Monaldi Arch Chest Dis
2014; 82: 29-34

ORIGINAL ARTICLE

Italian survey on prevalence and disease management of chronic heart failure and chronic obstructive pulmonary disease comorbidity in ambulatory patients. SUSPIRIUM study rationale and design

Survey Italiana su prevalenza e disease management dei pazienti affetti dalla comorbilità scompenso cardiaco e broncopneumopatia cronica ostruttiva. Razionale e disegno dello studio SUSPIRIUM

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ABSTRACT: ***Italian survey on prevalence and disease management of chronic heart failure and chronic obstructive pulmonary disease comorbidity in ambulatory patients. SUSPIRIUM study rationale and design. R. Griffo, A. Spanevello, P.L. Temporelli, P. Faggiano, M. Carone, G. Magni, N. Ambrosino, L. Tavazzi and on behalf of the SUSPIRIUM Investigators.***

Background. **Chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) are leading causes of morbidity and mortality worldwide. Through shared risk factors and pathophysiological mechanisms, CHF and COPD frequently coexist. The concurrent disease has important therapeutic implications and independently predicts worsened mortality, impaired functional status, and health service use. However, assessment of the comorbidity varies widely according to the population studied, diagnostic criteria and measurement tools applied. Both syndromes have been studied extensively but largely separately, mostly in the domain of the pulmonologist for COPD and in the domain of the cardiologist for CHF.**

Study objectives and design. **The aim of the study is to evaluate in an Italian outpatients setting (10 cardiology and 10 pulmonology centers from the same institution) the prevalence, clinical profile and the routine diagnostic, functional and therapeutic work-up applied by cardiologists and pulmonologists in the presence/suspicion of concurrent disease in patients in a stable phase of their disease. For this purpose, CHF and COPD outpatients will be enrolled in a multicenter, nationwide, prospective observational study. Risk estimation of comorbidity will be based on suspected, documented or patient-reported diagnosis of COPD/CHF. In the absence of documented concurrent diagnosis, each specialist will describe the diagnostic, functional and therapeutic work-up applied.**

Conclusion. **The design of the study focused on the diagnostic validation of the CHF-COPD comorbidity aims to provide relevant new information on the assessment of the coexistent condition in the cardiac and pulmonary outpatients setting and on specialty-related different diagnostic and therapeutic strategies of comorbidity utilized in real life clinical practice. The symptomatic and prognostic benefits resulting from a combined approach to CHF/COPD could outweigh those attainable by treating either condition alone.**

Keywords: chronic heart failure, chronic obstructive pulmonary disease, comorbidity, observational study.

Monaldi Arch Chest Dis 2014; 82: 29-34.

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Introduction

Chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) are leading causes of morbidity and mortality worldwide [1]. The prevalence of COPD (Global Initiative for COPD -GOLD- stage II or higher) ranges from 5-10% among adults [2] and one-year mortality in the

community is relatively low (3%) but higher following hospitalization (25%) [3, 4].

CHF is less common, affecting about 1-3% of the general population, but carries a worse prognosis with an annual mortality in stable community-living patients of 5-7% while the median survival following hospitalization remains just two years [5]. Approximately half of the patients have CHF with preserved ejection fraction and half left ventricular systolic dysfunction [6].

Each of these conditions has an important impact on quality of life and functional status and generates considerable health-care costs.

Through shared risk factors (including cigarette smoking and advanced age) and pathophysiological mechanisms ("cardiopulmonary continuum", low-grade systemic inflammation [7, 8]), CHF and COPD coexist more frequently than expected from the respective populations observed by the pulmonologist or the cardiologist, with important prognostic and therapeutic implications. However, the assessment of the prevalence of concurrent disease, i.e. COPD in CHF patients (Table 1) and CHF in COPD patients (Table 2) varies considerably according to the population studied (outpatients or in-hospital patients), cohort selection (administrative data, community dwellers, GPs registry), diagnostic criteria and measurement tools applied (clinical, pulmonary function tests, echocardiography, natriuretic peptides). Moreover, both syndromes have been studied extensively but largely separately with COPD in the domain of the pulmonologist and heart failure in the domain of the cardiologist.

As highlighted by Table 1, few studies have systematically examined pulmonary function in stable CHF outpatients using standardized criteria, and the

Table 1. Studies carried out assessing presence of COPD in CHF patients

Reference	Year	Country	N° Patients	CHF Cohort	COPD Prevalence %	Diagnosis	Prognosis
Boschetto [24]	2013	Italy	118	outpatients stable>65y	30	PFT	Mortality: no difference
De Blois [25]	2010	Norwey	4132	inpatients	17	"experienced data collectors"	Mortality: HR 1.18 (ns)
O'Kelly [26]	2012	UK	783	community	12.9	PFT or >2 prescription for ipratropium bromide	CHF Hospitalization: HR 1.56 p<.001 MACE: HR 1.23 p<.001 CV death/All-cause mortality: HR .96-1.02 (ns)
Macchia [10]	2012	Argentina	201	outpatients stable>60y	37.3	PFT	Mortality: HR 0.77 (p ns)
Doos [27]	2014	UK	10113	GPs registry	8	clinical	higher mean costs for hosp p<.001
Steinacher [9]	2012	Austria	89	outpatients	25	PFT	–
Kadam [28]	2013	UK	60660	GPs registry	2	Clinical	High costs + Hospitalization (p<.001)
Di Lenarda [14]	2003	Italy	2127	inpatients	41.3	Clinical PFT	–
Iversen [29]	2008	Denmark	532	inpatients	35	PFT	–
Mentz [17]	2012	–	5701	inpatients	25	Clinical evidence, history	In-hospital non CV mortality: HR 1.65, p<.01
Mentz [18]	2012	–	4133	inpatients	10	Clinical evidence, history, PFT	All cause mortality: HR 1.41 mortality/ CHF hospitalization: HR 1.29
Rusinaru [30]	2008	France	799	Inpatients	19.5	Clinical evidence, history, PFT	Mortality: HR 1.53 p<.001

Abbreviation:
COPD= chronic obstructive pulmonary disease; pts= patients; y= years; PFT= pulmonary function tests; HR= hazard ratio; GPs= general practitioners; CHF=chronic heart failure; MACE= major adverse cardiac event; CV=cardiovascular

Table 2. Studies carried out assessing presence of CHF in COPD patients

Reference	Year	Country	N° Patients	COPD Cohort	CHF Prevalence %	Diagnosis	Prognosis
Rutten [21]	2005	Netherland	405	outpatients stable>60y	20.5	Echo PFT	
Macchia [10]	2012	Argentina	218	outpatients stable>60y	17	Echo	Mortality HR 2.3 (p<.05)
Rutten [31]	2010	Netherland	2230	GPs registry	24.5	clinical	–
Boudestein [11]	2012	UK	405	GPs registry	20.5	Echo PFT	Mortality HR 2.1 (p<.01)
Cui [32]	2012	China	4960	inpatients	19.6	Hospital code	–
Mullerova [33]	2013	Meta-analysis	–	–	28-70	–	–

Abbreviations: see Table 1; echo= echocardiography

observed prevalence of COPD ranges from 25 [9] - 37.7% [10]. Still fewer are the studies regarding COPD outpatients (Table 2), and the prevalence of unrecognized CHF ranges from 17% (in highly selected cohorts in whom diagnosis was adjudicated retrospectively [10]) to 20.5% [11]. In Italy, to our knowledge, no studies on CHF prevalence in COPD outpatients exist. The few studies on the prevalence of COPD in CHF patients are based on observation from administrative registration [12, 13] (prevalence 23.6-26.5%) or on only hospitalized patients (41.3%) or in patients with acute heart failure admitted to cardiology departments or internal medicine units (29.7%) [14, 15]. Also several post-hoc analysis of large randomized controlled trials and registries evaluated prevalence and prognostic impact of CHF and COPD association in ambulatory cardiac patients, consistently showing the unfavourable implications of the comorbidity either for the constraint in the use of recommended treatments or for a worse outcome [16-19].

Concurrent COPD independently predicts mortality in patients with reduced or preserved ejection fraction, as reported recently [21] also following adjustment for beta-blocker utilization, while two studies examining the prognostic implication of concurrent CHF in COPD patients document a hazard ratio for mortality of 2.3-2.1 over a mean follow-up of 2-4 years [11, 21].

The presence of one syndrome in the presence of the other has important therapeutic implications (e.g. beta-blockers or beta2-agonist use); hence knowledge about the concomitant prevalence is clinically important. Both cardiologist and pulmonologist, respectively, need to improve their identification and management of concurrent COPD and CHF. The resulting symptomatic and prognostic benefits could outweigh those attainable by treating either condition alone.

In Italy, a national network exists of cardiac and pulmonary rehabilitation centers, frequently combined in the same institution, treating stable outpatients with, respectively, CHF and COPD. In this setting, we have designed a survey to investigate 1) the clinical prevalence of COPD in patients with stable CHF diagnosed by the cardiologist and, viceversa the prevalence of CHF in patients with stable COPD diagnosed by the pulmonologist; and 2) the routine diagnostic, functional and therapeutic work-up applied by cardiologist and pulmonologist in the presence/suspicion of concurrent disease.

Secondary objectives of the survey are 1) to verify the frequency and quality of self-reported diagnosis of concurrent disease; and 2) to compare the clinical profile (according to the relative severity of the reference disease) of the patients with vs. without comorbidity.

Study Design

The Italian **su**rvey on prevalence and di**s**ease management in **p**atients with heart fa**i**lure and chronic obst**r**uct**i**ve p**u**l**m**onary disease (SUSPIRIUM) study is a cross-sectional, observational, multicenter nationwide survey, with on-line web-based data collection. Its design corresponds to the survey's goal, i.e. to describe accurately in a representative number of 20 Italian cardiac and respiratory outpatient centers (10 pairs of cardiac and respiratory units from the same institution) the prevalence and the usual diagnostic, functional and therapeutic work-up applied by the cardiologist and pulmonologist in the presence/suspicion of concurrent disease in patients in a stable phase of their disease.

Each cardiac and respiratory participating center will enroll the first 2 consecutive outpatients/week with definite diagnosis of CHF or COPD (with or without self-reported or suspected or definite comorbidity) respectively observed in the outpatients department during the 8 months enrollment period. The diagnosis of CHF is according to the criteria recommended by the European Society of Cardiology (ESC) guidelines 2012 [22] and the diagnosis of COPD is according to diagnostic criteria of the Global Initiative for COPD diagnosis (GOLD 2011 [23]).

We estimated that in 8 months about 800-1000 patients (50% COPD and 50% CHF) will be enrolled by the centers: 80-100 patients/center (40-50 patients/cardiologist investigator, 40-50 patients/pulmonologist investigator).

During the specialist's examination, after providing informed consent, all patients will undergo the following examinations: collection of demographic, anthropometric characteristics, cardiac and respiratory risk profile (risk factors), clinical history including past cardiac or respiratory events and patient-reported (or documented history of) COPD or CHF, other comorbidities, and data from physical examination.

The risk estimation of comorbidity, by the specialist, will be based on suspected (history, symptoms, physical examination), documented (pulmonary function tests, imaging, natriuretic peptides formerly performed) or patient-reported diagnosis of COPD/CHF. In the absence of documented concurrent diagnosis, each specialist will describe the usual diagnostic, functional and therapeutic work-up applied and will report any specific diagnostic tests or specialist consultations have been planned to confirm or to exclude the presence of comorbidity.

The survey does not involve any diagnostic tests, care interventions or pharmacological treatments that are not part of the clinical practice and protocols routinely adopted by each single participating center.

The study protocol has been submitted for approval to local or institutional review board/ethic committees.

The investigators have been given adequate training in the survey procedures before the beginning of the study and during follow-up data collection.

The survey will be independently managed and the data will be analyzed by the Scientific Board.

Study Population

The study population will include stable outpatients of either sex consecutively observed with: i) COPD diagnosed in a pulmonology setting, based on GOLD 2011 diagnostic criteria [23]: symptoms (progressive dyspnea at rest worsening during exercise, chronic cough and sputum), history of exposure to risk factors, family history of COPD and spirometry evidence of airflow limitations (post bronchodilator FEV1/FVC <0.70); ii) CHF diagnosed in a cardiology setting, based on diagnostic principles of the ESC Guidelines for the diagnosis and treatment of Chronic Heart Failure 2012 [22]: symptoms (typically shortness of breath at rest or during exertion, and/or fatigue), signs of fluid retention (such as pulmonary congestion or ankle swelling) and objective evidence of an abnormality of the structure or function of the heart at rest: reduced left ventricular ejection fraction (LVEF) ≤40% or preserved LVEF and significant structural heart disease (LV hypertrophy/LA enlargement) and/or diastolic dysfunction.

The following exclusion criteria will be applied: i) unstable CHF patients, defined as follows: previous (three months) or scheduled cardiac surgery; acute coronary syndrome (STEMI, NSTEMI, UA) within the previous 3 months; percutaneous coronary or valvular intervention within the previous month; change in cardiovascular drug therapy within the previous month; hospitalization/emergency ward admittance for cardio-respiratory reasons within the previous 3 months; ii) unstable COPD patients, defined as follows: hospitalization/emergency ward admittance for cardio-respiratory reasons within the previous 3 months; change in respiratory drug therapy within the previous month.

Also excluded will be patients with psychiatric disorders; cardio-pulmonary congenital malformation; patients scheduled for heart and/or lung transplant; patients with malignant cancer in active treatment and patients who did not give their informed consent to participate in the survey.

Data collection

Web-based electronic case report forms (e-CRF) will be used for data entry and transferred via web to a central database through a dedicated section of the website. Access to the electronic survey forms will be restricted to the investigators previously identified by the study's Scientific Board. The on-line data collection instrument will be available for round-the-clock use and the data required for patients inserted in real-time, at any moment during the course of the survey. The data collection instrument has been designed according to a multiple-choice style, with jump menus or select boxes and obligatory items, in order to reduce the risk of confounding answers. The construction aimed to prevent in any way tracing the identity of the subjects whose clinical course is described in the survey. The e-CFR form has been designed to cater for the collection and analysis of data regarding only the patients' enrolment visit. The CRF is to be completed individually for each enrolled subject. The investigator has ultimate responsibility for the collection and reporting of all data entered on the CRF and for ensuring that data are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

Statistical methods and data analysis

We have estimated that in 8 months about 800-1000 patients (approximately 50% COPD and 50% CHF) will be screened by the 10 paired centers. Assuming a proportion of 20% for the prevalence of COPD in patients with CHF diagnosed by the cardiologist and the prevalence of CHF in patients with COPD diagnosed by the pulmonologist, we expect that about 160 to 200 patients will present both diagnoses (80-100 COPD+CHF and 80-100 CHF+COPD). Assuming a prevalence of patients with CHF+COPD of 20%, a sample size of 400-500 patients with CHF will yield an estimate of the prevalence with a confidence level of 90% and a statistical precision of 16.5% (confidence interval: ±3.3%). Similarly for patients with COPD diagnosis. All the data provided by the centers participating in the study will be collected in the web-based electronic validated database after a data cleaning and quality control. All computations will be carried out with SAS® statistical software (*SAS Institute Inc., Cary, North Carolina, USA - version 9.2*).

Enrolled patients will be analyzed as an overall group and by diagnosis group (CHF and COPD groups). All continuous variables will be expressed as mean and standard deviation (SD) calculated together

with the median and range, whereas categorical variables will be expressed as percentages. For the evaluation of the differences between the two subgroups (COPD+CHF and CHF+COPD), the distributions of the main numerical variables will be compared by the Student's t-test and the analysis of variance (ANOVA) while for categorical data the chi-square test and Fischer's test will be used. The significance level will be set at $p<0.05$. For the evaluation of the prevalence related to the primary and secondary objectives, proportions will be estimated and associated with a 95% confidence interval (binomial distribution).

The impact of the concurrent syndromes on functional capacity in the two subgroups (COPD and CHF) will be evaluated by the t-test: differences in mean values between patients with only COPD vs. COPD+CHF and with only CHF vs. CHF+COPD will be calculated.

The correctness of self-reported diagnoses will be explored and the percentage of incorrect self-reported and new diagnoses will be reported. The diagnostic performance of the different cardiologist and pulmonologist assessments of COPD and CHF respectively will be described.

Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and will follow generally accepted research practices such as *Good Clinical Practices* (GCP). The informed consent form is in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, will be prospectively approved by the institutional review board/ethic committees. The investigator will ensure that each study participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

Funding source

SUSPIRIUM was supported by Boehringer-Ingelheim with an unrestricted research grant.

Conclusion

Cardiologists and pulmonologists, respectively, must better identify and manage concurrent COPD and CHF. The purely observational design of this study aims to provide significant new information on the assessment of the coexistent condition in the cardiac and respiratory outpatients setting and on diagnostic and therapeutic strategies of comorbidity in real life clinical practice. The SUSPIRIUM study aims to give also new insights for improvement and implementation of simple clinical and diagnostic measures for the systematic screening of this severe comorbidity in cardiac and pulmonary patients.

Appendix SUSPIRIUM Organization

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Disclaimer: The Italian Association of on Cardiovascular Prevention and Rehabilitation (IACPR) endorses and assumes the full responsibility for the SUSPIRIUM study, not only for its design and formulation, but also for the overall conduct of the study, including data monitoring and utilization of the results.

Riassunto

Background. Lo scompenso cardiaco cronico (CHF) e la broncopneumopatia cronica ostruttiva (COPD) sono le più frequenti cause di morbilità e mortalità nel mondo. Attraverso fattori di rischio e meccanismi fisiopatologici condivisi, esse coesistono frequentemente nello stesso paziente e ciò condiziona una peggiore capacità funzionale, una maggiore mortalità e un più elevato consumo di risorse sanitarie. La loro compresenza ha inoltre significative ricadute sulla terapia. La prevalenza di CHF e COPD varia largamente in base alla popolazione studiata, al setting assistenziale (cardiologico o pneumologico) e ai criteri diagnostici e strumentali utilizzati.

Obiettivi e disegno dello studio. Lo scopo dello studio osservazionale SUSPIRIUM, multicentrico e prospettico, è valutare in un setting ambulatoriale, 10 centri cardiologici e 10 pneumologici nella stessa istituzione, la prevalenza, il profilo clinico e il percorso diagnostico e terapeutico applicato dai cardiologi e dagli pneumologi in presenza/sospetto di compresenza di CHF e COPD in pazienti stabili. La stima del rischio di comorbilità sarà valutata sulla presenza di una sospetta, documentata o riferita diagnosi di comorbilità. In assenza di documentata comorbilità, ciascun specialista descriverà il percorso diagnostico adottato.

Conclusioni. Lo studio potrà fornire nuove e rilevanti informazioni sulla prevalenza della comorbilità in pazienti stabili con CHF e COPD rispettiva-

mente osservati dai cardiologi e dagli pneumologi e sulle relative strategie diagnostiche e terapeutiche adottate. I benefici derivanti da una maggiore attenzione e integrazione degli specialisti sulla presenza o sospetto di comorbilità potrebbero avere conseguenze favorevoli sullo stato funzionale e sulla prognosi dei pazienti.

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