from this large amount of data included in the same registry despite its low incidence, it has been even more important to study certain clinical manifestations that only a small group of patients suffer. This is where PAH, ILD, and scleroderma renal crisis (SRC) would come in. The study of these continues to be difficult due to the limitation in the number of patients who suffer from it, but

it is no longer impossible. Furthermore, it allows the isolated study of these clinical manifestations in a homogeneous group of patients with SSc and not included in studies with other types of patients as occurs, for example, in studies of PAH including patients with idiopathic PAH and other subtypes. In this regard, several national registries dedicated to the study of pulmonary hypertension have emerged in recent decades. Two of them have focused on SSc-related PAH, such as the ItinerAIR-Sclérodermie registry and the PHAROS registry (Suppl. Tables 3 and 4 and Figs. 1 and 2). They are cohorts of patients with incident PAH patients and patients not yet diagnosed with PAH. The inclusion of patients without PAH is broader in the former, so the incidence of PAH in the French cohort is lower. These cohorts allow a more rigorous study of this organic condition but they need years to be able to gather a sufficient number of patients to allow their study given their low incidence. There are no similar registries for SSc-related ILD or SRC.

On the other hand, the limitations inherent in these registries have to be commented on. First, as in all multicenter studies, there is heterogeneity between centers in terms of knowledge of the disease, management. The constant feedback from scientific meetings minimizes these differences, but they are there. Second, they are databases with several predefined variables and not designed for a specific study. This sometimes limits the study in depth of a specific topic that requires data not present in the database. Third, the management of the SSc overlaps between several specialties, mainly Internal Medicine and Rheumatology, Dermatology, Pneumology, among others. The registries are usually endorsed on occasions by a single scientific society so that certain patients may not be represented in the registry and this could lead to a bias toward inclusion. Fourth, it is important that a registry has reference centers in SSc but also 2nd and 3rd level centers without so much experience in its management. This may not occur in all registries and the big picture of the SSc in that country would not faithfully reflect the real seriousness of the patients. Fifth, most of the registries are prospective, but not all. A registry with retrospective data runs the risk of committing an inclusion bias. If a rigorous search has not been carried out to include previously deceased patients, it will only be including patients who have arrived alive at the time of recruitment and therefore those patients with severe SSc and risk factors of bad outcomes will be minimized in oblivion. Besides, the information in retrospect is not always available and this leads to loss of information in the registry.

In conclusion, the registries have shown their benefits in terms of progress in knowledge, and in a few years and with a greater follow-up of patients will be able to continue providing very interesting data from which we will learn even more. We can see that this type of research can have a limit and we should think about going further. Some of these registries include blood and tissue biobanks. This opens the door to new lines of research not possible until now. International cooperation is increasingly common and some of the latest registries have been born on this basis. Finally, registries are the basis of many observational studies, but the example of the SPIN shows the possibility of conducting clinical trials on a cooperative and systematic international basis. All this is good news for a disease like SSc, orphaned in the last century and of which we know more every day that passes. Our patients will be grateful for it.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Supplementary data

Supplementary data are available at *Spanish Journal of Medicine* online (www.spanishjmed.com). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole author's responsability.

References

1. Steen VD, Powell D, Medsger TA Jr. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. Arthritis Rheum. 1988;31:196-203.
2. Greidinger EL, Flaherty KT, White B, Rosen A, Wigley FM, Wise RA. African-American race and antibodies to topoisomerase I are associated with increased severity of scleroderma lung disease. Chest. 1998;114:801-7.
3. Mayes MD, Lacey JV, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum. 2003;48:2246-55.
4. Black CM. Scleroderma--clinical aspects. J Intern Med. 1993;234:115-8.
5. Chandran G, Ahern MJ, Smith M, Roberts-Thomson PJ. A study of scleroderrna in South Australia: prevalence, subset characteristics and nailfold capillaroscopy. Aust NZ J Med. 1995;25:688-94.
6. Galluccio F, Walker UA, Nihtyanova S, Moinzadeh P, Hunzelmann N, Krieg T, et al. Registries in systemic sclerosis: a worldwide experience. Rheumatology. 2011;50:60-8.
7. Lynch BM, Stern EP, Ong V, Harber M, Burns A, Denton CP. UK scleroderma study group (UKSSG) guidelines on the diagnosis and management of scleroderma renal crisis. Clin Exp Rheumatol. 2016;34 Suppl 100:106-9.
8. Thoua NM, Bunce C, Brough G, Forbes A, Emmanuel AV, Denton CP. Assessment of gastrointestinal symptoms in patients with systemic sclerosis in a UK tertiary referral centre. Rheumatology (Oxford). 2010;49:1770-5.
9. Hughes M, Ong VH, Anderson ME, Hall F, Moinzadeh P, Griffiths B, et al. Consensus best practice pathway of the UK scleroderma study group: digital vasculopathy in systemic sclerosis. Rheumatology (Oxford). 2015;54:2015-24.
10. Denton CP, Humbert M, Rubin L, Black CM. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. Ann Rheum Dis. 2006;65:1336-40.
11. Williams MH, Handler CE, Akram R, Smith CJ, Das C, Smee J, et al. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. Eur Heart J. 2006;27:1485-94.
12. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum. 2006;54:3962-70.
13. Herrick AL, Lunt M, Whidby N, Ennis H, Silman A, McHugh N, et al. Observational study of treatment outcome in early diffuse cutaneous systemic sclerosis. J Rheumatol. 2010;37:116-24.
14. Nihtyanova SI, Brough GM, Black CM, Denton CP. Mycophenolate mofetil in diffuse cutaneous systemic sclerosis--a retrospective analysis. Rheumatology (Oxford). 2007;46:442-5.
15. Nihtyanova SI, Parker JC, Black CM, Bunn CC, Denton CP. A longitudinal study of anti-RNA polymerase III antibody levels in systemic sclerosis. Rheumatology (Oxford). 2009;48:1218-21.
16. Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, et al. The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. Rheumatology. 2008;47:1185-92.
17. Hanitsch LG, Burmester GR, Witt C, Hunzelmann N, Genth E, Krieg T, et al. Skin sclerosis is only of limited value to identify SSc patients with severe manifestations--an analysis of a distinct patient subgroup of the German systemic sclerosis network (DNSS) register. Rheumatology (Oxford). 2009;48:70-3.
18. Herrgott I, Riemekasten G, Hunzelmann N, Sunderkötter C. Management of cutaneous vascular complications in systemic scleroderma: experience from the German network. Rheumatol Int. 2008;28:1023-9.
19. Sunderkötter C, Herrgott I, Brückner C, Moinzadeh P, Pfeiffer C, Gerss J, et al. Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. Br J Dermatol. 2009;160:835-43.
20. Moinzadeh P, Riemekasten G, Siegert E, Fierlbeck G, Henes J, Blank N, et al. Vasoactive therapy in systemic sclerosis: real-life therapeutic practice in more than 3000 patients. J Rheumatol. 2016;43:66-74.
21. Mierau R, Moinzadeh P, Riemekasten G, Melchers I, Meurer M, Reichenberger F, et al. Frequency of disease-associated and other nuclear autoantibodies in patients of the German network for systemic scleroderma: correlation with characteristic clinical features. Arthritis Res Ther. 2011;13:R172.
22. Moinzadeh P, Aberer E, Ahmadi-Simab K, Blank N, Distler JH, Fierlbeck G, et al. Disease progression in systemic sclerosis-overlap syndrome is significantly different from limited and diffuse cutaneous systemic sclerosis. Ann Rheum Dis. 2015;74:730-7.
23. Moinzadeh P, Kuhr K, Siegert E, Mueller-Ladner U, Riemekasten G, Günther C, et al. Older age onset of systemic sclerosis accelerated disease progression in all disease subsets. Rheumatology (Oxford). 2020;59(11):3380-9.
24. Hunzelmann N, Moinzadeh P, Genth E, Krieg T, Lehmacher W, Melchers I, et al. High frequency of corticosteroid and immunosuppressive therapy in patients with systemic sclerosis despite limited evidence for efficacy. Arthritis Res Ther. 2009;11:R30.
25. Tyndall A, Mueller-Ladner U, Matucci-Cerinic M. Systemic sclerosis in Europe: first report from the EULAR Scleroderma Trials and Research (EUSTAR) group database. Ann Rheum Dis. 2005;64:1107.
26. Avouac J, Kowal-Bielecka O, Landewe R, Chwiesko S, Miniati I, Czirjak L, et al. European league against rheumatism (EULAR) scleroderma trial and research group (EUSTAR) recommendations for the treatment of systemic sclerosis: methods of elaboration and results of systematic literature research. Ann Rheum Dis. 2009;68:629-34.
27. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76:1327-39.
28. Hoffmann-Vold AM, Distler O, Murray B, Kowal-Bielecka O, Khanna D, Allanore Y, et al. Setting the international standard for longitudinal follow-up of patients with systemic sclerosis: a Delphi-based expert consensus on core clinical features. RMD Open. 2019;5:e000826.
29. Tyndall A, Ladner UM, Matucci-Cerinic M. The EULAR scleroderma trials and research group (EUSTAR): an international framework for accelerating scleroderma research. Curr Opin Rheumatol. 2008;20:703-6.
30. Beyer C, Distler JH, Allanore Y, Aringer M, Avouac J, Czirják L, et al. EUSTAR biobanking: recommendations for the collection, storage and distribution of biospecimens in scleroderma research. Ann Rheum Dis. 2011;70:1178-82.
31. Walker UA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR scleroderma trials and research group database. Ann Rheum Dis. 2007;66:754-63.
32. Czirják L, Nagy Z, Aringer M, Riemekasten G, Matucci-Cerinic M, Furst DE, et al. The EUSTAR model for teaching and implementing the modified Rodnan skin score in systemic sclerosis. Ann Rheum Dis. 2007;66:966-9.
33. Walker UA, Tyndall A, Czirják L, Denton CP, Farge-Bancel D, Kowal-Bielecka O, et al. Geographical variation of disease manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research (EUSTAR) group database. Ann Rheum Dis. 2009;68:856-62.
34. Jaeger VK, Tikly M, Xu D, Siegert E, Hachulla E, Airò P, et al. Racial differences in systemic sclerosis disease presentation: a European scleroderma trials and research group study. Rheumatology (Oxford). 2020;59:1684-94.
35. Saketkoo LA, Escorpizo R, Keen KJ, Fligelstone K, Distler O; EUSTAR. International classification of functioning, disability and health core set construction in systemic sclerosis and other rheumatic diseases: a EUSTAR initiative. Rheumatology (Oxford). 2012;51:2170-6.
36. Maurer B, Graf N, Michel BA, Müller-Ladner U, Czirják L, Denton CP, et al. Prediction of worsening of skin fibrosis in patients with diffuse cutaneous systemic sclerosis using the EUSTAR database. Ann Rheum Dis. 2015;74:1124-31.
37. Wu W, Jordan S, Graf N, de Oliveira Pena J, Curram J, Allanore Y, et al. Progressive skin fibrosis is associated with a decline in lung function and worse survival in patients with diffuse cutaneous systemic sclerosis in the European scleroderma trials and research (EUSTAR) cohort. Ann Rheum Dis. 2019;78:648-56.
38. Avouac J, Walker UA, Hachulla E, Riemekasten G, Cuomo G, Carreira PE, et al. Joint and tendon involvement predict disease progression in systemic sclerosis: a EUSTAR prospective study. Ann Rheum Dis. 2016;75:103-9.
39. Avouac J, Walker U, Tyndall A, Kahan A, Matucci-Cerinic M, Allanore Y, et al. Characteristics of joint involvement and relationships with systemic inflammation in systemic sclerosis: results from the EULAR scleroderma trial and research group (EUSTAR) database. J Rheumatol. 2010;37:1488-501.
40. Ingegnoli F, Ardoino I, Boracchi P, Cutolo M; EUSTAR co-authors. Nailfold capillaroscopy in systemic sclerosis: data from the EULAR scleroderma trials and research (EUSTAR) database. Microvasc Res. 2013;89:122-8.
41. Blagojevic J, Bellando-Randone S, Abignano G, Avouac J, Cometi L, Czirják L, et al. Classification, categorization and essential items for digital ulcer evaluation in systemic sclerosis: a DeSScipher/European scleroderma trials and research group (EUSTAR) survey. Arthritis Res Ther. 2019;21:35.
42. Mihai C, Landewé R, van der Heijde D, Walker UA, Constantin PI, Gherghe Am, et al. Digital ulcers predict a worse disease course in patients with systemic sclerosis. Ann Rheum Dis. 2016;75:681-6.
43. Elhai M, Avouac J, Walker UA, Matucci-Cerinic M, Riemekasten G, Airò P, et al. A gender gap in primary and secondary heart dysfunctions in systemic sclerosis: a EUSTAR prospective study. Ann Rheum Dis. 2016;75:163-9.
44. Koumakis E, Wipff J, Dieudé P, Ruiz B, Bouaziz M, Revillod L, et al. TGFβ receptor gene variants in systemic sclerosis-related pulmonary arterial hypertension: results from a multicentre EUSTAR study of European Caucasian patients. Ann Rheum Dis. 2012;71:1900-3.
45. Adler S, Huscher D, Siegert E, Allanore Y, Czirják L, DelGaldo F, et al. Systemic sclerosis associated interstitial lung disease individualized immunosuppressive therapy and course of lung function: results of the EUSTAR group. Arthritis Res Ther. 2018;20:17.

46. Kowal-Bielecka O, Chwiesko-Minarowska S, Bernatowicz PL, Allanore Y, Radstake T, Matucci-Cerinic M, et al. The arachidonate 5-lipoxygenase activating protein gene polymorphism is associated with the risk of scleroderma-related interstitial lung disease: a multicentre European scleroderma trials and research group (EUSTAR) study. Rheumatology (Oxford). 2017;56:844-52.
47. Hoffmann-Vold AM, Allanore Y, Alves M, Brunborg C, Airó P, Ananieva LP, et al. Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database. Ann Rheum Dis. 2021;80:219-27.
48. Wipff J, Coriat R, Masciocchi M, Caramaschi P, Derk CT, Hachulla E, et al. Outcomes of Barrett's oesophagus related to systemic sclerosis: a 3-year EULAR Scleroderma Trials and Research prospective follow-up study. Rheumatology (Oxford). 2011;50:1440-4.
49. Ghrénassia E, Avouac J, Khanna D, Derk CT, Distler O, Suliman YA, et al. Prevalence, correlates and outcomes of gastric antral vascular ectasia in systemic sclerosis: a EUSTAR case-control study. J Rheumatol. 2014;41:99-105.
50. Sobanski V, Giovannelli J, Allanore Y, Riemekasten G, Airò P, Vettori S, et al. Phenotypes determined by cluster analysis and their survival in the prospective European scleroderma trials and research cohort of patients with systemic sclerosis. Arthritis Rheumatol. 2019;71:1553-70.
51. Foeldvari I, Tyndall A, Zulian F, Müller-Ladner U, Czirjak L, Denton C, et al. Juvenile and young adult-onset systemic sclerosis share the same organ involvement in adulthood: data from the EUSTAR database. Rheumatology (Oxford). 2012;51:1832-7.
52. Hügle T, Schuetz P, Daikeler T, Tyndall A, Matucci-Cerinic M, Walker UA, et al. Late-onset systemic sclerosis--a systematic survey of the EULAR scleroderma trials and research group database. Rheumatology (Oxford). 2011;50:161-5.
53. Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi consensus study from EULAR scleroderma trials and research group. Ann Rheum Dis. 2011;70:476-81.
54. Minier T, Guiducci S, Bellando-Randone S, Bruni C, Lepri G, Czirják L, et al. Preliminary analysis of the very early diagnosis of systemic sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. Ann Rheum Dis. 2014;73:2087-93.
55. Jaeger VK, Wirz EG, Allanore Y, Rossbach P, Riemekasten G, Hachulla E, et al. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR study. PLoS One. 2016;11:e0163894.
56. Heijnen IA, Foocharoen C, Bannert B, Carreira PE, Caporali R, Smith V, et al. Clinical significance of coexisting antitopoisomerase I and anticentromere antibodies in patients with systemic sclerosis: a EUSTAR group-based study. Clin Exp Rheumatol. 2013;31 2 Suppl 76:96-102.
57. Rozman B, Cucnik S, Sodin-Semrl S, Czirják L, Varjú C, Distler O, et al. Prevalence and clinical associations of anti-Ku antibodies in patients with systemic sclerosis: a European EUSTAR-initiated multi-centre case-control study. Ann Rheum Dis. 2008;67:1282-6.
58. Lazzaroni MG, Cavazzana I, Colombo E, Dobrota R, Hernandez J, Hesselstrand R, et al. Malignancies in patients with anti-RNA polymerase III antibodies and systemic sclerosis: analysis of the EULAR scleroderma trials and research cohort and possible recommendations for screening. J Rheumatol. 2017;44:639-47.
59. Lazzaroni MG, Marasco E, Campochiaro C, DeVries-Bouwstra J, Gonzalez-Perez MI, Rojas-Serrano J, et al. The clinical phenotype of Systemic Sclerosis patients with anti-PM/Scl antibodies: results from the EUSTAR cohort. Rheumatology (Oxford). 2021;2021:keab152.
60. Schneeberger D, Tyndall A, Kay J, Søndergaard KH, Carreira PE, Morgiel E, et al. Systemic sclerosis without antinuclear antibodies or Raynaud's phenomenon: a multicentre study in the prospective EULAR scleroderma trials and research (EUSTAR) database. Rheumatology (Oxford). 2013;52:560-7.
61. Becker M, Graf N, Sauter R, Allanore Y, Curram J, Denton CP, et al. Predictors of disease worsening defined by progression of organ damage in diffuse systemic sclerosis: a European Scleroderma Trials and Research (EUSTAR) analysis. Ann Rheum Dis. 2019;78:1242-8.
62. Hachulla E, Clerson P, Airò P, Cuomo G, Allanore Y, Caramaschi P, et al. Value of systolic pulmonary arterial pressure as a prognostic factor of death in the systemic sclerosis EUSTAR population. Rheumatology (Oxford). 2015;54:1262-9.
63. Wirz EG, Jaeger VK, Allanore Y, Riemekasten G, Hachulla E, Distler O, et al. Incidence and predictors of cutaneous manifestations during the early course of systemic sclerosis: a 10-year longitudinal study from the EUSTAR database. Ann Rheum Dis. 2016;75:1285-92.
64. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR scleroderma trials and research (EUSTAR) database. Ann Rheum Dis. 2010;69:1809-15.
65. Fransen J, Popa-Diaconu D, Hesselstrand R, Carreira P, Valentini G, Beretta L, et al. Clinical prediction of 5-year survival in systemic sclerosis: validation of a simple prognostic model in EUSTAR centres. Ann Rheum Dis. 2011;70:1788-92.
66. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis. 2017;76:1897-905.
67. Castellví I, Elhai M, Bruni C, Airò P, Jordan S, Beretta L, et al. Safety and effectiveness of abatacept in systemic sclerosis: the EUSTAR experience. Semin Arthritis Rheum. 2020;50:1489-93.
68. Bruni C, Tashkin DP, Steen V, Allanore Y, Distler O, Grotts J, et al. Intravenous versus oral cyclophosphamide for lung and/or skin fibrosis in systemic sclerosis: an indirect comparison from EUSTAR and randomised controlled trials. Clin Exp Rheumatol. 2020; 38 Suppl 125: 161-8.
69. Jordan S, Distler JH, Maurer B, Huscher D, van Laar JM, Allanore Y, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European scleroderma trial and research (EUSTAR) group. Ann Rheum Dis. 2015;74:1188-94.
70. Bruni C, Praino E, Guiducci S, Bellando-Randone S, Furst DE, Matucci-Cerinic M. Hydroxychloroquine and joint involvement in systemic sclerosis: preliminary beneficial results from a retrospective case-control series of an EUSTAR center. Joint Bone Spine. 2017;84:747-8.
71. Elhai M, Meunier M, Matucci-Cerinic M, Maurer B, Riemekasten G, Leturcq T, et al. Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept: a EUSTAR observational study. Ann Rheum Dis. 2013;72:1217-20.
72. Hudson M, Thombs BD, Steele R, Watterson R, Taillefer S, Baron M, et al. Clinical correlates of quality of life in systemic sclerosis measured with the World Health Organization disability assessment schedule II. Arthritis Rheum. 2008;59:279-84.
73. Levis B, Kwakkenbos L, Hudson M, Baron M, Thombs BD; Canadian Scleroderma Research Group. The association of sociodemographic and objectively-assessed disease variables with fatigue in systemic sclerosis: an analysis of 785 Canadian scleroderma research group registry patients. Clin Rheumatol. 2017;36:373-9.
74. Rockwood MR, MacDonald E, Sutton E, Rockwood K, Baron M; Canadian Scleroderma Research Group. Frailty index to measure health status in people with systemic sclerosis. J Rheumatol. 2014;41:698-705.
75. El-Baalbaki G, Lober J, Hudson M, Baron M, Thombs BD; Canadian Scleroderma Research Group. Measuring pain in systemic sclerosis: comparison of the short-form McGill Pain Questionnaire versus a single-item measure of pain. J Rheumatol. 2011;38:2581-7.
76. Milette K, Hudson M, Körner A, Baron M, Thombs BD; Canadian Scleroderma Research Group. Sleep disturbances in systemic sclerosis: evidence for the role of gastrointestinal symptoms, pain and pruritus. Rheumatology (Oxford). 2013;52:1715-20.
77. Thombs BD, Jewett LR, Kwakkenbos L, Hudson M, Baron M; Canadian Scleroderma Research Group. Major depression diagnoses among patients with systemic sclerosis: baseline and one-month followup. Arthritis Care Res (Hoboken). 2015;67:411-6.
78. Baron M, Hudson M, Steele R; Canadian Scleroderma Research Group. Malnutrition is common in systemic sclerosis: results from the Canadian scleroderma research group database. J Rheumatol. 2009;36:2737-43.
79. Hudson M, Steele R, Lu Y, Thombs BD; Canadian Scleroderma Research Group, Baron M. Work disability in systemic sclerosis. J Rheumatol. 2009;36:2481-6.
80. Hudson M, Steele R, Lu Y, Thombs BD, Panopalis P, Baron M, et al. Clinical correlates of self-reported physical health status in systemic sclerosis. J Rheumatol. 2009;36:1226-9.
81. Baron M, Hudson M, Dagenais M, Macdonald D, Gyger G, El Sayegh T, et al. Relationship between disease characteristics and oral radiologic findings in systemic sclerosis: results from a Canadian oral health study. Arthritis Care Res (Hoboken). 2016;68:673-80.
82. Bernatsky S, Hudson M, Pope J, Markland J, Robinson D, Jones N, et al. Reports of abnormal cervical cancer screening tests in systemic sclerosis. Rheumatology (Oxford). 2009;48:149-51.
83. Levis B, Hudson M, Knafo R, Baron M, Nielson WR, Hill M, et al. Rates and correlates of sexual activity and impairment among women with systemic sclerosis. Arthritis Care Res (Hoboken). 2012;64:340-50.
84. Mansour S, Bonner A, Muangchan C, Hudson M, Baron M, Pope JE, et al. Low socioeconomic status (measured by education) and outcomes in systemic sclerosis: data from the Canadian Scleroderma Research Group. J Rheumatol. 2013;40:447-54.
85. Bernatsky S, Hudson M, Panopalis P, Clarke AE, Pope J, Leclercq S, et al. The cost of systemic sclerosis. Arthritis Rheum. 2009;61:119-23.
86. Hoa S, Hudson M, Troyanov Y, Proudman S, Walker J, Stevens W, et al. Single-specificity anti-Ku antibodies in an international cohort of 2140 systemic sclerosis subjects: clinical associations. Medicine (Baltimore). 2016;95:e4713.
87. Sharif R, Fritzler MJ, Mayes MD, Gonzalez EB, McNearney TA, Draeger H, et al. Anti-fibrillarin antibody in African American patients with systemic sclerosis: immunogenetics, clinical features, and survival analysis. J Rheumatol. 2011;38:1622-30.
88. Hudson M, Pope J, Mahler M, Tatibouet S, Steele R, Baron M, et al. Clinical significance of antibodies to Ro52/TRIM21 in systemic sclerosis. Arthritis Res Ther. 2012;14:R50.

89. Mejia Otero C, Assassi S, Hudson M, Mayes MD, Estrada-Y-Martin R, Pedroza C, et al. Antifibrillarin antibodies are associated with native North American ethnicity and poorer survival in systemic sclerosis. J Rheumatol. 2017;44:799-805.
90. Hudson M, Luck Y, Stephenson M, Choi MY, Wang M, Baron M, et al. Anti-HMGCR antibodies in systemic sclerosis. Medicine (Baltimore). 2016;95:e5280.
91. Mahler M, You D, Baron M, Taillefer SS, Hudson M; Canadian Scleroderma Research Group, et al. Anti-centromere antibodies in a large cohort of systemic sclerosis patients: comparison between immunofluorescence, CENP-A and CENP-B ELISA. Clin Chim Acta. 2011;412:1937-43.
92. D'Aoust J, Hudson M, Tatibouet S, Wick J; Canadian Scleroderma Research Group, Mahler M, et al. Clinical and serologic correlates of anti-PM/Scl antibodies in systemic sclerosis: a multicenter study of 763 patients. Arthritis Rheumatol. 2014;66 1608-15.
93. Mahler M, Satoh M, Hudson M, Baron M, Chan JY, Chan EK, et al. Autoantibodies to the Rpp25 component of the Th/To complex are the most common antibodies in patients with systemic sclerosis without antibodies detectable by widely available commercial tests. J Rheumatol. 2014;41:1334-43.
94. Hudson M, Satoh M, Chan JY, Tatibouet S, Mehra S, Baron M, et al. Prevalence and clinical profiles of 'autoantibody-negative' systemic sclerosis subjects. Clin Exp Rheumatol. 2014;32 6 Suppl 86:S-127-32.
95. Richard N, Hudson M, Wang M, Gyger G, Proudman S, Stevens W, et al. Severe gastrointestinal disease in very early systemic sclerosis is associated with early mortality. Rheumatology (Oxford). 2019;58:636-44.
96. Baron M, Hudson M, Steele R, Lo E; Canadian Scleroderma Research Group. Validation of the UCLA scleroderma clinical trial gastrointestinal tract instrument version 2.0 for systemic sclerosis. J Rheumatol. 2011;38:1925-30.
97. Zhang XJ, Bonner A, Hudson M; Canadian Scleroderma Research Group, Baron M, Pope J. Association of gastroesophageal factors and worsening of forced vital capacity in systemic sclerosis. J Rheumatol. 2013;40:850-8.
98. Steele R, Hudson M, Lo E, Baron M; Canadian Scleroderma Research Group. Clinical decision rule to predict the presence of interstitial lung disease in systemic sclerosis. Arthritis Care Res (Hoboken). 2012; 64:519-24.
99. Semalulu T, Rudski L, Huynh T, Langleben D, Wang M; Canadian Scleroderma Research Group, et al. An evidence-based strategy to screen for pulmonary arterial hypertension in systemic sclerosis. Semin Arthritis Rheum. 2020;50:1421-7.
100. Hoa S, Bernatsky S, Steele RJ, Baron M, Hudson M; Canadian Scleroderma Research Group. Association between immunosuppressive therapy and course of mild interstitial lung disease in systemic sclerosis. Rheumatology (Oxford). 2020;59:1108-17.
101. Caron M, Hudson M, Baron M, Nessim S, Steele R; Canadian Scleroderma Research Group. Longitudinal study of renal function in systemic sclerosis. J Rheumatol. 2012;39:1829-34.
102. Jung M, Bonner A, Hudson M, Baron M, Pope JE; Canadian Scleroderma Research Group (CSRG). Myopathy is a poor prognostic feature in systemic sclerosis: results from the Canadian Scleroderma Research Group (CSRG) cohort. Scand J Rheumatol. 2014;43:217-20.
103. Zheng B, Nevskaya T, Baxter CA, Ramey DR, Pope JE, Baron M, et al. Changes in skin score in early diffuse cutaneous systemic sclerosis are associated with changes in global disease severity. Rheumatology (Oxford). 2020;59:398-406.
104. Khimdas S, Harding S, Bonner A, Zummer B, Baron M, Pope J, et al. Associations with digital ulcers in a large cohort of systemic sclerosis: results from the Canadian scleroderma research group registry. Arthritis Care Res (Hoboken). 2011;63:142-9.
105. Hudson M, Fritzler MJ, Baron M; Canadian Scleroderma Research Group (CSRG). Systemic sclerosis: establishing diagnostic criteria. Medicine (Baltimore). 2010;89:159-65.
106. Ferdowsi N, Huq M, Stevens W, Hudson M, Wang M, Tay T, et al. Development and validation of the scleroderma clinical trials consortium damage index (SCTC-DI): a novel instrument to quantify organ damage in systemic sclerosis. Ann Rheum Dis. 2019;78:807-16.
107. Bacher A, Mittoo S, Hudson M, Tatibouet S; Canadian Scleroderma Research Group, Baron M. Systemic sclerosis in Canada's North American Native population: assessment of clinical and serological manifestations. J Rheumatol. 2013;40:1121-6.
108. Diab S, Dostrovsky N, Hudson M, Tatibouet S, Fritzler MJ, Baron M, et al. Systemic sclerosis sine scleroderma: a multicenter study of 1417 subjects. J Rheumatol. 2014;41:2179-85.
109. Simeón-Aznar CP, Fonollosa-Plá V, Tolosa-Vilella C, Espinosa-Garriga G, Ramos-Casals M, Campillo-Grau M, et al. Registry of the Spanish network for systemic sclerosis: clinical pattern according to cutaneous subsets and immunological status. Semin Arthritis Rheum. 2012;41:789-800.
110. Marí-Alfonso B, Simeón-Aznar CP, Guillén-Del Castillo A, Rubio-Rivas M, Trapiella-Martínez L, Todolí-Parra JA, et al. Hepatobiliary involvement in systemic sclerosis and the cutaneous subsets: characteristics and survival of patients from the Spanish RESCLE registry. Semin Arthritis Rheum. 2018;47:849-57.
111. Tolosa-Vilella C, Morera-Morales ML, Simeón-Aznar CP, Marí-Alfonso B, Colunga-Arguelles D, Rubio JL, et al. Digital ulcers and cutaneous subsets of systemic sclerosis: clinical, immunological, nailfold capillaroscopy, and survival differences in the Spanish RESCLE Registry. Semin Arthritis Rheum. 2016;46:200-8.
112. Sánchez-Cano D, Ortego-Centeno N, Callejas JL, Plá VF, Ríos-Fernández R, Tolosa-Vilella C, et al. Interstitial lung disease in systemic sclerosis: data from the Spanish scleroderma study group. Rheumatol Int. 2018;38:363-74.
113. García-Hernández FJ, Castillo-Palma MJ, Tolosa-Vilella C, Guillén-Del Castillo A, Rubio-Rivas M, Freire M, et al. Pulmonary hypertension in Spanish patients with systemic sclerosis. Data from the RESCLE registry. Clin Rheumatol. 2019;38:1117-24.
114. Pestaña-Fernández M, Rubio-Rivas M, Tolosa-Vilella C, Guillén-Del-Castillo A, Freire M, Vargas-Hitos JA, et al. Longterm efficacy and safety of monotherapy versus combination therapy in systemic sclerosis-associated pulmonary arterial hypertension: a retrospective RESCLE registry study. J Rheumatol. 2020;47:89-98.
115. Pestaña-Fernández M, Rubio-Rivas M, Tolosa-Vilella C, Guillén-Del-Castillo A, Colunga-Argüelles D, Argibay A, et al. The incidence rate of pulmonary arterial hypertension and scleroderma renal crisis in systemic sclerosis patients with digital ulcers on endothelin antagonist receptors (ERAs) and phosphodiesterase-5 inhibitors (PDE5i). Rheumatology (Oxford). 2021;60:872-80.
116. Arandia NI, Simeón-Aznar CP, Del Castillo AG, Argüelles DC, Rubio-Rivas M, Martínez LT, et al. Influence of antibody profile in clinical features and prognosis in a cohort of Spanish patients with systemic sclerosis. Clin Exp Rheumatol. 2017;35 Suppl 106:98-105.
117. Arandia NI, Espinosa G, Vilella CT, Del Castillo AG, Rivas MR, Freire M, et al. Serodiscordant patients with systemic sclerosis: when antibody does not correspond to skin involvement. Clin Exp Rheumatol. 2020;38 Suppl 125:106-114.
118. Trapiella-Martínez L, Díaz-López JB, Caminal-Montero L, Tolosa-Vilella C, Guillén-Del Castillo A, Colunga-Argüelles D, et al. Very early and early systemic sclerosis in the Spanish scleroderma Registry (RESCLE) cohort. Autoimmun Rev. 2017;16:796-802.
119. Simeón-Aznar CP, Fonollosa-Plá V, Tolosa-Vilella C, Espinosa-Garriga G, Campillo-Grau M, Ramos-Casals M, et al. Registry of the Spanish network for systemic sclerosis: survival, prognostic factors, and causes of death. Medicine (Baltimore). 2015;94:e1728.
120. Rubio-Rivas M, Simeón-Aznar CP, Velasco C, Marí-Alfonso B, Espinosa G, Corbella X, et al. Changes in the pattern of death of 987 patients with systemic sclerosis from 1990 to 2009 from the nationwide Spanish Scleroderma Registry (RESCLE). Clin Exp Rheumatol. 2017;35 Suppl 106:40-7.
121. Rubio-Rivas M, Corbella X, Pestaña-Fernández M, Tolosa-Vilella C, Guillen-Del Castillo A, Colunga-Argüelles D, et al. First clinical symptom as a prognostic factor in systemic sclerosis: results of a retrospective nationwide cohort study. Clin Rheumatol. 2018;37:999-1009.
122. Rubio-Rivas M, Corbella X, Guillén-Del-Castillo A, Vilella CT, Argüelles DC, Argibay A, et al. Spanish scleroderma risk score (RESCLESCORE) to predict 15-year all-cause mortality in scleroderma patients at the time of diagnosis based on the RESCLE cohort: derivation and internal validation. Autoimmun Rev. 2020;19:102507.
123. Morrisroe K, Huq M, Stevens W, Rabusa C, Proudman SM, Nikpour M, et al. Risk factors for development of pulmonary arterial hypertension in Australian systemic sclerosis patients: results from a large multicenter cohort study. BMC Pulm Med. 2016;16:134.
124. Quinlivan A, Thakkar V, Stevens W, Morrisroe K, Prior D, Rabusa C, et al. Cost savings with a new screening algorithm for pulmonary arterial hypertension in systemic sclerosis. Intern Med J. 2015;45:1134-40.
125. Richard N, Hudson M, Wang M, Gyger G, Proudman S, Stevens W, et al. Severe gastrointestinal disease in very early systemic sclerosis is associated with early mortality. Rheumatology (Oxford). 2019;58:636-44.
126. Fairley JL, Hansen D, Proudman S, Sahhar J, Ngian GS, Walker J, et al. Clinical characteristics and survival in systemic sclerosis-mixed connective tissue disease and systemic sclerosis-overlap syndrome. Arthritis Care Res (Hoboken). 2020;2020:24167.
127. Morrisroe K, Stevens W, Huq M, Prior D, Sahhar J, Ngian GS, et al. Survival and quality of life in incident systemic sclerosis-related pulmonary arterial hypertension. Arthritis Res Ther. 2017;19:122.
128. Morrisroe K, Stevens W, Huq M, Sahhar J, Ngian GS, Zochling J, et al. Validity of the workers productivity and activity impairment questionnaire: specific health problem (WPAI:SHP) in patients with systemic sclerosis. Clin Exp Rheumatol. 2017;35 Suppl 106:130-7.
129. Wodkowski M, Hudson M, Proudman S, Walker J, Stevens W, Nikpour M, et al. Clinical correlates of monospecific anti-PM75 and anti-PM100 antibodies in a tri-nation cohort of 1574 systemic sclerosis subjects. Autoimmunity. 2015;48:542-51.
130. Nikpour M, Hissaria P, Byron J, Sahhar J, Micallef M, Paspaliaris W, et al. Prevalence, correlates and clinical usefulness of antibodies to RNA polymerase III in systemic sclerosis: a cross-sectional analysis of data from an Australian cohort. Arthritis Res Ther. 2011;13:R211.
131. Patel S, Morrisroe K, Proudman S, Hansen D, Sahhar J, Sim MR, et al. Occupational silica exposure in an Australian systemic sclerosis cohort. Rheumatology (Oxford). 2020;59:3900-5.

132. Dougherty DH, Kwakkenbos L, Carrier ME, Salazar G, Assassi S, Baron M, et al. The scleroderma patient-centered intervention network cohort: baseline clinical features and comparison with other large scleroderma cohorts. Rheumatology. 2018;57:1623-31.
133. Becetti K, Kwakkenbos L, Carrier ME, Gordon JK, Nguyen JT, Mancuso CA, et al. Physical or occupational therapy use in systemic sclerosis: a scleroderma patient-centered intervention network cohort study. J Rheumatol. 2019;46:1605-13.
134. Levis AW, Harel D, Kwakkenbos L, Carrier ME, Mouthon L, Poiraudeau S, et al. Using optimal test assembly methods for shortening patient-reported outcome measures: development and validation of the cochin hand function scale-6: a scleroderma patient-centered intervention network cohort study. Arthritis Care Res (Hoboken). 2016;68:1704-13.
135. Kwakkenbos L, Cumin J, Carrier ME, Bartlett SJ, Malcarne VL, Mouthon L, et al. Factors associated with patient-reported likelihood of using online self-care interventions: a scleroderma patient-centered intervention network (SPIN) cohort study. BMJ Open. 2019;9:e029542.
136. Sommer SJ, Harel D, Kwakkenbos L, Carrier ME, Gholizadeh S, Gottesman K, et al. Assessing differential item functioning for the social appearance anxiety scale: a scleroderma patient-centred intervention network (SPIN) cohort study. BMJ Open 2020;10:e037639.
137. Thombs BD, Kwakkenbos L, Henry RS, Carrier ME, Patten S, Harb S, et al. Changes in mental health symptoms from pre-COVID-19 to COVID-19 among participants with systemic sclerosis from four countries: a scleroderma patient-centered intervention network (SPIN) cohort study. J Psychosom Res. 2020;139:110262.
138. Shanmugam VK, Frech TM, Steen VD, Hummers LK, Shah AA, Bernstein EJ, et al. Collaborative national quality and efficacy registry (CONQUER) for scleroderma: outcomes from a multicenter US-based systemic sclerosis registry. Clin Rheumatol. 2020;39:93-102.
139. Morgan ND, Shah AA, Mayes MD, Domsic RT, Medsger TA Jr., Steen VD, et al. Clinical and serological features of systemic sclerosis in a multicenter African American cohort: analysis of the genome research in African American scleroderma patients clinical database. Medicine (Baltimore). 2017;96:e8980.
140. Ferri C, Giuggioli D, Guiducci S, Lumetti F, Bajocchi G, Magnan L, et al. Systemic sclerosis progression investigation (SPRING) Italian registry: demographic and clinico-serological features of the scleroderma spectrum. Clin Exp Rheumatol. 2020;38 Suppl 125:S40-7.
141. Morrisroe K, Hudson M, Baron M, de Vries-Bouwstra J, Carreira PE, Wuttge DM, et al. Determinants of health-related quality of life in a multinational systemic sclerosis inception cohort. Clin Exp Rheumatol 2018;36 Suppl 113:53-60.
142. Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum. 2005;52:3792-800.
143. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006;173:1023-30.
144. Hachulla E, de Groote P, Gressin V, Sibilia J, Diot E, Carpentier P, et al. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis Rheum. 2009;60:1831-9.
145. Humbert M, Sitbon O, Yaici A, Montani D, O'Callaghan DS, Jaïs X, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J. 2010;36:549-55.
146. Sitbon O, Benza RL, Badesch DB, Barst RJ, Elliott CG, Gressin V, et al. Validation of two predictive models for survival in pulmonary arterial hypertension. Eur Respir J. 2015;46:152-64.
147. Hachulla E, Carpentier P, Gressin V, Diot E, Allanore Y, Sibilia J, et al. Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinérAIR-Sclérodermie study. Rheumatology (Oxford). 2009;48:304-8.
148. Hinchcliff M, Fischer A, Schiopu E, Steen VD; PHAROS Investigators. Pulmonary hypertension assessment and recognition of outcomes in scleroderma (PHAROS): baseline characteristics and description of study population. J Rheumatol. 2011;38:2172-9.
149. Hsu VM, Chung L, Hummers LK, Shah A, Simms R, Bolster M, et al. Risk factors for mortality and cardiopulmonary hospitalization in systemic sclerosis patients at risk for pulmonary hypertension, in the PHAROS registry. J Rheumatol. 2019;46:176-83.
150. Hsu VM, Chung L, Hummers LK, Wigley F, Simms R, Bolster M, et al. Development of pulmonary hypertension in a high-risk population with systemic sclerosis in the pulmonary hypertension assessment and recognition of outcomes in scleroderma (PHAROS) cohort study. Semin Arthritis Rheum. 2014;44:55-62.
151. Kolstad KD, Li S, Steen V, Chung L; PHAROS Investigators. Long-term outcomes in systemic sclerosis-associated pulmonary arterial hypertension from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry (PHAROS). Chest. 2018;154:862-71.
152. Bae S, Saggar R, Bolster MB, Chung L, Csuka ME, Derk C, et al. Baseline characteristics and follow-up in patients with normal haemodynamics versus borderline mean pulmonary arterial pressure in systemic sclerosis: results from the PHAROS registry. Ann Rheum Dis. 2012;71:1335-42.
153. Lammi MR, Saketkoo LA, Gordon JK, Steen VD. Changes in hemodynamic classification over time are common in systemic sclerosis-associated pulmonary hypertension: insights from the PHAROS cohort. Pulm Circ. 2018;8:2045893218757404.
154. Hinchcliff M, Khanna S, Hsu VM, Lee J, Almagor O, Chang RW, et al. Survival in systemic sclerosis-pulmonary arterial hypertension by serum autoantibody status in the pulmonary hypertension assessment and recognition of outcomes in scleroderma (PHAROS) registry. Semin Arthritis Rheum. 2015;45:309-14.
155. Chung L, Fairchild RM, Furst DE, Li S, Alkassab F, Bolster MB, et al. Utility of B-type natriuretic peptides in the assessment of patients with systemic sclerosis-associated pulmonary hypertension in the PHAROS registry. Clin Exp Rheumatol. 2017;35 Suppl 106:106-13.
156. Fischer A, Swigris JJ, Bolster MB, Chung L, Csuka ME, Domsic R, et al. Pulmonary hypertension and interstitial lung disease within PHAROS: impact of extent of fibrosis and pulmonary physiology on cardiac haemodynamic parameters. Clin Exp Rheumatol. 2014;32 6 Suppl 86:S109-14.
157. Lammi MR, Mathai SC, Saketkoo LA, Domsic RT, Bojanowski C, Furst DE, et al. Association between initial oral therapy and outcomes in systemic sclerosis-related pulmonary arterial hypertension. Arthritis Rheumatol. 2016;68:740-8.

Spanish Journal of Medicine

REVIEW ARTICLE

Fighting the tragedy of nursing homes in the COVID-19 pandemic

Máximo Bernabeu-Wittel[1,2], Lourdes Moreno-Gaviño[1], Dolores Nieto-Martín[1], Concepción Conde-Guzmán[1], Manuel Rincón-Gómez[1], Pablo Díaz-Jiménez[1], Luis Giménez-Miranda[1], Jara Ternero-Vega[1], Sonia Gutiérrez-Rivero[1], Ignacio Vallejo-Maroto[1], Reyes Aparicio-Santos[1], Carlos Jiménez-Juan[1], and Manuel Ollero-Baturone[1]*

[1]Department of Internal Medicine, Hospital Universitario Virgen del Rocío; [2]Department of Medicine, Universidad de Sevilla. Sevilla, Spain

Abstract

During the last months, the pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has hit cruelly elderly citizens living in nursing homes (NHs) across the world. As a matter of fact, NHs are highly vulnerable to the occurrence of this new coronavirus disease (COVID-19), which results in high lethality rates. In addition, most of the long-term care facilities are not yet prepared to manage with this new epidemiological and clinical scenario. In this article, we will review the impact of COVID-19 in NH, its causes and underlying factors, and the possible solutions of keeping SARS-CoV-2 at bay in NH from a triple perspective: the focus of public health policies and global measures, the operative level at NH institutions themselves, and the daily clinical scenario of clinicians and other health care workers.

Key words: Coronavirus disease-19. Severe acute respiratory syndrome coronavirus 2. Community-based long-term care. Frailty. Multimorbidity. Nursing homes.

Introduction

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is beating most countries in the world, with nearly 160 million of cases, and more than 3,290,000 deaths reported as of May 12, 2021[1]. The disease affects more frequently and severely elderly citizens; in fact, they make up around 30% of all cases, 45-50% of all hospitalizations, and 80% of all deaths[2,3]. In these age strata, SARS-CoV-2 disease (coronavirus disease [COVID-19]) lethality rate can reach up to 20-40%[4]. In virtually all countries, we have painfully experienced, that one of the most helpless environments for the expansion of SARS-CoV-2 are nursing homes (NHs)[5,6]. In these facilities, the impact of COVID-19 is a real danger that can be devastating[6,7].

In this article, we will review the impact of COVID-19 in NH, its causes and underlying factors, and the possible solutions for keeping SARS-CoV-2 at bay in NH from a triple perspective: public health, NH institutions themselves, and health care workers.

Impact of COVID-19 in NHs

Already from at the beginning of the pandemic, NH suffered from outbreaks of the disease. These outbreaks were always characterized by a “silent” entry of

Visual abstract available at https://spanishjmed.com/frame_esp.php?id=50

Correspondence:
*Máximo Bernabeu-Wittel
E-mail: wittel@cica.es

Date of reception: 03-02-2021
Date of acceptance: 20-05-2021
DOI: 10.24875/SJMED.21000004

Available online: 05-10-2021
Span J Med. 2021;1(3):154-161
www.spanishjmed.com

SARS-CoV-2 and a subsequent "explosion" of cases among both, residents and care professionals, affecting up to 60% and 30% of them, respectively[5]. More than 400 papers have been already published regarding COVID-19 in NH. The first well-documented outbreaks were described and analyzed in Singapore and the United States of America[7-9]. In all these early reports, the authors found high attack rates on residents and workers, with hospitalization and mortality rates over 50% and 30% of affected residents, respectively[7-9]. These experiences brought up the potential deleterious impact of COVID-19 in NH (and subsequently in local health-care systems) and suggested the fact that once SARS-CoV-2 enters into a long-term care facility, it has the potential to spread rapidly and widely. The main routes of entry of the virus into NH were visitors and workers. This fact underscores the importance of proactive actions to identify and exclude potentially infected staff and visitors, as well as early recognition of potentially infected patients, and implementation of appropriate infection prevention and control measures[5-9].

As SARS-CoV-2 progressively increased its incidence in the community, it was paralleled by more and more outbreaks in an increasing number of NH, until they became one of the hottest spots in the current pandemic[9-11]. This tragedy wave occurred in most world countries, with special virulence in those with more aged populations and a higher density of long-term care facilities. As a matter of fact, in the United States of America, it is calculated that more than 2300 NH had been affected until April 2020[12]. Another specially hit country is Spain, in which more than 20,000 citizens living in NH are estimated to have died during the first wave of COVID-19 pandemic[6,13].

In the last months, many clinicians and professional institutions have been warning society and authorities of the need to pay more attention and dedicate more resources to preventing and combating COVID-19 in long-term care facilities[14-17]. These recommendations had a heterogeneous influence among countries, but at less have contributed to highlight the vulnerability of these citizens toward this new disease, which has conditioned, that in many places, they are the priority population for starting vaccination programs[18,19]. The effectiveness of vaccination in these vulnerable populations has already been demonstrated; as of today, outbreaks in NH have virtually disappeared and the incidence and mortality of COVID-19 in citizens over 80 years of age has decreased drastically in Spain[19].

Causes and underlying conditions of the "perfect storm"

Three major features converging in NH can explain this experienced "perfect storm:" First, the characteristics of the resident population, second, the structural and professional peculiarities of the residential care model, and at last, the global tension and saturation of the health and social care systems at the peak of the pandemic.

The residents of NH are characterized by their old age, the presence of multiple and severe chronic diseases (such as advanced dementia, chronic heart failure, and others), a high burden of comorbidities, and elevated dependence rates. In these age strata, COVID-19 lethality rate can reach up to 50%[2,3]. This increased mortality may be explained in part by already known risk factors (frailty, infection acting as a trigger to decompensate other chronic conditions, immunosenescence, and development of geriatric syndromes' cascade). In fact, the impact of comorbidities in the outcome of multiple acute diseases has largely been demonstrated, and in a recent large multicenter cohort of patients with COVID-19, chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease, and obesity were associated with higher in-hospital mortality[20]. In addition, death-risk scores assessing multimorbidity issues like PROFUND index have proven their usefulness in the survival prediction of NH residents with COVID-19[21].

NHs, like other closed or half-closed institutions, are predisposed to epidemic outbreaks of airborne or contact pathogens as already widely documented[22,23]. The high dependence levels of residents for basic activities of daily living (such as bathing, dressing, feeding, or transfers) increase the likelihood of transmission through the care staff. But beyond these factors, SARS-CoV-2 pandemic has highlighted the main weaknesses of the social care systems. In many countries, NHs are located in the border of health-care and social services, and because of that, their connections and boundaries to both systems are somehow imprecise[5,6]. There are regulatory failures leading to lack of delimitation of responsibilities; funding shortfalls leading to structural problems and suboptimal staff training; a market-oriented model without strict quality control measures; and heterogeneous support from the health-care system, which frequently delegates its tasks to the NH teams themselves[24,25]. Under these circumstances, NH faced the pandemic lacking infrastructures and work flows to manage an epidemic of this magnitude; many of them were poorly connected with the health-care system; counted with lower staff ratio (usually planned to attend

Table 1. Public health measures carried out or proposed by different countries and institutions to prevent SARS-CoV-2 from entering NH

Public health measures	Field of action
Global, coordinated, coherent, and transparent plans for the management of COVID-19 in NH	Full society
Strengthen the integration of NH with the health-care system	Social and health care systems
Provide clinical teams (combining professionals from primary and hospital care) to attend possible outbreaks in NH	Health-care system
Prepare for separation of clean and contaminated spaces, circuits, professionals, and shifts in case of outbreaks, in NH	Social care system
Provide evacuation centers (campaign hospitals, medicalized hotels...) for outbreaks in NH with unavailability of separation measures	Social and health-care systems
Specific training programs to workers and managers of NH	Social Care System
Limit/ban any visit and entry to NH (family members, volunteers, providers...) when high community incidence rates	Full society
Strict control on health status and SARS-CoV-2 exposure of NH staff members	NH staff
Reinforcement/increase of NH staff to face higher workload, and possible decrease of personnel due to exposure to SARS-CoV-2	NH staff
Extreme prevention measures in the daily care of residents with a higher level of dependency	NH staff
Ensure support for and availability of adequate personal protective equipment	NH staff
Avoid unnecessary trips and outings. Promotion of telemedicine and e-health devices for medical revisions	NH population
Regular viral testing of NH staff and residents	NH staff and residents
Ongoing screening of all individuals who are admitted to NH	NH residents
Isolate or quarantine all admissions from hospitals or other high-risk areas, regardless of test results	NH residents
Massive vaccination of all NH residents	Health-care system

NH: nursing home.

"stable" residents); and had suboptimal staff training and expertise in managing patients with COVID-19. The time has come to rethink the role and place of NH in our societies on a global scale, and to work on a deeper integration of health and social care.

At last, the saturation of health care systems during the peak of the pandemic nearly reached the collapse, leading to an extreme lack of material and professionals in hospitals and primary care. All countries and citizens were aware of these disaster situations, which involved ethical issues, prioritizing measures, as well as resources allocation and reallocation to save most lives, and lives of severely ill patients with highest survival probability[26-30].

A global strategy is needed to fight the storm. Political measures and public health

The responses of country federations and the countries themselves to this new virus challenge have been heterogeneous. Countries articulating an early response, with more restrictive measures in terms of stopping the main routes of transmission, and more coherent, homogeneous and clear guidelines, developing actions in the main "hot spots," have obtained better results in terms of SARS-CoV-2 spread, morbidity, and mortality. In contrast, in countries that decided more permissive measures to generate herd immunity or to safeguard the economy, the impact of the epidemic has been much more devastating[31]. This proofs the importance of global political measures, which should always be guided by scientific knowledge. In this extraordinary situation, governments and institutions have to make difficult and complex decisions, but the ultimate goal should be to save as many lives as possible, even if many elements of our daily lives have to be given up.

Dealing with the tragedy of NH requires a coordinated response from society as a whole. National, regional,

Table 2. Different approaches to manage with COVID-19 outbreaks in nursing homes

Approach	Advantages	Disadvantages	Best use
On-site medicalization	- Efficacious - Reduces mortality and hospital referrals - Offers optimal palliative care to those residents in their end-of-life periods - Maintains preserves home feeling and usual caregivers	- Needs substantial number of health-care professionals and equipment	- Large sized NH - Large outbreaks - Palliative care NH
Evacuation of infected residents*	- Easy and fast	- Needs facilities reconditioning - Disconnection from home and usual caregivers - Potential stay of asymptomatic infected residents	- Medium-sized NH - Small outbreaks
Evacuation of non-infected residents	- Easy and fast	- Needs facilities reconditioning - Disconnection from home and usual caregivers - Potential evacuation of asymptomatic infected residents	- Medium-sized NH - Small outbreaks
Evacuation of all residents*	- Easy and fast - Allows an early NH disinfection	- Needs facilities reconditioning - Disconnection from home and usual caregivers - Potential transmission to other hosts beyond the NH	- Small-sized NH - Small outbreaks

*To medicalized facilities such as hotels, hospitals, or campaign hospitals. NH: nursing home.

and local governments need to develop a coherent and coordinated plan, devoting all necessary resources to preserving the health of NH residents. All public institutions, scientists, and the media must raise awareness among the public at large to avoid unnecessary exposure of the most frail populations to SARS-CoV-2. Finally at individual levels, the recommendations of the experts must be accomplished, and the authorities have to prioritize the enough resources to deal with COVID-19 in NH.

Focusing on specific public health measures, there are some which have been performed and/or proposed by some countries and institutions, as detailed in table 1[5-7,14-17,25,31-35]. These actions are oriented to three levels: to the political institutions and society as a whole to make the vulnerability of NH visible and to raise awareness among the entire population of the importance of devoting resources to these institutions; to the social and health systems to improve their coordination, teamwork, and cooperation actions; and finally, to workers and residents of NH to ensure the necessary structural changes in the centers, the professional skills in the prevention and management of COVID-19, the necessary equipment and protection measures, and the universal and regular screening of workers and residents.

Keeping at bay SARS-CoV-2 in the operative level. A pragmatic approach to manage NH outbreaks

The management of NH outbreaks has been also different during the pandemic. Most frequent approaches are detailed in table 2. In the last months, we have accumulated experience in the on-site medicalization programs in our area and will detail the main actions to develop such programs.

In the medicalization program of a NH with a COVID-19 outbreak, it is crucial to establish a relationship of trust among NH staff and health-care staff to carry out an optimal teamwork. When first facing with an outbreak, there are a lot of tasks to arrange, so it is useful to follow a checklist of priority actions. These can be summarized in nine:

1. Visiting the NH to identify the responsible person, evaluate needs, establish immediate measures, and plan the following, clearly assigning roles and responsibilities.
2. Evaluating material resources, equipment, expendables, and medication needs (informatics, a portable ultrasound device, oxygen therapy, material for blood extractions, intravenous and subcutaneous lines, intravenous fluids, intravenous drugs...); and providing the necessary.

3. Identifying the needs of health care workers (physicians and nurses). Mobilizing the coordinated team (primary care and hospital professionals) to provide clinical attention 24 h during 7 days in the week.
4. Locating a "clean room" for informatics equipment, clinical work, consulting and writing in electronic clinical charts, and administrative tasks. Establishing full connection with health-care electronic information systems.
5. Locating a secure locker room for NH staff and health care workers' dressing and undressing. Ensuring enough PPE supplies to all team members.
6. Universal SARS-CoV-2 testing to residents and staff members to detect active infections, by performing real-time polymerase chain reaction (RT-PCR) for the detection of specific viral ribonucleic acid (RNA) from nasopharyngeal swab smears. Repeating test after 7 days, or if symptoms development to not infected residents. Performing a meticulous epidemiological survey and follow-up to trace the outbreaks' origin and evolution.
7. Establishing a "clean area" with rooms and common spaces for uninfected residents, and a "contaminated area" with rooms and common spaces for residents with confirmed infection. Warranting the compulsory use of PPE to all members of the work team while remaining in the contaminated area.
8. Specific training of staff members in the management and care of COVID-19 patients. Separation of those working in the clean area and those working in the contaminated area, with prohibition to change shifts between professionals from these two areas. Proper clinical attention and quarantine of staff members with confirmed SARS-CoV-2 acute infection.
9. Ensuring common clinical management, and communication protocol to inform residents' families.

It may be practical to count with a "survival kit" of expendables and medications, to manage COVID-19 patients the first 48-72 h, until the supply circuit is operational. We detail this kit in table 3.

After controlling the outbreak, it is important to establish a demedicalization process. We consider that after 14 days of the last confirmed COVID-19 case, the NH is eligible for demedicalization. In this process, the following five requirements should be ensured: (1) A contingency plan with infection and prevention measures, active surveillance, actions in case of new infections, and provision of spaces and rooms for possible future "contaminated areas." (2) Urgent notification of the appearance of suspected cases compatible with

Table 3. "Survival kit" for the initial approach of COVID-19 outbreaks in nursing homes

"Survival kit"*	Number
Health care clothing	
- Personal protective equipment	20
- Gloves, surgical caps, and shoe covers (different sizes)	100, 100, 100
- FFP2 and surgical masks	50, 50
- Surgical gowns	20
- Hydroalcoholic gel	1000 mL
- Protection glasses	5
Medical devices	
- Oxygen nasal cannulas and different concentration masks	10, 10
- Portable oxygen concentrators	3
- Portable ultrasound dispositive	1
Intravenous fluids and associated material	
- Needles (subcutaneous, intramuscular, intravenous, and trocar)	20, 20, 20, 20
- Syringes (2 mL, 5 mL, and 10 mL)	20, 20, 20
- Intravenous lines	20
- Subcutaneous lines	10
- Dosimeters (Dosiflow®)	10
- Infusers	3
- Peripheral catheters (Abocath® 20 and Abocath® 22)	15, 15
- Dressings and adhesive tapes	30
- Chlorhexidine, 70° ethanol, or povidone iodine	1000 mL
- Saline 1000, 250, and 100 mL	5, 5, 5
- Glucose 5% 500 mL	3
- Glucosaline 500 mL	3
Medications	
COVID-19 supplies	
- Dexamethasone 4 mg (iv)	50
- Methyl-prednisolone 40 mg (iv)	500
- Furosemide 20 mg (iv)	100
- Metoclopramide 10 mg (iv/sc)	500
- Enoxaparin 20, 40, 60 mg (sc)	50, 100, 50
- Remdesivir	On request
- Tocilizumab	On request
Anti-bacterial supplies	
- Ceftriaxone 2 g (iv)	75
- Ceftriaxone 1 g (im)	30
- Levofloxacin 500 mg (iv)	75
- Levofloxacin 500 mg (tablets)	30
Respiratory supplies	
- Salbutamol (inhaler)	50
- Ipratropium (inhaler)	50
- Formoterol/budesonide (inhaler)	25
- Inhalation chambers	25
Other medications	
- Acetaminophen 1 g (iv)	500
- Acetaminophen 500 mg (tablets)	200
- Morphine 10 mg (iv/sc)	500
- Midazolam 15 mg, 50 mg (iv/sc)	100, 50
- Levomepromazine 25 mg (iv/sc)	20
- Haloperidol 5 mg (iv/sc)	50
- Scopolamine 0.5 mg (iv/sc)	200

*This "kit" is planned to cover the first 24-48 h of on-site medicalization of NH with COVID-19 outbreaks affecting initially 40-50 residents.

Table 4. Proposed death risk stratification approach in elderly patients living in nursing homes

Index score	Proposed approach
PROFUND ↓ and CURB-65 ↓	- Etiologic-pathogenic approach - Standard care*
PROFUND ↓ and CURB-65 ↑	- Etiologic-pathogenic approach - Intensified care#
PROFUND ↑ and CURB-65 ↓	- Symptomatic approach - Standard care*
PROFUND ↑ and CURB-65 ↑	- Symptomatic approach - Intensified care &

*Standard ward or nursing home; # including transfer to intensive care unit; & including the offer of palliation, palliative sedation, and spiritual care.

COVID-19. (3) Continuous training to staff members. (4). Staff members control through daily temperature measurement and a responsible declaration at the entrance to the workplace of not having symptoms compatible with COVID-19, and in case of symptoms onset, urgent notification. (5) Public and auditable weekly checklist of the infection control measures[5].

Managing and treating old frail patients with COVID-19. The daily clinical trench

Managing elderly frail patients with COVID-19 are a triple challenge.

First, their symptoms are more vague, unspecific, and similar to other acute conditions (many of them develop only geriatric syndromes such as delirium, falls, or neuromuscular dysphagia)[36,37]. Other typical COVID-19 symptoms such as fever, odynophagia, anosmia, or ageusia are also uncommon. Hence, a high suspicion level is needed to early recognize, confirm, isolate incidental cases, and avoid further transmission in NH.

Second, many of these patients suffer comorbidities or are indeed polypathological patients, whose conditions frequently get decompensated and need to be globally treated. It is common that these patients develop heart failure, bronchial hyperreactivity, and a variety of geriatric syndromes (immobilization, constipation, acute urinary retention, and among others), which need specific expertise in their integral management.

And third, a deep knowledge of multimorbidity, frailty, and geriatric medicine is needed to establish best clinical actions and treatments. An earlier symptoms recognition by well-trained professionals is needed to lead to earlier treatment and support measures; in this sense, treating very old patients with potentially acceptable life expectancy is safe and of benefit; otherwise, we could fall in a somehow nihilist deviation of clinical practice. Besides, a gentle attention to the most frail and terminally ill residents will enable a personalized care according to preferences of patients and families; the rush of a pandemic situation should not make palliative care invisible, on the contrary, an optimal palliative care has to be offered to this selected population to avoid futility and unnecessary iatrogenia[38].

Among the multiple COVID-19 prognostic scores, the presence of multimorbidity, chronic conditions, and functional status is often forgotten. However, in this population, chronic conditions are of similar relevance of severity of COVID-19 in determining patient's survival. This fact has been demonstrated also in many other acute and chronic diseases[39-41]. Hence, we propose the death risk stratification to be performed on two axis detailed in table 4[21]. The first dimension to assess should be the death risk due to basal status and severity of chronic conditions, by means of a co-morbidity tool like PROFUND index[42]; with this assessment, we could differentiate those patients with good life expectancy in which a nihilist practice should be avoided and an etiologic-pathogenic approach is the best choice; and those patients with basal severe illnesses or already in their end-of-life trajectory, in which futility and iatrogenia should be avoided and a more symptomatic approach is the best clinical practice. The second axis is the current death risk due to the severity of COVID-19, by means of a pneumonia severity tool like CURB-65 index[43]; standard care should be offered to patients with mild-moderate disease, while an intensified care with advanced measures (intensive care for those with good life expectancy and advanced palliative care for those who are already in their end-of-life process) is the best option for those with severe COVID-19[21].

At last, it may be useful to prepare a checklist of important issues to consider and consign in the daily clinical evaluation and care of all patients (such as clinical status, vital signs, global approach, treatments, patient and family preferences...). This checklist should be available to all members of the work team.

Conclusions

NHs are highly vulnerable to the occurrence of COVID-19 outbreaks, which are unfortunately burdened with high mortality rates among residents.

Three converging features can explain this "perfect storm:" The characteristics of the resident population, the structural and professional singularities of the residential care model, and the global tension and

saturation of the health and social care systems during pandemic peaks.

Dealing with the tragedy of NH requires a coordinated response from national, regional, local governments, and societies as a whole. Best results in terms of stopping transmission have been obtained with an early response, restrictive measures, and with coherent, homogeneous and clear guidelines, developing actions in the main "hot spots."

It is important to carefully plan the management of COVID-19 outbreaks in NH. The best choice will depend on the NH and outbreak size. Possible solutions are on-site medicalization programs or partial/total evacuation to other appropriate facilities.

Finally, an optimal clinical attention of these patients is of vital importance. They frequently develop non-specific symptoms as well as geriatric syndromes as manifestations of COVID-19, and their comorbidities often get decompensated. In their clinical approach, an exquisite prognostic stratification may be of considerable help.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for profit sectors.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Acknowledgments

Members of the RESICOVID Study Group are detailed below:

Reyes Aparicio-Santos[1], Máximo Bernabeu-Wittel*[1,2], Silvia Calzón-Fernández[3], Concepción Conde-Guzmán[1], Juan Delgado de la Cuesta[1], Pablo Díaz-Jiménez[1], Luis Giménez-Miranda[1], Sonia Gutiérrez-Rivero[1], Carlos Jiménez-Juan[1], Lourdes Moreno-Gaviño[1], Mª Mar Muñoz-García[4], Dolores Nieto-Martín[1], Manuel Ollero-Baturone[1], Manuel Rincón-Gómez[1], Jara Ternero-Vega[1], Ignacio Vallejo-Maroto[1]

[1]Internal Medicine Department, Hospital Universitario Virgen del Rocío; [2]Medicine Department, Universidad de Sevilla; [3]Centro de la Salud de Atención Primaria Los Bermejales, Distrito de Atención Primaria; [4]Epidemiology and Public Health Department, Distrito de Atención Primaria. Seville, Spain

References

1. European Centre for Disease Control and Prevention. COVID-19 Situation Update Worldwide, as of Week 18; 2021. Available from: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases. [Last accessed on 2021 May 16].
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.
3. Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, Lumbreras-Bermejo C, Ramos-Rincón JM, Roy-Vallejo E, et al. on behalf of SEMI-COVID-19 network. Clinical characteristics of patients hospitalized with COVID-19 in Spain: results from the SEMI-COVID-19 registry. Rev Clin Esp. 2020;220:480-94.
4. Ramos-Rincon JM, Buonaiuto V, Ricci M, Martín-Carmona J, Paredes-Ruíz D, Calderón-Moreno M, et al, SEMI-COVID-19 Network. Clinical characteristics and risk factors for mortality in very old patients hospitalized with COVID-19 in Spain. J Gerontol A Biol Sci Med Sci. 2021;76:e28-37.
5. Bernabeu-Wittel M, Ternero-Vega JE, Nieto-Martín MD, Moreno-Gaviño L, Conde-Guzmán C, Delgado-Cuesta J, et al. Effectiveness of a on-site medicalization program for nursing homes with COVID-19 outbreaks. J Gerontol A Biol Sci Med Sci. 2021;76:e19-27.
6. Bernabeu-Wittel M, Gómez-Huelgas R, Nieto-Martín MD, SEMI-COVID-19 Network. Time to stop the tragedy in Spanish nursing homes during the COVID-19 pandemic. J Am Geriatr Soc. 2021;69:320-2.
7. Fallon A, Dukelow T, Kennelly SP, O'Neill D. COVID-19 in nursing homes. QJM 2020;113:391-2.
8. Tan LF, Seetharaman SK. COVID-19 outbreak in nursing homes in Singapore. J Microbiol Immunol Infect. 2021;54:123-4.
9. McMichael TM, Currie DW, Clark S, Pogosjans S, Kay M, Schwartz NG, et al. Epidemiology of covid-19 in a long-term care facility in king county, Washington. New Engl J Med. 2020;382:2005-11.
10. Tseng TG, Wu HL, Ku HC, Tai CJ. The impact of the COVID-19 pandemic on disabled and hospice home care patients. J Gerontol A Biol Sci Med Sci. 2020;75:e128-9.
11. Quigley DD, Dick A, Agarwal M, Jones KM, Mody L, Stone PW. COVID-19 preparedness in nursing homes in the midst of the pandemic. J Am Geriatr Soc. 2020;68:1164-6.
12. Kwlatkowski M, Nadonly TL. At Least 2,300 Nursing Homes Have Coronavirus Cases-and the Reality is Likely Much Worse. Washington, DC: USA Today; 2020.
13. Rada AG. Covid-19: the precarious position of Spain's nursing homes. BMJ. 2020;369:m1554.
14. American Geriatrics Society. American geriatrics society policy brief: COVID-19 and nursing homes. J Am Geriatr Soc. 2020;68:908-11.
15. Davidson PM, Szanton SL. Nursing homes and COVID-19: we can and should do better. J Clin Nurs. 2020;29:2758-9.
16. Lloyd-Sherlock PG, Kalache A, McKee M, Derbyshire J, Geffen L, Gomez-Olive Casas F. WHO must prioritise the needs of older people in its response to the covid-19 pandemic. BMJ. 2020;368:m1164.
17. Gaur S, Dumyati G, Nace DA, Jump RL. Unprecedented solutions for extraordinary times: helping long-term care settings deal with the COVID-19 pandemic. Infect Control Hosp Epidemiol. 2020;41:729-30.
18. Anonymous. ECDC Releases COVID-19 Vaccination Rollout Strategies for EU/EEA. European Centre for Disease Prevention and Control. Available from: https://www.ecdc.europa.eu/en/news-events/ecdc-releases-vaccination-rollout-strategies-eueea. [Last accessed on 2021 May 15].
19. Anonymous. COVID-19 Vaccination Strategy in Spain; Update1. Spanish Ministry of Health; 2020. Available from: https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/vacunaCovid19.htm.
20. Docherty AE, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20133 UK patients in hospital with COVID-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. BMJ. 2020;369:m1985.

21. Bernabeu-Wittel M, Ternero-Vega JE, Díaz-Jiménez P, Conde-Guzmán C, Nieto-Martín MD, Moreno-Gaviño L, et al. Death risk stratification in elderly patients with covid-19. A comparative cohort study in nursing homes outbreaks. Arch Gerontol Geriatr. 2020;91:104240.
22. Sengstock DM, Thyagarajan R, Apalara J, Mira A, Chopra T, Kaye KS, et al. Multidrug-resistant *Acinetobacter baumannii*: an emerging pathogen among older adults in community hospitals and nursing homes. Clin Infect Dis. 2010;50(12):1611-6.
23. McKinnell JA, Singh RD, Miller LG, Kleinman K, Gussin G, He J, et al. The SHIELD orange county project: multidrug-resistant organism prevalence in 21 nursing homes and long-term acute care facilities in Southern California. Clin Infect Dis. 2019;69:1566-73.
24. Inzitari M, Risco E, Cesari M, Buurman BM, Kuluski K, Davey V, et al. Editorial: nursing homes and long term care after COVID-19: a new era? J Nutr Health Aging. 2020;24:1042-6.
25. Anonymous. Scarce, Late, and Bad. The Unacceptable Helplessness of Elderly Citizens Living in Nursing Homes of Spain During COVID-19 (Spanish). Doctors Without Borders (Médicos sin Fronteras); 2020. Available from: https://www.static.msf.es/web/archivos/cov-19/AAFF-MSF-Informe-COVID19-Residencias-BAJA-NOTA.pdf?_ga=2.163940604.2100051873.1600703801-1858459954.1600034663. [Last accessed on 2021 May 15].
26. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. JAMA. 2020;323:1545-6.
27. Steinberg E, Balakrishna A, Habboushe J, Shawl A, Lee J. Calculated decisions: COVID-19 calculators during extreme resource-limited situations. Emerg Med Pract. 2020;22:CD1-5.
28. Peterson A, Largent EA, Karlawish J. Ethics of reallocating ventilators in the covid-19 pandemic. BMJ. 2020;369:m1828.
29. Rosenbaum L. Facing covid-19 in Italy-ethics, logistics, and therapeutics on the epidemic's front line. N Engl J Med. 2020;382:1873-5.
30. Mannelli C. Whose life to save? Scarce resources allocation in the COVID-19 outbreak. J Med Ethics. 2020;46:364-6.
31. Warne DJ, Ebert A, Drovandi C, Hu W, Mira A, Mengersen K. Hindsight is 2020 vision: a characterisation of the global response to the COVID-19 pandemic. BMC Public Health. 2020;20:1868.
32. American Health Care Association. Guidance and Resorts. Available from: https://www.ahcancal.org. [Last accessed on 2021 May 15].
33. John A. Hartford Foundation. COVID-19 Resources for Nursing Homes and Long-term Care. Available from: https://www.johnahartford.org/dissemination-center/view/nursing-home-long-term-care-resources. [Last accessed on 2021 May 15].
34. The Society for Post-acute and Long-term Care Medicine/AMDA. AMDA Update on COVID-19. Available from: https://www.paltc.org/COVID-19. [Last accessed on 2021 May 15].
35. Centers for Disease Control and Prevention. Preparing for COVID-19 in Nursing Homes. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/long-termcare.html. [Last accessed on 2021 May 15].
36. Tay HS, Harwood R. Atypical presentation of COVID-19 in a frail older person. Age Ageing. 2020;49:523-4.
37. Ward CF, Figiel GS, McDonald WM. Altered mental status as a novel initial clinical presentation for COVID-19 infection in the elderly. Am J Geriatr Psychiatry. 2020;28:808-11.
38. Borasio GD, Gamondi C, Obrist M, Jox R, For The Covid-Task Force of Palliative Ch. COVID-19: decision making and palliative care. Swiss Med Wkly. 2020;150:w20233.
39. Greenfield S, Apolone G, McNeil BJ, Cleary PD. The importance of co-existing disease in the occurrence of postoperative complications and one-year recovery in patients undergoing total hip replacement. Med Care. 1993;31:141-54.
40. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chron Dis. 1973;27:387-404.
41. Lang CC, Mancini DM. Non-cardiac comorbidities in chronic heart failure. Heart. 2007;93:665-71.
42. Bernabeu-Wittel M, Ollero-Baturone M, Moreno-Gaviño L, Barón-Franco B, Fuertes A, Murcia-Zaragoza J, et al. Development of a new predictive model for polypathological patients. The PROFUND index. Eur J Intern Med. 2011;22:311-7.
43. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377-82.

Spanish Journal of Medicine

GUIDELINES AND CONSENSUS

Consensus 2021 for medical management of type 2 diabetes from the Diabetes, Obesity, and Nutrition Working Group of the Spanish Society of Internal Medicine

Francisco J. Carrasco-Sánchez[1], José M. Fernández-Rodríguez[2], Pedro P. Casado-Escribano[3], José P. Miramontes-González[4], Ricardo Gómez-Huelgas[5], María D. García-de-Lucas[6], Javier Ena[7], and Juana Carretero-Gómez[8] on behalf of the Diabetes, Obesity, and Nutrition Working Group of the Spanish Society of Internal Medicine*

Department of Internal Medicine, [1]Hospital Universitario Juan Ramón Jiménez, Huelva; [2]Hospital Carmen y Severo Ochoa, Cangas de Narcea, Asturias; [3]Hospital de la Princesa, Madrid; [4]Hospital Clínico Universitario de Valladolid, Valladolid; [5]Hospital Regional Universitario de Málaga, Instituto de Investigación Biomédica de Málaga (IBIMA), Universidad de Málaga, Málaga; [6]Hospital Costa del Sol, Marbella; [7]Hospital Marina Baixa, Villajoyosa, Alicante; [8]Hospital Universitario de Badajoz, Badajoz. Spain

Abstract

Type 2 diabetes (T2D) is a major health concern due to its high prevalence, severe morbidity, and elevated mortality. Medical antidiabetic treatment is constantly changing and becoming more complex. Many national and international societies have published recommendations for the medical treatment of T2D focused on patients' clinical situations instead of glycemic control. However, most consensus documents offer such comprehensive information that it can be difficult to apply and effectively put into practice. This document contains the necessary 2021 update of the consensus statement about recommendations for the medical management of T2D from the Diabetes, Obesity, and Nutrition Working Group of the Spanish Society of Internal Medicine. The aim of this consensus document is to facilitate therapeutic decision-making to improve diabetes patient care. By focusing on clinical conditions such as cardiovascular risk, heart failure, diabetic kidney disease, obesity and overweight, the elderly population, risk of hypoglycemia, and history of diabetes of more than 10 years, the consensus recommends selecting antidiabetic drugs according to the best available evidence. The document prioritizes the use of glucagon-like peptide-1 receptor agonists and sodium-glucose contransporter-2 inhibitors due to their additional cardiovascular and renal benefits beyond glycemic control.

Key words: Type 2 diabetes. Treatment. Cardiovascular disease. Heart failure. Obesity. Hypoglycemia. Chronic renal disease. Elderly.

Introduction

The prevalence of type 2 diabetes (T2D) mellitus is increasing exponentially worldwide. The International Diabetes Federation (IDF) estimates that 463 million adults aged 20-79 currently suffer from diabetes, or 1 in 11 of the global population, and 50% of these (232 million) are undiagnosed. The number of individuals with diabetes is likely to rise to 578 million by 2030, and to 700 million by 2045[1].

The prevalence of diabetes in Spain, according to the di@bet.es study, is 13.8% of the adult population. Of

Corrrespondence:
*Francisco J. Carrasco-Sánchez
E-mail: franciscoj.carrasco.sspa@juntadeandalucia.es

Date of reception: 28-03-2021
Date of acceptance: 07-06-2021
DOI: 10.24875/SJMED.21000010

Available online: 05-10-2021
Span J Med. 2021;1(3):162-170
www.spanishjmed.com

these individuals, 7.8% are aware of their T2D diagnosis (almost 3 million people) while 6% (more than 2.3 million) are unaware that they have the disease[2]. The aging population, the steady rise in obesity, and the negative aspects of unhealthy diets, such as the departure from the Mediterranean diet, are factors that influence this growing prevalence of diabetes around the world. Recent data from the di@bet.es cohort reports an incidence of diabetes of 11.6 cases per 1000 people/year, of which 3.7 cases per 1000 people/year know of their diagnosis and, most concerning, 7.9 cases per 1000 people/year are unaware of their disease. Incidence varies according to age and life stages, with very low prevalence among those under 30 years and in women of fertile age, and high prevalence among the elderly (25%)[3]. It is estimated that 35% of patients hospitalized in Internal Medicine departments in Spain receive a secondary diagnosis of diabetes[4,5]. These patients are typically elderly with a high comorbidity rate, and often present with established chronic kidney disease and cardiovascular disease (CVD)[5,6]. Furthermore, the risk of hypoglycemia, mainly as a result of illness, is high[7]. The prevalence of obesity in the general population is estimated at 23%, a figure similar to that found in patients treated by Internal Medicine services[8]. In diabetes patients, this number reaches 35% for obesity and 70% for overweight.

There are many national and international proposals for tackling T2D therapeutically which vary in complexity and applicability in daily clinical practice. To provide practical guidance on the choice of antidiabetic drugs, the diabetes, obesity, and Nutrition Working Group of the Spanish Society of Internal Medicine (Sociedad Española de Medicina Interna [SEMI]) published its recommendations in 2020 based on a critical review of the scientific literature[9]. This document updates those recommendations based on new findings published in 2020.

The proposals in this document do not intend to override clinicians' professional judgment and should only be applied following a medical assessment based on the doctor's own knowledge and common practice; treatment can be adjusted according to individual preference, comorbidities, and other health-care system and patient-related factors.

The main aim of this consensus is to present a short, practical document of recommendations for antidiabetic drug therapy, striking a balance between simplicity and scientific rigor, to help clinicians to make therapeutic decisions based on the best available evidence.

Material and methods

The first part of the consensus contains recommendations based on the most frequent clinical situations that patients experience: high/very high cardiovascular risk, heart failure (HF), diabetic kidney disease (DKD), obesity and overweight, aged 75 and over, high risk of hypoglycemia, and a history of diabetes of more than 10 years (Fig. 1). The second set of recommendations concerns the administration of treatment based on the patient's initial glycated hemoglobin (HbA1c) level, and the objectives to be agreed on with the patient (Fig. 2).

This 2021 update is based on a review of the revised recommendations for T2D drug treatment published by the American Diabetes Association (ADA) in January 2021[10]; in addition, we ran a bibliographical search published in 2020 filtered by "T2D" in combination with: "CVD," "HF," "DKD," "obesity," "elderly," "hypoglycemia," "glucagon-like peptide-1 receptor agonists GLP-1RAs," "sodium-glucose contransporter-2 (SGLT2) inhibitors," "DPP4 inhibitors," and "insulin."

The first version of this consensus was published in 2020 in *Revista Clínica Española* (online, June 2020)[9]. This updated version contains additional information from four clinical trials and two systematic reviews[11-17].

We used standard ADA classifications to test the quality of the evidence: A (clear evidence from randomized controlled trials); B (evidence from observational studies); C (evidence from non-controlled studies); and E (a consensus of experts or clinical experience)[18]. Each principal recommendation in our consensus is categorized and stated within parentheses by one of these letters.

The consensus draft was revised and approved by a committee of experts from SEMI's diabetes, obesity, and Nutrition Working Group, and a final consensus reached.

Results and recommendations

Metformin and lifestyle changes are still the main recommendations for treating T2D in the absence of intolerance or contraindication. In 75-80% of patients participating in cardiovascular safety studies, metformin was administered in combination with other antidiabetic drugs that were the focus of those studies (A).

High and very high cardiovascular risk

CVD in people with diabetes begins before diabetes is diagnosed; this concept, known as the

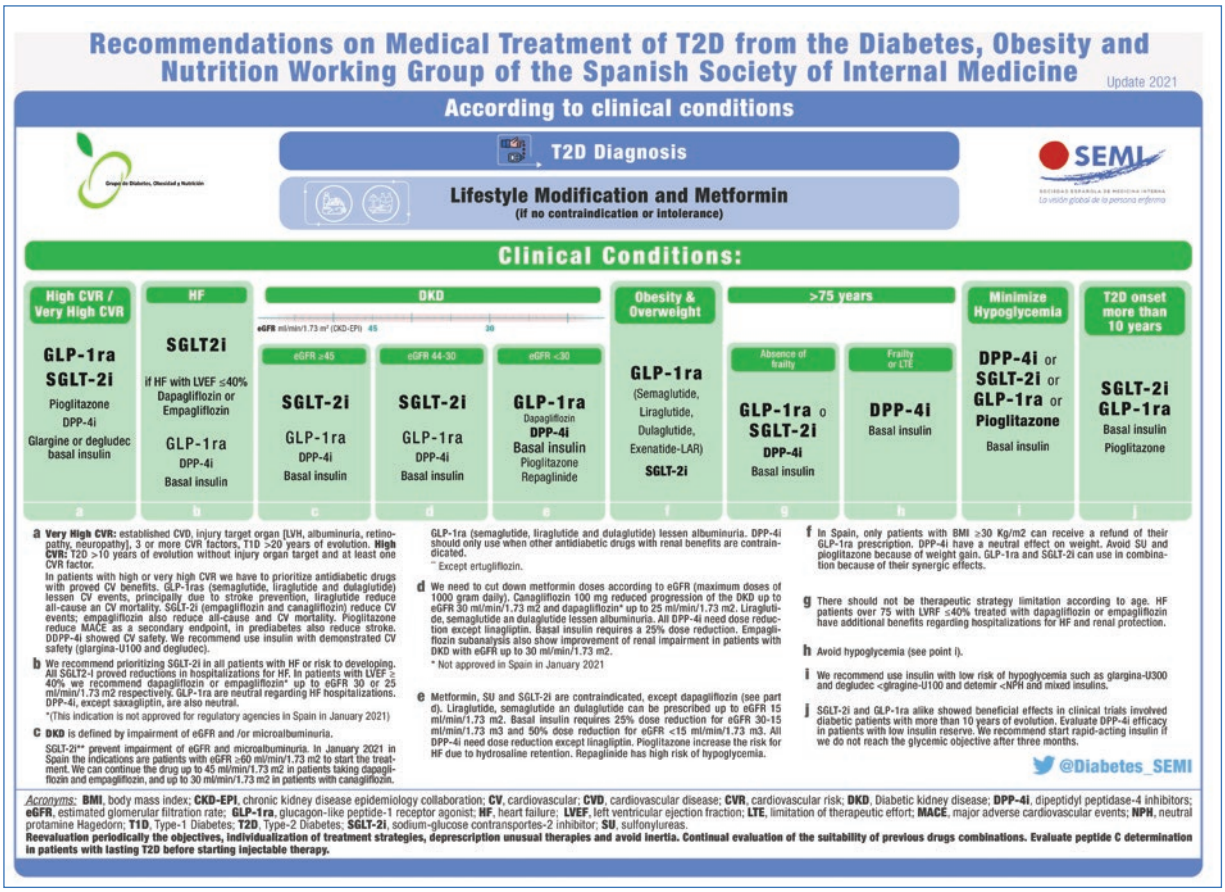

Figure 1. Recommendations on medical treatment of type 2 diabetes from the Diabetes, Obesity, and Nutrition Working Group of the Spanish Society of Internal Medicine.

cardiovascular continuum, advises that the diabetic patient be classified as high or very high cardiovascular risk regardless of the presence of established CVD. Patients are classified as high cardiovascular risk if they have a T2D history of more than 10 years in the absence of target organ damage, and with at least one additional cardiovascular risk factor. Diabetic patients are classified as very high cardiovascular risk if they have target organ damage, three or more additional cardiovascular risk factors, or established CVD[19].

Metformin is considered to be safe even for high and very high cardiovascular risk patients[20] (C). GLP-1RAs and SGLT-2 inhibitors are the drugs of choice, as their use is associated with a reduction in CVD events as compared to placebo (A).

In the LEADER trial, liraglutide, a GLP-1RA, reduced the primary combined endpoint of major adverse cardiovascular events (MACE) (hazard ratio [HR]: 0.87; 95% confidence interval [CI]: 0.78-0.97; p = 0.01). In the ungrouped analysis, the relative risk reduction (RRR) was 22% (p = 0.007) for CV mortality and 15% (p = 0.02) for total mortality[21]. In the SUSTAIN-6 study, semaglutide reduced MACE (HR 0.74; 95% CI: 0.58-0.95; p = 0.02) with 39% RRR (p = 0.04) for stroke[22]. Similarly, in the REWIND study, dulaglutide reduced MACE (HR 0.88; 95% CI: 0.79-0.99; p = 0.026) with 24% RRR (p = 0.017) for stroke[23]. Lixisenatide[24] and exenatide LAR[25] were neutral compared to standard treatment.

Regarding SGLT2 inhibitors, empagliflozin (EMPA-REG-OUTCOME trial) also reduced MACE (HR 0.86; 95% CI: 0.74-0.99; p = 0.04) with a 38% RRR (p < 0.001) for CV mortality and 32% (p < 0.001) for total mortality[26]. In the CANVAS study, canagliflozin reduced MACE (HR 0.86; 95% CI: 0.75-0.97 p = 0.02), not reaching statistical significance for the individual cardiovascular outcome components[27]. The DECLARE study on dapagliflozin found no statistical significance in the reduction of MACE[28].

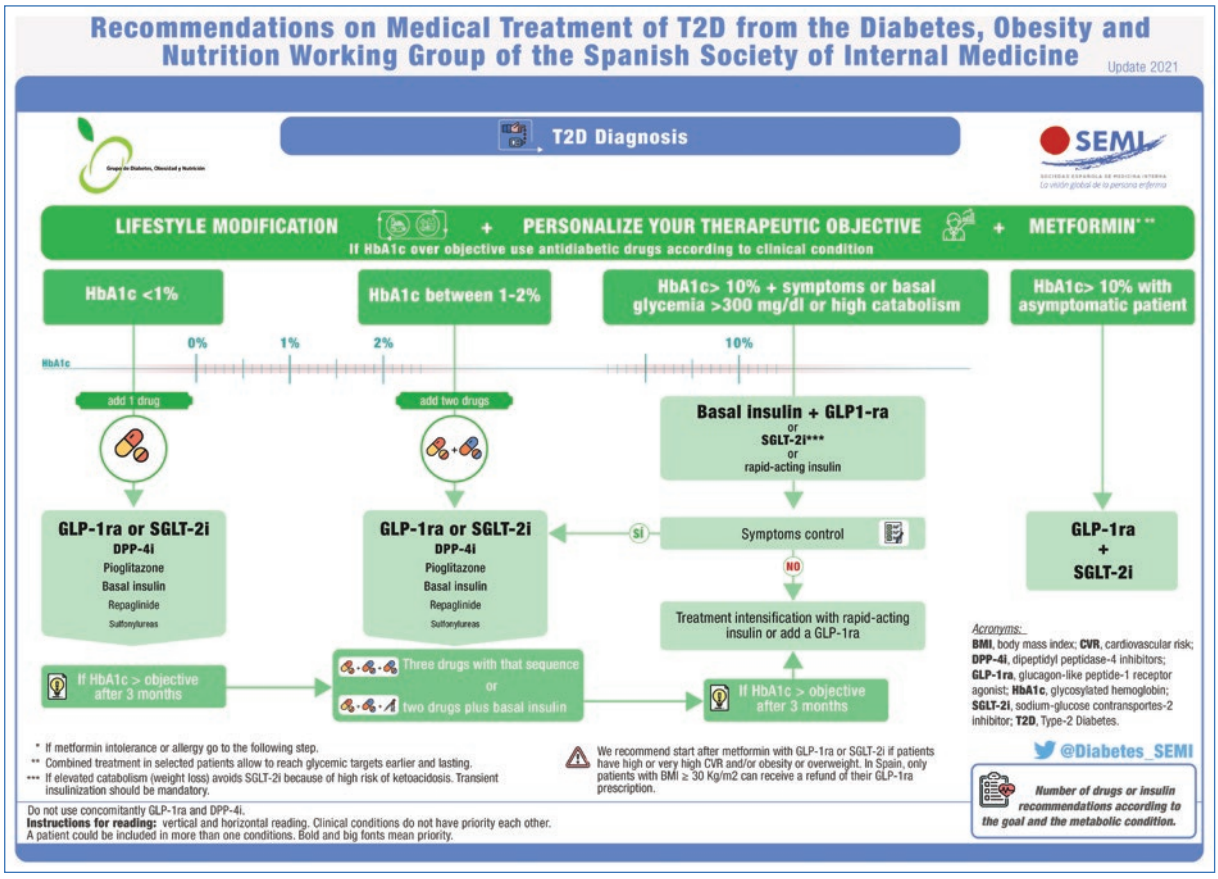

Figure 2. Recommendations on medical treatment of type 2 diabetes from the Diabetes, Obesity, and Nutrition Working Group of the Spanish Society of Internal Medicine.

The VERTIS-CV trial with ertugliflozin showed no reduction in cardiovascular events (HR 0.97; 95.6% CI: 0.85–1.11; p < 0.001 for non-inferiority) in a population similar to that of the EMPA-REG-OUTCOME study[11].

The PROactive study on pioglitazone found a 16% RRR (p = 0.027) in MACE as a secondary objective[29]. In a pre-diabetic population, treatment with pioglitazone was linked to a 24% RRR (p = 0.007) for the combined variable of stroke and/or heart attack[30] (A).

The CV safety of dipeptidyl peptidase-4 (iDPP4) enzyme inhibitors was not inferior to standard antidiabetic treatment (A). Although there are no trials directly addressing the CV safety of vildagliptin, a meta-analysis of studies supports its neutrality (B)[31]. The CAROLINA study on linagliptin was neutral versus glimepiride for MACE, with a higher rate of hypoglycemia in the glimepiride group (A)[32]. For basal insulin, glargine-U100 demonstrated CV safety in the ORIGIN study[33]; the DEVOTE study compared insulin degludec to glargine-U100 and no inferiority was found (A)[34] (Fig. 1).

Heart failure

SGLT2 inhibitors remain the drug of choice for patients with HF or those at risk of developing it (A). In the aforementioned cardiovascular safety studies, empagliflozin (HR 0.65; 95% CI: 0.50-0.85; p = 0.002), canagliflozin (HR 0.67; 95% CI: 0.52-0.87; p < 0.001), dapagliflozin (HR 0.73; 95% CI: 0.61-0.88; p = 0.0005), and ertugliflozin (HR 0.70; 95% CI: 0.54-0.90; p = 0.006) were indicated for a significant reduction in hospitalizations for HF[11,26-28].

The DAPA-HF study showed that dapagliflozin reduced the primary combined endpoint of cardiovascular mortality, hospitalizations for HF, and/or emergency room visits for HF in patients with reduced ejection fraction (EF ≤ 40%) and estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 regardless of the presence of diabetes (HR 0.74; 95% CI: 0.65-0.85; p = 0.00001)[35]. Similarly, in the EMPEROR-REDUCED study, empagliflozin reduced the primary combined endpoint of cardiovascular mortality, HF

hospitalizations with EF ≤ 40% and eGFR ≥ 20 mL/min/1.73 m^2 in patients with and without diabetes (HR 0.75; 95% CI: 0.65-0.86; p < 0.001)[13].

GLP-1RAs were neutral for HF hospitalizations, except for albiglutide (HR 0.71; 95% CI: 0.53-0.94; p < 0.0001) which reduced them[36] (A). iDPP4s were neutral, except for saxagliptin (HR 1.27; 95% CI: 1.07-1.51; p = 0.007), for HF hospitalizations[37]. Basal insulin analogs were neutral for HF hospitalizations in the above-mentioned studies[33,34] (A). Pioglitazone was contraindicated as it was associated with a rise in HF hospitalizations due to hydrosaline retention (A) (Fig. 1).

Diabetic kidney disease

All the studies (A) consistently reported that SGLT2 inhibitors reduce the risk of DKD progression, defined as the need for dialysis, kidney transplant or death by kidney failure (HR 0.67; 95% CI: 0.52-0.86; p = 0.0019), progression to terminal kidney disease (HR 0.65; 95% CI: 0.53-0.81; p < 0.0001), and severe kidney injury (HR 0.75; 95% CI: 0.66-0.85; p < 0.0001). In the eGFR subgroups analysis, the prevention of renal function deterioration and albuminuria decrease is persistent even with eGFR of 30-45 mL/min/1.73 m^2 (C). This effect occurs regardless of the presence of microalbuminuria and the use of renin-angiotensin system blockers[38].

Two studies assessed the renal benefits of SGLT2 inhibitors combined with renin-angiotensin system blockers. Both the CREDENCE study[39] with canagliflozin 100 mg in T2D, in which 60% of its patients had eGFR 30-59 mL/min/1.73 m^2, and the DAPA-CKD study[12] with dapagliflozin 10 mg in patients with or without diabetes, in which almost 90% of the patients had eGFR 25-59 mL/min/1.73 m^2, showed a significant reduction in DKD progression (A). The presence of DKD was less evident in the DECLARE-TIMI 58, CANVAS, and EMPA-REG OUTCOME studies, at 8%, 20%, and 26%, respectively.

Regarding GLP-1RAs, liraglutide (HR 0.78; 95% CI: 0.67-0.92; p = 0.003), semaglutide (HR 0.64; 95% CI: 0.46-0.88; p = 0.006), and dulaglutide (HR 0.85; 95% CI: 0.77-0.93; p = 0.0004) reduced renal events (eGFR deterioration, microalbuminuria, and renal death)[36] (A).

Other antidiabetic drugs showed no ability to prevent renal function deterioration. The use of metformin requires dose reduction in patients with eGFR <45 mL/min/1.73 m^2, and DPP4 inhibitors (except linagliptin) require dose adjustment depending on the eGFR. Pioglitazone is not recommended due to the risk of hydrosaline retention (A).

Metformin and sulfonylureas are contraindicated for eGFR < 30 mL/min/1.73 m^2. SGLT2 inhibitors should not be used with eGFR < 30 mL/min/1.73 m^2 but, as already mentioned, dapagliflozin continues to have renal benefits up to eGFR 25 mL/min/1.73 m^2 12 (A). Liraglutide, semaglutide, and dulaglutide can be used down to eGFR 15 mL/min/1.73 m^2 to continued good cardiovascular and renal effect (A). Basal insulin requires a 25% reduction for eGFR 15-30 mL/min/1.73 m^2 and 50% for eGFR < 15 mL/min/1.73 m^2. Repaglinide can be used with advanced DKD patients although it could increase the risk of hypoglycemia.

The recent FIDELIO-DKD study assessed the effect of finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, on renal and cardiovascular events in patients with kidney disease and T2D in optimum treatment with renin-angiotensin system blockers. Patients in the trial presented an albumin-creatinine ratio of 30-300 mg/g, and eGFR of 25-60 mL/min/1.73 m^2. Finerenone significantly reduced the primary composite outcome (renal failure, eGFR reduction ≥ 40% of basal, and/or renal death) (HR 0.82; 95% CI: 0.73-0.93; p = 0.001). It also reduced secondary outcomes, such as MACE and hospitalizations for HF (HR 0.86; 95% CI: 0.75-0.99; p = 0.034)[16]. The results were similar in the presence or absence of established CVD, (*p*-value for the interaction 0.85)[14] (A) (Fig. 1).

Overweight and obesity

Overweight and obesity are linked to an increase in cardiovascular events, HF, and total mortality[40]. GLP-1RAs are the drugs of choice. Weight reduction for the different drugs varies, with the hierarchy ranging from greater to lesser weight loss: semaglutide, liraglutide, dulaglutide, exenatide LAR, and lixisenatide (A).

SGLT2 inhibitors are associated with reduction in body weight, although of the lower intensity and less enduring effect in the long term (A). The combination of GLP-1RAs and SGLT2 inhibitors is recommended to achieve weight loss objectives (E).

Pioglitazone, sulfonylureas, glinides, and basal insulin analogs are linked to body weight gain[41]. The iDPP4s are neutral (A). The role of antidiabetic drugs in the treatment of non-alcoholic fatty liver disease (NAFLD) is currently under study, and could benefit patients receiving treatment with pioglitazone, GLP-1RAs, and/or SGLT2 inhibitors[42] (Fig. 1).

Patients over 75 years of age

Elderly patients are more vulnerable to the deleterious effects of hypoglycemia and other secondary effects, so the goals for controlling their blood glucose levels should be less stringent. Nevertheless, many of the aforementioned studies include additional benefits for elderly patients in terms of cardiovascular, renal, and HF prevention. The EMPA-REG OUTCOME study in patients > 75 years reported a reduction in cardiovascular mortality (HR 0.55; 95% CI: 0.32-0.94), HF hospitalizations (HR 0.45; 95% CI: 0.22-0.89), and renal events (HR 0.54; 95% CI: 0.37-0.79) that was higher than for the general population[43]. In the CANVAS study, the results were similar in patients > 65 years (HR 0.80; 95% CI: 0.67-0.95)[27]. The GLP-1RAs also showed beneficial effects in elderly patients[44].

In the DAPA-HF trial, patients > 75 years benefited most from the drop in hospitalizations for HF and/or cardiovascular mortality (HR 0.68; 95% CI: 0.53-0.88; p = 0.003) with fewer secondary effects than the placebo, especially in volume depletion and renal injury[45] (C). The EMPEROR-REDUCED trial found similar benefits for patients > 75 years (*p* for interaction = 0.54)[17] (C). As most findings for the elderly come from sub-studies of clinical trials, the level of evidence is classified as "C."

Any clinical assessment of elderly T2D patients should take into account functional, cognitive, and social factors. Age is not the only factor to consider in antidiabetic treatment, which should be less intensive for patients with functional, cognitive, and social impediments and/or poor prognosis. It is essential that the patient not develop acute hypoglycemia, so drugs that present a low risk of developing this condition should be administered; if insulin is required, it should be the safest form for this type of patient. Further details can be found in the Spanish Society of Internal Medicine's Consensus on T2D treatment for the elderly[46] (Fig. 1).

Hypoglycemia

Drugs with non-insulin dependent actions exhibit a low risk of hypoglycemia and are thus recommended: metformin, GLP-1RAs, SGLT2 inhibitors, and iDPP4 (E). Both glargine U300 and degludec achieve lower incidence of hypoglycemia as compared to levemir and glargine U100[34,47] (A) (Fig. 1).

Patients with long-term diabetes (> 10 years)

SGLT2 inhibitors[26-28] and GLP-1RAs[21-23] have been shown to be beneficial in cardiovascular safety studies in T2D patients who have had diabetes for 10 years or longer, as opposed to studies with sulfonylureas, metformin, or basal insulin analogs[48-51] (A) (Fig. 1).

Treatment according to HbA1c

Metformin continues to be the foundation of any antidiabetic treatment. This document recommends the number of drugs to be administered according to initial HbA1c and personalized therapeutic goals (E).

GLP-1RAs and/or SGLT2 inhibitors are recommended as a second line of treatment after metformin for the cardiovascular and renal benefits mentioned previously (A). Basal insulin analogs can be used whenever required, according to metabolic control, especially if insulin reserves are low, blood glucose level >300 mg/dL, cardinal symptoms of high catabolism or HbA1c >10% with hyperglycemia symptoms, or when there is a contraindication or intolerance to other therapies (E) (Fig. 2).

Discussion

This consensus gathers the recommendations of the diabetes, obesity, and nutrition working group of the SEMI for decision-making regarding drugs for T2D treatment, based on the best available evidence up to January 2021. Although this information is primarily for Internal Medicine practitioners, it can be used by clinicians in other specialties who deal with T2D patients at any level within the health system. The high prevalence and increased incidence of T2D means that doctors of any discipline might need to treat such patients across a range of scenarios in their daily clinical practice.

The first part of the algorithm should be interpreted horizontally, then vertically: select the patient's clinical situation or situations (horizontal) then decide which drug to use in this situation (vertical) (Fig. 1). Doctors must always evaluate the drug's contraindications, the dose to administer, and whether the indication conforms to the medical specifications, to avoid therapeutic inertia. The document offers some recommendations not included in the medical specification indications, at least in Spain, on eGFR threshold for initial use of most SGLT2 inhibitors, or regarding BMI for GLP-1RAs.

However, solid evidence from recent clinical trials suggests that these indications could soon be included following review by the health authorities.

In the recommendations for reducing cardiovascular events, we found no difference in the use of GLP-1RAs among patients with/without established CVD, as opposed to other consensuses. Current treatment of cardiovascular risk should focus on the cardiovascular continuum and avoid the discussion on primary and secondary prevention[52]. In fact, various trials with GLP-1RAs apply different criteria when classifying patients with or without established CVD. SUSTAIN-6 and LEADER include vascular stenosis > 50% at the coronary, carotid, and periphery level, moderate renal insufficiency, or stage 2/3 HF as established CVD. In contrast, these patients were not defined as having established CVD in the REWIND study[53].

Although the overall perception of SGLT2 inhibitors would suggest a class effect in cardiovascular event reduction, the DECLARE-TIMI study[28] with dapagliflozin did not reduce MACE in the total population; it did so in patients with a prior history of acute myocardial infarction[54]. The recent VERTIS-CV trial with ertugliflozin also failed to achieve a significant reduction in cardiovascular events[11].

The DECLARE-TIMI trial results were supposedly explained by the fact that there were fewer patients with established CVD and advanced DKD as compared to other studies with SGLT2 inhibitors. However, this is not a valid argument for the VERTIS-CV trial as almost the entire study population had established CVD. Thus, the class effect of reducing cardiovascular events in T2D patients is at least questionable, and the recommendation for SGLT2 inhibitor use in T2D patients should focus on those patients who have experienced this reduction. In contrast, the results of the study with dapagliflozin are the easiest to generalize[15].

When considering mechanisms of protection, SGLT2 inhibitors seem to generate cardiorenal benefits through hemodynamic mechanisms while GLP-1RAs would have anti-atherosclerosis effects; thus, both mechanisms are complementary, with additive effects on the cardiovascular risk continuum.

SGLT2 inhibitors have a class effect for reducing hospitalizations for HF. However, the percentage of HF patients before the initial studies was small, so the evidence is more robust for preventing the development of HF[55]. Regarding established HF, both dapagliflozin and empagliflozin show a reduction in hospitalizations and/or cardiovascular mortality in HF patients and reduced (< 40%) EF regardless of the presence of diabetes[17].

Despite the neutral results in the CAROLINA study[32], with a rise in hypoglycemia in the glimepiride treatment arm, sulfonylureas are not recommended for patients with high or very high cardiovascular risk as many clinical trials and observational studies have described an increased CV risk associated with the use of these antidiabetic drugs[56].

For DKD, current indications in the medical specifications in Spain continue to establish the threshold for SGLT2 inhibitors (except canagliflozin) at eGFR > 60 mL/min/1.73 m^2 for starting treatment, with a maintenance dosage at eGFR 45 mL/min/1.73 m^2. Based on the results of the CREDENCE study[39], which included patients with eGFR 30 mL/min/1.73 m^2, canagliflozin 100 can be administered to start treatment at eGFR 30 mL/min/1.73 m^2, and as a maintenance dosage for patients already in treatment even if the eGFR is lower. Results from the DAPA-CKD study support the use of dapagliflozin down to an eGFR of 25 mL/min/1.73 m^2 (this indication was not included in the medical specification when preparing this consensus). These findings emphasize the importance of most SGLT2 inhibitors in affording cardiorenal protection to moderate to severe DKD patients. More analyses of ertugliflozin for DKD patients are required to support its use to treat this disease. Although the results are promising, finerenone is not yet available for use in Spain.

GLP-1RAs reduce body weight for overweight and obese patients, but its use in Spain is only approved and financed for BMI ≥ 30 kg/m^2.

When treating elderly T2D patients, it is important to combine a functional, cognitive, and social approach with the clinical assessment. Regardless of age, patients who can function adequately should benefit from the same treatments and blood glucose control goals as younger subjects, with chronological age being no barrier to treatment. However, in patients with deteriorating functional and cognitive faculties or poor prognosis, the priority should be limitation of pharmacological treatment. In these patients, it is important to prevent the development of acute symptomatic hyperglycemia, and even more importantly, to avoid hypoglycemia. Physicians should use drugs with a low risk of producing hypoglycemia. In patients who need insulin, we should prioritize the new generation of basal insulins with low risk of hypoglycemia[46].

Regarding a blood glucose level approach (Fig. 2), it is important to set a HbA1c patient-centered goal. Lifestyle measures and metformin alike continue to be

the basis of any therapeutic plan. The algorithm helps us predict the use of one, two, or three drugs to achieve those therapeutic goals. Although insulinization is traditionally recommended for patients with HbA1c > 10% on diagnosis, GLP-1RAs and/or SGLT2 inhibitors together with metformin can often achieve correct metabolic control and may avoid the use of insulin, even temporarily. Patients with cardinal symptoms and/or hyperglycemia > 300 mg/dL should not be initially treated with SGLT2 inhibitors due to the risk of euglycemic ketoacidosis.

It is essential to identify insulinopenic patients who need substitution therapy with insulin, thus predicting metabolic failure if we initiate other therapies. However, the objective of this consensus is not to provide recommendations for basal bolus insulin regimen therapy and intensification with rapid insulin analogs in multiple doses.

The ultimate aim of this consensus is to provide guidelines for correct treatment to improve prognosis and reduces complications in T2D patients in any area of healthcare.

The advantage of this document is that it is clear, concise, and simple to use in daily clinical practice. Its main drawback is that it cannot provide in-depth answers to highly specific and/or special clinical situations. However, the balance between simplicity and scientific rigor means it can be widely applied as a consensus across the scientific and health-care community.

Author contribution statements

C-S F.J. coordinated the project. F-R J.M., C-G J., and C-S F.J. conceived of the idea, analyzed the data, wrote the manuscript, and designed the algorithms. All authors participated in the discussion and contributed to the final manuscript.

Funding

The project was supported by the Spanish Society of Internal Medicine.

Conflicts of interest

The authors declare no conflicts of interest regarding this article.

References

1. International Diabetes Federation. Diabetes Atlas. 9th ed. Brussels, Belgium: International Diabetes Federation; 2019. Available from: https://www.diabetesatlas.org/upload/resources/material/20200302_133351_IDFATLAS9e-final-web.pdf.
2. Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es study. Diabetologia. 2012;55:88-93.
3. Rojo-Martínez G, Valdés S, Soriguer F, Vendrell J, Urrutia I, Montanya E, et al. Incidence of diabetes mellitus in Spain as results of the nation-wide cohort di@bet.es study. Sci Rep. 2020;10:110.
4. Zapatero A, Gómez-Huelgas R, González N, Canora J, Asenjo A, Hinojosa J, et al. Frequency of hypoglycemia and its impact on length of stay, mortality, and short-term readmission in patients with diabetes hospitalized in internal medicine wards. Endocr Pract. 2014;20:870-5.
5. Ena J, Gómez-Huelgas R, Romero-Sánchez M, Gaviria AZ, Calzada-Valle A, Varela-Aguilar JM, et al. Hyperglycemia management in patients admitted to internal medicine in Spain: a point-prevalence survey examining adequacy of glycemic control and guideline adherence. Eur J Intern Med. 2015;26:392-8.
6. Zapatero-Gaviria A, Gómez-Huelgas R, Canora-Lebrato J, Ena-Muñoz J, Romero-Sánchez M, Mendez-Bailón M, et al. Analysis of hospitalizations by cardiovascular disease in the population with diabetes in Spain. Rev Clin Esp. 2019;219:124-9.
7. Ena J, Gaviria AZ, Romero-Sánchez M, Carretero-Gómez J, Carrasco-Sánchez FJ, Segura-Heras JV, et al. Derivation and validation model for hospital hypoglycemia. Eur J Intern Med. 2018;47:43-8.
8. Carretero Gómez J, Arévalo Lorido JC, Gómez Huelgas R, Vidal MT, Tembra MS, Aguilar JM, et al. Prevalencia de obesidad según la estadificación de Edmonton en las consultas de medicina interna. Resultados del estudio OBEMI. Rev Clin Esp. 2017;217:71-8.
9. Carrasco-Sánchez FJ, Fernández-Rodríguez JM, Ena J, Gómez-Huelgas R, Carretero-Gómez J. Medical treatment of Type 2 diabetes mellitus: recommendations of the diabetes, obesity and nutrition group of the Spanish society of internal medicine. Rev Clin Esp. 2021;221:101-8.
10. Care D, Suppl SS. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes 2021. Diabetes Care. 2021;44:S111-24.
11. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, et al. Cardiovascular outcomes with ertugliflozin in Type 2 diabetes. N Engl J Med. 2020;383:1425-35.
12. Heerspink HJ, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436-46.
13. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383:1413-24.
14. Filippatos G, Anker SD, Agarwal R, Pitt B, Ruilope LM, Rossing P, et al. Finerenone and cardiovascular outcomes in patients with chronic kidney disease and Type 2 diabetes. Circulation. 2021;143:540-52.
15. Castellana M, Procino F, Sardone R, Trimboli P, Giannelli G. Generalizability of sodium-glucose co-transporter-2 inhibitors cardiovascular outcome trials to the Type 2 diabetes population: a systematic review and meta-analysis. Cardiovasc Diabetol. 2020;19:1-10.
16. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, et al. Effect of finerenone on chronic kidney disease outcomes in Type 2 diabetes. N Engl J Med. 2020;383:2219-29.
17. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396:819-29.
18. Introduction: standards of medical care in diabetes-2020. Diabetes Care. 2020;43:S1-2.
19. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al.; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255-323. Erratum in: Eur Heart J. 2020;41(45):4317.
20. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with Type 2 diabetes. Diabetologia. 2017;60:1620-9.
21. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in Type 2 diabetes. N Engl J Med. 2016;375:311-22.
22. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with Type 2 diabetes. N Engl J Med. 2016;375:1834-44.
23. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in Type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394:121-30.
24. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, et al. Lixisenatide in patients with Type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373:2247-57.
25. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in Type 2 diabetes. N Engl J Med. 2017;377:1228-39.

26. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in Type 2 diabetes. N Engl J Med. 2015;373:2117-28.
27. Neal B, Perkovic V, Mahaffey KW, Matthews DR. Canagliflozin and cardiovascular and renal events in Type 2 diabetes. N Engl J Med. 2017;377:644-57.
28. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in Type 2 diabetes. N Engl J Med. 2019;380:347-57.
29. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with Type 2 diabetes in the PROactive study (PROspective pioglitAzone clinical trial in macrovascular events): a randomised controlled trial. Lancet. 2005;366:1279-89.
30. Kernan WN, Viscoli CM, Furie KL, Young LH, Inzucchi SE, Gorman M, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med. 2016;374:1321-31.
31. McInnes G, Evans M, Del Prato S, Stumvoll M, Schweizer A, Lukashevich V, et al. Cardiovascular and heart failure safety profile of vildagliptin: a meta-analysis of 17 000 patients. Diabetes Obes Metab. 2015;17: 1085-92.
32. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with Type 2 diabetes: the CAROLINA randomized clinical trial. JAMA. 2019;322:1155-66.
33. Gerstein HC, Bosch J, Dagenais GR, Díaz R, Jung H, Maggioni AP, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012;367:319-28.
34. Marso SP, Mcguire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, et al. Efficacy and safety of degludec versus Glargine in Type 2 Diabetes. N Engl J Med. 2017;377:723-32.
35. McMurray JJ, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381:1995-2008.
36. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with Type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019;8587:1-10.
37. Singh AK, Singh R. Heart failure hospitalization with DPP-4 inhibitors: a systematic review and meta-analysis of randomized controlled trials. Indian J Endocrinol Metab. 2019;23:128-33.
38. Neuen BL, Young T, Heerspink HJ, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2019;7:845-54.
39. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJ, Charytan DM, et al. Canagliflozin and renal outcomes in Type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295-306.
40. Costanzo P, Cleland JG, Pellicori P, Clark AL, Hepburn D, Kilpatrick ES, et al. The obesity paradox in Type 2 diabetes mellitus: relationship of body mass index to prognosis: a cohort study. Ann Intern Med. 2015;162:610-8.
41. Care D, Suppl SS. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2020. Diabetes Care. 2020;43: S98-110.
42. Ranjbar G, Mikhailidis DP, Sahebkar A. Effects of newer antidiabetic drugs on nonalcoholic fatty liver and steatohepatitis: think out of the box? Metabolism. 2019;101:154001.
43. Monteiro P, Bergenstal RM, Toural E, Inzucchi SE, Zinman B, Hantel S, et al. Efficacy and safety of empagliflozin in older patients in the EMPA-REG OUTCOME® trial. Age Ageing. 2019;48:859-66.
44. Onoviran OF, Li D, Smith ST, Raji MA. Effects of glucagon-like peptide 1 receptor agonists on comorbidities in older patients with diabetes mellitus. Ther Adv Chronic Dis. 2019;10:12;10:2040622319862691.
45. Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang CE, Tereshchenko S, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF. Circulation. 2020;141:100-11.
46. Gómez-Huelgasa R, Díez-Espinob J, Formigac F, Tejedord JL, Mañase LR, González-Sarmientoa E, et al. Tratamiento de la diabetes mellitus Tipo 2 en el paciente anciano. Rev Clin Esp. 2018;218:74-88.
47. Ritzel R, Roussel R, Giaccari A, Vora J, Brulle-Wohlhueter C, Yki-Järvinen H. Better glycaemic control and less hypoglycaemia with insulin glargine 300 U/mL vs glargine 100 U/mL: 1-year patient-level meta-analysis of the EDITION clinical studies in people with Type 2 diabetes. Diabetes Obes Metab. 2018;20:541-8.
48. Turner R. Effect of intensive blood-glucose control with metformin on complications in overweight patients with Type 2 diabetes (UKPDS 34). Lancet. 1998;352:854-65.
49. Gerstein HC, Miller ME, Byington RP, Goff DC Jr., Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in Type 2 diabetes. N Engl J Med. 2008;358:2545-59.
50. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with Type 2 diabetes. N Engl J Med. 2009;360:129-39.
51. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with Type 2 diabetes. N Engl J Med. 2008;358:2560-72.
52. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019;41:111-88.
53. Varin EM, McLean BA, Lovshin JA. Glucagon-like peptide-1 receptor agonists in adult patients with Type 2 diabetes : review of cardiovascular outcome trials. Can J Diabetes. 2019;44:68-77.
54. Furtado RH, Bonaca MP, Raz I, Zelniker TA, Mosenzon O, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in patients with Type 2 diabetes mellitus and previous myocardial infarction. Circulation. 2019;139:2516-27.
55. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in Type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393: 31-9.
56. Bain S, Druyts E, Balijepalli C, Baxter CA, Currie CJ, Das R, et al. Cardiovascular events and all-cause mortality associated with sulphonylureas compared with other antihyperglycaemic drugs: a Bayesian meta-analysis of survival data. Diabetes Obes Metab. 2017;19:329-35.