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Comorbidities and short-term prognosis in patients hospitalized for acute exacerbation of COPD. The ESMI study

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Conflict of interest

The authors declare no conflicts of interest

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INTRODUCTION

According to the definition of the Global Initiative for Obstructive Lung Disease (GOLD), chronic obstructive pulmonary disease (COPD) is an inflammatory disease, characterized by extrapulmonary manifestations in many patients[1]. Among these systemic manifestations are the presence of associated diseases, namely comorbidities that have a significant influence on health-related quality of life, use of resources, and prognosis. It is well known that COPD patients have an increased prevalence of cardiovascular disease, cancer and depression, in comparison to the general population, even after adjustment for other risk factors such as smoking or dyslipidemia[2]. These comorbidities are related with the systemic inflammation that characterizes the disease[3]. In fact, cardiovascular disease and cancer are frequent causes of death in COPD, particularly in moderate and mild severity COPD patients[4].

Although comorbidities may be present from the moment of the initial diagnosis[5,6], their frequency increases with COPD progression , and they are particularly common in patients with more advanced disease, such as those hospitalized for a COPD exacerbation[7]. In these patients comorbidity is related with a poor survival rate in subsequent years[8].

The main purpose of our study was to explore comorbidities associated with COPD in patients hospitalized for exacerbation, and to examine their effect on short-term mortality and hospital readmissions up to 3 months after discharge.

METHODS

The ESMI study (acronym for *EPOC en Servicios de Medicina Interna,* that is COPD in Internal Medicine Services, in Spanish) is a longitudinal, observational multicentre study, conducted in 70 emergency room and internal medicine services in Spain, that

included the first 10 consecutive patients seen for a COPD exacerbation during a one-year period (October, 2009 through October, 2010). Exacerbation was defined as a change in the symptoms of patients, beyond daily variations and requiring a change in regular medication[9]. Inclusion criteria were: 1) age above 40 years, 2) admission for COPD exacerbation, and 3) forced spirometry with a post-bronchodilator FEV_1 < 80% of predicted and an FEV_1/FVC <0.70. Exclusion criteria were: 1) a previous diagnosis of asthma or bronchiectasis as predominant disease, or other explainable cause of obstructive airflow limitation, 2) acute pulmonary oedema or pneumonia upon admission, 3) inability to perform spirometry or non-compliance with spirometric criteria, and 4) admission for reasons other than an exacerbation of COPD.

During admission, all patients were evaluated with a standardized questionnaire. Data collected included time from the first medical diagnosis of COPD, hospitalizations for COPD or other pathologies in the previous year and home status (family, alone, nursing home). Functional status at baseline was assessed with the Katz index[10]. Comorbidity was documented using the previously validated Charlson index, a standard scale with 15 chronic diseases graded for severity of disease[11]. For comparative analysis, a point was subtracted from the total score on the Charlson index, as all patients had COPD, which adds a point in this index. Additionally, comorbidity data were collected using a specific questionnaire which included pathologies that were considered relevant, whether included or not in the Charlson index. To calculate the total of comorbidities one point was added for each one of the following pathologies: ischemic heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, connective tissue disease, liver disease, kidney failure, diabetes mellitus, AIDS, hypertension, osteoporosis, sleep apnea syndrome, dyslipidemia, presence of psychological disorders (anxiety or depression), active malignancy (including leukemia and lymphoma),

arrhythmia, anemia and venous thromboembolic disease. Data on medical treatment previous to hospitalization, during hospitalization and upon discharge were also collected. Dyspnea was measured using the modified Medical Research Council (mMRC) scale, and length of stay was recorded. Patients were followed up to 3 months after discharge, and a spirometric test was performed, if this had not been done before. At this time survival, cause of death and time between hospital discharge and mortality were collected, and hospital readmissions for COPD or other causes were recorded.

STATISTICAL ANALYSIS

Qualitative variables were expressed as absolute frequencies and percentages, while quantitative variables were summarized as mean and standard deviation in the case of normally distributed or median otherwise. Comparison among means was made with the Student's t test for independent samples. The Mann-Whitney U test was used for variables not normally distributed. Chi^2 test or Fisher's exact test were used for the comparison of proportions. For time-dependent variables we used the Cox logistic regression and Kaplan-Meier statistics. Multivariate statistics were performed using a multiple logistic regression analysis or Cox, whenever indicated. The analysis was performed with SPSS 15.0, and all analyses were based on the bilateral hypothesis with statistical significance below 0.05.

The study was approved by the Clinical Investigation Ethics Committee of the Hospital Mútua de Terrassa (EO/0922_0709). All patients participated voluntarily and signed written informed consent forms.

RESULTS

Overall, 679 patients were screened, and 606 were included. Fifteen patients were excluded for having an incomplete minimum data set, and another 58 cases were unable to perform spirometry or did not fulfill spirometric criteria for COPD. In 48 cases, spirometry was not available within the 6 month period before admission and could not be performed between discharge and follow-up visit, but a prior diagnosis of COPD with spirometric confirmation was avalaible. These patients were included in the study of comorbidity, although spirometric data were considered as 'missing' in the current analysis (Figure 1). No differences existed between included and excluded patients in terms of age, sex, smoking history or dyspnea measured by the mMRC (data not shown).

Mean age of the studied population patients was 72.6 years (SD 9.9, range 41-94); 594 (89.9%) were men, and mean post-bronchodilator FEV_1 was 43% (21.2). A total of 94.2% patients were former smokers or ex-smokers with a mean average of 55.5 (28) packs/year. Regarding previous hospitalization, 71% of patients had required at least one admission for COPD exacerbation during the previous year, with a mean of 2.2 (1.5) and with a hospital duration of 19.4 (16.5) days, while 65.3% had been hospitalized for other reasons during the same period, with a mean of 2.51 (1.73). In 127 (21%) cases the current hospitalization was the first admission for COPD exacerbation, whereas in the remaining cases the first admission occurred a mean of 6.1 years earlier. No prior diagnosis of COPD was made in 7.6% of patients, while the mean time from the first diagnosis for the rest of the participants was 8.5 (6.4) years.

Regarding ambulatory control, 39% were followed mainly by their family doctor, while the rest were also controlled by pulmonologists (46%), internists (27%) or other specialists (8%); 4.6% did not undergo ambulatory controls until the current admission.

Only 11% were included in a program of ambulatory pulmonary rehabilitation. The main demographic, clinical and respiratory characteristics of the total population are shown in Table I.

The average score on the Charlson index was 3.1 (2). The most commonly observed comorbidities in this index were heart failure (32.8%), diabetes without complications (28.4%), and ischemic heart disease (20.8%). Regarding comorbidities not included in the Charlson index, the most frequent were arterial hypertension (63.4%), osteoporosis (16%), abdominal obesity (> 102 cm. in men and> 88 cm in women) (29%), dyslipidemia (34%), anemia (19.3%, of which 9% were considered iron deficiency) and psychological disorders—depression (15%) or anxiety (18.3%). Table II shows the main comorbidities grouped according to whether or not they are included in the Charlson index. Males had a higher score on the Charlson Index, 3.1±2 vs 2.5±2, but not when assessing the scale of total comorbidities. On the one hand, men with COPD also more frequently had previous ischemic heart disease ($p < 0.001$), myocardial infarction ($p < 0.001$), chronic renal failure ($p = 0.02$) and hypertension ($p = 0.02$); on the other hand, women had more osteoporosis ($p < 0.001$), anxiety ($p < 0.001$) and depression ($p < 0.001$). Regarding ambulatory treatment prior to current admission, 89.4% of the patients received long-acting beta agonists (LABA); 87.6% inhaled corticosteroids and 79.4% long-acting antimuscarinics. Other treatments were diuretics (54.5%), statins (40.3%), ACE inhibitors (30.4%), angiotensin II receptor antagonists (26.4%), β-Blockers (11.1%), antiplatelet drugs (36.6%), and warfarin or other anticoagulation drugs (18%).

A total of 69 patients (11.1%) were discharged from the emergency room (ER) without requiring conventional hospitalization. Patients who required conventional hospitalization, compared with those discharged home from ER, were older (73.2 vs.

67.7, P <0.001), with lower FEV_1 (42% vs. 52% p <0.001), a greater number of associated comorbidities (3.7 vs. 2.6., P <0.001), higher scores on the Charlson index (3.1 vs. 2.5., p < 0.01), more dyspnea measured with the mMRC scale (2.4 vs.2.0 p <0.001), more admissions for COPD in the previous year (1.7 vs. 1.5., P <0.001), lower pO_2 at the time of the visit to the ER (60 mmHg vs. 66 mmHg, P = 0.03), and higher functional dependency measured by the Katz index (5.2 vs. 5.7., p = 0.005). After adjusting all significant variables in a logistic regression analysis, the number of global comorbidities expressed numerically or the Charlson index, post-bronchodilator FEV_1 and the number of hospitalizations for COPD in the previous year maintained independent statistical significance.

The length of the stay in hospitalized patients was 9.3 (7.6) days, and this was also related with comorbidity measured with Charlson index or the total number of comorbidities (p <0.001), independently of FEV1, age, and gender.

Of the 606 included patients, 470 (78%) completed follow-up and outpatient visit at 3 months. Patients who could not attend the outpatient control had required more frequent hospital admission in the previous year (p <0.001), needed chronic home oxygen therapy more frequently (p <0.04), and more often suffered dementia (p <0.04), hemiplegia (p <0.03) or cardiac arrhythmia (p <0.001). However, there were no differences regarding age, functional status (Katz index), gender, Charlson index, or the total number of comorbidities.

The reasons for failure of follow-up control were death in 27 cases (20%), multiple hospital readmissions in 14 (10.3%), other reasons in 38 (28%) cases and missing in the rest (41.7%).

All-cause mortality at 3 months was therefore 4.5% (27/606). The causes of death were respiratory failure in 17 cases, stroke in 3, cardiovascular in 2, cancer in 2 and other

causes in 3. Mean follow-up for deceased patients was 40 days (28) (interquartile range 25%-75%:13-64 days). Mortality at 3 months was associated with age, number of hospital admissions for COPD or other causes in the previous year, greater dyspnea (mMRC), chronic home oxygen therapy, more functional dependence (Katz index), and comorbidities both measured with the Charlson index and total of comorbidities. Several conditions analyzed separately were also associated with increased mortality (Table III), namely ischaemic heart disease and chronic heart failure (Figures 2 and 3). The severity of COPD as measured by the postbronchodilator FEV1, stratified according to the GOLD classification, was also associated with decreased survival (Figure 4).

In a multivariate analysis (Table IV), it can be seen that increasing age (but with borderline non-significance), and then significantly reduced FEV_1 stratified according to GOLD guidelines, higher functional dependence measured with the Katz index, and increasing comorbidity measured with the Charlson index were independently associated with total mortality.

Data on readmissions are available for 484 surviving patients. Of these, 98 (20.2%) were readmitted for COPD within a 3-month period after discharge, with a mean frequency of 1.26 readmissions, while 68 (14%) were hospitalized for other reasons. Overall, 28% of patients had required at least one new hospitalization.

Readmissions for a new exacerbation of COPD were related with the number of hospitalizations for COPD during the previous year ($p < 0.0001$), dyspnea ($p < 0.004$), FEV_1 stratified according to the GOLD guidelines ($p < 0.001$), chronic home oxygen use ($p < 0.004$), presence of *cor pulmonale* (<0.002), functional dependence measured by the Katz index ($p < 0.0001$), and Charlson index stratified into 2 or more points (corresponding to 2 mild or 1 severe disease other than COPD), ($p = 0.02$).

Readmissions for other diseases were attributable in 15 cases (22%) to heart failure, 12 (18%) to infections, 7 (10%) to ischemic heart disease, 6 (9%) to bone fractures, 6 to stroke, and the rest to miscellaneous causes. Predictors of readmission for any cause were the Katz index ($p < 0.003$), and hospitalization during the previous year for both COPD and another cause (both $p < 0.001$). The baseline Charlson index stratified into two or more points was significantly higher in patients who required re-hospitalization ($p < 0.05$), independently of age, gender, and FEV_1.

DISCUSSION

Our study confirms the high prevalence of comorbidity in patients hospitalized for exacerbation of COPD and its importance in relation to short-term prognosis in this population, namely to the need for a readmission or mortality within 3 months after hospital discharge. Although previous studies have shown the relationship between comorbidity and post-hospital mortality, these studies have usually been based on long-term follow-up [7,12,13]. Other significant predictors of mortality such as age, FEV_1, dyspnea or functional dependence measured by the Katz index were also associated with mortality after a COPD hospitalization [8].

The most common comorbidities observed in our study were ischemic heart disease, affecting 20.8% of patients, of whom 11.6% had a previous myocardial infarction, heart failure in 32.8%, diabetes mellitus in 35.8%, arterial hypertension (63.4%), and dyslipidemia in 33.8%. This prevalence is slightly higher than what was observed in previous studies conducted with a similar methodology[14], but definitively greater than that reported in retrospective studies based on hospital databases[12].

In our study, comorbidity measured by the Charlson index or with an extended comorbidity questionnaire was confirmed as an independent predictor of mortality at 3 months after discharge, and was additionally related to an increased need for hospitalization after consultation for acute exacerbation in the emergency room, increased length stay in conventional hospitalization, and subsequent readmissions for COPD or other diseases.

Mortality was also higher in patients with cardiovascular disease, such as ischemic heart disease, heart failure, stroke, and peripheral vascular disease. The relationship between COPD and cardiovascular disease is well documented in the literature and in fact is a common cause of mortality in these patients [4,15]. Cohort studies show that patients with

COPD are twice as likely to have ischemic heart disease and four times as likely to suffer heart failure as age and gender-matched controls even after adjusting for various confounders[16]. Moreover, the risk of a cardiovascular event, particularly myocardial infarction, increases after an episode of COPD exacerbation [17]. Our patients have a very high prevalence of classic cardiovascular risk factors such as smoking exposure, hypertension, diabetes mellitus, dyslipidemia or abdominal obesity, among others. Therefore optimizing the treatment of comorbidity and cardiovascular risk factors should be a priority in the care of patients with COPD[18]. Of utmost priority, apart from optimizing any COPD treatment, is detecting and treating associated diseases, including cardiovascular risk factors. Treatment of osteoporosis, depression, and others should also be a priority in the care of COPD patients. Several retrospective studies have shown an association with reduced mortality with the use of statins, angiotensin converting enzyme inhibitors or beta blockers, all of which also tend to be underutilized in patients with COPD and ischemic heart disease [19-21]. The presence of depressive symptoms has also been associated with increased mortality in patients hospitalized for COPD, although again in longer-term studies[7,22].

Previous studies on comorbidity and its relationship with the risk of hospitalization and readmission in COPD have shown conflicting results. For example, regarding the need for hospitalization in patients visiting the emergency department for acute exacerbation, two studies conducted in Canada found no relationship between the presence of associated diseases and the need for hospitalization[23,24]. However, in both studies only limited numbers of comorbidities were considered, and one of them even excluded patients with concomitant heart failure, a condition that occurs in 30% of patients hospitalized for COPD[25]. In contrast, studies performed using validated tools to evaluate comorbidity such as the Charlson index have shown that the presence of comorbidity

and greater functional dependency are both predictors of hospitalization in both COPD and heart failure[26], results which are similar to those observed in the present study. Similarly, in our study the length of hospital stay was significantly higher in patients with more comorbidities, confirming data from previous studies[27,28].

Finally, comorbidity was also associated with an increased number of readmissions, either for COPD or other causes, in the 3 months after discharge. To our knowledge, no previous studies have demonstrated a relation between Charlson index and hospital readmissions[29-31], except a retrospective study based on an electronic hospital database. Unfortunately that study did not detail the observed comorbidities[32].

Our study has several limitations, the first being the small number of women included, similar to other studies performed in Spain. This is related to the secular trends of smoking in Spain, with most women exposed to active smoking only after the 1950s. A number of comorbidities in our study, such as osteoporosis and psychological disorders, are more common in women, while ischemic heart disease predominates in men, confirming the results of previous studies [25]. Second, most of the patients included in our study had been hospitalized in internal medicine departments, and probably were more likely to present a greater number of comorbidities than those hospitalized in respiratory services. In Spain, between 40 and 50% of exacerbations of COPD are treated in internal medicine services, which generally often see older patients with more comorbidities[33]. However, the observed mortality and readmissions at 3 months are similar to those reported in a study conducted in Spain with over 1,200 patients hospitalized in different units and hospitals[34]. Third, regrettably we have no full, protocolised mortality data of 55 patients who were lost to follow-up (accounting for 9% of the total sample tested). However these patients are comparable to the rest, so we have no evidence to suspect that mortality outcomes are different. As an additional

limitation, cardiac biomarkers (eg. Troponin or BNP), which have recently been highlighted as very important in predicting prognosis [35], were not measured in all participants. Finally, our study design did not take into account seasonality or type of AECOPD [36,37]. As per methods, each investigator included the first 10 consecutive patients seen for a COPD exacerbation during a one-year period (October, 2009 through October, 2010). More than half of patients were included in February, March and April (data not shown).

In summary, we confirm the presence of comorbidity in patients hospitalized for COPD is high and related to the later need for hospitalization, length of stay and hospital readmissions. Moreover, comorbidity is also related to survival, and some severe comorbidities, mainly cardiovascular, chronic kidney disease, depression and dementia, are by themselves associated with increased mortality as early as 3 months after discharge. Accurate evaluation and treatment of these associated diseases may improve the prognosis of these patients [18].

Author contributions:

Dr Almagro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Almagro contributed to the study design, analysis and interpretation of the data and writing of the manuscript

Dr. Soriano contributed to the study design, analysis and interpretation of the data and writing of the manuscript.

Dr. Murio contributed to the study design and writing of the manuscript.

Dr. Cabrera contributed to the data collection and review of the manuscript.

Dr. Diez contributed to the data collection and review of the manuscript.

Dr.Alonso contributed to the data collection and review of the manuscript.

Dr. Boixeda contributed to the data collection and review of the manuscript.

Table I

Demographic and clinical characteristics of COPD participants (n=606)

	Total
Age in years	72.6±9.9
Male sex	544 (89.8%)
BMI	27.8±5.3
Chronic oxygen therapy	237 (39.1%)
Cor pulmonale	142 (23.4%)
Dyspnea mMRC	2.3±1.1
Katz index	5.3±1.3
Home status	
Family	498 (82.2%)
Alone	78 (12.9%)
Nursing home	30 (4.8%)
Blood Gas analysis at admission	
Ph	7.4±0.6
pCO2 in mmHg	45.8±11.2
pO2 in mmHg	56.2±12
Blood Gas analysis at discharge	
Ph	7.41±0.4
pCO2 in mmHg	44.6±8.4
pO2 in mmHg	67.1±14.4
POSTBRONCHODILATOR SPIROMETRY	
FVC in ml.	2,239±885
FVC percent predicted	69±18.8
FEV1 in ml.	1,190±537
FEV1percent predicted	43±21.2
FEV1/FVC	55.6±31.2
SEVERITY GOLD SCALE	
Moderate	213 (44.8%)
Severe	209 (44.0%)
Very severe	53 (11.2%)

Note: Summary variables are presented as mean±standard deviation for quantitative variables, and count (percentage) for discrete variables. BMI= Body Mass Index

TABLE II

	Previous diagnosis	
Included in Charlson index	**number**	**%**
Ischemic heart disease	126	20.8
Heart failure	199	32.8
Peripheral vascular disease	102	16.8
Cerebrovascular disease	71	11.7
Dementia	22	3.6
Chronic obstructive pulmonary disease	606	100
Connective tissue disease	15	2.5
Ulcer disease	63	10.4
Liver disease (mild)	35	5.8
DM without organ damage	172	28.4
Kidney Disease (creatinine<3)	94	15.5
Hemiplegia	10	1.7
Kidney Disease (creatinine>3)	4	0.7
DM with organ damage.	45	7.4
Malignant solid tumor	73	12
Leukemia	2	0.3
Lymphoma	4	0.7
Liver Disease (severe)	3	0.5
Malignant solid tumor with metastases	7	1.2
AIDS	4	0.7
Not included in Charlson Index		
Acute Myocardial Infarction	70	11.6
Systemic Hypertension	384	63.4
Osteoporosis	96	15.8
Depression	91	15
Anxiety	111	18.3
Dyslipidemia	205	33.8
Obstructive Sleep Apnea	74	12.2
Atrial fibrillation	128	21.1
Sick Sinus Disease	4	0.7
Atrioventricular block	19	3.1
Iron deficiency anemia	54	8.9
Other anemias	63	10.4
Abdominal obesity	178	29.4
Thromboembolic disease	26	4.3
Lung Neoplasm	12	2
Gastrointestinal Neoplasm	9	1.5
Other Neoplasm	44	7.3

DM=diabetes mellitus

TABLE III

Crude Mortality Predictors at 3 months			
	p	R.R.	C.I. 95%
Age	<0.007	1.068	1.02-1.1
Hospitalization for COPD in previous year	<0.001	1.4	1.2-1.7
Hospitalization for other causes in previous year	<0.05	1.3	1.15-1.57
Dyspnea	<0.0001	2.36	1.57-3.55
Chronic Oxygen Therapy	<0.003	3.4	1.5-7.5
Charlson Index	<0.0001	1.35	1.18-1.57
Global Comorbidity Scale	<0,003	1.32	1.15-1.52
Katz Index	<0.0001	0,7	0.58-0.85
FEV1 stratified GOLD	<0.04	1.78	1.02-3.11
Ischemic heart disease	< 0.01	1.29	1.04-1.61
Heart failure	<0.01	2.31	1.05-5.1
Peripheral vascular disease	<0.002	3.83	1.71-8.57
Cerebrovascular disease	<0.006	3.44	1.49-7.99
Dementia	<0.001	5.17	1.76-15.28
Chronic kidney disease	<0.005	3.91	1.75-8.73
Hemiplegia	<0.0001	32.2	10.2-101
Depression	<0.012	3.24	1.24-7.36
Atrial fibrillation	<0.001	2.8	1.28-6.15

TABLE IV Mortality. Multivariate Analysis (Cox Regression)

	p	R.R.	I.C. 95%
Age	0.06	1.05	0.99-1.1
Katz index	0.04	0.78	0.60-0.98
FEV_1 *	0.03	1.95	1.05-3,62
Charlson index	0.003	1.23	1.09-1.55

*FEV_1 stratified according GOLD guidelines

Figure 1

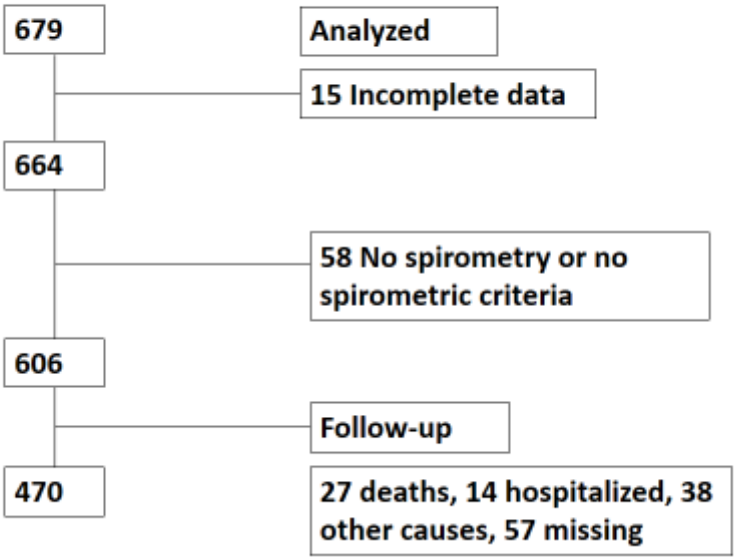
679
Analyzed
15 Incomplete data
664
58 No spirometry or no spirometric criteria
606
Follow-up
470
27 deaths, 14 hospitalized, 38 other causes, 57 missing

FIGURE 2

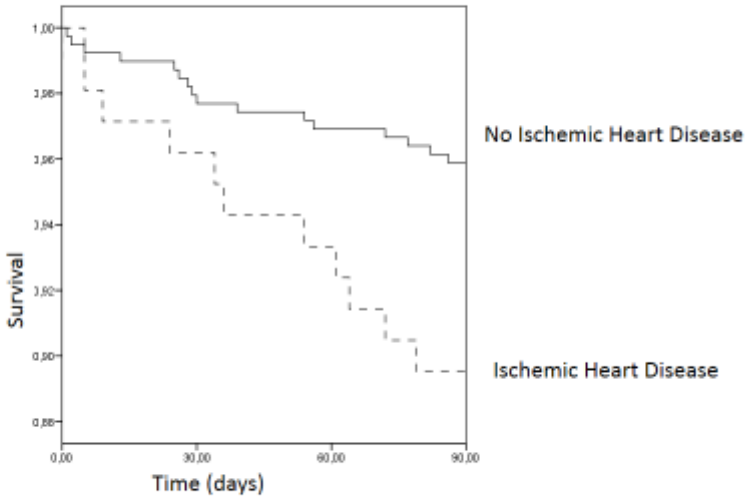

FIGURE 3

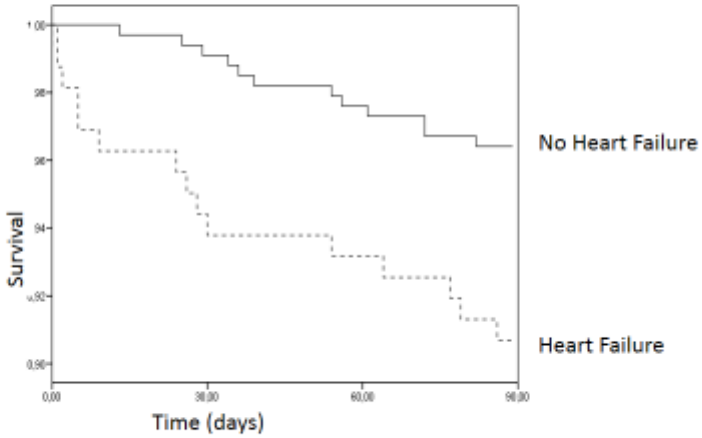

FIGURE 4

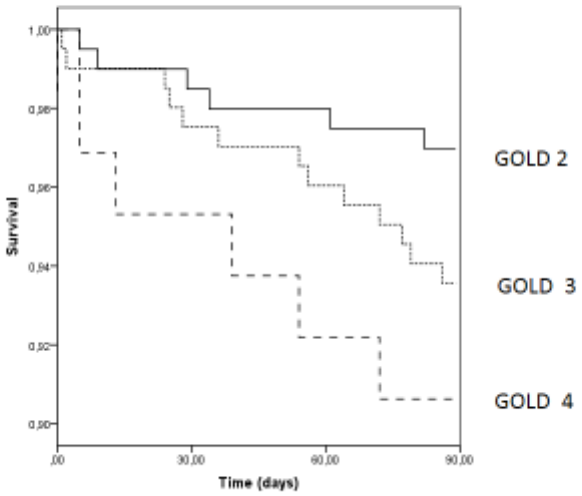
1,00
0,98
0,96
0,94
0,92
0,90
Survival
,00
30,00
60,00
90,00
Time (days)
GOLD 2
GOLD 3
GOLD 4

Figure legends

Figure 1. Flowchart and cause exclusion

Figure 2. Mortality and ischemic heart disease

Figure 3. Mortality and heart failure

Figure 4. Mortality and FEV_1(GOLD)

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