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Pattern of comorbidities and 1-year mortality in elderly patients with COPD hospitalized in internal medicine wards: data from the RePoSI Registry

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Abstract

Currently, chronic obstructive pulmonary disease (COPD) represents the fourth cause of death worldwide with significant economic burden. Comorbidities increase in number and severity with age and are identified as important determinants that influence the prognosis. In this observational study, we retrospectively analyzed data collected from the RePoSI register. We aimed to investigate comorbidities and outcomes in a cohort of hospitalized elderly patients with the clinical diagnosis of COPD. Socio-demographic, clinical characteristics and laboratory findings were considered. The association between variables and in-hospital, 3-month and 1-year follow-up were analyzed. Among 4696 in-patients, 932 (19.8%) had a diagnosis of COPD. Patients with COPD had more hospitalization, a significant overt cognitive impairment, a clinically significant disability and more depression in comparison with non-COPD subjects. COPD patients took more drugs, both at admission, in-hospital stay, discharge and 3-month and 1-year follow-up. 14 comorbidities were more frequent in COPD patients. Cerebrovascular disease was an independent predictor of in-hospital mortality. At 3-month follow-up, male sex and hepatic cirrhosis were independently associated with mortality. ICS-LABA therapy was predictor of mortality at in-hospital, 3-month and 1-year follow-up. This analysis showed the severity of impact of COPD and its comorbidities in the real life of internal medicine and geriatric wards.

Keywords COPD, comorbidities, elderly, internal medicine, in-hospital mortality · 3-month mortality · 1-year mortality

Introduction

Chronic obstructive pulmonary disease (COPD) represents an important leading cause of morbidity and mortality with high economic and social costs: according to the WHO, COPD is the fourth most common cause of death worldwide, and it is estimated to be the third by 2020; furthermore, the global burden of COPD is expected to increase in the

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coming years, due to the prevalence of smoking and aging of the world population [1].

Comorbidities are an essential component of COPD burden. Some of these are related to aging, others may have the same underlying mechanisms (e.g. systemic inflammation) or share common risk factors (e.g. smoking exposure), but all of them are able to afflict prognosis [2]. Some comorbidities occur more frequently in COPD patients, independently from pulmonary severity disease [3]. They increase in number and severity with age and have a major impact on the patient's quality of life, hospitalization and mortality [4]. In this sense, Divo and colleagues identified twelve comorbidities associated with increased mortality [5]. However, recommendations on management of respiratory diseases are based on evidence from studies with restrictive inclusion criteria or no representative enrollment [6, 7], thus not accounting for complicating effects from coexisting conditions and treatments. Therefore, their management and prevention might provide benefit in reducing the global cost load especially since international recommendations on COPD management do not systematically include the evaluation of comorbid conditions in the diagnostic approach or in the treatment decisions of the disease, thus focusing on isolated lung impairment rather than multimorbidity. Given this background, the aim of this study was to assess comorbidities and outcomes in a cohort of elderly patients with the clinical diagnosis of COPD, hospitalized in Internal Medicine and Geriatric Wards participating to the RePoSI (REgistro per lo studio delle POlipatologie e politerapie SImi) registry study.

Methods

Data collection and study population

Retrospectively, we analyzed the collected data within the frame of the RePoSI project in the recruitment weeks of 2010, 2012, 2014 and 2016. RePoSI is an independent and collaborative register, organized by the Italian Society of Internal Medicine (SIMI) and the Mario Negri Institute for Pharmacological Research. It involved the creation of a network of internal medicine and geriatric wards that collected information about polytherapy on elderly patients, affected by multiple diseases. Patients were eligible for RePoSI if: (1) they were admitted to one of the participating internal medicine wards during the 4 index weeks chosen for recruitment (one in February, one in June, one in September, and one in December); (2) their age was 65 years or older; (3) they gave informed consent. Each ward had to enroll at least ten consecutive eligible patients during each index week recording data on socio-demographic details, the main reason for admission and comorbidities, diagnoses, treatment

(including all drugs taken at hospital admission and recommended at discharge), clinical events during hospitalization and outcome. During those weeks, all participating centers had to complete the registration of all patients admitted, indicating those who were consecutively enrolled. For patients who were excluded, the reason had to be given. Also, data on mortality or any new hospitalization were collected, with a telephone interview performed by a physician to the patient or his/her relatives, 3-and 12 months after hospital discharge. Then, a final database was created and checked by the Mario Negri Institute for Pharmacological Research. The project's design is accessible at the related website [8]. Subjects were referred as having COPD if a diagnosis of the disease was reported in previous medical charts, or whether the diagnosis was posed at admission, as judged by the clinician. Given the nature of the study, the spirometric assessment was judged not to be a pre-requisite to confirm the diagnosis.

Socio-demographic and clinical characteristics

Socio-demographic variables such as age classes, marital status, living arrangement and need for assistance in daily living, were considered along with laboratory findings in patients with COPD compared to the ones without it. The following clinical characteristics were evaluated: respiratory and non-respiratory disease distribution at hospital admission (according to International Classification of Diseases-Ninth Revision); cognitive status and mood disorders (by the Short-Blessed-Test [SBT] [9] and the Geriatric-Depression-Scale [GDS] [10],respectively; performance in activities of daily living at hospital admission (measured by means of the Barthel Index [BI] [11]; severity and comorbidity index(assessed by the Cumulative-Illness-Rating-Scale CIRS-s and CIRS-c, respectively) [12], glomerular filtration rate (using the Chronic Kidney Disease Epidemiology Collaboration-formula [13]), length of hospital stay, drugs prescriptions (at admission, discharge, at 3 and 12 months follow-up), destination at discharge, in-hospital and 3-month and 1-year mortality rate. The association between variables and in-hospital, 3-month and 1-year mortality was analyzed.

Statistical analysis

Quantitative variables were summarized as mean (95% confidence intervals), and categorical variables as percentage. Patients with significant disability were selected according to a BI score of ≤ 40. Fisher's exact-test for contingency tables, z test and non-parametric Mann–Whitney U test were used when appropriate. A multivariate logistic analysis was used to assess the relationship between variables and in-hospital, 3-month and 1-year follow-up mortality. Variables were chosen according to the Hosmer–Lemeshow methodology

[14]. After univariate analysis, only variables with a $p < 0.20$ were included in the final model; then, through a backward process, variables were excluded until a significance level of $p < 0.20$ was reached for each variable. The application of Hosmer–Lemeshow test is a measure of how well the model fits the data without any choice of variables by researcher to put into the multivariate model. A two-tailed $p < 0.05$ was considered statistically significant. Stata Statistical Software2016, Release14 (Stata-Corp, College-Station, TX-USA) was used for database management and all the analyses.

Results

During the recruitment period, 4696 out of 4825 inpatients were eligible for this analysis (129 patients had missed variables); 932 (19.8%) presented with a diagnosis of COPD. Among them, 61% were male with a mean age of 80 years. Table 1 shows the demographic characteristics and modifiable risk factors of the two study groups.

Interestingly, almost half of the COPD in-patients had history of previous hospitalizations compared to only

Table 1 Socio-demographic characteristics and modifiable risk factors of the REPOSI elderly population according to Chronic Obstructive Pulmonary Disease (COPD) categorization

Variables	Inpatient with COPD	Inpatient without COPD	p
$N°$ of subjects	932	3764	–
Men (%)	61.0	46.1	< 0.0001
Age[a]	80.1 (79.6–80.5)	79.4 (79.1–79.6)	0.0064
Marital status (%)			0.724
Married	52.4	54.2	
Widow	38.6	36.4	
Separated	1.4	1.3	
Divorced	1.4	1.4	
Living arrangement (%)			0.444
Alone	23.5	22.7	
Spouse	43.9	45.2	
Sons	15.6	15.7	
Spouse and sons	7.2	6.9	
Other	9.4	8.5	
Previously Institutionalized (%)	6.0	5.6	0.5977
Previously Hospitalized (%)	46.2	35.0	0.0002
Caregiver (%)	58.6	51.1	< 0.0001
Spouse (%)	37.6	32.0	0.091
Brother/Sister (%)	3.0	3.4	
Son/Daughter (%)	42.9	47.9	
Son/Daughter in law (%)	0.6	1.5	
Grandson (%)	3.6	3.7	
Other (%)	12.4	11.4	
Never Smoked (%)	32.1	60.0	< 0.0001
ex-Smoker (%)	52.8	33.0	
Smoker (%)	15.0	7.0	
Never Alcohol (%)	47.8	58.8	< 0.0001
Alcohol (%)	38.9	26.0	
ex-Alcohol (%)	4.8	6.4	
Casual Drinking (%)	8.5	8.8	
BMI[a]	26.26 (25.87–26.65)	25.84 (25.67–26.01)	0.1332
Underweight patients (%)	4.2	3.9	0.6913
Optimal weight patients (%)	39.6	41.5	0.3021
Overweight patients (%)	34.1	35.6	0.4176
Class I obesity (%)	13.6	12.5	0.3766
Class II obesity (%)	3.7	3.0	0.2967
Class III obesity (%)	2.4	1.3	0.0136

[a]Data are reported as mean (95% confidence interval)

one-third of non-COPD inpatients. A significantly higher proportion of COPD subjects also showed history of alcohol consumption and were more often morbidly obese.

In-patients with COPD had a significantly higher cumulative illness rating scale for the evaluation of severity and comorbidity index ($p < 0.0001$ for both comparisons). As shown in Table 2, significant overt cognitive impairment was documented in almost half of in-patients with COPD, while a quarter needed positioning of urinary catheter. In-patients with clinically significant disability (BI ≤ 40) were 16.8% in comparison with individuals without COPD (13.9%, $p = 0.0291$). Moreover, GDS was shown to be more frequently abnormal (mean-score equal to 1.49). In addition, 21.2% had a probable depression (GDS > 2) as opposed to non-COPD individuals. COPD patients took more drugs than those without COPD, both at admission, at in-hospital stay, at discharge and at 3-and 1-year follow-up (Table 2).

Overall, disease distribution showed that arterial hypertension, ischemic heart disease, atrial fibrillation, heart failure, chronic renal failure, peripheral artery disease, overt hypertensive heart disease, anemia, rheumatic diseases, prostatic hypertrophy, osteoporosis, pneumonia, gastroesophageal reflux disease, respiratory failure, and cholelithiasis were more frequent in COPD patients (Table 3).

As shown in Table 4, subjects with COPD had significantly longer hospital stay; in addition, higher rates of re-hospitalization at 1-year after discharge were recorded.

Table 2 Laboratory and clinical characteristics of the REPOSI population at hospital admission according to Chronic Obstructive Pulmonary Disease (COPD) categorization

Variables	Inpatient with COPD	Inpatient without COPD	p
Systolic blood pressure (mm Hg)[a]	130.0 (128.7–131.3)	132.3 (131.6–133.1)	0.0089
Diastolic blood pressure (mm Hg)[a]	73.4 (72.7–74.1)	73.6 (73.2–73.9)	0.6558
Heart rate (bpm)[a]	80.0 (78.9–81.0)	78.8 (78.2–79.3)	0.0108
Body temperature (°C)[a]	36.89 (36.78–37.01)	37.99 (35.94–40.04)	0.0106
Fasting glucose (mg/dL)[a]	129.9 (126.0–133.8)	126.8 (124.7–128.8)	0.0247
Creatinine (mg/dL)[a]	1.28 (1.22–1.34)	1.26 (1.23–1.29)	0.0112
GFR(ml/min)[a]	58.9 (57.4–60.5)	59.4 (58.6–60.2)	0.3902
Mild decrease in GFR(ml/min)	37.7	41.2	0.0519
Moderate decrease in GFR(ml/min)	39.2	35.5	0.0340
Severe decrease in GFR(ml/min)	10.2	10.1	0.9257
Kidney Failure	2.6	3.7	0.0907
Hemoglobin (mg/dL)[a]	12.09 (11.94–12.23)	11.76 (11.68–11.83)	0.0002
Leucocytes (cells per microliter) ($\times 10^3$/uL) [a]	9.94 (9.40–10.47)	9.83 (9.19–10.46)	< 0.0001
Platelets (cells per microliter) ($\times 10^3$/uL) [a]	232.33 (226.03–238.63)	229.94 (226.26–233.63)	0.1314
Cholesterol (mg/dL)[a]	160.6 (157.3–163.9)	159.4 (157.6–161.1)	0.4738
Short Blessed Test score[a]	9.6 (9.1–10.2)	9.0 (8.7–9.3)	0.0169
Overt Cognitive impairment (Short Blessed Test score ≥ 10) (%)	39.4	35.1	0.0202
Need for urinary catheter (%)	25.5	21.7	0.0155
Barthel index score[a]	73.8 (71.8–75.7)	78.5 (77.5–79.4)	< 0.0001
Clinically significant disability (Barthel index ≤ 40) (%)	16.8	13,9	0.0291
Geriatric Depression Scale score[a]	1.47 (1.39–1.56)	1.37 (1.33–1.41)	0.0380
Probable Depression (Geriatric Depression Scale score > 2) (%)	21.2	17.7	0.0222
N° of drugs at hospital admission[a]	6.7 (6.5–6.9)	5.5 (5.4–5.6)	< 0.0001
N° of in-hospital drugs[a]	8.7 (8.4–9.1)	7.7 (7.5–7.8)	< 0.0001
N° of drugs at hospital discharge[a]	8.4 (8.1–8.7)	7.5 (7.4–7.6)	< 0.0001
N° of drugs at follow up 3 months[a]	7.4 (7.1–7.7)	6.4 (6.2–6.5)	< 0.0001
N° of drugs at follow up 1 year[a]	7.3 (6.6–7.9)	6.2 (5.9–6.5)	0.0020
Severity index (by CIRS) [a]	1.79 (1.77–1.82)	1.64 (1.63–1.65)	< 0.0001
Comorbidity index (by CIRS) [a]	3.66 (3.54–3.79)	2.90 (2.84–2.96)	< 0.0001

BMI Body Mass Index, *CIRS* cumulative illness rating scale

[a]Data are reported as mean (95% confidence interval)

Table 3 The most frequent clinical diagnoses (as percentage) in the REPOSI population according to Chronic Obstructive Pulmonary Disease (COPD) categorization (the table only shows the diagnoses which frequency was more than 5% at least in one group)

Variables	Inpatient with COPD (%)	Inpatient without COPD (%)	p
Arterial hypertension	65.8	57.5	< 0,0001
Diabetes	31.9	28.7	0.0567
Ischemic heart disease	31.1	20.8	< 0,0001
Atrial fibrillation	29.2	23.5	0.0003
Heart Failure	29.4	17.6	< 0,0001
Chronic renal failure	27.4	18.5	< 0,0001
Peripheral artery disease	19.5	13.5	< 0,0001
Cancer	19.1	18.9	0.8904
Overt hypertensive heart disease	17.4	11.9	< 0,0001
Anemia	17.1	21.3	0.0043
Rheumatic diseases	16.5	12.2	0.0045
Prostatic hypertrophy	16.0	10.2	< 0,0001
Gastritis	14.5	12.9	0.1965
Dementia	14.2	15.1	0.5046
Arthrosis	13.0	10.7	0.0510
Cerebrovascular disease	11.6	11.7	0.9721
Depression	9.9	8.9	0.3838
Vasculitis	9.0	8.8	0.8217
Osteoporosis	8.8	6.7	0.0297
Pneumonia	8.0	5.5	0.0042
Hypothyroidism	7.9	6.7	0.2013
Hypercholesterolemia	7.7	8.0	0.7434
Diverticulosis	7.6	9.2	0.1187
Gastroesophageal reflux disease	6.5	4.6	0.0144
Chronic hepatitis	6.0	5.5	0.7241
Respiratory failure	5.4	3.0	0.0005
Cholelithiasis	5.4	3.6	0.0159
Gallstones	5.3	4.2	0.2756
Carotid Atherosclerosis	4.9	5.6	0.6553
Anxiety	4.9	5.3	0.6430
Hepatic cirrhosis	3.5	4.9	0.0694

Table 4 Length of hospital stay, destination at hospital discharge, in-hospital and at follow-up mortality of the whole REPOSI population according to Chronic Obstructive Pulmonary Disease (COPD) categorization

Variables	Inpatient with COPD	Inpatient without COPD	p
Length of hospital stay[a] (days)	11.82 (11.21-12.43)	11.80 (11.34-12.25)	0.0183
In hospital mortality (%)	5.5	5.4	0.9293
3-month mortality (%)	9.6	9.4	0.8573
12-month mortality (%)	13.5	14.1	0.8392
Destination at discharge (3-month)			
Home (%)	88.5	89.4	0.5386
Home care (%)	3.4	3.2	0.7963
Institution (%)	3.4	4.2	0.4098
Rehospitalization (%)	4.7	3.2	0.0959
Destination at discharge (12-month)			
Home (%)	86.5	89.6	0.3383
Home care (%)	3.4	2.5	0.6200
Institution (%)	5.0	5.7	0.7668
Rehospitalization (%)	21.0	13.3	0.0261

[a]Data are reported as means (95% confidence interval)

In-hospital and within 1-year mortality did not differ between the two groups. However, when we assessed independent predictors of mortality, running univariate analysis (see appendix) and then multivariate analysis (Fig. 1) according to Hosmer–Lemeshow methodology, cerebrovascular disease and current ICS-LABA therapy were independently associated with in-hospital mortality. At 3-month follow-up, male gender, hepatic cirrhosis, and ICS-LABA therapy were predictors of mortality. At 1-year follow-up, ICS-LABA therapy was the only predictor of mortality. COPD exacerbation did not represent an independent predictor of mortality in older hospitalized people even if 43% of patients with COPD had exacerbation.

Discussion

In this observational study on the RePoSI registry, we assessed the distribution of comorbidities and the occurrence of outcomes in a population of elderly COPD in-patients admitted to the internal medicine and geriatric wards, with the aim to evaluate whether COPD subjects behave differently from non-COPD individuals. Overall, the current findings suggest that COPD subjects are at higher risk of death within the first year from admission to the hospital.

Although comorbidities are increasingly identified as important factors of COPD management and outcomes [15], studies specifically designed to evaluate the relationships between comorbidities and long-term outcomes in subjects with a diagnosis of COPD admitted to an internal medicine ward are scarce [16], and this is also true for several chronic diseases [17]. A recent study showed that the addition of comorbidities to age, BMI, blood markers and indexes such as smoking status, dyspnea assessment, airway obstruction produced a model, known as BARC index, that performed better than established index scores in predicting 1-year mortality [18]. Our analysis showed that COPD in-patients are more often older men, smokers or former smokers, and live with their relatives, in agreement with our previous findings [19]. Moreover, COPD patients are severe obese
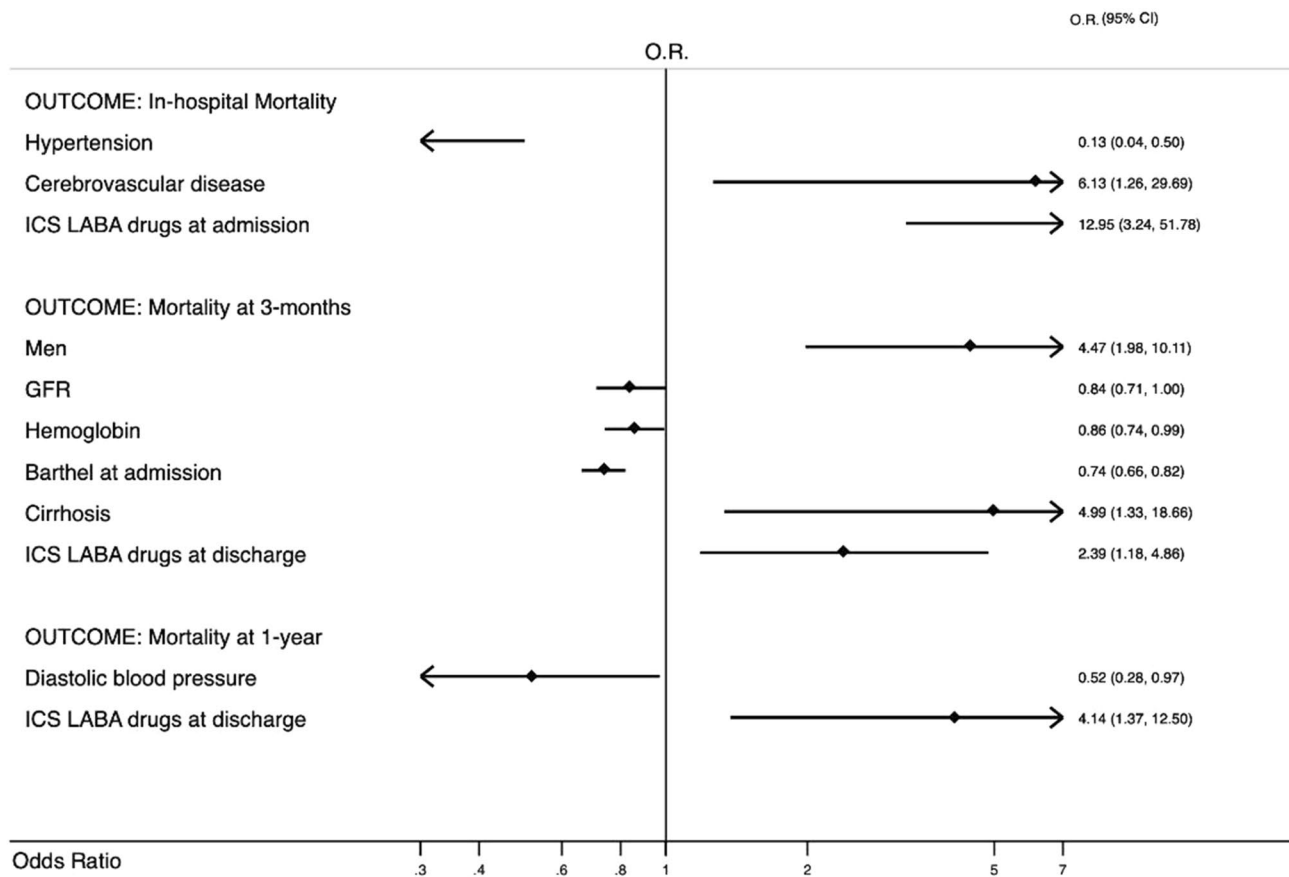
Fig. 1 Multivariate Analysis in COPD patients according to in-hospital, 3-month and 1-year mortality. *OR* odds ratio, *95% CI* 95% confidence interval, *ICS/LABA* Inhaled corticosteroids and long-acting beta2-agonists in combination, *GFR* Glomerular Filtration Rate calculated by CKD-EPI formula; GFR is referred to values every 10 ml/min; Barthel Index is referred to values every 10 points; Diastolic Blood Pressure is referred to values every 10 mmHg. Only the final model is shown according to Hosmer–Lemeshow methodology. For the selection of variables see appendix and statistical analysis section

consistently with recent data that seem to confirm that obesity is more common in COPD patients compared to subjects who do not have COPD [20]. Interestingly, individuals with a diagnosis of COPD had more frequent mood changes, indicating higher level of distress, in agreement with those from the NHANES study of 20.6% of subjects with COPD suffering from depression [21]. Shane et al. showed that up to 40% of patients with COPD had clinically significant depressive symptoms, a proportion higher than that recorded in other chronic diseases such as stroke, diabetes, coronary heart disease, arthritis, hypertension, and cancer [22]. Similarly, COPD patients showed worse cognitive impairment than non-COPD patients; in the study by Dodd et al., up to 57% of patients with COPD exacerbation had features of cognitive impairment [23]. A recent systematic review and meta-analyses outlined that one in four subjects with COPD has mild cognitive impairment [24]. In addition to affecting pharmacological treatment, comorbidities may impair the ability to use inhalation devices [25]; for example, cognitive impairments affect the ability to properly use the inhaled device, and anxiety and depression can reduce the adherence to treatment. It follows that the choice of the proper inhaler should also take into account the relative contribution of concomitant diseases in affecting the correct use of the device. It is commonly accepted that cognitive impairment and depression lead to progressive disability [19, 26], especially in oldest-old subjects [27, 28], thus potentially affecting short-and long-term outcomes. The current findings also show that the presence of anemia is associated with the frequency of exacerbations and increasing healthcare costs [29, 30]. The phenomenon is relevant in clinical practice: indeed, Cote et al. found that anemia was present in 17% of COPD inpatients [31]. The possible mechanism consists in persistent elevated interleukin levels, in particular IL-1, that interfere with the erythropoietin response [32].

The current analysis highlighted that COPD patients had a worse functional status than patients without COPD; this is of clinical importance, given that hospitalized elderly patients affected by pneumonia with a clinically significant disability were already shown to have higher mortality risk [33]. Lanièce et al. found that severe disability was the most important predictor of early re-admission among elderly inpatients [34]. Recent data showed that male gender, previously hospitalized, polypharmacy (more than 5 drugs), lower functional status and frailty, depression, heart diseases, COPD, urinary tract infection were associated to a higher risk of hospitalization [35]. Moreover, heart failure, diabetes and stroke were associated with a prolonged hospital stay (> 11 days) in hospitalized COPD patients [36]. The current findings on comorbidities distribution showed a significant prevalence of respiratory failure and respiratory conditions other than COPD, as well as cardiovascular diseases, chronic renal failure, prostatic hypertrophy,

rheumatic diseases, and gastroesophageal reflux disease. An interesting speculation on these findings comes from the theory of network medicine [37], based on which human diseases are not independent of each other, but rather the consequence of different biological processes that interact in this complex network, defined as "diseasome". In this regard, COPD is among the best scenario in which multiple factors such as chronic inflammation, aging-related changes, altered immune response, increased oxidative stress, consequences of smoke exposure and physical inactivity are variably interwound. Aging per se is characterized by chronic low-grade systemic inflammation, and is associated with multiple chronic conditions, including COPD [2, 38, 39]; interestingly, a relationship among systemic inflammation, comorbidities and COPD outcomes has been clearly documented [40]. Of note, ischemic heart disease, heart failure, myocardial infarction, diabetes, lung cancer, osteoporosis, metabolic syndrome, are all characterized by low-grade inflammation and frequently associated with COPD [41].

The question is whether, and to what extent, comorbidities affect mortality independent of lung disease. Using data from the multicenter observational study ECLIPSE, Agusti and colleagues [42] proposed the systemic inflammome, a network representation of systemic inflammation in individuals suffering from COPD, which may account, in a proportion of subjects who are persistently inflamed, for significantly higher rates of all-cause mortality. The prevalence of comorbidities in patients with COPD was assessed by Divo and collaborators [5], who identified specific comorbidities significantly associated with increased mortality. The relative contribution of each comorbidity to mortality and the relationships among comorbidities led to the so-called "comorbidome". Vanfleteren et al. [43] identified five clusters of comorbidities: ''cardiovascular'', ''cachectic'', ''metabolic'' and ''psychological'' and ''less comorbidity''. The authors however failed to find any association with mortality. Our findings indicate that cerebrovascular disease significantly increased the risk of death during hospitalization. On the other hand, cirrhosis and men gender were significantly associated with 3-month mortality. These observations are in agreement with Kim et al. that found a significant statistically association between COPD and increased risk of stroke [44], and with Divo et al. that found that the risk of death was strongly associated with different comorbidities including liver cirrhosis, suggesting a correlation with lifestyle and social behavior [5]. These data were also confirmed by Baty et al. that found a higher prevalence of alcoholic cirrhosis in their nationwide analysis of hospital admissions for COPD in Switzerland [45]. Moreover, our results are consistent with previous studies that identified comorbidities that were associated with COPD progression and exacerbation frequency, poor quality of life, higher mortality

and increase of costs management [5, 46, 47]. The current analysis highlights the role of the ICS-LABA regular treatment, which was independently associated with in-hospital, 3-month and 1-year follow-up mortality. This result was unchanged even if variables such as COPD exacerbation, heart failure, atrial fibrillation, ischemic heart disease, oral anticoagulants, anti-platelet drugs had been included into the model. In a recent meta-analysis, Horita et al. found that patients treated with LABA-LAMA had fewer exacerbations and a significantly lower risk of developing pneumonia in comparison with ICS-LABA [48].

In addition, Ernst et al. suggested a limit use of ICS and ICS-LABA in COPD patients on the basis of the evidence of adverse effects, especially severe pneumonia, leading to excess mortality [49]. Although the causes of mortality are not known, it cannot be excluded that chronic use of ICS was responsible for severe adverse events in compromised subjects. The lack of data on the dosage or the class of corticosteroids does not allow to draw firm conclusions on the contribution of the active drug. Similarly, it is plausible to hypothesize that LABA variably influenced the outcome.

A recent study showed the importance of BI as a strong predictor of 30-days, 3-and 12-month mortality in elderly patients with pneumonia [33]. Simonetti et al. found that pneumonia severity and low functional status are the main factors associated with mortality in elderly people with community acquired pneumonia [50]. Vitacca et al. suggested the utilization of a unique instrument, i.e. the BI-dyspnea, to provide a global assessment of disability evaluating both respiratory and motor impairment [51]. Formiga et al. demonstrated that a better functional status and a lower comorbidity conditions were independent predictors of mortality at 5-years in 85-year-old community-dwelling subjects [52]. In the current study, disability did not enter the multivariate analysis as independent predictor of mortality, although the Barthel score suggestive of physical impairment clearly distinguished the COPD phenotype (Fig. 1).

A possible explanation for the apparent discrepancy between studies lies in the lack of information on the lung functional impairment, which may variably affect the ability to interact with daily activities. It is therefore logical to hypothesize that disability is one of the strongest predictors of mortality also in COPD. Further studies are needed to confirm it.

With regard to the protective function of higher glomerular filtration rate, our data are consistent with those of Singanayagam et al. who established that chronic renal failure was significantly associated with increased short–term mortality in patients with COPD [53]. A potential explanation lies in the glomerular damage by arterial stiffness along with hypoxic damage to tubules and interstitium as possible mechanisms in the relationship between COPD and chronic renal failure [54].

We found that blood pressure had a protective role regarding in-hospital mortality. Our findings are in agreement with previous observations that showed a reverse association between higher blood pressure and mortality in oldest old patients [55, 56]. Moreover, recent analysis showed that in contrast to the general population, in frail elderly patients increased blood pressure is associated with reduced mortality. A possible explanation is that high blood pressure is necessary to maintain sufficient organ perfusion in a population of older subjects who are likely to have significant vascular damage [57, 58].

Regarding sex, our results are consistent with a previous study that showed in elderly hospitalized patients a male profile, smokers or former smokers, affected by COPD, coronary artery disease and cancer responsible for re-hospitalization and higher mortality [19, 59].

This observational study has some limits. First, there was no specific information about how the diagnosis of COPD was formulated (GOLD criteria, radiological criteria), and the severity of COPD was not taken into account. Given the lack of spirometric confirmation, it cannot be excluded that a proportion of subjects actually suffered from chronic diseases other than COPD. However, the observational nature of the design and the exploratory approach limit the weaknesses of the findings. Second, the lack of information on the appropriateness of prescriptions, and the opportunity to exclude potential confounders that goes beyond the scope of the RePoSI study. The major strength of the study is the multicenter design of the RePoSI register and the large number of participating centers resulting in a comprehensive sample of the elderly patients hospitalized in internal medicine and geriatric wards.

In conclusion, this study showed the impact of COPD and its comorbidities in the real-world scenario of internal and geriatric wards, identifying factors that are linked with short-and long-term outcomes. The current findings strongly support that the management of COPD patients should include identification and treatment of its comorbidities. This approach should be the first step for personalized care based on a multidimensional assessment of elderly patients affected by COPD.

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Compliance with ethical standards

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