Spanish Journal of Medicine

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Volume 2, Issue 1, January-March 2022

eISSN: 2696-5631

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ORIGINAL ARTICLE

Educational strategy to improve cardiovascular health and mitigate food insecurity: Rationale for the E-DUCASS program

Juan L. Romero-Cabrera[1,2‡], Isabel de-Castro-Burón[3‡], Elena Yubero-Serrano[1,2], Alberto Díaz-Cáceres[1,2], Alejandro Serrán-Jiménez[1,2], Javier Arenas-Montes[1,2], Juan F. Alcalá-Díaz[1,2], Ana M. Ortiz-Morales[1,2¶], and Pablo Pérez-Martínez[1,2¶]*

[1]Lipid and Atherosclerosis Unit, Instituto Maimónides de Investigación Biomédica de Córdoba – Hospital Universitario Reina Sofía/Universidad de Córdoba, Córdoba; [2]Centro de Investigación Biomédica en Red – Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid; [3]Communication Department, Instituto Maimónides de Investigación Biomédica de Córdoba, Córdoba. Spain

‡Equal first authors.

¶Equal last authors.

Abstract

Introduction and Objectives: Food insecurity is involved in the most important health problem worldwide: the rise in non-communicable diseases. It affects populations in poor countries and disadvantaged populations in affluent countries. Lifestyle improvement strategies are often costly and only effective in the short term. Our aim is to demonstrate that an educational program on a healthy lifestyle which increases health literacy could improve long-term health and mitigate food insecurity. **Methods:** This work will conduct a 24-month intervention to improve cardiovascular health, measured by the Life's Simple 7 criteria, in vulnerable families (460 individuals) at risk of food insecurity. It entails initial training through workshops (basic intervention model) followed by randomization into three groups: (1) no further intervention; (2) a traditional advanced intervention model every 3 months; and (3) an e-learning advanced intervention model every 15 days with YouTube videos or WhatsApp/text message. In a next step, we will explore if the lifestyle intervention improve families' food insecurity score according to the criteria established by the Food and Agriculture Organization and measured by the Food Insecurity Experience Scale (FIES). Finally, we will analyze which of the two advanced intervention models, either face to face or virtual, are more effective at improving cardiovascular health and food literacy. **Conclusions**: If this type of program – not very complex or costly – has favorable effects, it could be proposed as a model for improving these populations' state of vulnerability. The E-DUCASS program aims to use this strategy to improve cardiovascular health in vulnerable populations in a scientific, efficient, safe, and sustainable manner.

Keywords: Food insecurity. Cardiovascular health. Literacy. Vulnerable. E-learning.

Introduction

Food insecurity is involved in the most important health problem worldwide: the rise in non-communicable diseases. Food insecurity is defined as a "limited or uncertain availability of the quantity and quality of food necessary to meet individuals' nutritional requirements or the ability to acquire them in a socially and culturally acceptable manner." This situation, which is closely linked to an unhealthy food supply, affects populations in poor countries and more disadvantages population groups in affluent countries, such as Spain. It is the

Visual abstract available at https://www.spanishjmed.com/frame_esp.php?id=60

***Correspondence:**
Pablo Pérez-Martínez
E-mail: pabloperez@uco.es

Date of reception: 14-11-2021
Date of acceptance: 13-12-2021
DOI: 10.24875/SJMED.21000025

Available online: 25-01-2022
Span J Med. 2022;2(1):1-8
www.spanishjmed.com

consequence of a complex interaction among overexploitation of the land, climate change, population growth, and large corporations' pursuit of profits. Indeed, unhealthy diets currently pose a greater risk to morbidity and mortality than unprotected sex acts and alcohol, drug, and tobacco use combined[1].

An expert panel recently demonstrated that the consequences of food insecurity are different forms of pandemics, including malnutrition (obesity and undernutrition, with the latter understood as selective undernutrition of specific micronutrients) and global warming. They defined this situation as the "global syndemic"[2]. It is estimated that excess body weight affects two billion people worldwide, causing 4 million deaths and costing 2.8% of global GDP[3]. In addition, these pandemics are closely linked to the development of non-communicable diseases, which makes the global syndemic the main threat to the health and economy of modern societies[4]. Addressing this problem will require an enormous effort, with the commitment of many governments, institutions, researchers, industries, and public and private foundations in accordance with the guidelines agreed on in the 2015 United Nations Climate Change Conference, held in Paris, or the conferences held in Madrid and Glasgow.

Although the root of this problem is apparently unable to be meaningfully addressed by the initiatives of individuals or single institutions, health researchers and professionals should not shirk taking on joint responsibility for implementing initiatives against the global syndemic. These initiatives include searching for educational and nutritional strategies to fight the consequences of food insecurity, especially in light of the already evident failure of the enormous amount of resources and strategies squandered in the fight against obesity and non-communicable diseases from traditional clinical or experimental perspectives. In this regard, it should be called into question whether many of science's resources should focus on untangling the complex biological mechanisms that underlie said diseases, as they have to date, or if an effort should also be made to develop direct, population-based research strategies to mitigate the impact of diseases linked to the syndemic.

In addition to the aforementioned relationship between food insecurity and obesity and undernutrition, food insecurity has also been consistently linked to behavioral disorders in children[5], worse academic achievement[6], stunted growth[7], non-alcoholic fatty liver disease[8], type 2 diabetes mellitus[9,10], progression of chronic kidney disease[11], depression[12], peripheral arterial disease[13], cardiorenal syndrome, and mortality, among other entities[14]. Considering this broad spectrum of diseases, it is unsurprising that this food insecurity is associated with cardiovascular health and lifestyle[15-17], including type 2 diabetes mellitus, hypertension, hyperlipidemia, or sleep problems[18].

The evidence that low health literacy affects the health status of individuals and the community must lead to health empowerment also being a priority alongside the great health and sustainable development challenges on global agendas[19]. Recently, various studies have been published that demonstrate the efficacy of health literacy interventions as a tool for improving education on cardiovascular disease[20,21] and heart failure[22]. Within this concept, food literacy or basic food culture is defined as the basic education that all individuals should have on food in its multiple dimensions (health, culture, gastronomy, comfort, price, etc.) that prepare them to practice suitable habits and follow an adequate diet within the environment and conditions in which they live to be able to reach an optimal state of health and quality of life[23,24]. In this context, the challenge currently faced is implementing sustainable, structured food literacy interventions that improve the education of vulnerable, at-risk populations, and, secondarily, reduce food insecurity[25].

Prior experience of other programs

Multiple health programs have demonstrated positive impacts on cardiovascular risk markers through programs aimed at improving lifestyle. One of the best studied is the Fifty-Fifty Program[26], led by Professor Valentín Fuster. It demonstrated a positive impact on participants' health, mainly through improvements in their diet, an increase in physical activity, and smoking cessation in the case of smokers, leading to an improvement in quality of life. However, these types of programs normally have limitations, given that they require a significant amount of financial resources for their implementation, especially in settings without resources and if they seek to endure and remain suitable overtime.

Paradoxically, there is little information on the impact of these types of approaches on the populations' food insecurity status, despite the fact that it is an underlying problem for many of these subjects. Therefore, it would be of interest to know if food insecurity could also be mitigated through literacy on a healthy lifestyle, given that this strategy would influence certain behaviors it depends on, such as harmful habits (tobacco and alcohol use), a sedentary lifestyle, or consumption of

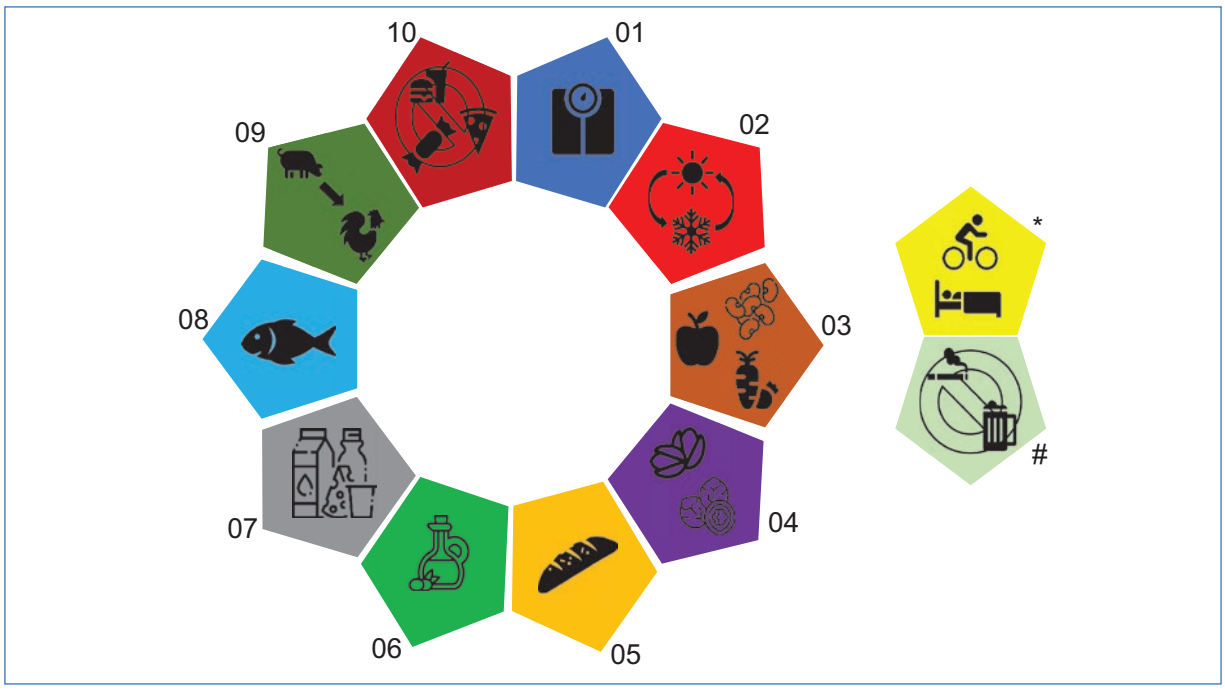

Figure 1. Healthy lifestyle recommendations. Graphical material for the participants of the E-DUCASS program.

unsuitable foods due to a dearth of information. Likewise, it would be of interest to seek alternatives that can improve this vulnerable population's lifestyle at a financially sustainable cost so that the research not only demonstrates potential benefits but also shows these benefits can be sustained in a manner that is inexpensive and able to be extrapolated to large populations. Finally, it should be determined if education on a healthy lifestyle affects the degree of food insecurity in the population studied.

Purpose of the E-DUCASS program

A commission comprising experts from 14 countries convened with the aim of developing a strategy against the global syndemic recently issued a call to society – including scientists – to develop joint strategies in the fight against this serious problem humanity is facing. Taking into account that 30% of global warming is linked to diet, it seems reasonable to focus on vulnerable populations, fostering healthy lifestyles centered on the promotion of healthy, sustainable diets[4,27].

In this context, the purpose of the E-DUCASS program is to improve the lifestyle of a population at risk of food insecurity with an educational intervention on health literacy that takes into account planetary health criteria (Fig. 1). The intervention would involve later reinforcement so that it is sustainable both overtime and financially so that it may be extrapolated to larger populations. To do so, two alternatives will be explored to determine which is most worthwhile for maintaining the benefits of the initial intervention on improving cardiovascular health and food insecurity in the aforementioned population. Most lifestyle improvement strategies are costly and, if they are conducted over a limited period of time, their benefits are only proven in the short term. Therefore, our hypothesis is that an educational program for a vulnerable population that promotes a planetary health lifestyle and consists of an initial basic intervention with later reinforcement that increases health literacy could improve their long-term health status and even mitigate their food insecurity.

Aims of the E-DUCASS program

The main aim is to conduct an intervention consisting of an educational program aimed at improving cardiovascular health status, measured through the American Heart Association's Life's Simple 7 criteria, in a vulnerable population consisting of families (460 individuals) at risk of food insecurity. The 24-month intervention will involve an initial health literacy training period through workshops that encourage individuals to modify their health habits (basic intervention model). Once this training is complete, participants will be randomized into three groups: (1) no further intervention; (2) follow-up

with motivational, low-cost workshops every 3 months (traditional advanced intervention model), and (3) follow-up with educational workshops every 15 days with videos on a YouTube channel or WhatsApp/text messages (e-learning advanced intervention model).

The following secondary aims are proposed: (1) Demonstrate if the lifestyle intervention improved families' food insecurity score according to the criteria established by the Food and Agriculture Organization (FAO) and measured by the Food Insecurity Experience Scale (FIES), specifically in terms of item 3 (having eaten only a few kind of foods), which refers to diet quality. (2) Analyze which of the two advanced intervention models, either face to face or virtual, is more effective at improving cardiovascular health and food literacy in the aforementioned vulnerable population.

Methods

Population and study design

The study will be conducted at the Maimónides Biomedical Research Institute of Córdoba (IMIBIC, for its initials in Spanish) and the Reina Sofía University Hospital along with Córdoba City Hall's Community Social Services Centers in Distrito Sur, Moreras, and Barriada de las Palmeras, where screening, selection, and recruitment of the volunteers who will participate in the study will take place.

The sample size has been calculated based on the following assumptions: for the main outcome variable of the study, an improvement on the score of the Life's Simple 7 criteria will be used, with a change of 20% from the baseline test considered significant[28]; alpha risk: 0.05; difference in percentage between comparisons of 20%; power (1-ß): 0.90; estimated losses: 10%; and two-tailed contrast. Based on these premises, 117 patients per group are needed. With the aim of minimizing possible losses and increasing the study's power, a total of 460 participants (families) will be included. Recruitment will be conducted among the general population without debilitating diseases or diseases whose severity entails a life expectancy of < 5 years.

Description of the intervention and health literacy strategy

The 24-month intervention will consist of an initial training period involving informational workshops that encourage individuals to modify their health habits (basic intervention model). The first phase of the program will consist of an 8 h educational intervention that will involve two workshops taught by experts to all volunteers. The first workshop will attempt to encourage individuals to change their habits, learn the phases through which these changes will pass, and learn how they will improve their health (chronic diseases related to lifestyle). The second workshop will focus on encouraging healthy behaviors to reduce risk factors associated with disease (unhealthy diet, overweight/obesity, sedentarism, harmful habits, and blood pressure). Once this training is complete: the volunteers will be randomized into three groups: (1) no further intervention; (2) follow-up with motivational, low-cost workshops every 3 months (traditional advanced intervention model), and (3) follow-up with educational workshops every 15 days with videos on a YouTube channel or WhatsApp/text messages (e-learning advanced intervention model).

The results of the health evaluations at the end of each intervention period will allow for determining if the improvements initially obtained are maintained with the later interventions and, if so, whether the online intervention achieves similar outcomes to the face-to-face intervention. The workshops will include recommendations based on planetary health lifestyle guidelines, indicated below, which include healthy diet recommendations that follow the planetary health diet criteria defended by Willet et al.[1] (Table 1).

The efficacy of this program is predicated on an adequate understanding of the messages and acceptance of the behavior guidelines based on a good interpretation of the message communicated. Only with clear knowledge of why and what the measures are for will they be integrated into individuals' behavior. Therefore, specific training aimed at improving health literacy will be provided, especially on aspects closely related to cardiovascular disease and its risk factors. The training will go in depth on the main measures that can be used to fight it, in which lifestyle plays a fundamental role. In these patients, health literacy will be evaluated through the Short Assessment of Health Literacy for Spanish-Speaking Adults[29] and their knowledge about cardiovascular diseases will also be assessed[21,30,31]. In addition, specific training will also be provided to improve food literacy[32]. A nutritionist will prepare a series of low-cost menus that includes local, seasonal food, allowing for improving diet quality at a very low cost so that it is affordable for the volunteers. All these materials will be adapted to a digital format with the aim of disseminating them through other channels of information (short educational videos with health messages that will be published on a YouTube

Table 1. List of healthy lifestyle recommendations

Number	Recommendations
1.	Periodically monitor your weight and aim to maintain it at a healthy level. Do not consume foods that are high in calories or which contain added sugars.
2.	Eat a varied diet. Cook at home and use the least amount of salt possible (< 5 g/day). Food should be seasonal and local or as local as possible.[a]
3.	Fruit and vegetables should be served at least 5 times/day. Eat legumes at least 2 or 3 times/week.
4.	Eating unsalted nuts at least 2 times/week is healthy. They should not be eaten for dessert as a substitute for fruit.
5.	The bread and grains eaten daily should be whole grain. White bread and other foods prepared with grain flour, such as precooked pizza and processed pastries and baked goods, should be eliminated from our diet as they are ultra-processed foods.[b]
6.	Cook and dress foods with extra virgin olive oil. This should be the biggest source of fat in our diet. Butter and margarine can be consumed occasionally (once per week).
7.	Eggs, fresh cheese, milk, or yogurt can be consumed daily. The latter two should not contain added sugars. Never eat dairy products as a substitute for fruit.
8.	Fish is an important source of protein and omega-3 fatty acids. Therefore, it should be a part of our diet. Children and women of childbearing age should avoid eating large fish.
9.	Reduce consumption of red meat such as beef, pork, and lamb as much as possible[b] substitute it for chicken (2-3 times/ week). Cold cuts tend to be ultra-processed and should likewise be avoided.[c]
10.	Ultra-processed foods, whether meat or other products; chips; and the majority of precooked foods are not recommendable.[c]
*	Increase physical activity, consumption of organic food, contact with nature, and sleep (7-8 h/night); use public transportation, a bicycle, or walk; do activities that you enjoy and find relaxing.
#	Reduce sedentarism, do not smoke, and avoid being around people smoking. Alcohol has been shown to favor cancer and cognitive decline, among other problems. Therefore, it should be avoided as much as possible. Every little change you make will improve your health.

[a]Food's contribution to global warming depends both on its production and transportation. Therefore, we should eat seasonal, local food, avoiding food produced far away. In addition, seasonal foods are richer in nutrients and conserve their natural flavors.
[b]Red meat and its derivatives are a very important cause of global warming, water consumption, and land degradation. Therefore, they should be avoided and consumption of foods rich in vegetable protein, such as legumes and whole grain cereals, as well as animal protein such as eggs, dairy products, fish, or chicken should be increased.
[c]Ultra-processed foods, whether meat or other products, and the majority of precooked foods contain ingredients such as added sugars or trans fats, which favor the development of chronic diseases such as cancer, diabetes, obesity, and cardiovascular diseases. Therefore, they should not be included in our diet.

channel, text messages, or WhatsApp messages). In this regard, recent evidence suggests the efficacy of using technology and social networks in vulnerable populations to improve health literacy and prevent risk of cardiovascular diseases by promoting a healthy lifestyle[33].

Follow-up on the population: after conducting the initial training, participants will be randomized into three intervention models, as indicated above. (1) A model with no further intervention. These patients will be given annual appointments to reevaluate them, take new anthropomorphic measurements, and collect new biological samples (12 and 24 months). (2) In the traditional advanced intervention model (low cost), an intervention with group dynamics will be performed. Participants will meet every 3 months to share experiences, common problems, knowledge on health habits, changes in their habits, and to provide mutual support. To do so, participants will be organized into groups of approximately 15 people. The group meetings will last for approximately 90-120 min and will be held quarterly. Participants will share improvements in their health habits and difficulties they faced. During these reflections, in which participants will be able to seek support and encouragement from others, the group members will propose achievable lifestyle improvement goals. (3) An e-learning advanced intervention model consisting of follow-up with educational workshops every 15 days through videos on a YouTube channel or WhatsApp/text messages.

The advanced intervention models 2 and 3 will last for 24 months, the same as the basic intervention model 1. Patients will be given annual appointments to reevaluate them, take new anthropomorphic measurements, and collect new biological samples (12 and 24 months).

Evaluation of cardiovascular health, lifestyle, and food insecurity

To conduct the cardiovascular health evaluation, the Life's Simple 7 criteria, a validated, widely used method proposed by the American Heart Association, will be used[28]. It includes seven risk factors that people can improve through lifestyle changes to achieve ideal cardiovascular health: body mass index, smoking status, healthy diet, moderate physical activity ≥ 150 min/week, total cholesterol < 200 mg/dL, systolic blood pressure < 120 mmHg, diastolic blood pressure < 80 mmHg, and basal blood glucose < 100 mg/dL. These measures have something in common: they are not expensive, and anyone can make changes to improve them. Each of the seven risk score items is scored based on the targets achieved as poor (0 points), intermediate (1), or ideal (2). The total sum of points on the LS7 allows for establishing three categories: inadequate (0-4), average (5-9), and optimal (10-14). In addition, specific cutoff points are established for the population between 12 and 19 years of age and those older than 20 years of age.

Food insecurity experienced by individuals or households will be measured using the FIES for the family, as defined by the United Nations FAO. The FIES provides a new validated, worldwide standard to measure the experience of food insecurity that has international support. The FIES[34] includes eight items:

1. You were worried you would not have enough food to eat;
2. You were unable to eat healthy and nutritious food;
3. You ate only a few kinds of foods;
4. You had to skip a meal;
5. You ate less than you thought you should;
6. Your household ran out of food;
7. You were hungry but did not eat;
8. You went without eating for a whole day.

With repeated measurements of the FIES in the same population on an individual or family level, it is possible to monitor on the trends and changes in food insecurity levels overtime.

Determination of anthropometric measurements and biochemical parameters

A detailed medical history will be taken at baseline, including the most relevant health problems along with a basic examination that includes weight, height, waist circumference, blood pressure, and heart rate. At baseline, 12 months, and at the end of the intervention (24 months), dry chemistry techniques will be used for capillary blood analysis (2 μL) after a 12 h fast to determine biochemical parameters (cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and blood glucose). Roche's Cobas B 101 system will be used for the lipid panel and the Accu-Chek Inform II system will be used for measuring blood glucose levels. Both systems are for professional use in clinical laboratories and are specially designed to provide quick, reliable results (Roche Diagnostics).

Statistical analysis of the data

SPSS v.24-0 (SPSS Inc., Chicago, Illinois, USA) and R v.3.3.0 will be used for the statistical analysis of the data. A level of $p < 0.05$ will be considered statistically significant. When the variables do not follow a normal distribution, a log transformation of the data will be used for their analysis. Continuous variables will be compared using Student's t-test and analysis of variance (ANOVA), depending on whether there are two or more groups in each comparison. The association among categorical variables will be analyzed using the Chi-square test. To determine the effect of the diets consumed on the various parameters studied, the repeated measures ANOVA test followed by a *post hoc* Bonferroni multiple comparisons test will be used to identify the differences among each group.

Ethical aspects of the research

The study will be conducted in accordance with the fundamental principles set forth in the Declaration of Helsinki (1964), the European Convention on Human Rights and Biomedicine (1997), and UNESCO's Universal Declaration of Human Rights (1997) and pursuant to the requirements set forth in Spanish legislation on biomedical research, personal data protection, and bioethics.

Discussion

There are compelling local and national reasons for conducting a project such as E-DUCASS. The deprivation index of Spanish municipalities was published several years ago and, along with it, Spain's National Institute of Statistics (INE, for its initials in Spanish) published the results of the "Urban Indicators" project, which arose from the European Urban Audit project and includes information on the living conditions in the main

Spanish cities. This report indicated that of the 15 neighborhoods with the lowest mean annual income per resident, four were in the city of Córdoba. These neighborhoods were Parque Azahara-Palmeras, Polígono del Guadalquivir, Sector Sur, and El Higuerón-Majaneque-Alameda del Obispo area. Of them, the most disadvantaged neighborhood was Parque Azahara-Palmeras, where the mean per capita income was 6,207 Euros. This situated it among the five poorest neighborhoods in the country, in contrast to the richest neighborhood of El Viso, in Madrid, with an income of 42,819 Euros (https://www.ine.es/jaxiT3/Tabla.htm?t=10849).

On the other hand, in contrast to this unfortunate precariousness, Córdoba is home to the Maimónides Institute of Biomedical Research of Córdoba (IMIBIC, for its initials in Spanish). It is one of 33 biomedical institutes accredited as a center of excellence in healthcare research by the Carlos III Institute of Health (ISCIII) as a multidisciplinary research space in which scientists from the university and health-care fields work together and whose activity should be oriented toward improving citizens' health and the social and economic development of Córdoba Province, according to its mission statement. Given that our mission implores us to conduct real-world, translational research in line with this social commitment, we believe that we should lead a strategy aimed at promoting and improving the populations' health through research projects that serve as a driving force for fighting society's health problems. This is precisely what is required by the principles of the Responsible Research and Innovation (RRI) policy, a new theoretical framework for research and innovation in Europe. This model is gaining force as a strategy to align scientific and technological progress with socially desirable and acceptable aims. In practice, RRI is implemented as a series of actions that include the participation of multiple actors and the public in research and innovation, allowing for easier access to scientific results, the incorporation of gender and ethics in the content and the process of research and innovation, and formal and informal scientific education.

In this context, the E-DUCASS project aims to conduct real world, translational, clinical-epidemiological research that is in line with its commitment to society. During the development of this project, the opinions of various actors in society, including the citizenry, were considered. The project addresses one of the most important topics in modern societies: the need to attend to vulnerable populations who suffer from health inequalities. Therefore, leading a strategy aimed at promoting and improving the population's health can serve as a driving force, bringing together the efforts of various institutions to fight against this serious problem that affects populations in Spain and abroad. Through this program, we are responding to the principles of the RRI policy.

Given that our hypothesis assumes trust in educational strategies to improve health and seeks to ensure they are affordable, we believe that our research's repercussions on society will be significant, given that it can offer tools to extrapolate these strategies to other populations in a similar situation. In light of the foregoing, its potential social benefits have been clearly proven, given that the returns from this research could have effects on a large target population. Furthermore, the current problem of global warming will be taken into account in the training program and nutrition education strategy, as we will emphasize guidelines that are in line with recently published lifestyle recommendations, especially in regard to the consumption of local, plant-based foods.

Conclusions

If this type of program – not very complex or costly – has favorable effects, it could be proposed as a model for improving these populations' state of vulnerability. The E-DUCASS program aims to use this strategy to improve cardiovascular health in vulnerable populations in a scientific, efficient, safe, and sustainable manner.

Acknowledgments

The authors would like to thank Jesús Campos Reyes, the social worker of E-DUCASS program for his work. We also acknowledge the implication of the E-DUCASS program in recruiting the participants, organizing workshops, and facilitating the accessibility to this vulnerable population.

Funding

The E-DUCASS program has received research grants from the Institute of Health Carlos III (ISCIII), Ministry of Science, Innovation and Universities of Spain (PI20/01413 to Pablo Pérez-Martínez). The CIBEROBN is an initiative of the Instituto de Salud Carlos III, Madrid. JLRC has received a research grant "Río Hortega" from Instituto de Salud Carlos III. The funding source had no role in the study design, data analysis or interpretation, or writing of the manuscript.

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 the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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.

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Spanish Journal of Medicine

ORIGINAL ARTICLE

Respiratory infections in nursing home residents: A retrospective analysis of characteristics and prognostic factors

Juan M. Antón-Santos[1,2], Yolanda Majo-Carbajo[1,2], María de-Castro-García[1,2], M. Pilar García-de-la-Torre-Rivera[1,2], M. Rosario Burón-Fernández[1,2], Carolina Medina-de-Campos[2], Alberto Rando-Caño[2], and Pilar Cubo-Romano[1,2]*

[1]Internal Medicine Department; [2]Complex Chronic Patients and Hospital-at-Home Unit. Hospital Universitario Infanta Cristina, Parla, Madrid, Spain

Abstract

Introduction and Objectives: Hospitalization for respiratory events is common in nursing home residents (NHR). Pneumonia in NHR has different features, is more severe, and appears in more dependent patients. Aspiration pneumonia is usually misdiagnosed as infective pneumonia. Hospital-at-Home (HaH) has emerged as an alternative to conventional hospitalization. We decided to study respiratory admissions in NHR and the safety of our HaH program. **Methods**: Retrospective study of all consecutively hospitalized NHR with a respiratory crisis, discharged from 2016 to 2017. Univariate analysis was used for differences between aspiration and infection, multivariate analysis to check for prognostic factors. **Results:** 301 episodes were included in the study. Patients (mean age 86.4 years) showed numerous comorbidities (hypertension 80.7%, dementia 70.8% and chronic heart failure 41.5%), high degree of dependence (Barthel Index 12.7, Katz 5.3), and poor prognosis (high-risk PROFUND 91.7% and high-risk PALIAR 76.7%). Severity was high by Pneumonia Severity Index (97% groups ≥ 4) and CURB65 (89.4% ≥ 2) indexes. Antibiotics were used in 288 episodes, 67 covering MDR bacteria. Aspiration was associated with dementia and dysphagia, scored higher on CURB65, and showed worse prognosis: In-hospital mortality 27.5% versus 15.1% and 1-year survival 20.8% versus 38.6%. 55 episodes (18.3%) were treated in HaH, with the lower mortality than conventional hospitalization. After multivariate analysis, HaH and chronic oxygen therapy showed protective role, whereas CURB65, altered mental status (both as referral symptom or physical finding), leukocytosis and acidemia proved deleterious. **Conclusions**: NHR hospitalized for respiratory events are highly complex, comorbid, and dependent. Aspiration carries worse prognosis than infection. HaH care leads to better outcomes, whereas altered mental status, acidemia, leukocytosis, and CURB65 confer worse prognosis.

Keywords: Nursing home residents. Respiratory infections. Aspiration pneumonia. Hospital-at-home.

Introduction

The number of nursing homes residents (NHR) has continually increased in the last decades, leading to higher burdens of morbidity. Infections are the leading cause of hospitalization[1]. Pneumonia is the second most common infection in NHR, and the main cause of hospital referral[2], hospitalization and death[3-6]. Patients with pneumonia acquired in nursing homes (NH) are different from community-acquired pneumonia (CAP)[7,8], regarding their demographics (older, higher burden of underlying diseases, and poorer functional status[7,8]), their presentation (higher prevalence of extrapulmonary manifestations such as mental confusion or

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***Correspondence:**
Juan M. Antón Santos
E-mail: jmanton.hugf@salud.madrid.org

Date of reception: 08-11-2021
Date of acceptance: 01-02-2022
DOI: 10.24875/SJMED.21000023

Available online: 21-03-2022
Span J Med. 2022;2(1):9-23
www.spanishjmed.com

gastrointestinal symptoms, higher degree of hypoxemia, or altered consciousness[8-11]), and their evolution (incidence and mortality rate similar to hospital-acquired-pneumonia [HAP][12]). Thus, nursing-home-acquired-pneumonia (NHAP) was described as a subgroup of healthcare-acquired-pneumonia (HCAP); broad spectrum antibiotherapy covering multidrug-resistant (MDR) microorganisms was recommended for HCAP[13]. Highly variable etiology of NHAP was found, both usual[7,8,12,14] and MDR[15,16] bacteria as the leading causes. However, HCAP was found not to be predictive of MDR etiology[17], and broad spectrum antibiotherapy has failed to the lower NHAP mortality, adding to the HCAP controversy[18]. Recent pneumonia guidelines recommended abandoning this categorization and emphasized local epidemiology and validated risk factors to guide MDR coverage[19].

NHR are also prone to aspirations, and thus can develop aspiration pneumonitis and aspiration pneumonia[20]. Despite its high prevalence, aspiration events in NH had been less studied and is prone to misconceptions. In the 1980's, a high prevalence of anaerobic bacteria was described in aspiration pneumonia[21,22]. In the past four decades, the epidemiology of aspirations has changed, with a higher proportion of NHR and overall better oral health, thus changing the microbiological isolations[20,23]. Algorithms to differentiate aspiration pneumonitis from aspiration pneumonia had been proposed[24,25], although they are not widely used, so aspiration pneumonitis are often misdiagnosed and treated as aspiration pneumonia. Moreover, the differences between infectious pneumonia and aspiration pneumonia in NH have not been sufficiently studied. As a result, respiratory crisis in NHR is usually treated as a uniform entity, disregarding the differences in both the etiology and the host, and leading to probably inadequate antibiotic treatments.

To address the growing care necessities of NHR, different initiatives have been launched. At University Hospital Infanta Cristina we arranged the "Liaison Unit" ("Unidad de Enlace") to coordinate the care of NHR, including circuits for quick consultation, Hospital-at-Home (HaH) care, and traditional hospitalization. As hospitalizations for respiratory crisis were common, a local study was needed.

The main objectives of our study were: (1) to describe the respiratory events leading to hospitalization in NHR; (2) to compare the differences between aspiration and infectious events; (3) to investigate prognostic factors for mortality, and (4) to determine the security in terms of mortality of HaH care at NH.

Methods

Setting

This study was conducted at Hospital Universitario Infanta Cristina, a secondary-level university public hospital of 187 beds in Spain. Its sanitary area included a total of 13 NH at the time of the study.

Design

This study was a retrospective review of hospital medical charts of patients coming from NH and hospitalized for the treatment of a respiratory infection or aspiration event, discharged from January 1, 2016, to December 31, 2017. Patient was selected by searching for ICD-10 codes for respiratory tract infections (j06.9, j15.xxx, j13, j20.9, j22, j98.8, j69, and j98.01) or aspiration events (t17.xxx, j69) in the discharge codification database.

A data collection chart was developed, including all the variables deemed necessary for the study. Chart review was done by one of two data abstractors (JMAS and YMC). Anonymized data were entered into a protected database. Data collected included demographics and comorbidities; clinical data and physical findings at emergency room evaluation; results from complementary explorations (including cultures); clinical management (including antimicrobial treatment received); and hospital outcome. All charts were reviewed to check for long-term survival, but patients were not directly contacted after hospital discharge.

Study population

All consecutive episodes of respiratory infections in NHR requiring hospitalization and discharged during the study period were included in the study.

Definitions

All variables and definitions were selected before data collection.

Aspiration events were defined as witnessed, unwitnessed (using the criteria by Pick[26]) or suspected (using the criteria by Mylotte[24]). A witnessed aspiration event was defined as a history of choking after emesis or eating. An unwitnessed aspiration event was defined

as the development of compatible symptoms (at least one of either a new infiltrate on chest radiograph [CXR], new tachypnea new fever, or a change in mental status not explained by another cause) within 24 h of a witnessed episode of emesis, coughing while eating, displacement of a feeding tube, or the presence of vomitus or tube feeding on a pillow or clothing. A suspected aspiration[24] was defined when the criteria for definite aspiration event were not met, but there was a sudden onset of symptoms and signs of lower respiratory tract infection (dyspnea, tachypnea, hypoxemia, and fever) in a previously stable resident, in the context of at least one of the following: tube feeding, objective evidence of dysphagia, or a CXR with an infiltrate consistent with aspiration (lower lobe infiltrate). Patients with either witnessed, unwitnessed or suspected aspiration were considered to have an aspiration event, whereas patients with no history of aspiration were considered as infectious events.

Radiographic infiltrates were defined similarly to previous studies[24], with a slight modification: as CXR readings by radiologists were not available for every patient, in those cases the emergency-room clinician interpretation was used. An infiltrate was considered present on CXR if one of the following was described: possible or definite pneumonia, localized air-space disease, or consistent with pneumonia. CXR officially read as questionable infiltrate, atelectasis, or pleural effusion were not considered infiltrates unless a second CXR or thoracic ultrasonography on admission confirmed the diagnosis.

The diagnosis was categorized into four groups according to the presence or absence of aspiration events and confirmed radiographic infiltrates: acute bronchitis (neither infiltrates nor aspiration event), bacterial pneumonia (infiltrates without aspiration), bronchoaspiration (aspiration event without infiltrates) or aspiration pneumonia (aspiration event plus infiltrates).

Several scales were calculated from data review. Functional status was determined by Katz Activities of Daily Living (ADL) score and Barthel Index (BI). Severity of infection was assessed by Pneumonia Severity Index (PSI), CURB65 score, and qSOFA (quick Sequential Organ Failure Assessment) index. Two validated medium-term prognostic scales were also evaluated: PROFUND Index[27,28] and PALIAR Index[29,30].

Quantitative variables were generally categorized as normal or abnormal upon admission. Age on admission was segmented in four groups: < 70 years; 70-79 years; 80-89 years; and ≥ 90 years.

Outcomes

Hospital outcome (discharge or death) was the main endpoint for the study. Hospital length of stay (LOS) was calculated from the date of admission and the date of discharge. Survival after discharge and readmission during the first 30 days were secondary endpoints for the analysis.

Statistical analysis

First, a descriptive analysis was made using two categorizations (a dichotomic categorization into aspiration events vs. infectious events, and a four-group categorization as described in definitions).

Quantitative variables were expressed as means and SD. Continuous variables were tested for normal distribution using Kolmogorov–Smirnov. Categorical variables were expressed as absolute frequencies and percentages. p values were obtained for cuantitative variables using Student t-test for two group comparisons, and ANOVA or Kruskal–Wallis test for four-group comparisons, and Pearson Chi-square or Fisher exact test for categorical variables. A two-sided $p < 0.05$ was considered significant.

Univariate analysis was performed to explore possible risk factors for death, using binomial logistic regression. Variables associated ($p < 0.10$) either with aspiration (potential confounding factors) or with death were included in a backward-stepwise multivariate logistic regression model for mortality. Survival analysis was deemed unnecessary, as there were no censored cases, and time until death or discharge was not considered relevant.

We used SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) for all analyses.

Results

A total of 301 episodes (from 212 patients) were discharged during the study period. There were 152 respiratory infections (81 acute bronchitis and 71 pneumonia) and 149 aspiration events (78 uncomplicated aspiration events and 71 aspiration pneumonia). 182 happened in females (60.5%), with a mean age of 86.4 years (85.8% over 80 years). The main comorbidities were hypertension (HTA) (80.7%), dementia (70.8%), chronic heart failure (CHF) (41.5%), and diabetes (38.5%). A low functional status was observed (mean BI 12.7 ± 17.9 and mean Katz Index 5.3 ± 1.2); however, only 20.6% of them had any validated functional status score

Table 1. Description of patient characteristics: main results from univariate analysis by mechanism of event, aspiration versus infectious

	Global	Infectious (n = 152)	Aspiration (n = 149)	p-value
Demographics and comorbidities				
Age (years)	86.4 ± 7.1	87.6 ± 6.6	85.1 ± 7.4	p = 0.002
Sex (male)	119 (39.5%)	52 (34.2%)	67 (45%)	p = 0.037
Hypertension	243 (80.7%)	132 (86.8%)	111 (74.5%)	p = 0.007
Chronic heart failure	125 (41.5%)	80 (52.6%)	45 (30.2%)	p < 0.001
Atrial fibrillation	101 (33.6)	71 (46.7%)	30 (20.1%)	p < 0.001
Ischemic cardiopathy	65 (21.6%)	43 (28.3%)	22 (14.8%)	p = 0.004
Diabetes	116 (38.5%)	55 (36.2%)	61 (40.9%)	NS
Stroke	77 (25.6%)	33 (21.7%)	44 (29.5%)	p = 0.120
Chronic obstructive pulmonary disease	44 (14.6%)	17 (11.2%)	27 (18.1%)	p = 0.089
Chronic domiciliary oxygenotherapy	76 (25.2%)	44 (28.9%)	32 (21.5%)	p = 0.136
Chronic non-invasive mechanical ventilation	21 (7.0%)	10 (6.6%)	11 (7.4%)	NS
Dementia Global Deterioration Scale	213 (70.8%) 5.2 ± 1	87 (57.2%) 4.8 ± 1	126 (84.6%) 5.5 ± 0.9	p < 0.001 p = 0.001
Dysphagia	81 (26.9%)	6 (3.9%)	75 (50.3%)	p < 0.001
Nasogastric tube	10 (3.3%)	0 (0%)	10 (6.7%)	p = 0.001
Gastrostomy feeding	5 (1.7%)	1 (0.7%)	4 (2.7%)	NS
Chronic kidney disease	73 (24.3%)	46 (30.3%)	27 (18.1%)	p = 0.14
Functional and prognostic indexes				
Any functional scale obtained at admission	62 (20.6%)	28 (18.4%)	34 (22.8%)	NS
Katz Index Katz Index 6	5.3 ± 1.2 188 (62.5%)	4.8 ± 1.5 68 (44.7%)	5.7 ± 0.7 120 (80.5%)	p < 0.001** p < 0.001
Barthel Index Barthel Index < 30	12.7 ± 17.9 243 (80.7%9	18.9 ± 20.5 105 (69.5%)	6.3 ± 11.9 138 (92.6%)	p < 0.001** p < 0.001
PROFUND Index High risk PROFUND (groups 3&4)	11.3 ± 3.2 275 (91.7%)	11 ± 3.4 131 (86.8%)	11.5 ± 3 144 (96.6%)	NS** p = 0.002
PALIAR Index High risk PALIAR (groups 3&4)	7.1 ± 3.9 231 (76.7%)	6.3 ± 3.9 99 (65.1%)	7.9 ± 3.8 132 (88.6%)	p < 0.001 p < 0.001
Referral symptoms				
Aspiration Witnessed Unwitnessed Suspected	149 (49.5%) 41 (13.6%) 18 (6.0%) 90 (29.9%)	0 (0%) 0 (0%) 0 (0%) 0 (0%)	149 (100%) 41 (27.5%) 18 (12.1%) 90 (60.4%)	p < 0.001 p < 0.001
Cough	116 (38.5%)	79 (52%)	37 (24.8%)	p < 0.001
Desaturation	194 (64.5%)	73 (48%)	121 (81.2%)	p < 0.001
Altered consciousness	140 (46.5%)	47 (30.9%)	93 (62.4%)	p < 0.001
Tachycardia	27 (9.0%)	9 (5.9%)	18 (12.1%)	p = 0.062
Physical examination				
Respiratory exertion	129 (42.9%)	52 (34.2%)	77 (52.4%)	p = 0.002

(continues)

Table 1. Description of patient characteristics: main results from univariate analysis by mechanism of event, aspiration versus infectious *(continued)*

	Global	Infectious (n = 152)	Aspiration (n = 149)	p-value
Altered consciousness	150 (49.8%)	53 (34.9%)	97 (66%)	p < 0.001
Rales	138 (45.8%)	67 (44.1%)	71 (48.3%)	NS
Bronchoespasm	110 (36.5%)	63 (41.4%)	47 (32%)	p = 0.089
Pit edema	67 (22.3%)	44 (28.9%)	23 (15.6%)	p = 0.006
Systolic blood pressure (mmHg)	126.8 ± 23.2	127.8 ± 23.1	125.8 ± 23.3	NS
Tachycardia > 100 lpm	97 (12.3%)	39 (25.7%)	56 (37.6%)	p = 0.026
Tachypnea (> 20 rpm)	84 (27.9%)	49 (32.2%)	35 (23.5%)	p = 0.091
Desaturation (SpO_2 < 90%)	128 (42.5%)	69 (45.4%)	81 (54.4%)	p = 0.120
Pressure ulcers	118 (39.3%)	51 (33.6%)	67 (45.3%)	p = 0.038
Complementary tests				
Alveolar infiltrates (on CXR)	142 (47.2%)	71 (46.7%)	71 (47.7%)	NS
Acidemia	61 (20.3%)	28 (18.4%)	33 (22.1%)	NS
PO_2 (mmHg)	55.1 ± 21.3	54.4 ± 20.5	55.8 ± 22.2	NS
PCO_2 (mmHg)	44.5 ± 12.4	45.1 ± 12.5	44 ± 12.3	NS
Hypercapnia (> 45 mmHg)	115 (38.2%)	63 (41.4%)	52 (34.9%)	NS
Metabolic acidosis (HCO_3 < 22)	36 (12%)	15 (9.9%)	21 (14.1%)	NS
Creatinine (mg/dL)	1.34 ± 0.84	1.36 ± 0.92	1.33 ± 0.75	NS
Urea (mg/dL)	77 ± 52.1	71.9 ± 49	82.2 ± 54.9	p = 0.105**
Hypernatremia (Na > 145)	78 (25.9%)	25 (16.4%)	53 (35.6%)	p < 0.001
Glucose (mg/dL)	161.1 ± 84.1	154.8 ± 72.1	167.5 ± 94.6	NS
Leukocytosis (> 12500×10^6/L)	125 (42.2%)	50 (32.9%)	75 (52.1%)	p = 0.001
Reactive C-Protein	94 ± 84.7	90.3 ± 81.6	98 ± 88.2	NS
Severity indexes				
PSI PSI group 5	141.5 ± 29.6 186 (61.8%)	140.2 ± 29.5 91 (59.9%)	143 ± 29.7 95 (63.8%)	NS NS
CURB65 Index CURB65 ≥ 3	2.4 ± 0.8 143 (47.5%)	2.3 ± 0.7 57 (37.5%)	2.6 ± 0.8 86 (57.8%)	p < 0.001 p = 0.002
qSOFA index qSOFA ≥ 2	0.9 ± 0.7 53 (17.6%)	0.8 ± 0.7 19 (12.5%)	1 ± 0.7 34 (22.8%)	p = 0.004 p = 0.004
Initial treatment				
Palliative approach (n = 301)	10 (3.3%)	2 (1.3%)	8 (5.5%)	p = 0.046
Corticosteroids (n = 292)	179 (61.3%)	96 (64.4%)	83 (58%)	NS
Antibiotic therapy (n = 301)	288 (96.6%)	150 (98.7%)	138 (94.5%)	p = 0.046
Combined therapy	82 (27.2%)	53 (34.9%)	29 (19.5%)	p = 0.003
MDR-directed antibiotic therapy (n = 274)	67 (24.5%)	35 (24.1%)	32 (24.8%)	NS
Length of antibiotic treatment (days)	8.6 ± 4	9.1 ± 3.9	8.1 ± 4.1	p = 0.056
Adicional tests				
Repeated chest X-rays	130 (43.2%)	69 (45.4%)	61 (40.9%)	NS

(continues)

Table 1. Description of patient characteristics: main results from univariate analysis by mechanism of event, aspiration versus infectious *(continued)*

	Global	Infectious (n = 152)	Aspiration (n = 149)	p-value
Thoracic POCUS	37 (12.3%)	28 (18.4%)	9 (6%)	p = 0.003
Blood cultures	103 (34.2%)	49 (32.2%)	53 (35.6%)	NS
Sputum cultures	23 (7.6%)	18 (11.8%)	4 (2.7%)	p = 0.006
Urinary antigens	40 (13.3%)	26 (17.1%)	13 (8.7%)	p = 0.060
Evolution				
Length of stay (days)	6 ± 5.8	6.5 ± 7	5.4 ± 4.1	p = 0.108
Hospital-at-Home care	55 (18.3%)	23 (15.1%)	32 (21.5%)	NS
In-Hospital death	64 (21.3%)	23 (15.1%)	41 (27.5%)	p = 0.009
Survival				
Readmission < 30 days	73 (24.3%)	43 (28.3%)	30 (20.1%)	p = 0.099
Death or readmission < 30 days	137 (45.5%)	66 (43.4%)	71 (47.7%)	NS
Alive 1 month after discharge (n = 300)	190 (63.3%)	109 (71.7%)	81 (54.7%)	p = 0.002
Alive 3 months after discharge (n = 291)	151 (51.9%)	93 (62.8%)	58 (40.6%)	p < 0.001
Alive 6 months after discharge (n = 287)	121 (42.2%)	74 (50.3%)	47 (33.6%)	p = 0.004
Alive 1 year after discharge (n = 270)	81 (30%)	54 (38.6%)	27 (20.8%)	p = 0.001
Length of survival after discharge (days)	97.7 ± 169.2	136.2 ± 203.2	63.9 ± 124.1	p = 0.001**

Cualitative variables are expressed as n (%), cuantitative variables as mean ± standard deviation. Comparison among groups were made using Student t-test for cuantitative variables (** Kruskal–Wallis) and Chi-Square for cualitative variables. p > 0.15 is simplified as NS.
CxR: chest X-rays; POCUS: Point-of-Care UltraSonography; MDR: multidrug-resistant; NS: not significant.

registered on admission. Estimated prognosis was poor when calculated either by PROFUND (91.7% groups 3 or 4) or PALIAR (76.7% groups 3 or 4) indexes. No patient had advance directive document.

The main reasons for emergency-room referral were dyspnea (74.4%), low peripheral saturation (64.5%), and altered mental status (46.5%). Clinical examination showed mainly altered consciousness (49.8%), rales (45.8%), respiratory exertion (42.9%), and low oxygen saturation (42.5%); bronchospasm was present on 36.5% episodes, whereas fever (14.6%), tachycardia (12.3%), or tachypnea (27.9%) were uncommon. Infiltrates and pleural effusions were present on 47.2% and 18.1%, respectively. A high clinical severity was assessed both by PSI (97% groups ≥ 4) and CURB65 (89.4% ≥ 2) indexes, but not by qSOFA (17.6% ≥ 2).

Table 1 (and supplementary table 1) summarizes global data and shows the differences according to the mechanism; table 2 (and supplementary table 2) shows differences according to the diagnosis. Some comorbidities, such as HTA, CHF, atrial fibrillation (AF), and chronic kidney disease (CKD), were more common in infectious episodes, whereas dementia, dysphagia, or low functional status were more frequently present in aspiration events. The main symptoms at referral also differed, cough being more frequent in infections, whereas low oxygen saturation and altered consciousness were more common in aspirations. Hypotension was less common in uncomplicated bronquitis. On physical examination, only pleural effusions (more common in infections) and hypernatremia and leukocytosis (more common in aspirations) showed differences. Clinical severity was not different according to PSI, but aspirations scored worse on CURB65 and qSOFA indexes.

The main treatments were antibiotics (288 cases, 96.6%), oxygen (295 cases, 99.7%), corticosteroids (61.3%), and bronchodilators (84.3%); ten patients were directed to palliative care at admission (3 of them survived). Antibiotic treatment consisted of monotherapy on 192 episodes (63.8%) and polytherapy on 82 (27.2%). Spectrum of antibiotics was directed to MDR bacteria on 67 episodes (24.5%), whereas 17 patients received

Table 2. Characteristics of patients: Main results from univariate analysis by diagnosis

	Acute bronchitis (n = 81)	Bacterial pneumonia (n = 71)	Broncho-aspiration (n = 78)	Aspiration pneumonia (n = 71)	p-value
Demographics and comorbidities					
Age (years)	88.4 ± 5.8	86.8 ± 7.4	85.7 ± 6.5	84.5 ± 8.3	p = 0.006
Sex (male)	20 (24.7%)	32 (45.1%)	28 (35.9%)	39 (54.9%)	p = 0.001
Hypertension	72 (88.9%)	60 (84.5%)	57 (73.1%)	54 (76.1%)	p = 0.045
Chronic heart failure	47 (58.0%)	33 (46.5%)	23 (29.5%)	22 (31.0%)	p = 0.001
Atrial fibrillation	37 (45.7%)	34 (47.9%)	15 (19.2%)	15 (21.1%)	p < 0.001
Ischemic cardiopathy	22 (27.2%)	21 (29.6%)	8 (10.3%)	14 (19.7%)	p = 0.017
Diabetes	34 (42.0%)	21 (29.6%)	28 (35.9%)	33 (46.5%)	NS
Stroke	14 (17.3%)	19 (26.8%)	37 (34.6%)	17 (23.9%)	p = 0.093
Chronic obstructive pulmonary disease	10 (12.3%)	7 (9.9%)	12 (15.4%)	15 (21.1%)	NS
Chronic domiciliary oxygenotherapy	26 (32.1%)	18 (25.4%)	14 (17.9%)	18 (25.4%)	NS
Chronic non-invasive mechanical ventilation	8 (9.9%)	2 (2.8%)	5 (6.4%)	6 (8.5%)	NS
Dementia Global Deterioration Scale	40 (49.4%) 4.5 ± 1.2	47 (66.2%) 5.1 ± 0.8	65 (83.3%) 5.4 ± 0.9	61 (85.9%) 5.5 ± 1	p < 0.001 p < 0.001**
Dysphagia	1 (1.2%)	5 (7.0%)	44 (56.4%)	31 (43.7%)	p < 0.001
Nasogastric tube	0 (0.0%)	0 (0.0%)	6 (7.7%)	4 (5.6%)	p = 0.011
Gastrostomy feeding	1 (1.2%)	0 (0.0%)	2 (2.6%)	2 (2.8%)	NS
Chronic kidney disease	29 (35.8%)	17 (23.9%)	16 (20.5%)	11 (15.5%)	p = 0.024
Functional and prognostic indexes					
Any functional scale obtained at admission	15 (18.5%)	13 (18.3%)	16 (20.5%)	18 (25.4%)	NS
Katz Index Katz Index 6	4.5 ± 1.5 25 (30.9%)	5.2 ± 1.4 43 (60.6%)	5.7 ± 0.6 61 (78.2%)	5.7 ± 0.7 59 (83.1%)	p < 0.001** p < 0.001
Barthel Index Barthel Index < 30	25.5 ± 22 46 (56.8%)	11.4 ± 15.5 59 (84.3%)	6.3 ± 11.3 74 (94.9%)	6.3 ± 12.6 64 (90.1%)	p < 0.001** p < 0.001
PROFUND Index High risk PROFUND (groups 3&4)	10.3 ± 3.3 67 (82.7%)	11.9 ± 3.2 64 (91.4%)	11.4 ± 2.5 78 (100%)	11.6 ± 3.5 66 (93%)	p = 0.016 p < 0.001
PALIAR Index High risk PALIAR (groups 3&4)	5.2 ± 3.4 44 (54.3%)	7.5 ± 4.1 55 (77.5%)	7.9 ± 3.9 67 (85.9%)	7.9 ± 3.6 65 (91.5%)	p < 0.001 p < 0.001
Referral symptoms					
Aspiration Witnessed Unwitnessed Suspected	0 (0%) 0 (0%) 0 (0%) 0 (0%)	0 (0%) 0 (0%) 0 (0%) 0 (0%)	78 (100%) 24 (30.8%) 9 (11.5%) 45 (57.7%)	71 (100%) 17 (23.9%) 9 (12.7%) 45 (63.4%)	p < 0.001 p < 0.001
Cough	49 (60.5%)	30 (42.3%)	15 (19.2%)	22 (31%)	p < 0.001
Desaturation	34 (42%)	39 (54.9%)	65 (83.3%)	56 (78.9%)	p < 0.001
Hypotension	1 (1.2%)	9 (12.7%)	9 (11.5%)	9 (12.7%)	p = 0.035
Altered consciousness	16 (19.8%)	31 (43.7%)	45 (57.7%)	48 (67.6%)	p < 0.001
Tachycardia	3 (3.7%)	6 (8.5%)	8 (10.3%)	10 (14.1%)	NS

(continues)

Table 2. Characteristics of patients: Main results from univariate analysis by diagnosis *(continued)*

	Acute bronchitis (n = 81)	Bacterial pneumonia (n = 71)	Broncho-aspiration (n = 78)	Aspiration pneumonia (n = 71)	p-value
Physical examination					
Respiratory exertion	25 (30.9%)	27 (38%)	35 (46.1%)	42 (59.2%)	p = 0.004
Altered consciousness	21 (25.9%)	32 (45.1%)	47 (61.8%)	50 (70.4%)	p < 0.001
Rales	32 (39.5%)	35 (49.3%)	36 (47.4%)	35 (49.3%)	NS
Bronchoespasm	46 (56.8%)	17 (23.9%)	25 (32.9%)	22 (31%)	p < 0.001
Pit edema Tachycardia > 120 lpm Tachypnea (> 20 rpm)	24 (29.6%) 10 (12.3%) 32 (39.5%)	20 (28.2%) 2 (2.8%) 17 (23.9%)	13 (17.1%) 12 (15.4%) 18 (23.1%)	10 (14.1%) 13 (18.3%) 17 (23.9%)	p = 0.049 p = 0.029 p = 0.059
Desaturation (SpO_2 < 90%)	38 (46.9%)	31 (43.7%)	34 (43.6%)	47 (66.2%)	p = 0.017
Temperature (ºC)	37 ± 0.7	37.2 ± 0.8	37.1 ± 0.8	37.2 ± 0.9	NS
Pressure Ulcers	23 (28.4%)	28 (39.4%)	41 (53.2%)	26 (36.6%)	p = 0.015
Complementary tests					
pH	7.39 ± 0.06	7.41 ± 0.07	7.39 ± 0.08	7.41 ± 0.08	NS
Acidemia	17 (21%)	11 (15.5%)	20 (25.6%)	13 (18.3%)	NS
PO_2 (mmHg)	57.2 ± 20.3	51.3 ± 20.6	58.8 ± 24.4	52.5 ± 19.2	p = 0.114
PCO_2 (mmHg)	47.7 ± 13.6	42.1 ± 10.5	44.9 ± 13.3	42.9 ± 11.2	p = 0.033
Hypercapnia (> 45 mmHg)	39 (48.1%)	24 (33.8%)	29 (37.2%)	23 (32.4%)	NS
HCO_3 (mEq/L)	28 ± 6.1	25.9 ± 4	25.7 ± 5.4	27 ± 9.5	p = 0.137
Metabolic acidosis (HCO_3 < 22)	7 (8.6%)	8 (11.3%)	16 (20.5%)	5 (7%)	p = 0.048
Creatinine (mg/dL)	1.43 ± 1.13	1.29 ± 0.59	1.34 ± 0.78	1.31 ± 0.71	NS
Urea (mg/dL)	74.9 ± 56.9	68.5 ± 38.6	87.5 ± 63.1	76.4 ± 43.6	NS**
Sodium (mmol/L)	139.9 ± 7.1	141.5 ± 8.3	142.9 ± 10.5	143.9 ± 7.6	p = 0.017**
Hypernatremia (Na > 145)	10 (12.3%)	15 (21.1%)	24 (30.8%)	29 (40.8%)	p < 0.001
Glucose (mg/dL)	148.2 ± 58	162.3 ± 85	177.1 ± 116.5	156.8 ± 61.3	NS
Leukocytosis (> 12500×10^6/L)	22 (27.2%)	28 (39.4%)	35 (45.5%)	40 (59.7%)	p = 0.001
Reactive C-Protein	63.1 ± 57.5	120.3 ± 93.3	82.3 ± 76.7	118.3 ± 98	p < 0.001**
Severity indexes					
PSI PSI group 5	138.8 ± 29.7 49 (60.5%)	141.7 ± 29.3 42 (59.2%)	143.5 ± 29.2 50 (64.1%)	142.3 ± 30.4 45 (63.4%)	NS NS
CURB65 Index CURB65 ≥ 3	2.2 ± 0.7 27 (33.4%)	2.3 ± 0.8 30 (42.2%)	2.6 ± 0.8 42 (53.9%)	2.6 ± 0.8 44 (54.0%)	p < 0.001 p = 0.044
qSOFA index qSOFA ≥ 2	0.7 ± 0.6 6 (7.4%)	0.8 ± 0.7 13 (18.3%)	0.9 ± 0.7 17 (21.8%)	1.1 ± 0.7 17 (23.9%)	p = 0.011 p = 0.098
Initial treatment					
Palliative approach (n = 301)	1 (1.2%)	1 (1.4%)	6 (7.7%)	2 (2.8%)	p = 0.077
Corticosteroids (n = 292)	55 (68.8%)	41 (59.4%)	46 (62.2%)	37 (53.6%)	NS
Antibiotic therapy (n = 301) Combined therapy	80 (98.8%) 25 (30.9%)	70 (98.6%) 28 (39.4%)	70 (92.1%) 14 (17.9%)	68 (97.1%) 15 (21.1%)	p = 0.077 p = 0.012

(continues)

Table 2. Characteristics of patients: Main results from univariate analysis by diagnosis *(continued)*

	Acute bronchitis (n = 81)	Bacterial pneumonia (n = 71)	Broncho-aspiration (n = 78)	Aspiration pneumonia (n = 71)	p-value
MDR-directed antibiotic therapy (n = 274)	16 (20.5%)	19 (28.4%)	11 (16.2%)	21 (34.4%)	p = 0.071
Additional tests					
Blood cultures	22 (27.2%)	27 (38%)	21 (26.9%)	32 (45.1%)	p = 0.076
Sputum cultures	11 (13.6%)	7 (9.9%)	1 (1.3%)	3 (4.2%)	p = 0.033
Urinary antigens	6 (7.4%)	20 (28.2%)	4 (5.1%)	9 (12.7%)	p < 0.001
Evolution					
Length of stay (days)	6.8 ± 8.4	6.1 ± 5.2	4.7 ± 3.8	6.2 ± 4.2	p = 0.123
Hospital-at-Home care	12 (14.8%)	11 (15.5%)	15 (19.2%)	17 (23.9%)	NS
In-Hospital death	10 (12.3%)	13 (18.3%)	21 (26.9%)	20 (28.2%)	p = 0.045
Survival					
Readmission < 30 days	27 (33.3%)	16 (22.5%)	13 (16.7%)	17 (23.9%)	p = 0.102
Death or readmission < 30 days	37 (45.7%)	29 (40.8%)	34 (43.6%)	37 (52.1%)	NS
Alive 1 month after discharge (n = 300)	62 (76.5%)	47 (66.2%)	46 (59.7%)	35 (49.3%)	p = 0.005
Alive 3 months after discharge (n = 291)	54 (68.4%)	39 (56.5%)	32 (43.2%)	26 (37.7%)	p = 0.001
Alive 6 months after discharge (n = 287)	44 (55.7%)	30 (44.1%)	26 (35.6%)	21 (31.3%)	p = 0.014
Alive 1 year after discharge (n = 270)	29 (39.2%)	25 (37.9%)	15 (22.1%)	12 (19.4%)	p = 0.016
Length of survival after discharge (days)	118.2 ± 151.1	153.1 ± 242.5	76.3 ± 138.9	50.6 ± 105.6	p = 0.008**

Cualitative variables are expressed as n (%), cuantitative variables as mean ± standard deviation. Comparison among groups were made using ANOVA for cuantitative variables (** Kruskal–Wallis) and Chi-Square for cualitative variables. p > 0.15 is simplified as NS
CxR: chest x-rays; POCUS: Point-of-Care UltraSonography; MDR: multi-drug resistant; NS: not significant.

antibiotics unidentified on clinical charts or discharge reports. There were no significant differences in antibiotic coverage between aspirations and infections, but the severity by CURB65 index correlated with broad-spectrum therapy (6.5%, 24.8%, 25.2%, and 53.3% for CURB65 scores 1, 2, 3, and 4, respectively). A secondary CXR was obtained in 120 episodes (43.2%), and 37 (12.3%) were reevaluated by Point-Of-Care UltraSonography (POCUS). Microbiological samples were not commonly obtained: Blood cultures in 103 episodes (only eight positives, 7.8%), sputum culture in 22 episodes (11 positives, 50%), and urinary antigens in 39 episodes (eight positives, 20%).

Of 301 episodes, 55 were transferred to HaH care (18.3%), and overall 64 died (21.3% mortality rate). Average LOS (including HaH) was 6 ± 5.8 days. Readmission on the first 30 days occurred in 73 cases (24.3%). Survival was present on 190 (63.3%), 151 (51.9%), 121 (42.2%), and 81 (30%) cases, respectively, at months 1st, 3rd, 6th, and 12th after hospital discharge. Aspirations showed worse survival rates (20.8% vs. 38.6% at 1 year) and lower length of survival (63.9 vs. 136.2 days), especially when aspiration pneumonia was diagnosed (19.4% 1-year survival rate, survival after discharge only 50.6 days).

Table 3 (and supplementary table 3) shows the univariate analysis of mortality. Mortality was associated with the antecedent of not using oxygen chronically, and neared signification for CHF and stroke. Low functional status in Katz or BI and a high PALIAR score also correlated with mortality, whereas PROFUND index did not. Description at referral of either aspiration, no cough, altered mental status or tachycardia, clinical findings at emergency room of respiratory exertion and altered mental status, and complementary findings of acidemia, metabolic acidosis, hypernatremia, and leukocytosis, also conferred worse mortality. All severity scores (PSI, CURB, and qSOFA) correlated with worse mortality. Patients who survived were more prone to have been treated with corticosteroids or a defined

Table 3. Main results of univariate analysis of differences by survival status

	Global	Survivors (n = 237)	Non-survivors (n = 64)	p-value
Demographics and comorbidities				
Age (years)	86.4 ± 7.1	86.3 ± 7	86.7 ± 7.7	NS
Sex (male)	119 (39.5%)	91 (38.4%)	28 (43.8%)	NS
Hypertension	243 (80.7%)	193 (81.4%)	50 (78.1%)	NS
Chronic heart failure	125 (41.5%)	105 (44.3%)	20 (31.3%)	p = 0.060
Ischemic cardiopathy	65 (21.6%)	52 (21.9%)	13 (20.3%)	NS
Diabetes	116 (38.5%)	94 (39.7%)	22 (34.4%)	NS
Stroke	77 (25.6%)	66 (27.8%)	11 (17.2%)	p = 0.083
Chronic domiciliary oxygenotherapy	76 (25.2%)	67 (28.3%)	9 (14.1%)	p = 0.020
Chronic non-invasive mechanical ventilation	21 (7.0%)	20 (8.4%)	1 (1.6%)	p = 0.055
Dementia Global Deterioration Scale	213 (70.8%) 5.2 ± 1	163 (68.8%) 5.1 ± 1	50 (78.1%) 5.5 ± 1	p = 0.145 p = 0.037
Dysphagia	81 (26.9%)	66 (27.8%)	15 (23.4%)	NS
Nasogastric tube	10 (3.3%)	8 (3.4%)	2 (3.1%)	NS
Gastrostomy feeding	5 (1.7%)	2 (0.8%)	3 (4.7%)	p = 0.066
Functional and prognostic indexes				
Any functional scale obtained at admission	62 (20.6%)	43 (18.1%)	19 (29.7%)	p = 0.043
Katz Index Katz Index 6	5.3 ± 1.2 188 (62.5%)	5.2 ± 1.3 136 (57.4%)	5.7 ± 0.9 52 (81.3%)	p = 0.001** p = 0.021
Barthel Index Barthel Index < 30	12.7 ± 17.9 243 (80.7%9	14.9 ± 18.8 184 (77.6%)	4.4 ± 10.1 59 (93.7%)	p < 0.001** p = 0.038
PROFUND Index High risk PROFUND (groups 3&4)	11.3 ± 3.2 275 (91.7%)	11.2 ± 3.3 214 (90.3%)	11.5 ± 2.7 61 (96.8%)	NS** p = 0.096
PALIAR Index High risk PALIAR (groups 3&4)	7.1 ± 3.9 231 (76.7%)	7 ± 4 174 (73.4%)	7.6 ± 3.5 57 (89.1%)	NS p = 0.009
Referral symptoms				
Aspiration Witnessed Unwitnessed Suspected	149 (49.5%) 41 (13.6%) 18 (6.0%) 90 (29.9%)	108 (45.6%) 32 (13.5%) 12 (5.1%) 64 (27%)	41 (64.1%) 9 (14.1%) 6 (9.4%) 26 (40.6%)	p = 0.009 p = 0.044
Cough	116 (38.5%)	102 (43%)	14 (21.9%)	p = 0.002
Altered consciousness	140 (46.5%)	95 (40.1%)	45 (70.3%)	p < 0.001
Tachycardia	27 (9.0%)	16 (6.8%)	11 (17.2%)	p = 0.010
Physical examination				
Respiratory exertion	129 (42.9%)	90 (38.1%)	39 (61.9%)	p = 0.001
Altered consciousness	150 (49.8%)	102 (43.2%)	48 (76.2%)	p < 0.001
Systolic blood pressure (mmHg)	126.8 ± 23.2	127.5 ± 23.7	124.2 ± 21.1	NS
Tachycardia (> 100 lpm)	97 (12.3%)	71 (30%)	24 (37.5%)	NS
Tachypnea (> 20 rpm)	84 (27.9%)	64 (27%)	20 (31.3%)	NS
Pulse oxymetry (%)	89.9 ± 6.3	90.3 ± 6.2	88.5 ± 6.9	p = 0.06

(continues)

Table 3. Main results of univariate analysis of differences by survival status *(continued)*

	Global	Survivors (n = 237)	Non-survivors (n = 64)	p-value
Desaturation (SpO_2 < 90%)	128 (42.5%)	114 (48.1%)	36 (56.3%)	NS
Complementary tests				
Alveolar infiltrates (on CXR)	142 (47.2%)	109 (46%)	33 (51.6%)	NS
pH	7.4 ± 0.07	7.4 ± 0.07	7.38 ± 0.08	p = 0.082**
Acidemia	61 (20.3%)	42 (17.7%)	19 (29.7%)	p = 0.035
PO_2 (mmHg)	55.1 ± 21.3	54.9 ± 20.8	55.8 ± 23.4	NS
PCO_2 (mmHg)	44.5 ± 12.4	44.5 ± 12.2	44.8 ± 13.4	NS
Hypercapnia (> 45 mmHg)	115 (38.2%)	91 (38.4%)	24 (37.5%)	NS
HCO_3 (mEq/L)	26.7 ± 6.5	27 ± 6.5	25.4 ± 6.4	p = 0.093
Metabolic acidosis (HCO_3 < 22)	36 (12%)	20 (8.4%)	16 (25%)	p < 0.001
Creatinine (mg/dL)	1.34 ± 0.84	1.29 ± 0.74	1.53 ± 1.11	p = 0.074**
Urea (mg/dL)	77 ± 52.1	71.8 ± 41.9	96.1 ± 77	p = 0.05**
Hypernatremia (Na > 145)	78 (25.9%)	54 (22.8%)	24 (37.5%)	p = 0.017
Potassium (mmol/L)	4.5 ± 0.8	4.4 ± 0.8	4.6 ± 0.9	p = 0.054
Glucose (mg/dL)	161.1 ± 84.1	159.9 ± 80	165.8 ± 98.6	NS
Total white cell count (x10^6/L)	13158 ± 13109	12071 ± 5878	17180 ± 25835	p = 0.01
Leukocytosis > 12500	125 (42.2%)	90 (38.6%)	35 (55.6%)	p = 0.016
Hemoglobin (g/dL)	11.9 ± 1.8	11.9 ± 1.7	12.1 ± 2.2	NS**
Reactive C-Protein	94 ± 84.7	90.1 ± 83.4	109.6 ± 88.7	p = 0.130
Severity indexes				
PSI PSI group 5	141.5 ± 29.6 186 (61.8%)	139.3 ± 29.7 138 (58.2%)	150 ± 27.5 48 (75%)	p = 0.01 p = 0.049
CURB65 Index CURB65 ≥ 3	2.4 ± 0.8 143 (47.5%)	2.4 ± 0.7 102 (43.0%)	2.8 ± 0.8 41 (64.1%)	p < 0.001 p < 0.001
qSOFA index qSOFA ≥ 2	0.9 ± 0.7 53 (17.6%)	0.8 ± 0.7 36 (15.1%)	1.1 ± 0.6 17 (26.6%)	p < 0.001 p = 0.004
Initial treatment				
Palliative approach (n = 301)	10 (3.3%)	3 (1.3%)	7 (11.3%)	p < 0.001
Corticosteroids (n = 292)	179 (61.3%)	148 (64.3%)	31 (50%)	p = 0.04
Antibiotic therapy (n = 301) Combined therapy	288 (96.6%) 82 (27.2%)	233 (98.7%) 68 (28.7%)	55 (88.7%) 14 (21.9%)	p < 0.001 p < 0.001
MDR-directed antibiotic therapy (n = 274)	67 (24.5%)	56 (24.1%)	11 (26.2%)	NS
Length of antibiotic treatment (days)	8.6 ± 4	9.6 ± 3.4	3.9 ± 3.1	p < 0.001
Evolution				
Length of stay (days)	6 ± 5.8	6.2 ± 5.9	4.9 ± 5.3	p = 0.091
Hospital-at-Home care	55 (18.3%)	52 (21.9%)	3 (4.7%)	p = 0.005

Cualitative variables are expressed as n (%), cuantitative variables as mean ± standard deviation. Comparison among groups were made using Student t-test for cuantitative variables (** Kruskal–Wallis) and Chi-square for cualitative variables. p > 0.15 is simplified as NS.
CxR: chest x-rays; MDR: multidrug resistant; NS: not significant.

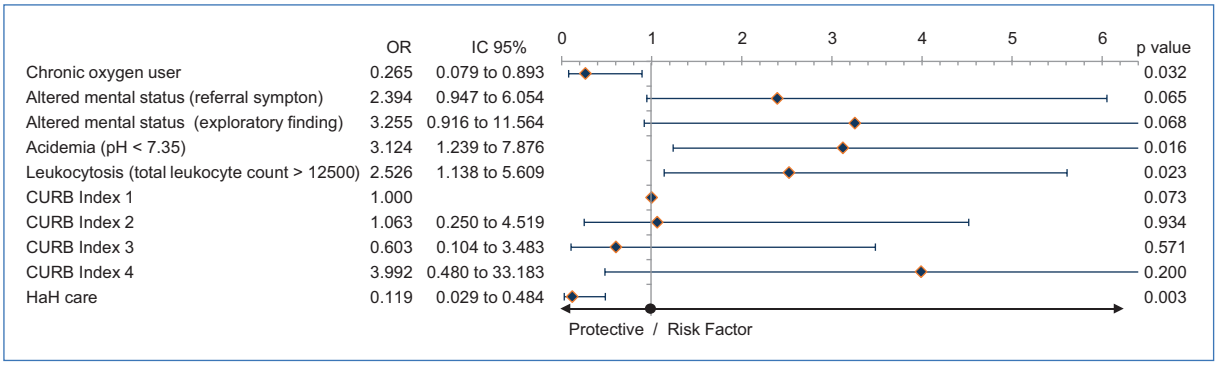

Figure 1. Multivariate analysis of in-hospital mortality. Final model for mortality included two protective factors (chronic oxygen-user and HaH care) and five deleterious factors (altered mental status both as referral symptom or physical examination finding, acidemia, leukocytosis, and CURB65 index). Global prediction was 87.6%.

antibiotic. Undefined antibiotherapy correlated with decease, but MDR-spectrum did not.

A multivariate logistics regression was modeled to control possible confounders. Variables independently associated with mortality are shown on figure 1: chronic oxygen therapy (OR 0.265, CI 95% 0.079-0.893) and HaH care (OR 0.119, CI 95% 0.029-0.484) were protective, whereas acidemia and leukocytosis were deleterious. Altered consciousness and CURB65 were included but did not retain significance. The model correctly categorized 87.6% of the cases. Interestingly, age was not relevant for mortality.

A sensitivity analysis was made by forcing some indexes or antibiotics into the model, with none of the aforementioned variables falling from the model, while maintaining similar OR.

Conclusions

Here, we present one of the largest series of respiratory events leading to hospitalization in NHR in Spain, while also being, to the best of our knowledge, the first to provide insight into the different respiratory events. Carratalá described a series of 126 NHAP hospitalized in 3 years[15], whereas Polverino reported 150 cases in 10 years[13], both at large university hospitals (900 and 1200 beds, respectively). The demographic shift in recent years, with an increasingly older population, has led to higher burden on hospitalization wards: Sanchez[31] found 38% of pneumonias admitted to be NHAP (119 of 313 in just 9 months). The unusually high NH number in our sanitary area has allowed us to gather information on 301 respiratory events (including 142 pneumonia) in only 2 years despite ours being a much smaller hospital.

NHR hospitalized because of respiratory events are elderly, highly comorbid and have a low functional status, as in previous studies[31]. Most charts on revision included subjective expressions such as “dependent for ADL” or “severely frail”. However, only one in five patients had a functional status score properly recorded on admission, and none of them had a frailty score. Frailty has long demonstrated prognostic value independent from age or dependence[32]. In the elderly, comprehensive geriatric assessment leads to better outcomes[33], and should be emphasized, both at emergency room and hospital wards[34]. On the other hand, 70.8% of the patients had dementia, 91.7% showed a poor prognosis on PROFUND index, and none of them had advanced directives. In Spain, advanced directives are less common than in English-speaking countries, and are veritably scarce in demented people. In contrast, in a cohort of NHR in USA with dementia and respiratory infections, Do-Not-Resuscitate and Do-Not-Hospitalize directives were recorded in 64.4% and 2.7% of NH residents[35]. It has been pointed that Advanced-Care-Planning (ACP) in NHR neither correlates with the lower rates of referral or hospitalization, neither with goal-concordant care[36]. ACP is necessary although not sufficient. Not having advanced directives is a sure way to low-value end-of-life care, and thus should be emphasized in NH residents.

In our cohort, the main referral reasons were dyspnea, low peripheral saturation, and altered mental status. Fever, tachycardia, or tachypnea were scarce both as referral symptoms and exploratory findings. It has long been known that older patients have different clinical presentations, and it may well explain the lower performance of some mortality scores in the elderly[37], as they usually rely on tachycardia/tachypnea. In our

series, qSOFA scored ≥ 2 or more in only 17.6% of the patients.

To elucidate the pattern of disease in NHR, we decided to include in our study not only radiological pneumonia (47% of the patients) but also radiologically unaffected patients. Most previous studies[12,14] had focused on NHAP, but our findings show a higher mortality for "uncomplicated" aspirations than bacterial pneumonia in NHR. It is due time to broaden the picture and include the whole range of respiratory events leading to hospitalizations.

In the previous studies, the difference between aspiration pneumonitis and aspiration pneumonia has been emphasized[24]. Protocols for the management of respiratory events in NH residents recommend withholding antibiotics in aspiration pneumonitis and repeating CXR at 72 h[25]. However, local protocols for respiratory infections at our hospital do not include these points, so nearly all patients had antibiotic treatment upon hospital admission, and CXR were only repeated on a clinical worsening. As it was impossible to differentiate aspiration pneumonitis from pneumonia, at the design phase it was decided to label all aspirations with confirmed infiltrates as aspiration pneumonia, knowing that some of them would be aspiration pneumonitis.

Our study shows that roughly half of the respiratory events were aspiration events, with a different profile. Patients with aspiration events had higher rates of dementia, dysphagia and tube or gastrostomy feeding, and worse scores on both ADL indexes, whereas infectious events were more common with cardiological comorbidities. Basal prognosis from PROFUND or PALIAR was also worse in aspirations. Aspirations usually showed less cough but more desaturation, tachypnea and altered consciousness, and worse scores on qSOFA and CURB65 indexes. Aspirations conferred worse prognosis on univariate analysis (64.1% vs. 45.6%), whereas radiological infiltrates did not. It is quite common at emergency room to overemphasize the importance of pneumonia, whilst minimizing the role of aspirations. As aspirations confers worse prognosis, in NHR it should be the other way round. To provide high-value care, the causative mechanism of a respiratory event should be clearly described.

Most patients were treated with antibiotics, whereas only 10 patients received palliative care, reflecting a highly aggressive standard-of-care at emergency room. Most patients had poor prognosis (76.7% based on PALIAR and 91.7% on PROFUND), so palliative care should have been considered more often. This aggressive approach is not universal; in a study comparing respiratory events in NH residents from the USA and the Netherlands, severity of dementia and dependence correlated with the lower antibiotic usage in both cohorts, whereas severity of illness correlated with more antibiotic treatment in the USA and lesser in the Dutch cohort[35]. More than a century ago, Sir William Osler wrote: "Pneumonia may well be called the friend of the aged. Taken off by it in an acute, short, not often painful illness, the old man escapes those 'cold gradations of decay' so distressing to himself and to his friends"[38]. With our aggressive approach, we may be depriving our elders the chance to die mercifully. When the end of life is near, the line between medical futility and medical nihilism is often very narrow. Efforts should be made to provide high-value care; this involves talking to NHR in advance to discover their priorities, and considering carefully whether an aggressive or supportive treatment is more desirable in their context (frailty, dependence, and mid-term prognosis).

In our multivariate model, two factors showed protective association and five were deleterious factors. Chronic usage of oxygen was counter-intuitively protective. The most likely explanation is that, respiratory failure being one of the main reasons for hospital admission, chronic oxygenotherapy identified chronic respiratory failure, which has lower short-term mortality. Altered consciousness both as referral symptom or physical finding conferred worse prognosis. In other studies, the inability to ingest fluids correlated with mortality[39]; our study did not register that factor, closely related to altered consciousness. CURB65 index was also included (albeit not significant), whereas qSOFA, PSI, and age fall from the model. As tachypnea and hypotension were uncommon, it is not surprising that qSOFA performed poorly in NHR; as all NHR are elder, it is unsurprising that both age and PSI, highly age-dependent, lost predictive power.

Most interestingly, HaH care was also a strong protective factor (OR 0.119, CI95% 0.029 to 0.484). In a case–control study in Australia, HaH for NHAP led to better intra episode mortality (6.7% vs. 31.9%, univariate p = 0.001)[40]. It can be argued that the more severe patients probably kept hospitalized, leading to a selection bias. supplementary table 4 shows nearly no differences: HaH patients had a similar degree of dependence, a slightly poorer prognosis and higher acute severity, so the selection bias should work against HaH. We explored this potential bias by excluding patients who died at hospital in the first 24, 48, and 72 h after admission, but not those who died at HaH (supplementary table 5). In all three models, HaH remained a protective factor after

multivariate analysis, although with a slightly lower protection. Thus, we can conclude that our model of HaH care is safer than conventional hospitalization, as was previously better proven[41].

Our study was conducted when the ATS-IDSA guidelines still recommended broad-spectrum therapy for NHAP[13]. However, only one quarter of our patients received broad-spectrum antibiotherapy, and it was not related to worse mortality. Higher usage of broad-spectrum coverage was seen with increasing CURB65 index, so it could be a surrogate for higher severity. We tested antibiotics into the multivariate model: both the number and the spectrum of antibiotherapy were rejected. This suggests that it is the frailty of the host and not the profile of the bacterial agent which leads to higher mortality.

The main strengths of our study are: (1) the consecutive inclusion, which limits selection bias, (2) the large size of the sample in a short time, thus limiting changes in the standard-of-care, and (3) the existence of the "liaison unit," thus ensuring fluid contact with NH and allowing us information on the evolution despite there not being a prospective follow-up.

The main limitations of our study are its observational design and its hospital inception. Being a retrospective observational study, causality cannot be inferred from our data. As we only included patients hospitalized for respiratory events, patients with less severe episodes not needing hospitalization were not analyzed, while a selection bias (from local admission criteria) was introduced; to complete the whole picture, more studies including all respiratory crisis not needing hospital referral are needed. Our data collection lacked several important features, which should be considered both in general treatment and in further studies: differentiation of aspiration pneumonia and pneumonitis, frailty indexes, and risk of multidrug-resistant etiology indexes.

Funding

None.

Acknowledgments

Juan Torres Macho, former Medical Director, critically contributed to develop our Liasion Unit and HaH at NH programs and suggested the necessity for this study.

Conflicts of interest

None.

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 declare that no patient data appear in this article and have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Supplementary data

Supplementary data are available at Spanish Journal of Medicine (10.24875/SJMED.21000023). 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 responsibility of the authors.

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Spanish Journal of Medicine

ORIGINAL ARTICLE

Computed tomography attenuation values of pleural fluid are useless for differentiating transudates from exudates

José M. Porcel[1], Graciela Bagüeste[1], Marina Pardina[2], Paula Sancho-Marquina[1], and Silvia Bielsa[1]*

[1]Pleural Medicine Unit, Department of Internal Medicine, IRBLleida; [2]Department of Radiology, Hospital Universitario Arnau de Vilanova. Lleida, Spain

Abstract

Background and objective: The aim of this study was to evaluate the accuracy of computed tomography (CT) attenuation values in differentiating transudates from exudates; a controversial issue in the literature. **Methods:** A total of 317 consecutive patients with pleural effusions (PE) who underwent both CT and thoracentesis during their hospitalization period were retrospectively analyzed. CT attenuation values were measured in Hounsfield units (HU) and classification of effusions as transudates or exudates was based on the underlying disease. **Results:** Median CT attenuation values were significantly higher in 217 patients with exudates than in 100 with transudates (6.43 HU vs. 0.67 HU; $p < 0.001$), but these differences disappeared in non-contrast CT explorations (3.78 HU vs. −0.38 HU; $p = 0.166$). At the best cutoff value of ≥ 4 HU, CT identified exudates with a sensitivity of 69%, specificity of 66%, likelihood ratio positive of 2, and likelihood ratio negative of 0.47. **Conclusions:** CT attenuation values of pleural fluid are not able to confidently discriminate between transudative and exudative PE and, therefore, should not influence the decision to perform a diagnostic thoracentesis.

Keywords: Transudates. Exudates. Computed tomography.

Introduction

Differentiation between transudates and exudates represents the first step down the diagnostic pathway of a pleural effusion (PE). This is usually accomplished through the analysis of pleural fluid (PF) which should always be interpreted in the specific clinical context[1]. While transudates are mostly due to heart failure and, less commonly, cirrhosis, exudates are secondary to a wide variety of causes such as cancer and infections[2]. Computed tomography (CT) is ordered in a significant proportion of patients with undiagnosed PEs and, oftentimes, may reveal an unexpected PE when performed for other reasons. In both situations, radiologists often give information on CT attenuation values of PF in an attempt to narrow down the differential diagnosis of the PE. However, this CT parameter has been shown to be unhelpful for separating benign and malignant PEs[3]. Moreover, the few studies that have explored the role of CT attenuation values for transudate-exudate discrimination have reached different conclusions, included relatively small sample populations, and, more importantly, used Light's criteria[4] as the gold standard for identifying transudates and exudates[5-8]. Although it is true that Light's criteria are universally employed to uncover the transudative or exudative nature of a PE, the fact remains that they misclassify 25-30% of transudates as exudates[9]. We present our experience with the utilization of CT attenuation values for transudate-exudate discriminating purposes in a large sample population,

Visual abstract available at https://www.spanishjmed.com/frame_esp.php?id=63

***Correspondence:**
José M. Porcel
E-mail: jporcelp@yahoo.es

Date of reception: 25-01-2022
Date of acceptance: 02-02-2022
DOI: 10.24875/SJMED.22000001

Available online: 21-03-2022
Span J Med. 2022;2(1):24-27
www.spanishjmed.com

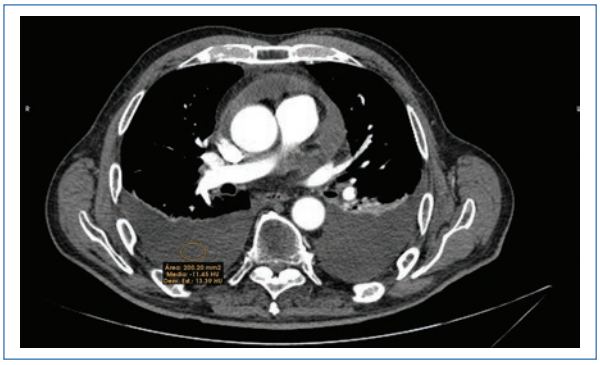

Fig 1. Contrast-enhanced CT showing a median fluid attenuation value of –11.45 HU (circle) in a patient with acute pleuro-pericarditis.

with the avoidance of the inappropriate use of Light's rule as a definitive criterion for labeling transudates.

Patients and methods

We retrospectively reviewed the electronic records of all consecutive inpatients who underwent a diagnostic thoracentesis in our center from January 2019 to April 2021, for whom a CT was ordered during hospitalization according to the attending physician criteria. The Local Ethics Committee approved the study protocol (CEIC No. 1965).

We obtained demographic data (age and sex), time lapse between CT and thoracentesis, categorization of the PF into a transudate or an exudate according to the Light's criteria, CT attenuation values of the PF in Hounsfield units (HU), and final diagnoses. Patients with PEs secondary to dual or multiple causes were excluded from the analysis.

The presence of a transudate or an exudate was established by the patient's final diagnosis through physician judgment and investigators' consensus (i.e., we assumed that the patient had the type of effusion, whether transudate or exudate, that is typically associated with the underlying disease). The causes of PEs were determined by well-established clinical criteria[10]. Specifically, the diagnosis of heart failure relied on clinical grounds (i.e., medical history, physical examination, chest radiograph, echocardiography —if performed—, response to diuretics, and patient follow-up of at least 3 months to confirm resolution of the PE).

CT examinations were performed with either a 16- or 64-multiple detector CT scanner (Phillips Brilliance, Eindhoven, The Netherlands) using standard parameters. In most cases (87%), intravenous contrast agents (iobitridol or iopromide) were administered. CTs were reviewed by an expert thoracic radiologist (M.P.) who was blinded of clinical data and who estimated PF attenuation values using a circular region of interest (ROI) of 190-210 mm^2 in size over three slices (Fig. 1). The three measurements were taken from three different levels (superior, middle, and inferior), whenever possible, and the average of these HU values was calculated. Anatomical structures other than PF (e.g., ribs, lung, and pleural thickening) were explicitly excluded from ROIs.

Continuous variables were expressed as medians (25^{th} and 75^{th} quartiles). For between-group comparisons, Mann–Whitney U and Kruskal–Wallis tests were used, whichever were appropriate. Receiver operating characteristic (ROC) analyses and Youden index selected the optimal discriminating CT attenuation value for transudates-exudates, for which sensitivities, specificities, and likelihood ratios (LR) with their corresponding 95% confidence intervals (CI) were calculated. Relationships between PF biochemistries and CT attenuation values were assessed using Spearman's correlation coefficient. The level of significance was set at $p < 0.05$ (two-tailed). Analyses were performed in SPSS 24.0.

Results

The 317 patients in the study were 73 (62-83) years of age, 60% were male, 100 had transudates, and 217 had exudates. The main patient characteristics are displayed in table 1. Heart failure accounted for 81% of transudates and cancer for nearly half of exudates. Diagnostic thoracenteses were performed a median of 1 day within undergoing CT.

Median CT attenuation values were significantly higher in patients with exudates than in those with transudates (6.43 HU vs. 0.67 HU; $p < 0.001$). This difference remained when analyzing the subgroup of patients (i.e., 195 exudates and 80 transudates) in whom CT was performed with the administration of a contrast agent (6.58 HU vs. 0.87 HU; $p < 0.001$), but it disappeared in non-contrast CT examinations (3.78 HU vs. –0.38 HU; $p = 0.166$). Notably, there were no statistical differences between the median CT attenuation values of 75 patients with true transudates (i.e., concordance between the cause of the PE and the categorization by Light's criteria) and 25 patients with transudates that were misclassified by Light criteria as exudates (–0.24 HU vs. 3.93 HU; $p = 0.129$). The same was true with regard to the comparison of four exudates miscategorized

Table 1. Patient characteristics

Characteristic	Transudates (n = 100)	Exudates (n = 217)	p-value
Age, years	80 (71-86)	70 (59-77)	< 0.001
Female sex	44 (44)	84 (39)	0.372
Etiology of PE			
Heart failure	81 (81)	-	
Hepatic hydrothorax	10 (10)	-	
Miscellaneous	9 (9)	7 (3.2)	
Cancer	-	97 (44.7)	
Pneumonia	-	49 (22.6)	
Post-surgery	-	24 (11)	NA
Pericardial diseases	-	16 (7.4)	
Tuberculosis	-	8 (3.7)	
Systemic autoimmune diseases	-	6 (2.7)	
Pulmonary embolism	-	5 (2.3)	
Idiopathic	-	5 (2.3)	
Chest radiograph			
Bilateral effusions	60 (60)	33 (15)	< 0.001
Large effusions	15 (15)	81 (37)	< 0.001
Light's criteria categorization			
Transudates	75 (75)	4 (1.8)	NA
Exudates	25 (25)	213 (98.2)	
Lag time from CT to thoracentesis, days	1 (–1-3)	1 (–1-4)	0.387
Pleural fluid attenuation values, HU			
All CTs	0.67 (–3.75-6.17)	6.43 (2.31-10.28)	< 0.001
Contrast-enhanced CT	0.87 (–3.4-6.18)	6.58 (3-10.35)	< 0.001
Non-contrast-enhanced CT	–0.38 (–4.19-6.17)	3.78 (–2.68-9.12)	0.166

Data are presented as median (quartiles) or numbers (%).
CT: computed tomography; HU: hounsfield units; NA: not applicable; PE: pleural effusion.

as transudates by Light's criteria and the remaining 213 exudates (6.65 HU vs. 6.43 HU; p = 0.904).

HU values correlated moderately with PF protein (r = 0.494) and lactate dehydrogenase (r = 0.298) concentrations (p < 0.01). At the optimal cutoff point of ≥ 4 HU, CT had a sensitivity of 69% (95% CI 63-75), specificity of 66% (95% CI 56-75), LR positive of 2 (95% CI 1.5-2.7), LR negative of 0.47 (95% CI 0.37-0.6), odds ratio of 4.35 (95% CI 2.63-7.2), and area under the curve (AUC) of 0.718 (95% CI 0.658-0.778) for the identification of pleural exudates. These figures were similar when only taking contrast-enhanced CT examinations into consideration (data not shown).

Discussion

This study shows that the measurement of CT attenuation values lacks enough ability to discriminate pleural transudates from exudates. Therefore, this parameter information should not influence the decision to perform a thoracentesis when clinically indicated. In fact, finding a PE with a CT attenuation ≥ 4 HU only increases by 15% the pre-test probability of having an exudate (LR = 2), whereas values < 4 HU decrease this probability by around 15% as well (LR negative = 0.47). These changes in probability (both directions) are not sufficient to be considered clinically meaningful.

Only four studies have previously addressed the accuracy of CT in characterizing PEs on the basis of attenuation values[5-8] (Table 2). Whereas one study favored the consideration of this parameter after reporting an AUC of 0.912[7], the remaining three studies[5,6,8], in line with our results, reinforced the imprecision of HU values because of significant overlapping between transudates and exudates. Discrepancies may partially be explained by the imbalanced distribution of certain etiologies in the evaluated populations. For example, pleural infections (parapneumonics/empyema) accounted for 30-51% of exudates in the studies that did not support the diagnostic role of HU values[5,6,8], whereas they represented 79% of exudates in the only favorable study[7]. In general, the use of intravenous contrast protocols did not seem to much affect CT attenuation values in the previous series as opposed to our findings, but in any case assessment

Table 2. Studies evaluating CT attenuation values for transudate-exudate discrimination

Study	No. of transudates/ exudates	Best cutoff CT attenuation value (HU)[a]	Sensitivity, %	Specificity, %	AUC
Nandalur et al., 2005[5]	44/101	> 13.4	83.2	70.5	0.78
Abramowitz et al., 2009[6]	22/78	< 8.5	55.1	68.2	0.582
Çullu et al., 2013[7]	30/76	> 8.5	85	86.7	0.912
Yalçin-Safak et al., 2017[8]	33/95	≥ 5	72	70	0.740
Current study	100/217	≥ 4	69	66	0.718

[a]For labeling exudates.
AUC: area under the curve; CT: computed tomography; HU: hounsfield units.

of pleural surfaces on CT examinations is better achieved with delayed phase or venous phase intravenous contrast administration[3].

Other than the larger sample size, the strength of this study is the use of the final clinical diagnosis as the reference standard for labeling transudates and exudates, thus circumventing the relatively low specificity of Light's criteria for exudates. It had, however, a retrospective design with the application of a CT protocol for calculating HU for which there may not necessarily be a general agreement. It may be difficult to improve the design of the future studies since radiation exposure to CT is not justified in the diagnostic work-up of a significant proportion of PEs.

In conclusion, CT attenuation values are not reliable for categorizing a PE as either transudate or exudate and, therefore, they should not deter clinicians from performing a diagnostic pleural tap.

Funding

None.

Conflict of interest

The authors declare that they have no conflict 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.

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Spanish Journal of Medicine

REVIEW ARTICLE

The interplay between kidney function and multimorbidity: A scoping review

Giorgi Beridze[1], Davide Liborio Vetrano[1,2], and Amaia Calderón-Larrañaga[1,2]*

[1]Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet-Stockholm University; [2]Stockholm Gerontology Research Center. Stockholm, Sweden

Abstract

Kidney function impairment and multimorbidity are complex, highly prevalent, long-term conditions that place a significant burden on individuals and healthcare systems. In this scoping review, we aimed to (I) map research focusing on the interplay between kidney function and multimorbidity, (II) identify inconsistencies and gaps in the available knowledge, and (III) propose future directions for research that would address these concerns. PubMed database was used to identify 354 articles published before December 2021, out of which 26 were selected to be included in this review. Current evidence supports an association between multimorbidity and kidney function impairment, although there is a paucity of longitudinal studies, and existing studies are methodologically heterogenous in terms of measurement of kidney function and multimorbidity. Network and cluster analyses point at chronic kidney disease (CKD) playing an important role in the context of multimorbidity by being a highly centralized condition with links to several other conditions. Finally, the presence of CKD within multimorbidity combinations is associated with an increased risk of negative health outcomes, such as mortality and hospitalization. Existing evidence on kidney function impairment and multimorbidity points toward relevant and frequent interactions between the two conditions. Further longitudinal studies are needed to assess causal pathways and elucidate mechanisms underlying these relationships, which will ultimately lead to a better management and reduced burden among older patients suffering from these two highly prevalent, debilitating conditions.

Keywords: Multimorbidity. Renal insufficiency. Chronic. Aging.

Background

Multimorbidity, defined as the co-occurrence of two or more chronic conditions within an individual, often challenges the daily practice of physicians, who –in the absence of specific guidelines for multimorbidity– need to adapt clinical decision schemes to consider antagonisms or potential therapeutic synergies among all interacting health problems and their treatments[1]. Partly as a result of these challenges, people with multimorbidity are at a greater risk of adverse health outcomes, beyond what one would expect from the summed effect of single conditions[2]. Furthermore, diseases tend to aggregate in the same person due to shared risk factors and/or similar pathophysiological mechanisms, which leads to multimorbidity patterns characterized by chronic disorders that systematically cluster together beyond chance[3,4]. Persons with multimorbidity have poorer functional and cognitive status, lower quality of life, higher chances of suffering from

Visual abstract available at https://www.spanishjmed.com/frame_esp.php?id=64

***Correspondence:**
Giorgi Beridze
E-mail: giorgi.beridze@ki.se

Date of reception: 24-12-2021
Date of acceptance: 27-01-2022
DOI: 10.24875/SJMED.21000027

Available online: 21-03-2022
Span J Med. 2022;2(1):28-33
www.spanishjmed.com

psychological distress and depressive symptoms, and shorter survival compared to non-multimorbid persons[2], while specific multimorbidity patterns have been shown to differentially impact the risk of disability[5], dementia[6], unplanned hospitalizations[7], and institutionalization[8].

Chronic kidney disease (CKD), that is, a persistent and irreversible decline in kidney function, is a highly prevalent condition that accompanies multimorbidity, present in 11% of the overall population and 40% of older adults[9]. CKD also represents the paradigm for which the one-disease-one-guideline approach often leads to conflicting therapeutic goals[10,11]. Indeed, a reduced kidney function is *per se* a risk factor for other diseases (e.g., atherosclerosis, anemia), and its complications impact therapeutic decisions and treatment efficacy for other comorbidities. At the same time, other comorbidities (e.g., hypertension, diabetes) can be the causes of an impairment in kidney function, further increasing the disease burden of CKD[8].

Taking into consideration that both kidney function impairment and multimorbidity are highly prevalent and tend to coexist in the older population[9], exploring the associations between these two conditions could reveal novel pathways and therapeutic targets to alleviate the aforementioned complications and optimize their management and care. However, before all else, several methodological challenges in the assessment and operationalization of both kidney function impairment and multimorbidity need to be considered. Multimorbidity has so far been operationalized as chronic disease counts, patterns of diseases, and/or weighted indices[12,13], while kidney function is generally monitored using estimations of the glomerular filtration rate (eGFR) for which, depending on the study population and setting, several different, often poorly concordant equations are used[14].

To the best of our knowledge, previous attempts at synthesizing the evidence in this area have largely focused on individual comorbidities of CKD[15], which may fail to capture potential synergistic effects among all coexisting chronic conditions. In light of this, it is particularly important to critically appraise and synthesize the literature exploring the interplay between kidney function impairment and multimorbidity. Given these premises, this scoping review aims to: (I) systematically map research conducted in this area, (II) identify inconsistencies and gaps in the available knowledge, and (III) propose future directions for research that would address these concerns.

Methods

The review follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist. To be included in the review, papers needed to explicitly focus on both kidney function and multimorbidity. Peer-reviewed journal papers were included if they were written in languages spoken by authors (English, Spanish or Italian); involved human participants; included a measure of kidney function or otherwise relevant diagnosis; and operationalized multimorbidity as the co-occurrence of multiple chronic conditions. Papers were excluded if they did not fit the aims of the study, were not quantitative, studied acute changes in kidney function, or focused on comorbidities of an index disease other than CKD. To identify relevant publications, the PubMed database was searched from inception to December 3, 2021. A librarian was consulted regarding the search terms, while the final search strategy was drafted by the authors. All three authors jointly developed a data charting form and continuously discussed the results. The full search strategy is presented hereby: *("chronic kidney disease"[Title/Abstract] OR "renal insufficiency"[Title/Abstract] OR "chronic kidney failure"[Title/Abstract] OR "glomerular filtration rate"[Title/Abstract]" OR "eGFR"[Title/Abstract] OR "creatinine"[Title/Abstract] OR "kidney function*"[Title/Abstract] OR "renal function*"[Title/Abstract]) AND ("multiple chronic disease*"[Title/Abstract] OR "multiple chronic condition*"[Title/Abstract] OR "multimorbid*"[Title/Abstract] OR "multi-morbid*"[Title/Abstract]).*

Results

A total of 354 papers were identified from the electronic database search, 324 of which were excluded after title and abstract screening. Of the 30 remaining titles, four were excluded after full-text screening. The remaining 26 studies were included in the review. The flowchart of the appraisal process, along with reasons for exclusion at full-text stage, is presented in figure 1. The studies included in the review are described in supplementary table 1.

Current epidemiological evidence points to three main lines of research in this area as described below.

CKD in the context of other diseases

Twelve studies examined the coexistence and interactions of CKD with other chronic diseases, nine of

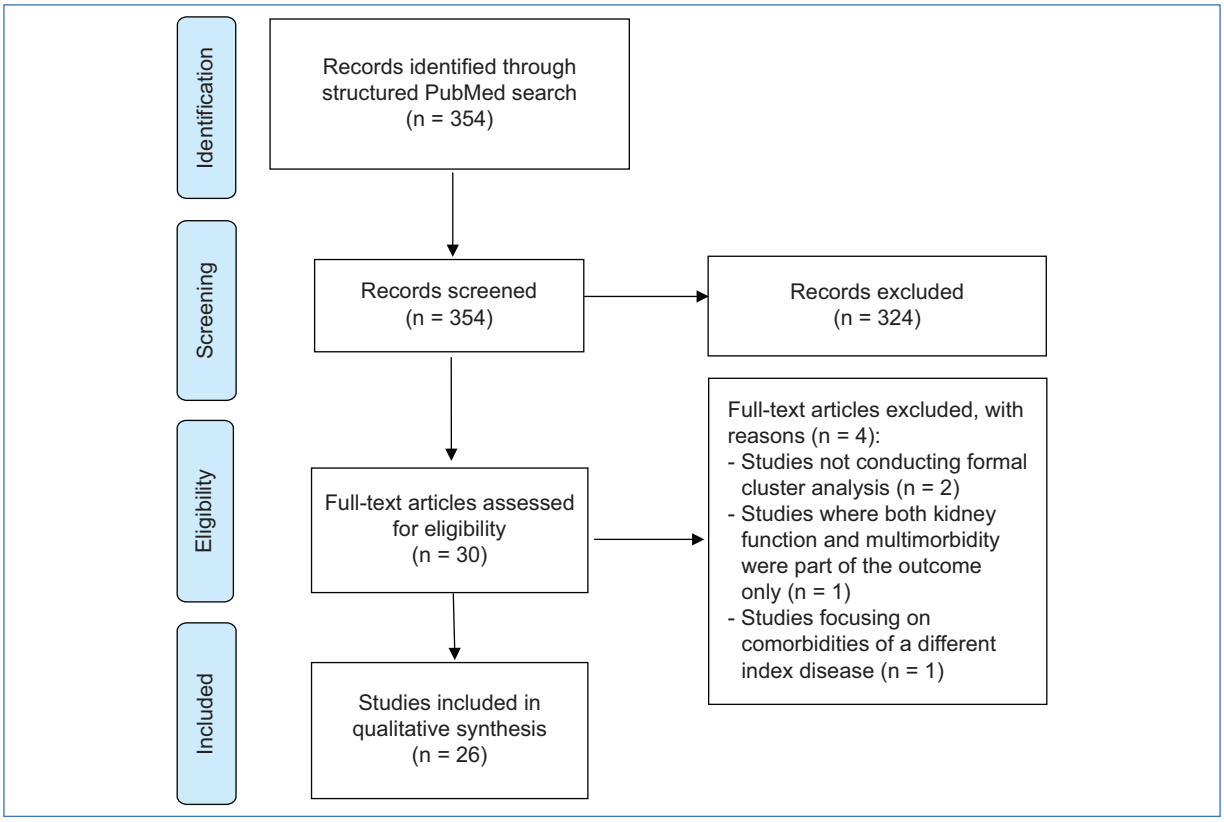

Figure 1. Flowchart of the search process.

which conducted cluster analysis, and three used network analysis[16-24]. The studies were from Europe (k = 7), North America (k = 3), and Asia (k = 1). One study combined cohorts from Europe and Asia. The number of chronic conditions considered in these studies ranged from 13 to 60.

Results from chronic disease cluster analyses (k = 9) are presented in table 1. Six studies used population-based samples, two studies used a sample of people living with HIV, and one study used a cohort of patients with heart failure. CKD most frequently clustered with hypertension (in 73% of studies containing hypertension in their list of conditions), atrial fibrillation (60%), and diabetes (45%). Corsonello et al. further looked at the differences in multimorbidity patterns when taking CKD severity (eGFR < 45 or < 30 mL/min/1.73 m^2) into account, and concluded that the strength of observed associations increased together with CKD severity[17].

Results from network analyses (k = 3) point at CKD being central and highly connected in multimorbidity networks of patients with heart failure and/or COPD[25], and cardiovascular disease[26]. The latter study also stratified multimorbidity networks by age and found that CKD was among the top five most connected conditions between the ages of 21 and 70 and remained highly connected at older ages.

Bidirectional associations between kidney function and multimorbidity

Cross-sectional studies

We identified five studies that examined the association between kidney function and multimorbidity cross-sectionally[27-31]. Four studies were conducted among CKD patient cohorts in Europe (k = 2) and Asia (k = 2), while one was based on ambulatory data from a statutory health insurance company in Germany.

Three studies looked at the association between eGFR (continuous) and multimorbidity. A study from the UK found that in a cohort of patients with impaired renal function (CKD stages 1-5), there was an inverse association between eGFR at study entry and the odds of multimorbidity, defined as the co-occurrence of two or more diseases[28]. Another study in the UK reported

Table 1. Summary of studies looking at chronic kidney disease in the context of other diseases (i.e., studies using cluster analysis).

Author	Statistical method	Hyper-tension	Heart failure	Ischemic heart disease	Cerebro-vascular diseases	Atrial fibrilla-tion	Bradycar-dias	Heart valve disease	Peri-pheral artery disease	Dementia	Osteopo-rosis	Sensory impair-ments	Dia-betes	Gout	Anemia	Chronic pain	Thyroid diseases	Non-sensory eye diseases	Peptic ulcer disease	COPD	Dyslipi-demia
Bisquera et al., 2021	Multiple Correspondence Analysis and Hierarchical Cluster Analysis	×	✓	✓	✓	✓			✓	✓	✓		×		×	×				×	
Corsonello et al., 2020 (SPPB 5-12)	Hierarchical Agglomerative Clustering	✓	×	×	×	×				×	×	✓	×		×					×	
Corsonello et al., 2020 (SPPB 0-4)	Hierarchical Agglomerative Clustering	✓	×	×	×	×				×	✓	✓	✓		✓					×	
Formiga et al., 2013	Hierarchical Cluster Analysis	✓	✓	×	✓	✓			×	×		✓	✓		×					×	×
Kim et al., 2012	Exploratory Structural Equation Modelling	✓	×	×									✓	✓					×	×	×
Lai et al., 2021 (Switzerland)	Hierarchical Agglomerative Clustering	✓		✓	×	✓			×	×			×			×	×		×	×	
Lai et al., 2021 (Hong Kong)	Hierarchical Agglomerative Clustering	✓		×	×	✓			×	×			×			✓	×		×	×	
Matesanz-Fernández et al., 2020	Multiple Correspondence Analysis	×	✓	×	×	✓		✓		×			×		×		×				
Tromp et al., 2018	Latent Class Analysis	✓		✓	×	×			×	×			✓		✓				×	×	
Villen et al., 2020	Principal Component Analysis and Multiple Correspondence Analysis	×	✓	✓	✓	✓	✓	✓	×	×	×	×	×	×	✓	×	×	✓	×	×	×
Yang et al., 2021	Hierarchical Cluster Analysis	✓	✓	✓	×	×	×		×	×	✓		✓		✓		✓		ü	✓	✓

✓ indicates that this condition clustered with CKD; × indicates that this condition did not cluster with CKD; Empty cell indicates that the disease was not considered in this study.
SPPB: short physical performance battery (higher score indicates better physical performance); COPD: chronic obstructive pulmonary disease.

similar findings; however, this was a cohort of patients with CKD stage 3 and multimorbidity was operationalized as three or more diseases in their analyses[27]. On the other hand, a study from Taiwan conducted among patients with CKD stages 3-5 did not find such an association[29].

One study from Japan explored the association between reduced eGFR (< 60 mL/min/1.73 m^2) and the number of chronic diseases out of a list of 23 conditions[30]. They found a dose-response relationship between the number of comorbidities and the odds of reduced eGFR, and stratified analysis suggested cardiovascular multimorbidity to be the main driver of these associations. Likewise, Schaffer et al. reported that the observed prevalence of renal insufficiency was higher than expected among people with severe multimorbidity (seven or more conditions)[31].

Longitudinal studies

We did not identify any longitudinal study that assessed the relationship between kidney function and future multimorbidity burden/trajectories. However, we identified three studies that looked at the association between multimorbidity and the evolution of kidney function[23,29,32]. The studies were conducted in Europe (k = 2) and Asia (k = 1), and operationalized multimorbidity as the count of chronic diseases (k = 2) and as patterns of chronic diseases (k = 1).

In a cohort of patients with stage 3-5 CKD in Taiwan, Lee et al. found that having three or more chronic conditions was associated with a steeper decline in eGFR and higher hazard of dialysis initiation over the 10 year follow-up period[29]. Similar results were obtained in a study using UK Biobank data, where they looked at major adverse kidney events (MAKE) as the outcome[32]. This study defined MAKE as the first of the following endpoints to occur: the need to receive long-term kidney replacement therapy, doubling of serum creatinine, fall of eGFR to < 15, or 30% decline in eGFR compared to baseline. The dose-response relationship between the number of long-term conditions and MAKE was more pronounced when only cardiometabolic multimorbidity was considered. Villen et al. used data on 60 chronic disease groups from Spanish electronic health registers to group individuals into multimorbidity patterns, and observed their kidney function evolution over a 5-year period[23]. There were significant differences in the risk of incident kidney function impairment (defined as reductions in eGFR below 60 mL/min/1.73 m^2) across the ten identified patterns, with the highest risk observed for the "Cardio-Circulatory and Renal" and "Minority Metabolic Autoimmune-Inflammatory" patterns.

CKD, multimorbidity and health outcomes

We identified ten studies that looked at the association between multimorbidity (including CKD) and negative health outcomes (Table 2)[22,23,33-40]. The studies were conducted among multimorbid populations in Europe (k = 7), USA (k = 1) and Asia (k = 1). One study was conducted at eleven different centers in Europe, USA and Israel. Seven studies looked at multimorbidity patterns using data-driven approaches, while three studies looked at multimorbidity combinations.

The most frequently studied endpoints were related to hospital care utilization. Studies looking at the outcomes of all-cause readmissions and emergency hospitalizations concluded that multimorbidity combinations including CKD consistently showed higher rates of hospital admissions across several European cohorts included in these studies[34,40]. Similar findings were observed in studies exploring potentially avoidable hospitalizations and healthcare costs as outcomes. Multimorbidity patterns containing CKD were among the highest drivers of potentially avoidable readmissions in two studies[34,35], and a study from the UK found that, among patients with multimorbidity, the combination of CKD and hypertension contributed to nearly one third of total secondary costs, while the combination of heart failure, CKD and hypertension was the strongest predictor of costs associated with potentially preventable admissions[39].

Another studied endpoint was mortality. Evidence from three studies suggests that multimorbidity patterns and disease combinations containing CKD are associated with the highest risk of mortality[22,33,38]. The other conditions making up these combinations frequently included hypertension, diabetes, and coronary heart disease.

Furthermore, a study conducted among a population of veterans with CKD found differences in the risk of mortality, hospitalization and emergency department visits depending on whether the multimorbidity pattern included a condition discordant to CKD or not[36]. In other words, when comparing patients with equal number of comorbidities (CKD being one of them), the presence of one or more apparently pathophysiologically discordant (e.g., heart failure and osteoporosis) or apparently unrelated (e.g., cancer and dementia) conditions amplified the risk of the aforementioned outcomes in every single case.

Finally, CKD seems to play an important role in other outcomes, such as severe SARS-CoV-2 infection and liver function impairment. Among the most commonly

occurring multimorbidity combinations in the UK Biobank cohort, the dyad of CKD and diabetes was associated with the highest risk of severe SARS-CoV-2 infection (defined as death or hospitalization due to COVID-19)[37]. Liver function impairment was explored in a Spanish study based on electronic health records, where out of 10 multimorbidity patterns, the one including CKD (Cardio-Circulatory and Renal pattern) had the second highest risk of incident liver function impairment (abnormal finding in at least one of: alkaline phosphatase, alanine transaminase and gamma-glutamyl transpeptidase)[23].

Discussion

The scientific literature on kidney function impairment and multimorbidity has witnessed an expansion in the past decades, however, among the twenty-six studies included in this scoping review, most focused on CKD as a component of multimorbidity rather than on the bi-directional associations between the two conditions. Despite the paucity of epidemiological evidence, findings from cross-sectional and longitudinal studies seem to point toward multimorbidity (particularly cardiovascular) constituting a risk factor for kidney function impairment. On the other hand, the absence of longitudinal studies and conflicting findings from cross-sectional studies preclude us from making conclusions about kidney function impairment constituting a risk factor for multimorbidity. Whether this is due to a lack of longitudinal data sources containing repeated measures of both kidney function and multimorbidity or to the weaker strength of this hypothesis remains to be elucidated.

The evidence is stronger for the important role of kidney function impairment as part of the overall multimorbidity burden. Indeed, whether looking at multimorbidity patterns or networks, CKD repeatedly emerges as a central component with strong links to multiple other conditions, primarily hypertension, atrial fibrillation, and diabetes. Results from these cluster and network analyses may serve as hypothesis generating for future research, since not all conditions that CKD was found to relate to may be considered concordant comorbidities based on current knowledge. Exploring whether these conditions are causally linked to one another and, if so, understanding the chronological order among them might pave the way for new interventions to address the burden of multimorbidity, particularly considering the important role CKD-associated patterns play in predicting important health outcomes such as mortality and hospitalization.

However, a detailed characterization of the association between kidney function impairment and multimorbidity remains difficult due to several issues that need to be addressed. The assessment of kidney function impairment needs to be carefully considered, particularly among older adults, who make up the majority of study populations included in our scoping review. Indeed, GFR is estimated to decrease by 10 mL/min/1.73 m^2 per decade after the age of 40[41]. At the same time, it remains challenging to distinguish between physiological and pathological declines in renal function. In fact, some experts strongly advocate for a lowering of the commonly accepted eGFR threshold of 60 mL/min/1.73 m^2 when diagnosing CKD in older adults[42]. Another important factor to consider is the dependency on GFR-estimating equations due to the cumbersome nature of measuring GFR in non-specialist settings. Considering that these equations tend to perform best in settings similar to their development cohorts, the Modification in Renal Disease (MDRD) equation employed by several studies in this review may not provide the most accurate estimate of GFR as older and multimorbid individuals were under-represented in this development cohort[43]. Indeed, several studies have compared GFR estimates from MDRD and other equations to the gold standard measured GFR (i.e., clearance of an ideal exogenous marker), and MDRD has consistently shown to underperform by overestimating GFR among older adults[44].

Studies have also employed several different operationalizations of multimorbidity, such as the presence of >2 conditions or aggregation of specific types or groups of chronic conditions. While the definition based on disease counts offers a simple interpretation, the commonly accepted threshold of >2 diseases may have a weak discriminatory capability among older adults. For instance, in a Swedish study with comprehensive information about 60 chronic disease groups, up to 9 out of every 10 participants aged 60 and above were classified as multimorbid using this definition, leading to a “ceiling effect” that fails to take into account the heterogeneity of multimorbidity in this population[12]. The disease clustering approach may be more informative of potential relationships between diseases in terms of their common etiology and/or impact on prognosis and treatment. Still, as shown in our synthesis of articles connecting kidney function impairment and multimorbidity, whether by choice or necessity, the list of chronic conditions considered across studies is almost never identical. Alternative ways of capturing the development and

Table 2. Summary of studies looking at CKD, multimorbidity and health outcomes

Outcome	Author	Main finding
Mortality	Ferrer et al., 2017	The most important pattern for predicting mortality was the combination of atrial fibrillation, CKD, and visual impairment at 3 years, and hypertension, CKD and malignancy at 5 years.
	Jani et al., 2019	Among patients with 3 and ≥ 4 chronic conditions, combinations that included CKD had the greatest impact on mortality.
	Tromp et al., 2018	Among patients with heart failure the multimorbidity pattern that included CKD had the highest risk of the combined outcome (all-cause mortality or hospitalization) compared to all other patterns.
	Bowling et al., 2017	Among patients with CKD, at every level of multimorbidity, those with one or more discordant/unrelated conditions had a higher risk for mortality, hospitalization and emergency department visits compared to those with concordant conditions.
Hospital care utilization		
All-cause readmission	Aubert et al., 2019[35]	Among the 20 combinations of comorbidities with the highest OR for 30-day all-cause readmission, 7 included CKD.
Emergency hospitalization	Sullivan et al., 2021	At equal number of chronic conditions, multimorbid patients with CKD had 2-3 times higher rates of hospitalization compared to those without CKD.
Potentially avoidable readmission	Aubert et al., 2019[34]	Among the 20 combinations of comorbidities with the highest OR for potentially avoidable readmission, 10 included CKD.
Potentially avoidable readmission	Aubert et al., 2019[35]	Among the 20 combinations of comorbidities with the highest OR for potentially avoidable readmission, 11 included CKD.
Healthcare costs	Stokes et al., 2021	The combination of CKD + hypertension made up a large proportion of total secondary costs, while the triad of heart failure + CKD + hypertension had the highest costs from potentially avoidable emergency admissions.
Other outcomes		
Abnormal liver function	Villen et al., 2020	Out of 10 multimorbidity patterns, the patterns that included CKD had the highest risk of incident liver function impairment.
Severe SARS-CoV-2 infection	Chudasama et al., 2021	Among all combinations of most commonly co-occurring conditions, the combination of CKD + diabetes had the highest risk of severe SARS-CoV-2 infection (hospitalization or death due to COVID-19).

CKD: chronic kidney disease; OR: odds ratio.

progression of multimorbidity have been recently suggested[45], and should be further tested in the context of the kidney function-multimorbidity binomial.

We believe that results from our review can be informative to public health researchers as well as medical professionals caring for multimorbid patients. Besides mapping the evidence available to date regarding the complex relationship between kidney function impairment and multimorbidity, we have detected the following areas that in our opinion require further research efforts. First, the establishment of more rigorous and clinically meaningful definitions and operationalizations of kidney function impairment and multimorbidity, particularly among populations of older adults, to increase the scientific validity and comparability of studies. Second, the design and execution of high-quality longitudinal studies looking at the bi-directional association between kidney function and multimorbidity, preferably within the same study, with the aim to address the methodological challenges raised earlier and ascertain causal links. Third, the identification of mechanistic pathways underlying the associations between the two conditions including, but not limited to, biomarkers and drug-related factors, so as to increase their diagnostic and prognostic capacity. Finally, the role of CKD within multimorbidity clusters and networks in predicting important functional (e.g., muscle strength and walking speed) and person-centered (e.g., quality of life) outcomes needs to be better understood, to facilitate the detection of high-risk multimorbid patients requiring special attention.

Conclusions

The evidence on kidney function impairment and multimorbidity has recently expanded and points toward relevant and frequent interactions among these two conditions. A bidirectional association seems plausible; however, study design limitations and methodological heterogeneity preclude us from making definitive statements at this point. Further longitudinal studies are needed to assess causal pathways and elucidate mechanisms underlying these relationships, which will ultimately lead to a better management and reduced burden among older patients suffering from these two highly prevalent, debilitating conditions.

Funding

This work was supported by specific grants obtained from the Swedish Research Council (2016-00981); the Swedish Research Council for Health, Working Life and Welfare (2017-01764); and Karolinska Institutet's Strategic Young Scholar Grants in Epidemiology or Biostatistics (SFO-EPI). The financial sponsors played no role in the design, execution, analysis and interpretation of data, or writing of the study.

Conflicts of interest

The authors declare 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 (10.24875/SJMED.21000027). 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 responsibility of the authors.

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