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"Remote telemonitoring supported by an artificial intelligence algorithm for the early detection of heart failure and COPD exacerbations"

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CHAPTER 1: INTRODUCTION

The progressive aging of the global population has led, over the last decades, to a significant increase in the number of elderly patients affected by multiple chronic conditions such as diabetes mellitus, chronic obstructive pulmonary disease (COPD), heart failure, chronic kidney disease and cancer.

The growing prevalence of chronic diseases in the population inevitably results in an increase in outpatient visits, emergency department admissions and hospitalizations, consequently leading to higher healthcare costs for national health care systems.

In this context, telemedicine represents a valuable tool to support healthcare system, increasingly contributing to the continuity of care, particularly in the post-hospital discharge phase and in the long-term management of elderly patients with chronic diseases.

The European Community defined telemedicine as early as 2008 as “the provision of healthcare services through the use of information and communication technologies in situations where the healthcare professional and the patient, or two healthcare professionals, are not in the same location.”

Telemedicine involves the secure remote transmission of medical information and data in the form of text, audio, images, recordings, or other types of content, aimed at prevention, diagnosis, treatment, monitoring of medication adherence and patient follow-up[1].

According to the document *Guidelines for the Development of Telemedicine*, developed by the Ministry for Innovation and

Technologies and the Ministry of Health, several application areas of telemedicine can be identified[1]:

- Remote telemonitoring
- Televisits
- Intra-specialist teleconsultation
- Teleradiology with machine learning
- Telerehabilitation
- Tele-emergency services

Over the past twenty years, both at the European and Italian levels, telemedicine has experienced a progressive and significant expansion.

In some countries, this development has been particularly noteworthy.

In Sweden, as early as 2008, more than 75% of hospitals were using e-health applications.

In Norway, the diffusion of telemedicine was driven by low population density and the need to provide healthcare across vast and geographically dispersed areas, leading to the early adoption of services such as teleradiology, teledermatology, teleconsultations between general practitioners and specialists, remote electrocardiogram reporting, and distance medical education[2].

Similarly, in Spain, over the last fifteen years, regional healthcare systems have promoted the development of e-health through shared strategies, identifying telemedicine as a priority axis of innovation.[3]

In the United Kingdom, the relevance of telemedicine was confirmed by the implementation of the *Whole System Demonstrator Programme* in 2008, one of the largest clinical studies on this topic, involving more than 6,000 patients with chronic diseases and demonstrating benefits in terms of reduced hospitalizations and improved care management[1].

In France, telemedicine was formally recognized as an integral part of the national health service in 2010. In Italy, numerous telemedicine programs have been developed at both national and regional levels, culminating in the establishment of the National e-Care Observatory in 2007. Initially focused on home care, this organization progressively expanded its scope to include all telemedicine applications with the aim of defining shared reference models and improving access to digital health services[1].

The development of telemedicine in Italy underwent further significant implementation during the SARS-CoV-2 pandemic, driven by limitations on outpatient services[4].

During this period, telemedicine enabled a reduction in diagnostic and treatment initiation times, ensured more frequent monitoring of frail and chronically ill patients, and contributed to lowering infection risk through home-based care.[4]

Experiences gained during this period highlighted that telemedicine does not represent only an emergency solution but rather a structural and sustainable model of healthcare delivery.

Italy has invested approximately €1.5 billion through the National Recovery and Resilience Plan (PNRR) in telemedicine and digital health, with the aim of creating a national telemedicine platform and providing care to hundreds of thousands of patients[1].

In 2023, a contract was signed for a national platform, making Italy one of the first European countries to implement telemedicine on a centralized scale, although significant regional heterogeneity remains, particularly in terms of digital literacy[1].

Telemedicine represents a valuable support for peripheral hospitals, which are often lacking specialized units, by enabling remote reporting and interpretation of radiological examinations, delivery of specialist consultations, electrocardiographic reporting, and remote interrogation of implanted devices such as pacemakers and defibrillators[5,6].

Telemedicine promotes the decentralization of healthcare from hospitals to the community through innovative, patient-centered care models.

Recent scientific evidence has further confirmed the effectiveness of telemedicine. Randomized controlled trials, systematic reviews and meta- analyses published in recent years have demonstrated that, in many clinical settings, telecare outcomes are comparable to those of traditional face-to face care.

In particular, in the management of diabetes mellitus, telemonitoring has been associated with improved control of clinical parameters, such as reductions in HbA_{1c} levels, as well as increased treatment adherence.

Additional evidence indicates that telehealth programs targeting patients with multiple comorbidities significantly improve quality of life, especially in physical and functional domains, by promoting disease self-management and reducing inappropriate use of emergency services[6].

In the neurological field, telemedicine has also demonstrated relevant benefits, contributing to improved motor and non-motor outcomes in patients with neurodegenerative diseases and reducing depressive and anxiety symptoms in the elderly population[1].

Overall, the benefits of telemedicine include reduced healthcare expenditure, fewer avoidable hospitalizations, improved access to care, optimized physician–patient communication and enhanced continuity of care.[6]

In the home care setting, telemedicine ensures equitable access to qualified healthcare services even in remote or underserved areas, delivering medical care directly to patients' homes[7–10].

The management of elderly patients and chronic diseases represents one of the priority areas for telemedicine application, as it enables improvements in quality of life through continuous monitoring solutions and self-management strategies.[11]

However, for these tools to be fully integrated into clinical practice, it is essential to guarantee high standards of data security and personal data protection, ensuring confidentiality, protection against unauthorized access and reliability of technological infrastructures[1].

Finally, telemedicine can contribute to optimize the management of home-based pharmacological therapy, improving treatment adherence and increasing patient awareness of their health status.[12]

1.2 MANAGEMENT OF THE TWO MOST COMMON CHRONIC DISEASES IN THE ELDERLY: HEART FAILURE AND COPD

1.2.1 HEART FAILURE IN THE ELDERLY

Heart failure is a clinical syndrome caused by structural and/or functional cardiac abnormalities resulting in elevated intracardiac pressures and/or inadequate cardiac output at rest or during exertion. It is characterized by typical symptoms such as dyspnea and peripheral edema, sometimes accompanied by clinical signs including elevated jugular venous pressure and pulmonary crackles. [13]

The incidence of heart failure in the adult population in Europe is approximately 5 cases per 1,000 persons per year[14–17].

The prevalence of heart failure in the adult population is estimated to range between 1% and 2%.

However, many epidemiological studies include only recognized and diagnosed cases and the true prevalence is likely underestimated.[18]

The prevalence of heart failure increases markedly with age, rising from approximately 1% in individuals younger than 55 years to over 10–20% in those aged over 70 years.[19,20]

Together with COPD and type 2 diabetes mellitus, heart failure represents one of the chronic conditions in the elderly with the greatest impact on the population, due to its clinical course characterized by frequent exacerbations, hospitalizations and increased mortality, leading to a substantial rise in healthcare expenditure related to patient care.[21]

Identification of the underlying etiology of cardiac dysfunction is crucial for both diagnosis and treatment of heart failure.

In most cases, heart failure in the elderly is attributable to myocardial dysfunction (systolic, diastolic, or both) secondary to ischemic heart disease, hypertensive heart disease, hypertrophic obstructive cardiomyopathy or infiltrative diseases such as wild-type transthyretin cardiac amyloidosis. Additionally, valvular heart disease (mitral and aortic) and cardiac arrhythmias such as atrial fibrillation or tachy-brady syndrome, may cause the development of heart failure.[1]

Heart failure is classified according to left ventricular systolic function, as assessed by transthoracic echocardiography, into:

- **Heart failure with reduced ejection fraction (HFrEF):** LVEF $\leq$ 40%

- **Heart failure with mildly reduced ejection fraction (HFmrEF):** LVEF 41–49%
- **Heart failure with preserved ejection fraction (HFpEF):** LVEF ≥ 50%

The diagnosis of heart failure is clinical. Measurement of serum natriuretic peptides, particularly N-terminal pro–brain natriuretic peptide (NT-proBNP), represents the gold standard biomarker for the diagnosis and monitoring of heart failure.[22] Transthoracic echocardiography plays a central role in the etiopathogenetic differential diagnosis of heart failure and guides therapeutic decision-making.[23]

Pharmacological therapy is the cornerstone of treatment for heart failure with reduced ejection fraction, aiming to reduce mortality, prevent heart failure–related rehospitalizations and improve clinical status, functional capacity and quality of life.

In patients with HFrEF, treatment focuses on modulation of the renin–angiotensin–aldosterone system and the sympathetic nervous system through the use of angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor–neprilysin inhibitors (ARNIs), beta-blockers and mineralocorticoid receptor antagonists (Spironolactone)[24,25].

This therapeutic approach has been shown to improve survival, reduce hospitalization risk and alleviate symptoms.[24,25]

In the absence of contraindications or intolerance (e.g., hypotension), the combination of an ACE inhibitor/ARNI or a soluble guanylate cyclase stimulator such as Vericiguat, a beta-blocker and a mineralocorticoid receptor antagonist is recommended as foundational therapy for heart failure.

In patients with HFrEF and a QRS duration ≥130 ms, cardiac resynchronization therapy with implantable cardioverter-defibrillator (CRT-D) implantation may be considered, except in patients with severe comorbidities and a life expectancy of less than one year.[13]

Patients with heart failure and preserved ejection fraction differ from those with reduced or mildly reduced ejection fraction by being generally older, more frequently female and more commonly affected by atrial fibrillation, chronic kidney disease and other non-cardiovascular comorbidities.[13]

Equally important is the identification and management of underlying risk factors, etiology and concomitant comorbidities. In patients with advanced heart failure (NYHA class IV) with severe and persistent symptoms, refractory to optimized medical therapy or device-based therapy and in the absence of severe right ventricular dysfunction and/or severe tricuspid regurgitation, implantation of a ventricular assist device may be indicated in selected patients with stable psychosocial conditions.[13]

Elderly patients affected by heart failure, including those with stable and well-controlled symptoms, require close follow-up to ensure continuous optimization of therapy, early identification of symptom progression and comorbidities and timely modification of care strategies.

This approach aims to reduce the risk of heart failure exacerbations and subsequent hospitalizations, which, particularly in elderly patients, significantly increase the risk of adverse outcomes such as infections, disability, immobilization, institutionalization and death.[13,26]

Telemonitoring offers the advantage of enabling frail patients to remotely provide digital health information, thereby supporting and optimizing healthcare delivery directly at home while minimizing outpatient visits and travel to healthcare facilities.

This is particularly beneficial for elderly individuals, for whom mobility limitations, disability and dependence on caregivers even for short-distance travel often represent significant barriers to access to care.[27,28]

1.2.2 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN THE ELDERLY

Chronic Obstructive Pulmonary Disease (COPD) is currently the third leading cause of death worldwide, with a prevalence of approximately 12% in the adult population in Europe, rising to as high as 35% among elderly individuals.[29,30,31,32]

COPD is a disease characterized by persistent airflow limitation associated with a chronic inflammatory response of the lower airways, usually progressive, to noxious particles and gases.[31]

The clinical presentation of COPD is heterogeneous. The most common respiratory symptoms include dyspnea, cough and sputum production, whereas atypical symptoms may include fatigue, peripheral edema, chest pain, confusion and dizziness[31].

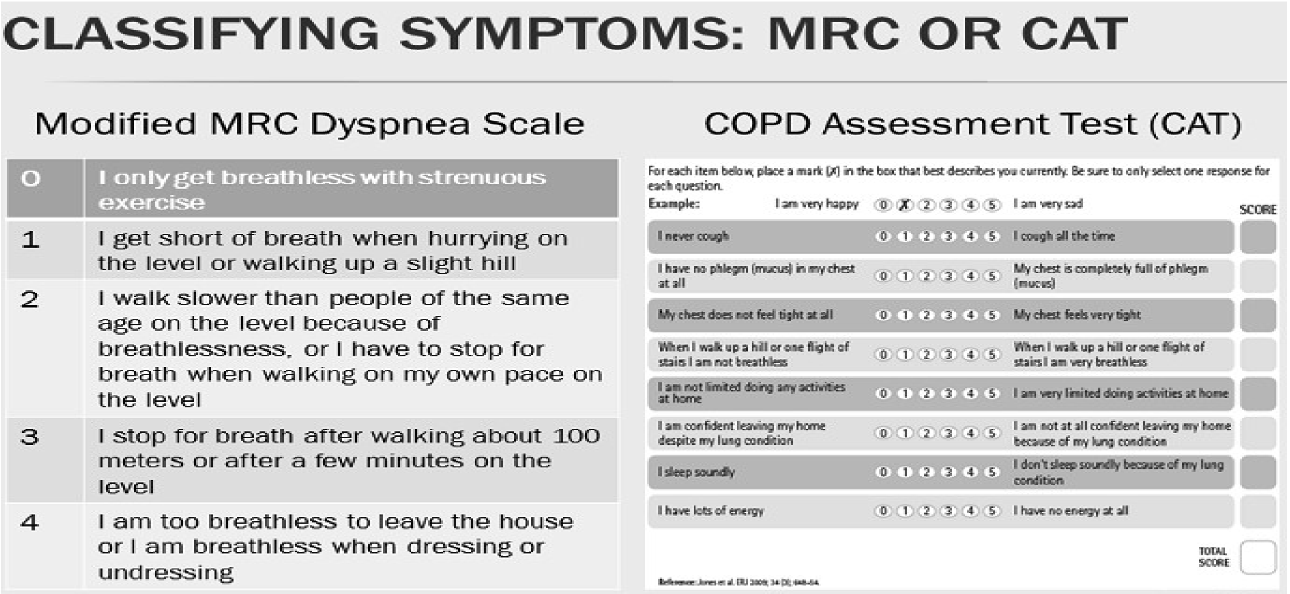
The main risk factor for COPD is cigarette smoking; however, other environmental exposures may contribute, including biomass fuel smoke and ambient air pollution[31].

In addition to environmental exposures, host-related factors predispose individuals to COPD, such as genetic abnormalities and impaired lung development.

Established risk factors for COPD include tobacco smoking, prolonged exposure to wood and biomass combustion, occupational exposure to organic and inorganic dusts, genetic factors such as inherited alpha-1 antitrypsin deficiency, as well as genetic variants encoding matrix metalloproteinase-12 (MMP-12) and glutathione S-transferase.[31]

Chronic comorbid conditions frequently occur in elderly patients affected by COPD including cardiovascular diseases, sarcopenia, metabolic syndrome, osteoporosis, depression, anxiety and lung cancer, all of which contribute to increased morbidity and mortality.

Spirometry is the diagnostic gold standard for COPD. A post-bronchodilator forced expiratory volume in one second to forced vital capacity ratio (FEV_1/FVC) <0.70 confirms the presence of persistent airflow obstruction[33]. According to the GOLD 2026 guidelines, COPD severity stratification is not based solely on the degree of airflow obstruction but also incorporates the ABE clinical staging, which evaluates the number of exacerbations per year, the number of hospitalizations per year and patient-reported dyspnea and symptom burden assessed using validated questionnaires including the COPD Assessment Test (CAT™), the modified Medical Research Council (mMRC) dyspnea scale and the Clinical COPD Questionnaire (CCQ©).[34,35.]



CLASSIFYING SYMPTOMS: MRC OR CAT

Modified MRC Dyspnea Scale

0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on the level or walking up a slight hill
2	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level
3	I stop for breath after walking about 100 meters or after a few minutes on the level
4	I am too breathless to leave the house or I am breathless when dressing or undressing

COPD Assessment Test (CAT)

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example:	I am very happy	0 X 2 3 4 5	I am very sad	SCORE
	I never cough	0 1 2 3 4 5	I cough all the time	
	I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
	My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
	When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
	I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
	I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
	I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
	I have lots of energy	0 1 2 3 4 5	I have no energy at all	
			TOTAL SCORE	

Figure n.1: Mmrc and CAT scale

The severity of airflow limitation, defined as the spirometric stage, is estimated

based on post-bronchodilator FEV_1 and classified as follows:

- **GOLD 1 (Mild):** $FEV_1 \geq 80\%$ predicted
- **GOLD 2 (Moderate):** $50\% \leq FEV_1 < 80\%$ predicted
- **GOLD 3 (Severe):** $30\% \leq FEV_1 < 50\%$ predicted
- **GOLD 4 (Very severe):** $FEV_1 < 30\%$ predicted

Figure 2. ABE Classification of COPD according to GOLD 2026 Guidelines

In COPD, bronchodilator medications are fundamental for symptom relief and reduction of exacerbation risk. Among the most commonly used bronchodilators are β_2-agonists, including short-acting β_2-agonists (SABAs) such as Salbutamol, Fenoterol, and Terbutaline, and long-acting β_2-agonists (LABAs) such as Formoterol, Salmeterol, Indacaterol, Olodaterol and Vilanterol. These agents relax bronchial smooth muscle by stimulating β_2-adrenergic receptors, increasing intracellular cyclic AMP, leading to symptom improvement, reduced exacerbation rates and fewer hospital admissions.[36,38]

Antimuscarinic agents are also widely used in COPD management, including short-acting muscarinic antagonists (SAMAs) such as Ipratropium and Oxitropium and long-acting muscarinic antagonists (LAMAs) such as Tiotropium, Aclidinium, Glycopyrronium bromide and Umeclidinium[38].

In addition to inhaled bronchodilator and corticosteroid therapy, patients experiencing frequent exacerbations despite optimized and regular triple inhaled therapy may benefit from Roflumilast, a phosphodiesterase-4 inhibitor.

In hyper-eosinophilic phenotypes (>300 eosinophils/μL), biologic therapies such as Mepolizumab and Dupilumab may be considered.

Non-pharmacological treatments, including patient education, physical exercise, nutritional support, pulmonary rehabilitation and telemonitoring, play a crucial role in improving the natural history of the disease.

COPD is a complex and highly heterogeneous condition characterized by multiple clinical phenotypes, highlighting the increasing importance of personalized and precision medicine approaches tailored to individual patients and focused on the treatment of specific treatable traits.[39]

Elderly patients with COPD experience a progressive decline in health status with frequent exacerbations and require regular outpatient follow-up with continuous reassessment of treatment selection and dosage[40].

This includes evaluation of therapy adherence, correct use of inhalation devices, potential drug–drug interactions and management of multiple comorbidities such as cardiovascular disease, chronic kidney disease, osteoporosis, cognitive impairment and sensory deficits, all of which influence adherence and therapeutic response.[41,42]

However, the frequent outpatient visits required for optimal disease management are often hampered by long waiting times, disability, and the constant need for caregiver support—even for short-distance travel.

In this context, remote telemonitoring emerges as a valuable tool for delivering medical and nursing care directly to the patient's home, offering opportunities for televisits, review of diagnostic tests and remote data acquisition from implantable or external devices such as loop recorders and pacemakers, continuous glucose monitoring systems, and remote review of home ventilation devices.

CHAPTER 1.3: TELEMONITORING

Remote telemonitoring is a specific application of telemedicine that involves the measurement and acquisition of selected patient vital parameters directly from the home environment.

This is made possible through the use of medical devices and artificial intelligence–based applications which, once configured and managed by healthcare professionals, are able to record, recognize and transmit patient vital signs either synchronously or asynchronously.

These parameters include heart rate, body weight, oxygen saturation, blood pressure and blood glucose levels. The system can identify values outside predefined ranges and automatically alert the treating physician[1].

This type of service allows time savings without compromising patient–clinician interaction by providing a continuous flow of clinical information.

As a result, telemonitoring contributes to reduce healthcare costs, enables elderly patients to remain in their home setting and allows physicians to personalize treatment according to patient preferences and the availability of healthcare services.

Telemonitoring facilitates access to care regardless of the patient's geographical location and reduces inappropriate emergency department visits as well as avoidable hospitalizations.

It is estimated that the Italian National Health Service spends approximately €3,500 per patient per year on COPD exacerbations, resulting in a total annual expenditure of nearly €7 billion.[7]

In addition, telemonitoring can improve the organization and management of patient data collection and enhance communication and collaboration among specialists working in geographically distant areas[1].

The success of telemonitoring programs depends on multiple factors, including the organizational structure of telemonitoring services, the usability and simplicity of the technology employed, patient adherence, patient autonomy and particularly in elderly populations the availability of a caregiver capable of providing continuous support in the use of monitoring devices. Continuous monitoring reassures patients by increasing their awareness and engagement in adapting healthcare management to daily life. It also has a positive impact on patients' acceptance of new technologies and digital health solutions as the devices provided are generally easy to use and cost-effective.[1]

1.3.1 Telemonitoring in Heart Failure

Several clinical trials conducted in patients affected by heart failure have reported encouraging results, suggesting that telemonitoring may reduce hospitalization rates and, consequently, healthcare costs related to hospital admissions, while also contributing to an improvement in patients' quality of life.[43,44,45]

In patients affected by heart failure, both teleconsultation and telemonitoring have been associated with a reduction in all-cause mortality and hospitalizations related to heart failure.

Telemonitoring has proven effective in the early detection of initial signs of clinical decompensation, ranging from the identification of oxygen desaturation and increases in body weight to the assessment of changes in intrathoracic impedance.

The latter represents an indirect estimate of volume overload and increased filling pressures and can be measured through ventricular or pulmonary artery electronic sensors integrated into implantable devices such as implantable cardioverter-defibrillators (ICDs) or cardiac resynchronization therapy devices with defibrillator function (CRT-D). The early identification of alterations in vital parameters, which often precede the onset of overt clinical symptoms, allows timely adjustment of pharmacological therapy, potentially preventing the progression to severe clinical conditions requiring hospitalization[46].

In elderly patients, heart failure is characterized by frequent episodes of decompensation that often lead to repeated hospital admissions throughout the year, with high rates of morbidity and mortality.

Readmission rates range from 20–30% within 30 days after discharge and may reach up to 50% at six months[46].

The high rate of hospitalizations for heart failure reflects not only the progression and advanced stage of the underlying disease but more frequently poor adherence to pharmacological therapy, particularly in elderly patients with polypharmacy. suboptimal treatment regimens, inadequate patient self-care and insufficient support systems.

Therefore, in patients affected by heart failure, telemonitoring may represent an important tool for the long-term management of chronic disease and acute exacerbations, supporting clinical monitoring that is often challenging within standard care pathways due to patient frailty.

This includes mobility limitations related to physical disability and the need for continuous caregiver assistance.

However, although the available data are promising, current evidence does not yet allow definitive conclusions regarding the effectiveness of telemonitoring in preventing hospitalizations and reducing all-cause mortality in elderly patients with heart failure.

Several studies on remote telemonitoring in heart failure have been published in adult populations; however, only a limited number have specifically enrolled elderly patients. Most studies have involved small or medium-sized cohorts, short follow-up periods and the use of a single type of device or monitoring strategy, often based solely on the measurement of individual vital parameters such as heart rate or oxygen saturation.[47,48]

Despite these limitations, current scientific evidence suggests that telemonitoring may be effective in reducing hospitalization rates for heart failure and for all causes.[48,49]

1.3.2 Telemonitoring in Chronic Obstructive Pulmonary Disease

Despite the unquestionable advantages associated with the use of telemonitoring, the current scientific literature has reported inconsistent and non-univocal results regarding its application in patients with chronic obstructive pulmonary disease (COPD).

Remote telemonitoring in this patient population appears to have a limited role in the prevention of acute exacerbations, hospitalizations and in reducing mortality. Only a few clinical trials have demonstrated a reduction ranging from 10% to 65% in mortality and hospitalization rates among elderly patients with COPD; however, these findings have generally failed to reach statistical significance.[50,51]

These inconclusive results may be partly attributed to the marked heterogeneity in the clinical presentation of patients with COPD, the advanced stage of disease in many of the enrolled subjects—some of whom were awaiting palliative care—the small sample sizes and the need to provide patients with a broader and more personalized model of care.

In this context, telemonitoring should be considered an integral component of a comprehensive and innovative care pathway, together with digital sharing of laboratory, radiological and instrumental examinations, telephone consultations and home nursing support, complementing rather than replacing usual care.

Furthermore, despite the increasing prevalence of COPD in the elderly population, relatively few studies have specifically investigated the effectiveness of telemonitoring in older patients[50,51].

These studies have generally enrolled small cohorts with highly heterogeneous clinical characteristics, short follow-up periods and the use of the same telemonitoring devices—typically including a pulse oximeter and traditional monitoring systems aimed solely at the measurement of selected vital parameters.

Such approaches are often not tailored to the needs of elderly patients and fail to account for the clinical heterogeneity that characterizes COPD.

Given the high frequency of exacerbations in elderly patients with COPD often severe and associated with multiple comorbidities and limited social support—multiparametric telemonitoring systems (including oxygen saturation, heart rate, respiratory rate and physical activity or movement), customized to individual patient characteristics and needs, may provide clinicians with a more holistic assessment of patient status.

This approach may allow earlier detection of initial signs of exacerbation, serving as a valuable adjunct to traditional models of care and clinical management.[50,51]

1.4 Study Objectives

The primary objective of this study was to evaluate the effectiveness of a remote monitoring system supported by an artificial intelligence algorithm in the early detection of exacerbations in patients affected by chronic obstructive pulmonary disease (COPD) and heart failure.

The secondary aim was to assess the sensitivity, specificity and overall accuracy of the algorithm.

CHAPTER 2: THE EXPERIMENTAL STUDY

Materials and Methods

The Clinical Study

2.1 Study Population

This study is a single-center, prospective, randomized clinical trial conducted in Policlinico Campus Biomedico in Rome.

Patients enrolled in the study were identified at the Geriatrics and Pulmonology outpatient clinics of the Policlinico Campus Biomedico in Rome through a preliminary review of electronic medical records.

Eligible patients were subsequently contacted and invited to attend an outpatient visit. During this visit, participants were informed about the study protocol and assessed for eligibility based on the predefined inclusion and exclusion criteria. All eligible patients who agreed to participate provided written informed consent prior to enrollment.

2.2 Inclusion and Exclusion Criteria

2.3

The following patients were included in the study:

- patients aged 65 years or older;
- patients affected by heart failure classified as New York Heart Association (NYHA)

class I-II–III, according to the 2023 update of the European Society of Cardiology (ESC) guidelines[13];

- patients with a diagnosis of chronic obstructive pulmonary disease (COPD) classified as stage A–B–E[31].

The following patients were excluded from the study:

- patients with metastatic neoplastic disease;
- patients with end-stage renal disease;
- patients with a life expectancy of less than 6 months and moderate-to-severe
- cognitive impairment (Mini-Mental State Examination [MMSE] score < 18)[52];
- patients who were not independent in instrumental activities of daily living and who lacked a caregiver capable of providing continuous 24-hour assistance during telemonitoring measurements. Prior to the initiation of the clinical trial, an outpatient meeting was held with patients affected by both heart failure and COPD, as well as

with their caregivers, in the form of a focus group.

The aim was to assess patients' needs and expectations regarding the telemonitoring program, in order to design a telemonitoring pathway that would be well accepted by both patients and caregivers and that would maximize patient adherence.

Based on the outcomes of the focus group and the available scientific evidence, multiparametric telemonitoring equipment was selected and subsequently provided to the participants.

During an outpatient evaluation, all patients included in the study underwent medical history assessment with collection of major comorbidities, review of previous clinical documentation and current pharmacological therapy and a comprehensive physical examination. In addition, a multidimensional geriatric assessment was performed, including evaluation of cognitive function using the Mini-Mental State Examination (MMSE)[52] and assessment of functional autonomy using the Lawton and Brody Instrumental Activities of Daily Living (IADL) scale.[53,54]

2.3 Study Design

Telemonitoring with an Artificial Intelligence Algorithm in Patients with heart Failure and COPD

Patients enrolled in the telemonitoring group were provided with a bluetooth-enabled pulseoximeter to perform percutaneous measurements of oxygen saturation and heart rate on a daily basis every 8 hours, within predefined time slots, excluding nighttime hours.

Measurements obtained by the patients using the bluetooth pulse oximeter were transmitted to an application installed on the patients' smartphones and uploaded to a telemonitoring digital platform accessible to the physician.

In this study, the *BPCOmedia* artificial intelligence algorithm was used for telemonitoring. During the first five days of measurements (training phase), the algorithm "adapts" to each individual patient by identifying their personal baseline pattern of normality.

This pattern is derived from the interaction between heart rate and oxygen saturation parameters, allowing the algorithm to identify measurements outside the individualized normal range as alarm signals.

In the event of abnormal measurements falling outside the predefined range, the algorithm classifies the event as an alert or warning.

Patients were then contacted by telephone by the healthcare professionals involved in the study and interviewed regarding their clinical status and the presence of any newly developed symptoms. Patients were also instructed to perform additional measurements in the event of new-onset symptoms.

2.4 Follow-up

During the follow-up period, significant alterations in vital parameters detected in the study group were recorded and analyzed.

These alterations were identified as “alerts” by the telemonitoring algorithm BPCOmedia and subsequently confirmed through telephone calls aimed at assessing patients’ clinical status, symptoms and signs related to exacerbation events of COPD and heart failure occurring at the time of the alert.

In the event of out-of-range measurements, patients were contacted by the study medical team to confirm the recorded values and to collect clinical information in order to determine whether modifications to pharmacological therapy were required or whether an additional follow-up visit should be scheduled.

In cases of particular clinical severity that could not be managed at home, patients were referred to the Emergency Department.

Healthcare personnel responsible for the study performed daily remote monitoring of patients enrolled in the telemonitoring group from monday to friday.

The telemonitoring system tested in this study does not represent a traditional telemonitoring approach based only on the simple detection and transmission of patients' vital parameters to the treating physician. Instead, it relies on an artificial intelligence algorithm, BPCOmedia, structured on a Petri net architecture, able of identifying interactions between the monitored parameters (heart rate and oxygen saturation) on an individualized, patient-specific basis and detecting deviations from the personalized measurement range which are flagged as "alerts."

In addition, patients were contacted monthly by telephone even in the absence of algorithm-generated alerts in order to identify any exacerbations that may not have been detected by the algorithm.

2.4 Data Analysis

Descriptive statistics were used to summarize the study variables.

Continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on whether they followed a normal distribution, while categorical variables were reported as percentages. Comparisons between the two groups were performed using the Student's *t*-test for continuous variables and the chi-square test for categorical variables. The risk of developing adverse outcomes (exacerbations, hospitalizations, and all-cause mortality related to heart failure or COPD) was evaluated using Kaplan–Meier survival curves and differences between groups were assessed with the log-rank test. Cox proportional hazards models were also constructed to estimate hazard ratios (HRs) with corresponding 95% confidence intervals (95% CIs). All statistical analyses were performed using the R statistical software (version 4.1.2; Vienna, Austria).

CHAPTER 4: Results

A total of 40 patients were enrolled in the study, including 18 patients with COPD and 22 patients with heart failure.

During the follow-up period, among telemonitored patients with heart failure, two exacerbations and two hospitalizations were recorded, with no deaths observed. In the group of telemonitored patients affected by COPD, one exacerbation and one hospitalization related to COPD occurred, and no deaths were recorded.

HEART FAILURE POPULATION

A total of 22 patients affected by heart failure were enrolled in the study.

The mean age of the patients was 78.68 years (SD 9.6), and 54.5% of the study population were women.

In addition to heart failure, patients were affected by the following comorbidities: arterial hypertension in 95.45% (21 patients), ischemic heart disease in 40.9% (9 patients), atrial fibrillation in 54.5% (12 patients), dyslipidemia in 100% (22 patients), diabetes mellitus in 50% (11 patients), and chronic kidney disease in 31.8% (7 patients).

The mean Activities of Daily Living (ADL) score was 5.82 (SD ± 0.5), and the mean Instrumental Activities of Daily Living (IADL) score was 7.55 (SD ± 0.8).

The mean CAT score was 12.78 (SD ± 0.5), while the mean mMRC dyspnea scale score was 1.33 (SD ± 0.77).

The mean duration of follow-up was 18 months.

	Heart failure patients
Age (mean, SD)	**78.6 (+- 9.9)**
Gender(n,%)	**Male: 10 (45.5%)** **Female: 11 (54.5%)**
ADL (mean, SD)	**5.82 (+-0.5)**
IADL (mean, SD)	**7.55 (+- 0.8)**

Arterial hypertension (n, %)	**21 (95.45%)**
Chronic kidney disease (n, %)	**7 (31.8%)**
Ischemic heart disease (n, %)	**9 (40.9%)**
Atrial fibrillation (n, %)	**12(54.5%)**
Dyslipidemia (n,%)	**22(100%)**
Diabetes mellitus (n, %)	**11(50%)**
Benign prostatic hyperplasia (n, %)	**7(31.8%)**
depression (n, %)	**2(9%)**

Table n.1: Characteristics of heart failure popolution

During the follow-up period, a total of two heart failure exacerbations and two heart failure–related hospitalizations were recorded, with no deaths observed (Table 2).

Total Events	**Telemonitoring period**	**Previous Year**
Exacerbations	**2**	**22**
Hospitalizations	**2**	**22**
Deaths	**0**	**0**

Table 2. Total number of events during the telemonitoring period compared with the previous year

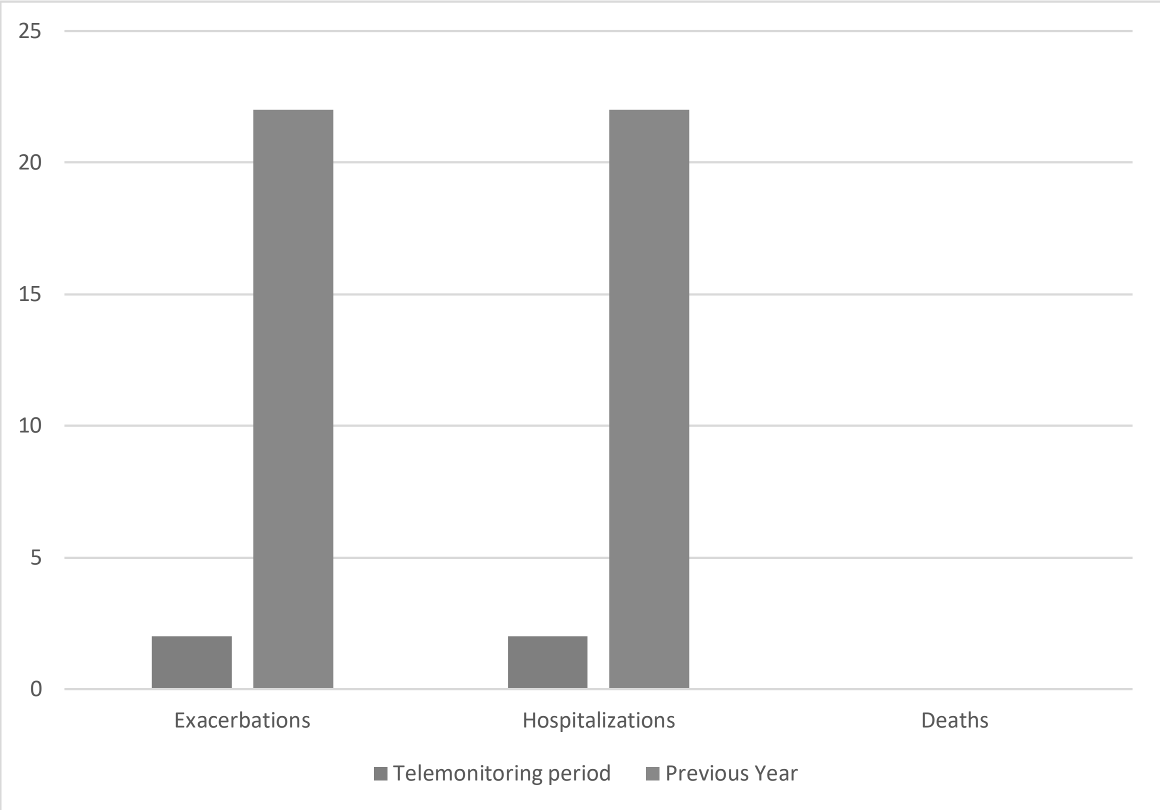


Figure 3. Comparison of heart failure–related exacerbations, hospitalizations, and deaths during the telemonitoring year and the previous year

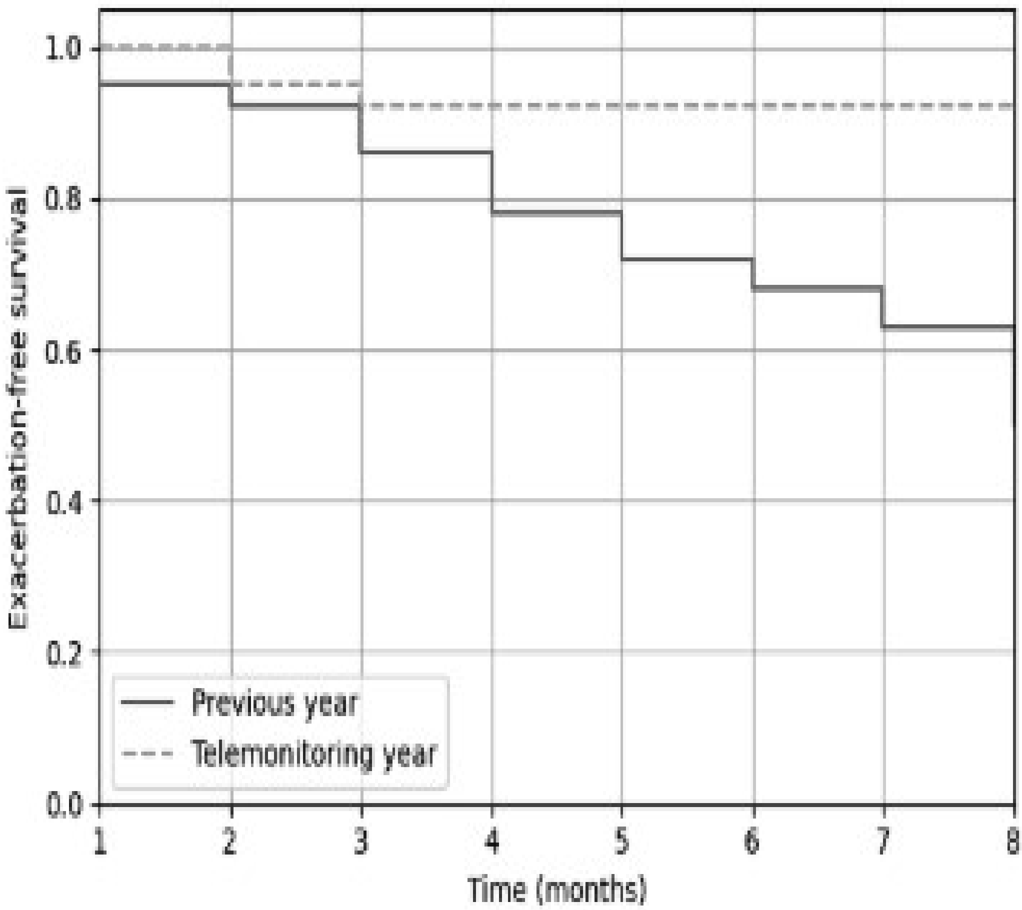


Figure 4. Risk of heart failure exacerbations during the telemonitoring period compared with the previous year

In Figure 4, the Kaplan–Meier curve shows that patients in the telemonitoring group had a lower risk of exacerbation compared with the year preceding telemonitoring ($p = 0.001$).

The Kaplan–Meier curve in Figure 5 shows that the risk of hospitalization in patients with heart failure during the telemonitoring period was lower

compared with the previous year (p = 0.001).

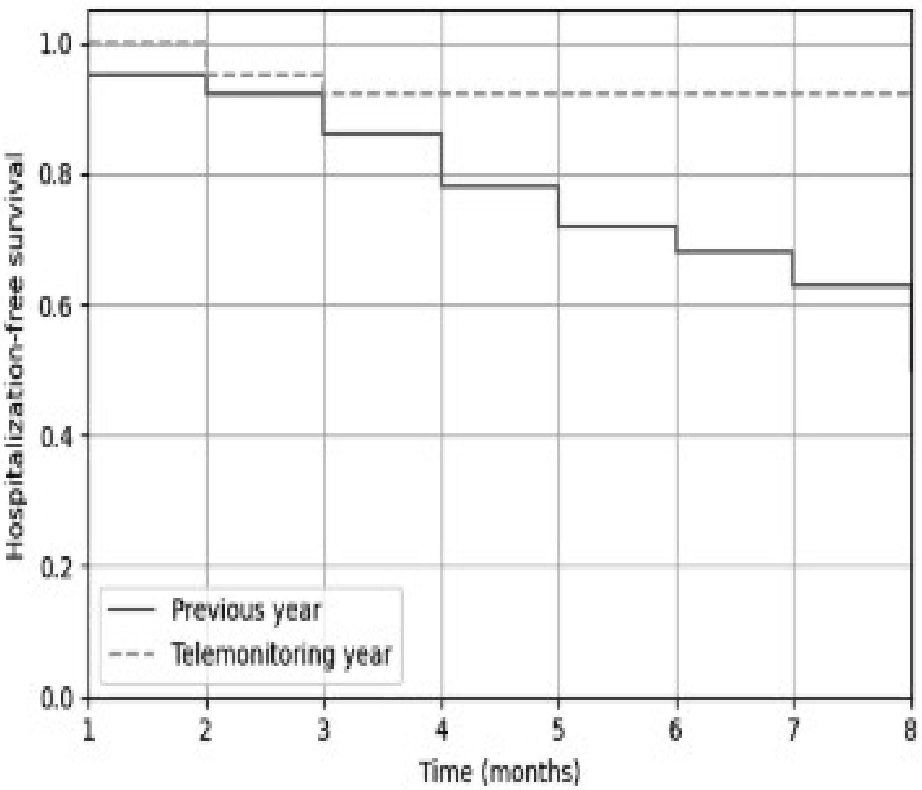


Figure 5. Risk of hospitalization over time in patients with heart failure

	HR (IC 95%)
Heart failure exacerbations	**0.09 (0.02-0.39)**
Heart failure hospitalizations	**0.09 (0.02-0.39)**

Table 3. Heart failure exacerbations and hospitalizations hazard ratio

Cox proportional hazards models showed that patients during the

telemonitoring year experienced a 91% reduction in the risk of exacerbations and hospitalizations compared with the previous year (HR 0.09, 95% CI 0.02–0.39).

COPD POPULATION

The study population affected by COPD consisted of 18 patients, with a mean age of 72.8 years (SD ± 9.59). Women accounted for 61% of the study population. In addition to COPD, patients were affected by the following comorbidities: arterial hypertension in 72.2% (n = 13), hypothyroidism in 16.6% (n = 3), ischemic heart disease in 16.6% (n = 3), atrial fibrillation in 5.55% (n = 1), dyslipidemia in 100% (n = 18), diabetes mellitus in 50% (n = 9), and chronic kidney disease in 11.1% (n = 2). The mean activities of daily living (ADL) score was 5.89 (SD ± 0.47), while the mean instrumental activities of daily living (IADL) score was 7.7 (SD ± 0.65).

	COPD patients
Age (%, SD)	72.8 (+-9.59)
Gender (n, %)	Male 7 (39%) Female 11 (61%)
ADL (mean, SD)	5.89 (+- 0.47)
IADL (mean, SD)	7.78 (+- 0.65)
Arterial hypertension (n, %)	13 (72.2%)
Chronic kidney disease (n, %)	2 (11.1%)
Ischemic heart disease (n,%)	3 (16.6%)
Atrial fibrillation (n, %)	1 (5.55%)
Diabetes mellitus (n, %)	9(50%)
Benign prostatic hyperplasia (n,%)	3(16%)
Depression (n,%)	1(5.55%)
Anemia (n,%)	2 (11.1%)

Table n. 4: Characteristics of heart failure popolution

During the follow-up period, a total of one COPD exacerbation and one hospitalization were recorded, with no deaths. (Table 6)

Total Events	Telemonitoring period	Previous year
Exacerbations	1	15
Hospitalizations	1	15

Table 6. Total number of COPD events

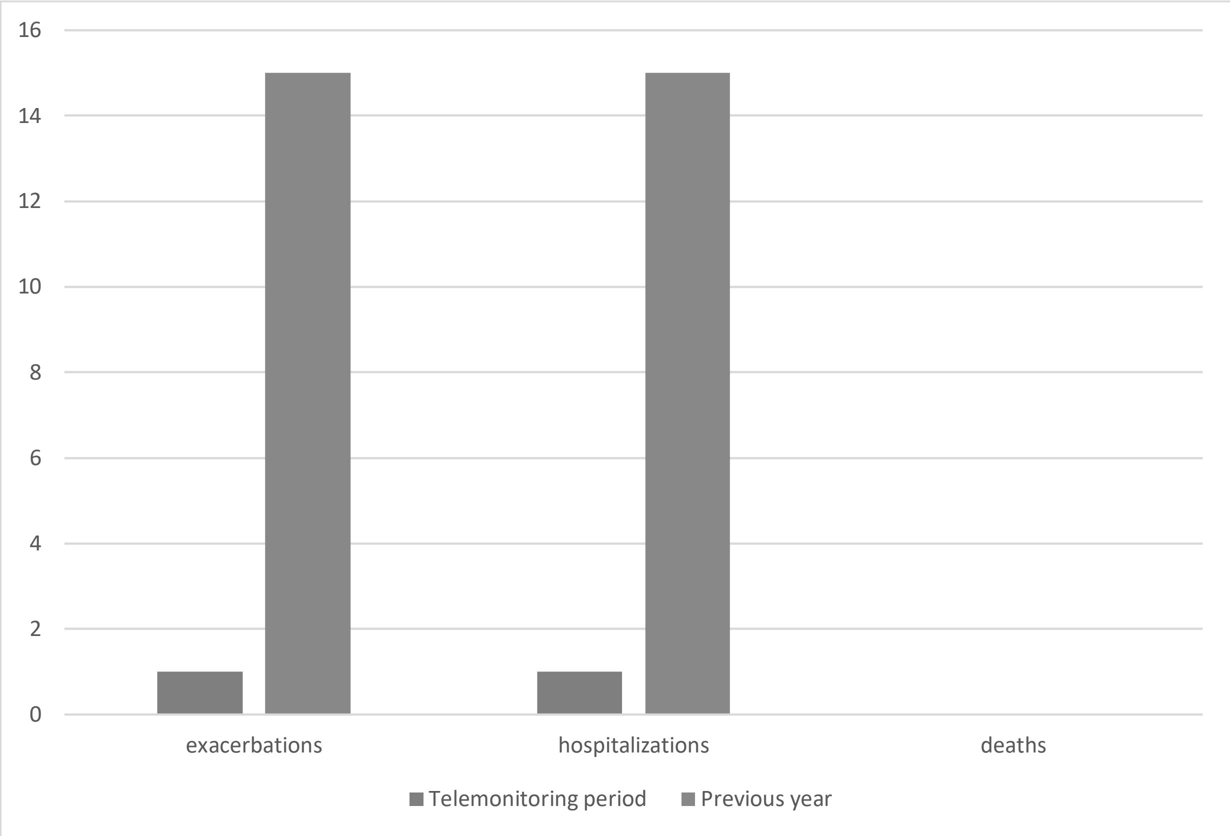


Figure 7. Cumulative incidence of mortality, hospitalizations, and composite outcome in COPD patients undergoing telemonitoring compared with the previous year

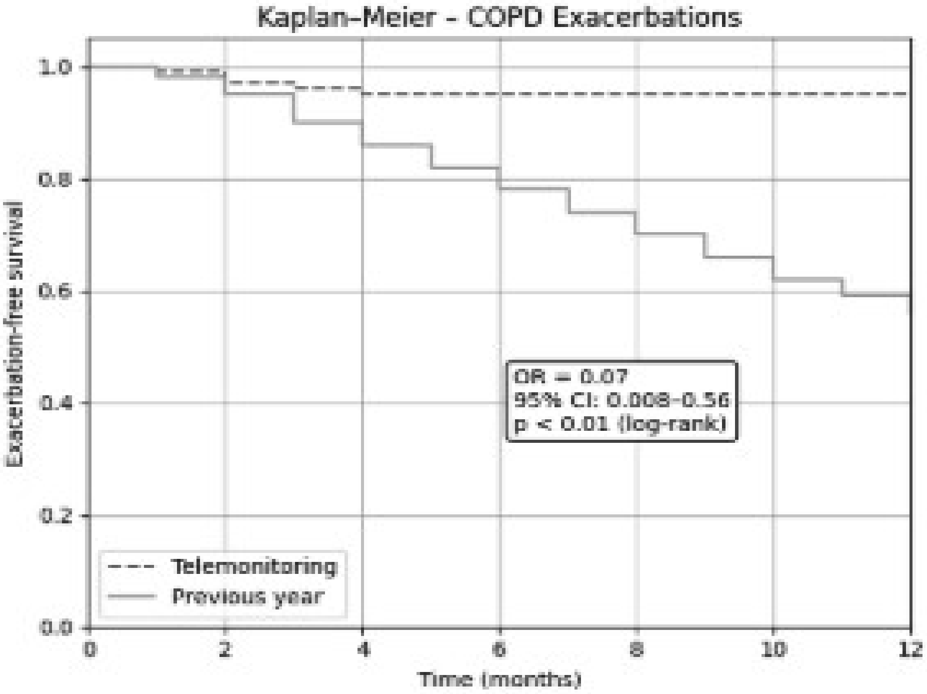


Figure 8. Risk of exacerbation over time in COPD patients undergoing telemonitoring compared with the previous year

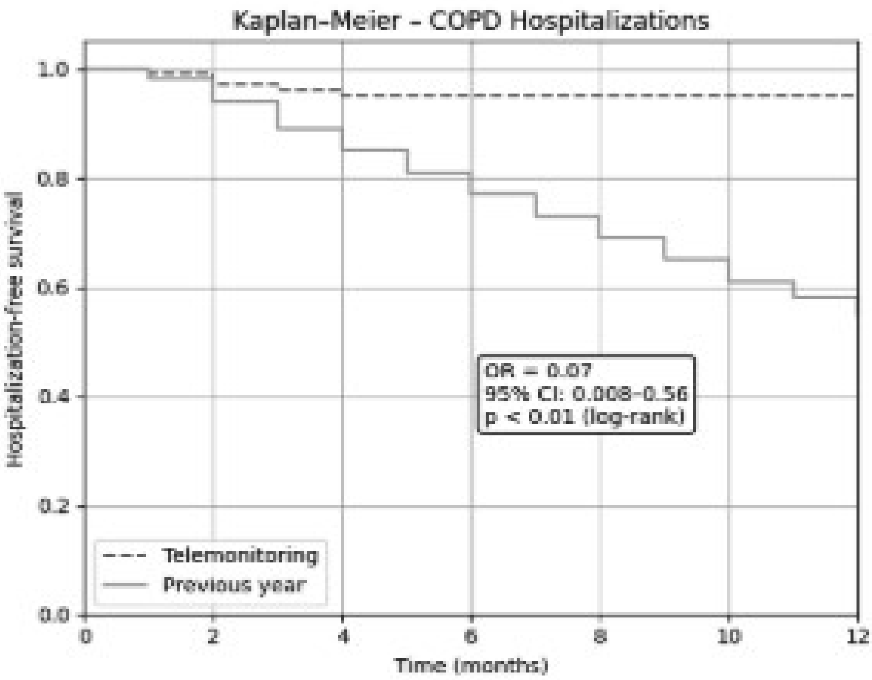


Figure 9. Risk of hospitalization over time in COPD patients undergoing telemonitoring compared with the previous year

	HR (95% CI)
COPD exacerbations	**0.067 (0.008–0.56)**
COPD hospitalizations	**0.067 (0.008–0.56)**

Table 6. Risk of negative outcomes in patients with COPD

The Cox regression models confirmed that telemonitoring reduced the risk of exacerbations and hospitalizations by 93% ($p = 0.009$).

DISCUSSION

The present study showed that remote telemonitoring supported by the BPCOmedia artificial intelligence algorithm in patients affected by heart failure appears to significantly reduce the risk of exacerbations and hospitalizations due to heart failure. Similar results were also observed in telemonitored patients with COPD.

The results obtained in patients affected by heart failure in our study are consistent with those reported by Koehler et al. regard to the reduction in hospitalizations but differ with respect to the significant reduction in exacerbations, which was not observed in the Koehler trial.[55]

The discrepancy in results may be primarily attributable to the small sample size and the relatively short follow-up of the present study, as well as to differences in the telemonitoring modalities adopted. Not all remote telemonitoring systems are comparable. In the multicenter study by Koehler et al., the analyzed population was not only larger (1.571 patients with NYHA class II– III heart failure), but patients were monitored using a traditional system based on a simple detection of vital parameters without the use of an artificial intelligence algorithm able to identify a patient-specific parametric range through a Petri net–based model and to signal clinically meaningful deviations as alerts. However, the structured intervention following alerts was comparable between the two studies.

In our study, when an alert was generated, patients were first contacted by telephone and, if deemed necessary, scheduled for an outpatient assessment. This approach may reduce exacerbations but at the cost of increased healthcare utilization, including more outpatient visits. This type of telemonitoring requires closer patient surveillance and greater involvement of dedicated medical and nursing staff. To confirm these findings in a larger population, a multicenter study design is clearly warranted.

The results of the present study are in contrast with the large multicenter trial by Ong et al. on this topic, which did not demonstrate a reduction in heart failure exacerbations in telemonitored patients at 180 days after discharge.[56]

In the study by Ong et al., a large cohort of 1,437 patients transmitted daily measurements of heart rate, blood pressure and body weight to a dedicated nurse[56]. Telemonitoring was again based on simple vital parameter recording combined with nurse-led telephone coaching in the event of abnormal values; thus, the type and modality of telemonitoring differed substantially from those used in our study.

In the group of patients with COPD, our AI-supported remote telemonitoring system also demonstrated a significant reduction in exacerbations and hospitalizations among elderly patients.

Data from previous studies focusing on elderly populations are limited and highly heterogeneous. The marked clinical heterogeneity of COPD likely contributes—more so than in heart failure—to the inconsistent results reported regarding the effectiveness of telemonitoring systems.

As highlighted in the meta-analysis by Prof. Pedone et al. which analyzed 12 randomized controlled trials involving populations with a mean age between 65 and 73 years, most studies in this field were small, used heterogeneous parameters and technologies, and showed that traditional remote telemonitoring in elderly patients with COPD did not reduce either mortality or hospitalizations.[57]

Only a few telemonitoring studies have been conducted specifically in elderly patients with COPD, such as the randomized controlled trial by Persson et al. and the non-randomized trial by Esteban et al., both of which reported reduced mortality in telemonitored COPD patients compared with usual care, in agreement with the results of the present study.[49,51]

However, the telemonitoring approaches differed, as the study by Esteban et al. combined vital sign monitoring with telephone interviews and patient education on disease management.[49]

Although the results of this study are encouraging, several limitations must be acknowledged, including the small sample size, the short follow-up duration and the monocentric design. A longer follow-up would have allowed the observation of a greater number of events and potentially demonstrated a stronger effect of telemonitoring compared with usual care, while the involvement of multiple centers would have enabled the recruitment of a larger patient population, thereby increasing the robustness of the findings.

Enrollment in the telemonitoring programs, in particular for the elderly where studies are lacking, was challenging due to the requirements that telemonitored patients must have adequate practical skills, functional autonomy in ADLs and IADLs, no moderate-to-severe cognitive impairment and the ability to correctly use the monitoring device, albeit simple to operate.

This is a crucial aspect because in Italy only 45% of the popolution is digitally literate, in particular in elderly and there are many digital divide between the regions, both due to infrastructural issues and the lack of digital skills[58].

The digital divide seems to be linked to a generation factor as highlighted by the national statistical surveys. [59,60]

To fill this digital gap, many digitazion programs have been promoted in recent years.

Elderly popolution often exhibit reduced digital skills, reduced attention, a visual-spatial impairment which make adherence to telemedicine and telemonitoring programs difficult.

The role of the caregiver in telemonitoring programs is essential in particular in this type of study.

The presence of a caregiver capable of supporting the patient during the three daily measurements— mainly during the training phase of the algorithm -was essential and this has not always be possible.

Many patients, despite being affected by heart failure and COPD, could not be enrolled because they were too frail, were candidates for care settings such as hospice or long-term care facilities, or used mobile phones (e.g., Brondi devices) that were not compatible with the BPCOmedia application. These limitations prevented testing the algorithm in a larger population. The relatively short duration of follow-up, particularly in patients with heart failure, was also influenced by the fact that patients—especially those with heart failure—tend to adhere to telemonitoring primarily during the acute phase of exacerbation and often discontinue it once clinical stability is achieved. This behavior contrasts with that of patients with COPD, for whom remote telemonitoring more frequently becomes an integral part of long-term disease management and contributes to increase patient awareness of their conditions.

CHAPTER 7: CONCLUSIONS

In conclusion, our study, in partial agreement with previous literature, demonstrated the usefulness of remote telemonitoring in reducing exacerbations and hospitalizations in both patients with COPD and those with heart failure.

The study also suggests that, in order to be effective, remote telemonitoring systems should be supported by artificial intelligence and require a high level of integrated medical care, particularly in clinically heterogeneous conditions such as COPD, where the need to provide precision medicine clearly emerges. Considering the prevalence, clinical impact and healthcare resource consumption associated with heart failure and COPD in the elderly population, further trials are needed in the future.

These studies should include larger study populations, involve multiple recruitment centers, extend follow-up periods, and employ new telemonitoring devices that are even simpler and more efficient, in order to confirm and strengthen these findings.

CHAPTER 7: A SIMILAR EXPERIENCE – A TELEMONITORING STUDY IN SARDINIA

During my PhD, I also focused on the analysis of data from a similar telemonitoring study conducted in patients with COPD in the Sardinia region, using remote telemonitoring supported by the artificial intelligence algorithm BPCOmedia.

A randomized, multicenter, prospective study was conducted in Lanusei, Sardinia, to evaluate the effectiveness of a telemonitoring system supported by the artificial intelligence algorithm BPCOmedia (EP 3394365) for the early identification of COPD exacerbations.

During the study year, 102 patients with COPD were enrolled: 54 received remote telemonitoring (mean age 69.8 years, SD ± 9.14; 76% male) and 46 received standard care (mean age 74.8 years, SD ± 9.14; 67.3% male).

Alerts were reviewed daily by a dedicated nurse through a dedicated platform.

In the event of an alert, patients were contacted by the physician and interviewed by phone regarding the onset of any new symptoms.

The need to modify pharmacological therapy was assessed on an individual basis. When necessary, additional outpatient visits were scheduled, and in more severe cases patients were referred to the Emergency Department.

Telemonitored patients were functionally more independent (ADL 5.9 vs 5.13; IADL 7.2 vs 6.6). Patients were also affected by heart failure (5.5% in the telemonitoring group vs 1.73% in the control group), arterial hypertension (63% vs 80.4%), ischemic heart disease (24.07% vs 45.6%), diabetes mellitus (22% vs 26.8%), chronic kidney disease (12.9% vs 10.8%), atrial fibrillation (16.6% vs 23.9%), benign prostatic hyperplasia (24.07% vs 43.47%), and obesity (26.9% vs 19.5%).

During the study year, there was a 67% reduction in exacerbations (RR 0.33, 95% CI 0.22–0.49) and a 71.6% reduction in hospitalizations (RR 0.28, 95% CI 0.057–1.4) compared with the control group.

Compared with the year preceding the study, the telemonitoring group experienced a 55.5% reduction in the exacerbation rate (RR 0.44, 95% CI 0.29–0.66, p = 0.0001) and a 60% reduction in the hospitalization rate (RR 0.40, 95% CI 0.078–2.06, p = 0.27).

These results suggest that remote telemonitoring supported by the BPCOmedia artificial intelligence algorithm represents an effective support tool for patients with COPD. However, limitations of this study include the small sample size, the short follow-up period, and the single-center design.

A multicenter study will be necessary to validate these preliminary findings.

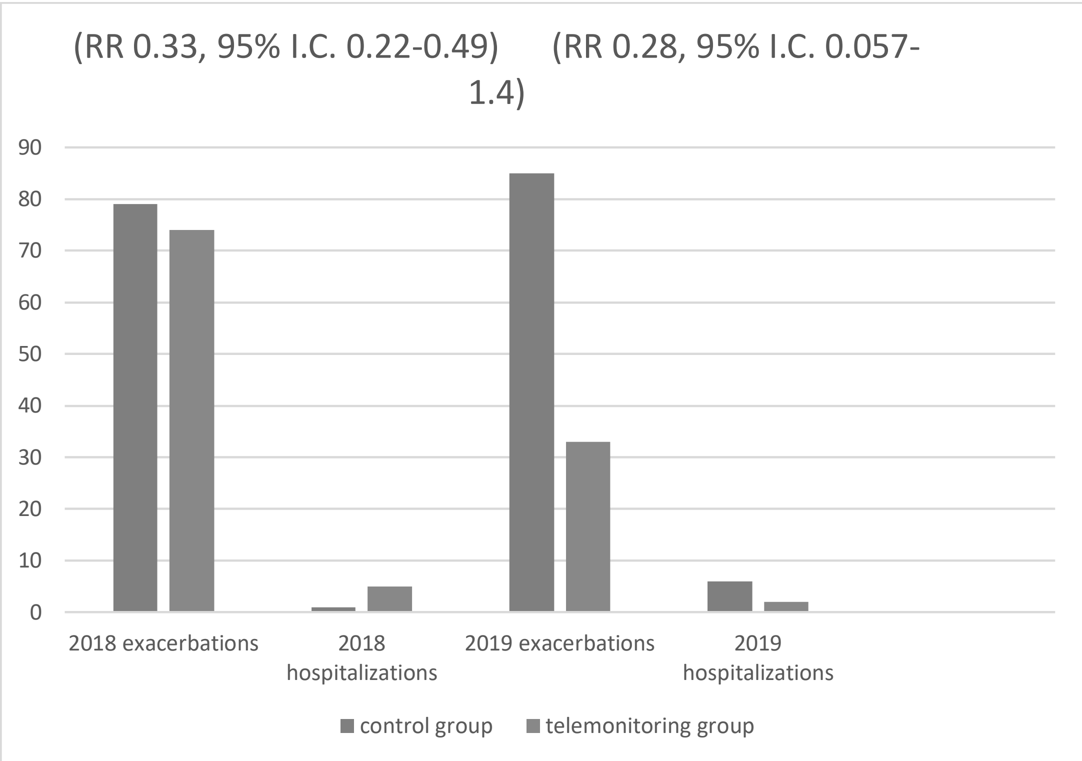


Figure n.10: The risults of Sardinia study

CAPITOLO 9: REFERENCES

1. Linee Guida Nazionali Telemedicina
2. R.Elford et al. Telemedicine in northern Norway JTelemedTelecare. 1997;3(1):122. DOI: 10.1258/1357633971930139
3. De la Torre-Díez I et al. Cost-utility and cost-effectiveness studies of telemedicine, electronic, and mobile health systems in the literature: a systematic review. Telemed J E Health. 2015 Feb;21(2):81-5. doi: 10.1089/tmj.2014.0053.
4. Coffey, J.D. et al. Implementation of a mulsite, interdisciplinary remote patient monitoring program for ambulatory management of patients with COVID-19. NPJ Digit. Med.4, 123 2021
5. Enno T Van der Velde et al. Remote monitoring of patients with implanted devices: data exchange and integration Eur J Prev Cardiol. 2013 Jun;20(2 Suppl):8-12. doi: 10.1177/2047487313487483b.
6. AbrarZulfiqar et al. Focus on the Different Projects of telemedicine Centered on the Elderly In France AgingSci. 2019;11(4):202 215.doi:10.2174/1874609812666190304115426
7. R.W. Dal Negro COPD: The Annual Cost-Of-Illness during the last two decases in Italy, and its Mortality PredictivityPowerHealthcare 2019, 7(1),35; https://doi.org/10.3390/healthcare7010035)
8. Zhonghua Wai Ke Za Zhi. W Tian Exploration and prospect of 5G application in telemedicine 2020 Jan 1;58(1):1-4. doi: 10.3760/cma.j.issn.0529-5815.2020.01.001. DOI: 10.3760/cma.j.issn.0529-5815.2020.01.001
9. José Luis Monteagudo et al. Envisioning patient safety in Telehealth: a research perspective Health Technol. (2014) 4:79–93 DOI 10.1007/s12553-014-0078-7

10. Peter A. Clark1 et al. Telemedicine: Medical, legal and ethical perspectives Med Sci Monit, 2010; 16(12): RA261-272 PMID: 21119593

11. Saeideh Goharinejad et al. Review of Systematic Reviews in the FieldofTelemedicine DOI: 10.47176/mjiri.35.184MedJIslamRepubIran. 2021Dec29; 35:184. doi:10.47176/mjiri.35.184. eCollection 2021.

12. Monika Fekete et al. Role of new digital technologies and telemedicine in pulmonary rehabilitation Smart devices in the treatment of chronic respiratory diseases Wien Klin Wochenschr.2021Nov

13. Linee guida ESC scompenso cardiaco 2023 Update

14. Inglis SC et al. Structured telephone support or non-invasive telemonitoring for patients with heart failure. Cochrane Database SystemRev2015Oct31(http://doi.wiley.com/10.1002/14651858.CD007228.pub3

15. Conrad N, Judge A, Tran J, et al. Temporal trends and patterns in heart failure incidence:population-based study of 4 million individuals. Lancet 2018; 391(10120): 572 – 580

16. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev. 2017; 3(1): 7–11.

17. Meyer S, Brouwers FP, Voors AA, et al. Sex differences in new-onset heart failure. Clinical Research in Cardiology 2015; 104: 342–350

18. Roger VL. Epidemiology of heart failure. Circ Res 2013;113: 646 659

19. Van Riet EE et al. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. Eur J Heart Fail. 2014; 16: 772–77

20. Van Riet EE et al. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016; 18: 242 – 252

21. Dunlay SM et al. Hospitalizations after heart failure diagnosis: a community perspective. J Am Coll Cardiol 2009;54: 1695–702

22. Dat Vu Nguyen et al. Prognostic value of NT-proBNP in the new era of heart failure treatment PLoS One. 2024 Sep 13;19(9):e0309948. doi: 10.1371/journal.pone.0309948. eCollection 2024.PMID: 39269956

23. Galderisi M et al. EACVI Scientific Documents Committee. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2017;18: 1301 1310

24. Cleland JG et al. PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure study. Eur Heart J 2006;27 :2338

25. Cleland JGF et al. Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of doubleblind randomized trials. Eur Heart J 2018; 39:26

26. Martín-Lesende I et al. Mortality in a cohort of complex patients with chronic illnesses and multimorbidity: a descriptive longitudinal study. J.BMC Palliat Care. 2016 Apr 12; 15:42. doi: 10.1186/s12904-016-0111-x.PMID: 27068572

27. Pedone C et al. Efficacy of a Physician-Led Multiparametric Telemonitoring System in Very Old Adults with Heart Failure.J Am Geriatr Soc. 2015 Jun;63(6):1175-80. doi: 10.1111/jgs.13432. Epub 2015 Jun 1PMID: 26031737

28. Aronow WS et al. Comparative Effectiveness of Disease Management With Information Communication Technology for Preventing Hospitalization and Readmission in Adults With Chronic Congestive Heart Failure. J Am Med Dir Assoc. 2018 May 2. pii: S1525-8610(18)30149- X. doi: 10.1016/j.jamda.2018.03.012.

29. Halpin DMG, Celli BR, Criner GJ, et al. The GOLD Summit on chronic obstructive pulmonary disease in low- and middle-income countries. Int J Tuberc Lung Dis 2019; 23(11): 1131-41

30. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet. 2004 Aug 14-20;364(9434):613-20.

31. Linee guida GOLD 2026

32. Buist AS et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007; 370(9589): 741-50

33. Colak Y et al. Prognostic significance of chronic respiratory symptoms in individuals with normal spirometry. Eur Respir J 201954(3)

34. Yasemin Ceyahn et al. The effects of breathing exercises and inhaler training in patients with COPD on the severity of dyspnea and life quality: a randomized controlled trial. Trials. 2022 Aug26;23(1):707.doi:10.1186/s13063-022-06603-3

35. Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis MRC breathlessness score BMJ 1960; 2: 1662

36. Bartolomé R Celli et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study DOI: 10.1164/rccm.200712-1869OC

37. Jean Bourbeau et al. Benefit/Risk Profile of Single. Inhaler Triple Therapy in COPD. Int J Chron Obstruct Pulmon Dis.2021 Mar 1:16:499-517.doi:10.2147/COPD.S291967

38. Charlie Strange et al. Exacerbations and Real- World Outcomes After Single-Inhaler Triple Therapy of Budesonide/Glycopyrrolate/Formoterol Fumarate, Among Patients with COPD: Results from the EROS (US) Study Int J Chron Obstruct

Pulmon Dis. 2023 Oct 12:18:2245-2256.doi:10.2147/COPD.S432963. eCollection2023

39. Treatable traits COPD: Xie et al. Toward Precision medicina in COPD: phenotypes, endotypes, biomarkers and treatable traits, Respiratory Research (2025) 26:274 https://doi.org/10.1186/s12931-025-033

40. Andrea Corsonello et al. Treating COPD in Older and Oldest Old Patients Curr PharmDes. 2015;21(13):167289. doi:10.2174/1381612821666150130121229.

41. Sven Stieglitz et al. COPD in elderly patients Pneumologie.2025 May;79(5):382-394. doi:10.1055/a-1849-4555. Epub 2025 May 12.

42. Jane Li Marlien Varnfield Rajiv Jayasena Home telemonitoring for chronic disease management: Perceptions of users and factors influencing adoption DOI: 10.1177/1460458221997893

43. Polisena J, Tran K, Cimon K, Hutton B, McGill S, Palmer K, Scott RE. Home telemonitoring for congestive heart failure: a systematic review and meta-analysis. J Telemed Telecare 2010;16: 68–76

44. Klersy C. et al. A meta-analysis of remote monitoring of heart failure patients. J Am Coll Cardiol 2009;54: 1683–1694

45. Ayesha Hasan and al. Telemonitoring in chronic heart failure European Heart Journal (2011) 32, 1457–1464 doi:10.1093/eurheartj/ehr005

46. Michael K Ong et al. Effectiveness of Remote Patient Monitoring After Discharge of Hospitalized Patients With Heart Failure: The Better Effectiveness After Transition -- Heart Failure (BEAT-HF) Randomized Clinical, Better Effectiveness After Transition–Heart Failure (BEAT-HF) Research Group
DOI: 10.1001/jamainternmed.2015.7712

47. Michael K Ong et al. Is telemonitoring effective in older adults affected by heart failure? A meta-analysis focused on this population D. JAMA Intern Med. 2016 Mar;176(3):310-8.

48. Hans Lennart Persson et al. “Elderly patients with COPD require more health care than elderly heart failure patients do in a hospital-based home care setting” Int J Chron Obstruct Pulmon Dis. 2019Jul16;14: 15691581doi:10.2147/COPD.S207621. eCollection 2019

49. Cristóbal Esteban et al. Outcomes of a telemonitoring-based program (telEPOC) in frequently hospitalized COPD patients DOI: 10.2147/COPD.S115350

50. Claudio Pedone et al. Efficacy of multiparametric telemonitoring on respiratory outcomes in elderly people with COPD: a randomized controlled trial BMC Health Services Research 2013, 13:82Journal of Telemedicine andTelecareVolume 27, Issue 1, January 2021, Pages 46-53, https://doi.org/10.1177/1357633X19858178

51. L Persson et al. a telemonitoring system lead to decreased hospitalization in elderly patients? Observational Study Int J Chron Obstruct Pulmon Dis . 2016 Nov 24;11: 2919-2930. doi: 10.2147/COPD.S115350. eCollection 2016

52. Cochrane Review Summary: Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations 2017 Nov;18(6):527-528. doi: 10.1017/S1463423617000202. Epub 2017 Jun 5.

53. Inmaculada Tornero-Quiñones et al. Int J Environ Res Public Health. 2020 Feb 5;17(3):1006.doi: 10.3390/ijerph17031006.Functional Ability, Frailty and Risk of Falls in the Elderly: Relations with Autonomy in Daily Living DOI: 10.3390/ijerph17031006

54. Parmalee PA et al.: Validation of the Cumulative Illness Rating Scale in a geriatric residential population. J Am Geriatr Soc 1995; 43:130-137.

55. Koehler et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. Lancet. 2018;392(10152):990–1000. doi:10.1016/S0140-6736(18)31995-0)

56. Michael K Ong et al. Effectiveness of Remote Patient Monitoring After Discharge of Hospitalized Patients With Heart Failure: The Better Effectiveness After Transition -- Heart Failure (BEAT-HF) Randomized Clinical TrialDOI: 10.1001/jamainternmed.2015.7712 JAMA Intern Med. 2016 Mar;176(3):310-8

57. Claudio Pedone et al. Systematic review of telemonitoring in COPD: an update Pneumonol Alergol Pol. 2015;83(6):476-84. doi:10.5603/PiAP.2015.0077

58. M. Vainieri et al. Tracking the digital health gap in elderly: A study in Italian remote Health Policy. 2023 Jul:133:104842. doi: 10.1016/j.healthpol.2023.104842. Epub 2023 May 25)

59. Eurostat. Eurostat regional yearbook. 2022

60. Istat. Cittadini e ict. 2019.