

Standards of care and clinical predictors in patients hospitalised for a COPD exacerbation - The Italian SOS (Stratification Observational Study)

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ABSTRACT: *Standards of care and clinical predictors in patients hospitalised for a COPD exacerbation - The Italian SOS (Stratification Observational Study).* M. Lusuardi, F. Blasi, C. Terzano, C. Cricelli, N. Crispino, L. Comarella, F. De Benedetto, C.M. Sanguinetti, L. Allegra, C.F. Donner.

Background and aims. Hospitalisations for chronic obstructive pulmonary disease (COPD) exacerbations are major events in the natural history of the disease in terms of survival, quality of life and risk of further episodes of exacerbation. The aims of study were to evaluate:

1. adherence to recommended standards of care; and
2. clinical factors influencing major outcomes during hospitalisation for an episode of COPD exacerbation and within a 6-month follow-up.

Methods. An observational, prospective study was conducted in 68 centres. Assessment of standards of care included diagnostic procedures (such as pulmonary function tests and microbiology) and management options (such as drug therapies, vaccinations and rehabilitation). Outcome measures relevant to the hospitalisation were: survival, need for mechanical ventilation, and length of stay (LOS). Outcomes at 6-months were: survival, exacerbations and hospitalisations for an exacerbation. Multi-

variate logistic regression was applied to evaluate the relation between clinical factors and outcomes.

Results. 931 patients were enrolled. Only 556 patients (59.7%) were diagnosed COPD and stratified for severity with the support of spirometry ($FEV_1/VC \leq 0.7$) and were considered for outcome analysis. Among treatments, pulmonary rehabilitation and anti-smoking counselling were applied infrequently (14.5 and 8.1% of patients, respectively). Within six months 63 COPD patients (17.7%) had at least one episode of exacerbation prompting a further hospitalisation and 19 died (5.3%). Predictor of mortality was the co-morbidity Charlson index (odds ratio, OR 10.3, $p=0.03$ CI:1.25-84.96). A further hospitalisation was predicted by hospitalisation for an exacerbation in the previous 12 months (OR 3.59, $p=0.003$ CI:1.54-8.39).

Conclusions. Standards of care were far lower than recommended, in particular 40% of patients were labelled as COPD without spirometry. COPD patients with a second hospitalisation in 12 months for an exacerbation had about 3 times the risk of suffering a new episode and hospitalisation in the following six months.

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Introduction

Hospitalisations for chronic obstructive pulmonary disease (COPD) exacerbations are major events in the natural history of the disease in terms of survival, quality of life and risk of further episodes of exacerbation [1-8]. From a societal

point of view they represent the main cost in relation to health care resources due to COPD [9], and account for about 10% of all hospitalisations [10]. The ICE (Italian Costs for Exacerbation in COPD) study confirmed that COPD is a disease with high costs: even at a conservative estimate COPD is responsible for about 6% of the total health care ex-

penditure, the largest share of costs being for hospitalisation [11].

Different studies have focused on factors influencing the risk and the outcomes of an exacerbation, in an attempt to plan strategies for minimising the individual and socio-economic impact of COPD exacerbations. Several clinical factors associated with an exacerbation have been reported as predictors of major outcome measures (in particular, survival and hospitalisation): they include lower FEV₁, hypoxaemia, lower albumin, lower Body Mass Index (BMI), longer disease duration or shorter time since the first hospitalisation [1-8]. Multidimensional grading systems, such as the BODE (BMI, Obstruction, Dyspnea, Exercise), seem to offer a better prediction of clinical outcomes than individual measures [12, 13].

Hospitalisation per se is a major predictor of poor survival, of re-exacerbation risk and re-admission to hospital [7]. On the other hand, in large hospitals with more respiratory consultants and better quality organised care, mortality and length of stay are lower [14, 15].

Among treatment factors, under-prescription of Long Term Oxygen Therapy (LTOT) or rehabilitation are both risk factors for a worse outcome [4]. Different pharmacologic trials have suggested better outcomes in patients on regular treatment with inhaled corticosteroids [16] or tiotropium [17]. Last but not least, a reduced hospitalisation rate for COPD exacerbation seems largely influenced by organisational factors, such as integrated/planned care supported by information technology and involving different levels of the health care system [18].

Since medical interventions and organisational factors may influence the risk and the outcomes of a COPD exacerbation, correct knowledge of the actual standards of care and of the main risk factors in each population and health system is mandatory.

The primary aim of the Italian "SOS (*Stratification Observational Study*) on COPD" was to evaluate the standards of care and clinical factors influencing major outcome measures such as survival, length of stay (LOS), and intensive care unit (ICU) admission, during hospitalisation for an episode of COPD exacerbation in a cohort of patients representative of the Italian COPD population.

The secondary aim was to estimate the risk of a new episode of exacerbation, hospital admission or death during a 6-month follow up.

Materials and methods

Study Design and Subjects

An observational, prospective study involving 68 pneumology centres evenly distributed throughout Italy was conducted. Enrolment of patients commenced in October 2004 and lasted for 4 months. The enrolment period had a follow-up interval of 6 months; visits took place after 1 and 6 months at the centre and a phone call was performed after 3 months from hospital discharge.

The first 20 consecutive patients of both sexes, aged ≥ 45 years who were admitted to each centre for a COPD exacerbation having had a chest X-ray negative for pneumonia, tuberculosis or pulmonary cancer, were enrolled. A COPD exacerbation was defined according to GOLD guidelines, i.e. increased breathlessness, possibly accompanied by wheezing and chest tightness, increased cough and sputum, change of the colour and/or texture of the sputum, and fever [16].

To evaluate actual practice versus standards of care as derived from GOLD guideline recommendations [16], the study did not foresee any definite protocol of patient management, i.e. each centre agreed to perform all diagnostic and treatment procedures as per their usual practice consolidated in time.

In relation to ethical considerations, the study was approved by each local review board. The written consent of each patient was formally requested and obtained regarding the use of personal data for research.

Data collection

AT HOSPITAL ADMISSION

Demographic and case-history data were collected for all patients including age, sex, socioeconomic status, risk factors for COPD (in particular smoking and occupational history) and COPD history with particular regard to hospitalisations in the previous 3 months, use of medications for COPD, use of antibiotics and non-pharmacological therapies. Comorbidity was measured for all patients with the Charlson index [19].

Physical examination, spirometric, biochemical and microbiological examinations upon admission were also recorded. Investigators were recommended to record pulmonary function tests preferably obtained in a stable phase of the disease in the 12 months before or 6 months following the index hospitalisation. For a correct COPD diagnosis and severity stratification a FEV₁/VC ≤ 0.7 post-bronchodilator was required.

Outcome measures relevant to the hospital stay were: mortality, need for mechanical ventilation, and length of hospital stay (LOS).

AT FOLLOW-UP

During follow-up visits (at 1 and 6 months) data on COPD exacerbations and hospitalisations related or not to COPD were collected.

During the telephone interview at 3 months from discharge, data on COPD exacerbations and hospitalisations related or not to COPD and deaths were collected.

Outcome measures relevant to the follow up were survival, new episodes of exacerbation and new hospitalisations for an exacerbation.

Statistical Analysis

Analyses were carried out using SAS® System software (8.2, TS level 02 Mo).

For continuous variables, mean and standard deviation or median with inter-quartile range were calculated as necessary. For dichotomic variables, absolute frequencies and percentages were calculated. Association between each outcome (mortality, need of mechanical ventilation, re-exacerbation, re-admission for exacerbation) and demographic and clinical variables was assessed using multivariate logistic regression models. Factors found to be significant on bivariate logistic regression or judged to be clinically relevant were included in the multivariate models and selected using backward stepwise procedure ($P < 0.05$ to enter into the model, $P < 0.10$ to remain). The risk of developing the event in the presence of a particular factor was evaluated in terms of odds ratio (OR), calculated with the corresponding 95% confidence interval (CI). Results were considered statistically significant at $P < 0.05$.

Results

A total of 931 patients were enrolled at hospital admission for an episode of COPD exacerbation, most of them coming directly from home (92.5%), while 5.9% of patients came from non pneumological hospital units, and 1.2% from nursing homes or long term health care facilities; 667 were males (71.6%), the mean age was 72.2 years (± 8.7 SD, standard deviation). Active smoking was still present in 149 patients (16.0%), the majority having ceased at least 6 months before (565, 60.7%); mean pack-years were 66.3 (± 35.2). About one out of five patients (200, 21.5%) were stated to have never smoked, while in 17 (1.8%) cases data on smoking habit was not obtained.

Exposure to passive smoking and to professional pollutants was present in 240 (25.8%) and 142 (15.3%) patients respectively, but only 71 among the never-smokers had been exposed to either passive smoking and/or occupational pollutants; therefore in 130 patients (13.9%) no exposure to usual exogenous risk factors was demonstrable.

In about 2/3 of the case series (637 patients, 68.4%) the diagnosis of COPD was already known, hence 294 patients (31.6%) had never been evaluated for COPD before the index hospital admission.

Mean Body Mass Index (BMI) was 26.9 (± 5.6). Respiratory function data was available for 556 patients (59.7%) and are reported in table 1. Following post-bronchodilator spirometry, COPD severity stages according to GOLD showed the following distribution: stage 0 at risk, 96 cases (17.3% of cases with spirometry), stage I mild, 15 cases (2.7%), stage II moderate 138 (24.8%), stage III severe 230 (41.7%), and stage IV very severe 75 (13.5%).

In the 12 months before admission 717 subjects (77.0%) had manifested at least one other episode of COPD exacerbation, the mean number of episodes being 2.43 (± 1.48). Only 58.4% patients had received annual influenza vaccination, while patients receiving pneumococcal vaccine in the previous 5 years represented only 12.6%.

In the 3 months before admission 539 patients (57.9%) had been hospitalised at least once for another episode of exacerbation, the mean number of episodes being 1.62 (± 1.16); 144 patients (15.5%) had been hospitalised in the 3 months prior for other causes than COPD (mean number of episodes, 1.15 \pm 0.52).

In 404 patients (43.4%) COPD was complicated by acute on chronic or acute respiratory failure. Before admission 310 patients (33.3%) were already on long-term oxygen therapy. The number of uncomplicated COPD patients with at least one concomitant extra-pulmonary disorder was 269 (29%). The mean number of co-morbidities was 2.11 (range 1-10), the distribution of the Charlson Index being 1 in 35.7%, 2 in 20.1%, and ≥ 3 in 22.6% of cases (21.7% not reported). Of 673 patients (72.3%) with at least one co-morbidity 370 (54.9%) had cardio-vascular disorders (heart failure or coronary or peripheral artery disease), 83 (27.2%) had diabetes, 70 (10.4%) cerebrovascular disorders, 43 (6.4%) chronic renal failure, 43 (6.4%) gastro-duodenal ulcer, 29 (4.3%) liver disorders, other conditions being represented less frequently.

Clinical evaluation of patients revealed worsening cough in 697 (74.9%), increasing volume of expectoration in 652 (70.0%), purulence in 492 (52.8%), and colour modification of sputum in 552 (59.3%). Only 97 (10.3%) had manifested increased temperature ≥ 37.5 °C (average temperature 36.8 \pm 0.7 °C). Mean respiratory frequency was 22.1 \pm 5.4 breaths per minute, and mean heart rate was 92.4 \pm 16.1 beats per minute. Mean blood

Table 1. - Respiratory function data, obtained in a stable phase (spirometry available for 556 patients, residual volume for 336, and CO transfer for 145 patients) and blood gas values at admission (896 patients, 96.2%). Data as mean \pm standard deviation (SD)

Respiratory function data	Mean \pm SD
FEV ₁ (L)	1.13 \pm 0.50
FEV ₁ % predicted	48.4 \pm 19.6
FVC (L)	2.05 \pm 0.71
FVC% predicted	68.1 \pm 20.6
VC (L)	2.24 \pm 0.76
VC% predicted	72.2 \pm 21.1
FEV ₁ /VC%	54.1 \pm 14.9
Residual Volume (L)	3.33 \pm 1.28
Residual Volume% predicted	142.7 \pm 51.1
DLCO (mLCO x min x mmHg)	13.0 \pm 9.5
DLCO% predicted	57.6 \pm 20.9
Blood gas values	
PaO ₂ (mmHg)	59.9 \pm 13.7
PaCO ₂ (mmHg)	47.8 \pm 13.8
pH	7.40 \pm 0.06
HbSO ₂ (%)	88.4 \pm 8.9

Abbreviations: FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; VC: vital capacity; DLCO: diffusing lung capacity for CO; PaO₂ partial arterial tension of O₂; PaCO₂ partial arterial tension of CO₂; HbSO₂: oxyhaemoglobin saturation.

pressure was $140.3 \pm 20.6 / 81.7 \pm 11.2$ mmHg for systolic and diastolic pressure respectively. Critical signs, such as mental confusion, tremors, decompensated right heart failure, lethargy and use of accessory respiratory muscles, were found in 97 (10.4%), 95 (10.2%), 248 (26.3%), 42 (4.5%), and 256 (27.5%) cases, respectively.

Blood gas values at admission are shown in table 1.

At least one sample for microbiological study was obtained in 683 patients (73.4%) of which 279 sputum (40.8%), 71 bronchial aspirates (10.4%), 11 blood cultures (1.6%), the remaining cases being not specified in records. Pathogens were isolated in no more than 55% of samples. The bacteria most frequently isolated in the sputum (only 32.7% of positive cases) were *Ps. aeruginosa*, 5.4%, *H. influenzae* 3.2%, *Enterobacteriaceae* 2.9%, *S. aureus* 2.5%, *M. catarrhalis* 1.8%. In the bronchial aspirates (54.8% of positive cases) *H. influenzae* was most frequently isolated (16.9%), followed by *H. parainfluenzae* (8.5%), *Ps. aeruginosa* e *S. pneumoniae* (each 7.0%), *S. aureus* and *M. catarrhalis* were 4.2% each. Serology and molecular biology were utilised in only 2.5 and 0.4% of cases, respectively.

At admission, usual drug therapy was modified in 96.8% of patients with a very scattered distribution of the different combinations of respiratory drugs, both topical and systemic. Among the 3 most represented combinations short acting β_2 agonists + corticosteroids + anticholinergic by inhalation + oral steroids was prescribed in 7.5% of patients, the same combination + theophylline in 5.1%, and β_2 agonists + corticosteroids + anticholinergic by inhalation (no drugs by general route) in 3.8% of cases. Given that the large majority of patients (89.3%) received an antibiotic treatment, if we consider the number of cases with a microbiological evaluation (see above) the drug would have been targeted in no more than one third of subjects. The main classes of antibiotics were cephalosporins (24.1% of all treatments), fluoroquinolones (22.4%), penicillin + β -lactamase inhibitor (16.6%), and macrolides (5.5%) as monotherapy; the most represented combinations were penicillins + β -lactamase inhibitor + fluoroquinolones (5.4%), cephalosporins + fluoroquinolones (4.9%), and cephalosporins + macrolides (3.1%). Apart from bronchodilators, corticosteroids and antibiotics, 525 patients (56.4%) received other drug or non-pharmacologic treatments, mainly represented by pulmonary rehabilitation (14.5% of the global population), anti-smoking counselling (8.1% of total co-

hort but 51.0% of current smokers), oxygen therapy (43.3%), non-invasive mechanical ventilation (12.7%, mean duration 6.9 days, range 1-30), and invasive mechanical ventilation (1.5%, mean duration 7.75 days, range 2-28).

Admission to a respiratory intensive care unit was necessary in 36 patients (3.9%) with a mean length of stay of 6.9 ± 6.0 days (range 1-28).

The percentage of patients receiving a definite respiratory treatment as prescribed in hospital is shown in figure 1.

Death occurred in 17 patients (1.8% of the global case series, 9 patients for respiratory failure, 4 for cardiovascular failure and 2 for other causes, 12 had pre-existing chronic respiratory failure). Three patients died on invasive ventilation in ICU, 6 on non-invasive ventilation in ICU or ward.

The mean length of stay (LOS) was 12.0 ± 7.1 (SD) days, range 1-75; the number of cases with a LOS >12 days was 302 (32.4%).

An analysis of factors predicated on the main outcome measures (survival, length of stay, and need for mechanical ventilation) was conducted only for those 458 patients with a diagnosis of COPD confirmed by spirometry ($FEV_1/VC \leq 0.7$ post-bronchodilator). The number of patients dying in hospital was too low to enable a reliable univariate logistic regression analysis on survival. The odds ratios of factors significantly predicting a LOS >12 days (mean LOS) or the need for mechanical ventilation are reported in table 2.

During the 6-month follow up 355 patients (77.5% of the cohort of patients with a correct diagnosis of COPD) were evaluated at the first month, 342 (74.7%) at the third month and 322 (70.3%) at the sixth month. The total number of patients who had died at 6 months was 19 (5.3% of the follow up cohort).

A major outcome measure at follow up was re-hospitalisation for a new episode of COPD exacerbation. A total number of 63 patients (17.7% of all COPD subjects evaluable for such an outcome) had at least one episode of COPD exacerbation prompting a new hospitalisation. Bivariate logistic

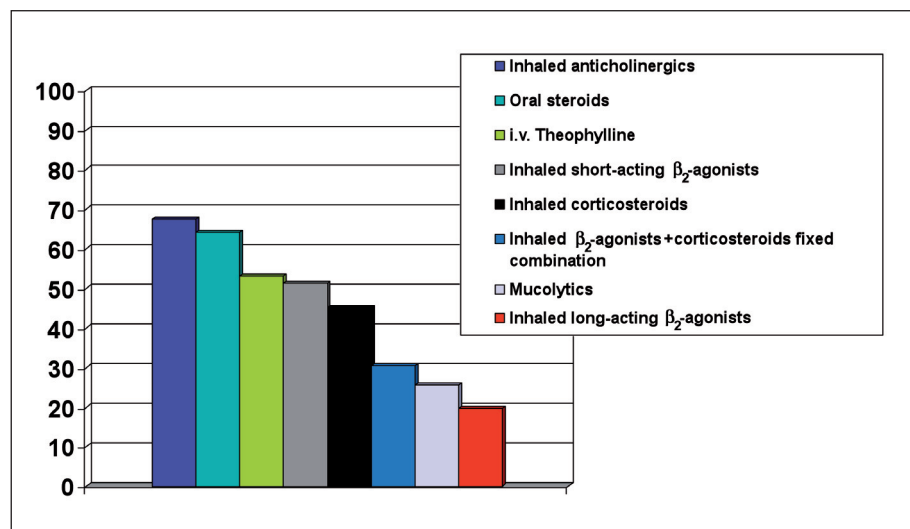


Fig. 1. - Percentage of patients receiving a definite respiratory treatment as prescribed in hospital (in decreasing order); for the main groups of non-fixed combination see "results"

Table 2. - The odds ratios (OR) of factors significantly predicting a mean LOS >12 days or the need for mechanical ventilation

<i>Predict a LOS > 12 days</i>	P value	Odds Ratio	Confidence Interval 95%
Cigarette smoking (No vs. Yes)	0.005	0.312	0.137-0.709
Haemoglobin (for each mg/dL of reduction) *	0.02	1.239	1.032-1.487
PaO ₂ ≤60 mmHg (Yes vs. No)	0.004	2.245	1.295-3.889
<i>Predict the need for mechanical ventilation</i>			
pH ≤7.35 (Yes vs. No)	<0.001	21.337	6.035-75.445
Mental confusion (Yes vs. No)	0.01	9.908	1.689-58.143
PaO ₂ ≤60 mmHg (Yes vs. No)	0.005	13.405	2.219-80.963
BMI * (for each unit increase above normal)	0.035	1.123	1.008-1.251
Red blood cells * (n x 10 ⁹ /dL, for each "n" unit decrease)	0.005	2.977	1.381-6.419

* Continuous variable.

regression analysis identified the following factors significantly increasing the risk of re-hospitalisation within 6 months: lower FEV₁% predicted (OR 1.019, $p=0.01$ CI:1.005-1.035), and previous hospitalisations for a COPD exacerbation in the 12 months before (OR 2.73, $p=0.001$ CI: 1.49-4.9).

A multivariate analysis was conducted using the main significant variables as reported above. The predictors at 6 months that reached a statistically significant level for the outcome "new episode of COPD exacerbation" were the Charlson index (1 vs >1) [OR 1.71, $p=0.05$ CI: 1.01-2.91], hospitalisation for a COPD exacerbation in the previous 12 months [OR 2.84, $p=0.0005$ CI: 1.59-5.1], age (<60 vs >80 years) [OR 0.23, $p=0.017$ CI: 0.07-0.77], and COPD severity according to GOLD (very severe vs moderate) [OR 3.31, $p=0.006$ CI: 1.41-7.81].

In the case of the outcome mortality the only significant predictor was the co-morbidity Charlson index (OR 10.3, $p=0.03$ CI: 1.25-84.96). The outcome hospitalisation was significantly predicted by hospitalisations for a COPD exacerbation in the previous 12 months (OR 3.59, $p=0.003$ CI: 1.54-8.39).

Discussion

The SOS study analysed a large cohort of COPD patients during and for 6 months after an episode of hospitalisation for an exacerbation, to evaluate actual clinical practice versus standards of care derived from international guideline recommendations, and to identify factors associated with a number of major outcomes such as survival, hospitalisation, length of stay, and further episodes of exacerbation.

The mean age of our population is similar to that reported in most other papers in the literature, a more important difference being the level of FEV₁ about 10% predicted better than that reported in the majority of papers [1-8]. One possible explanation is in the recommendation given to investigators to register as baseline respiratory function data obtained in a stable phase in the 12 months before or 6 months after admission, since patients are often unable to perform a reliable spirometry during an exacerbation.

Quite surprisingly, only 60% of patients had a diagnosis correctly based on spirometry, the figure being similar to that of audit data reported in the literature [20-23]. Therefore according to current practice in hospital, at least in the case of Italy and the UK, about 40% of cases of COPD are defined only on a clinical basis.

The presence of definite risk factors, i.e. exposure to smoking or occupational/environmental pollutants, was absent in about 14% of the population. Data in the literature report a percentage of lifetime non-smokers with COPD from 5.5 [24] to 20% [25, 26] but in many cases with other known risk factors. A risk of COPD overdiagnosis in never-smoker elderly subjects must not be overlooked [27]. Rather disturbing is the fact that about 1/3 of patients were diagnosed with COPD for the first time only at the index hospitalisation, i.e. diagnosis was obtained very late in the natural course of the disease.

The distribution of severity stages according to GOLD showed that about 1 in 4 cases was of moderate degree, and 55% were severe or very severe. A quota of 20% at stage 0/stage 1 GOLD is very surprising and poses a question of correct differential diagnosis between COPD and asthma or restrictive disorders.

The mean number of exacerbation episodes was comparable to average data in the literature (2.4 episodes per year) [28].

The main clinical factors characterising an exacerbation were dyspnea and worsening cough and expectoration volume (in about 3/4 of the population), quite in agreement with the definition of an exacerbation as reported by GOLD guidelines [16].

Standards of care

In 73% of cases sampling for microbiology investigation was obtained but the reduced rate of positive results (54% or less according to the type of sampling) and the well known problem of airways chronic colonisation stress the unresolved question of the real usefulness of microbiology in the clinical management of COPD exacerbations [29]. In our study about 1/3 of patients could have

received a targeted antibiotic according to an antibiogram, but this is a theoretical figure since many treatments are started empirically and are not changed if not unsuccessful. From an epidemiological point of view it is interesting to note the higher prevalence of Gram-negative bacteria, as expected from the average severity degree [29]. Real standards of care are difficult to define in this area, anyway this is a point in favour of obtaining nevertheless microbiological data; if seldom useful in the individual case, it can still be important for guiding local epidemiology-based empirical treatments.

In relation to drug treatments during the hospital stay it is very difficult to identify definite criteria given the large distribution of different combinations. It seems that the most frequent behaviour was to potentiate bronchodilator treatment and administer corticosteroids by oral or parenteral route in agreement with GOLD guidelines [16]. Among bronchodilators, i.v. theophylline represented a very frequent option (53.1% of cases) despite the fact that GOLD guidelines consider methylxanthines as second line for the low therapeutic index [16]. The main classes of antibiotics used were fluoroquinolones and cephalosporins underlining a difference with respect to European guidelines where penicillin or penicillin + β -lactamase inhibitor are recommended as the first choice and fluoroquinolones as the second, apart from cases at risk for *P. aeruginosa* [30].

It is very important to underline in this section that several aspects of the diagnostic or treatment practice appear far distant from what is recommended by international guidelines: spirometry available only in 59.7% of cases, pulmonary rehabilitation prescribed to only 14.5% of subjects, anti-smoking counselling to only 8.1% (but representing 50% of current smokers), influenza and pneumococcal vaccination to only 58% and 13% respectively. Also performance indicators, in particular the 6-min walking test, and dyspnea scales were underutilised, with the result that we could calculate a composite score such as the BODE only in a minority of patients (about 10%) and so were prevented from testing this as a prognostic factor in our population.

It is curious to note that all patients underwent a chest X-ray (necessary to exclude pneumonia), the large majority were assessed for arterial blood gases, but many had not undergone or were not asked to undergo spirometry to confirm COPD at least after the exacerbation episode. Similar data was reported by Roberts [20] for spirometry in relation to UK hospitals, but a better attitude emerged in Italian compared to UK hospitals versus smoking cessation (50% versus 30%), although it was lower than desired. A positive point was the total coverage of patients with chronic respiratory failure with long-term oxygen therapy (or non-invasive mechanical ventilation in a minority of patients with ventilatory failure).

Outcomes

In-hospital survival compares favourably with respect to data obtained from other countries, in-

hospital mortality being about 4 times lower [2, 6, 8, 22, 23]. Conversely, a very large, unselected, case series from the USA showed a similar mortality during hospitalisation, far lower than other studies carried out in the USA [31]. The differences are probably due to admission criteria, i.e. a large unselected population, such as in Patil's and our studies, versus case series of more severe patients selected according to a definite study design, or according to the type of hospital performing the study (e.g. tertiary referral centers are more likely to admit more severe patients).

The length of stay was on average longer in Italian hospitals (mean 12, median 9 days) than in the UK (mean 8.7, median 6 days) [22] or USA (median 9 days) [2]. Price *et al.* [22] demonstrated a relationship between organisational scores and LOS. In our study the contribution of organisational aspects or treatments to LOS was not assessed. Whether there is a relationship between longer LOS and better survival would probably merit further investigation.

The identification of factors influencing the major outcomes during the index hospitalisation underlined the importance of co-morbidities, hypoxaemia, respiratory acidosis, anemia, mental confusion, and tobacco smoking.

At follow up survival of COPD patients compared favourably with respect to other data in the literature showing a death rate at 6 months 2 to 4 times higher [2, 5, 8], the most probable explanation being the different inclusion criteria and baseline severity of patients. Survival at follow up was mainly influenced by the Charlson index, i.e. co-morbidities. The risk of a new exacerbation was significantly associated with previous hospitalisations, advanced age, disease severity and co-morbidities.

In COPD patients requiring hospitalisation for a new exacerbation, risk factors for re-hospitalisation were mainly low FEV₁, and previous hospitalisation(s) for a COPD exacerbation in the previous year.

All the above risk factors have been variously reported in the literature [1-8], but according to our data the most reproducible and consistent risk factor seems to be previous hospital admission for a COPD exacerbation, in agreement with a recent study from Soler-Cataluña JJ *et al.* [7]. As a consequence, for a correct allocation of health care resources patients discharged from hospital after a COPD exacerbation should probably be admitted to home care or outpatient programmes with active surveillance, according to recent recommendations [18].

Are the risk factors underlined by our study amenable to prevention or early intervention? In our study, interventions known to have a preventive action, such as vaccinations, were underprescribed. Also in the case of rehabilitation the number of patients enrolled in a programme of pulmonary rehabilitation was very low, despite scientific evidence of their efficacy in reducing the risk of re-hospitalisation for COPD [32].

The strengths of our study were the prospective collection of data, and the large cohort of uns-

elected patients enrolled at multiple hospital centers. It can be presumed that non-selected cohorts are more representative of a population of COPD patients [31] and probably more useful for the correct allocation of health care resources at a general level.

Among the weaknesses of our study we should mention the short follow up (6 months, mainly due to the resources available) and a significant number of subjects with questionable COPD diagnosis according to spirometry performed in a stable phase.

In conclusion, an important gap was found between current standards of care and recommendations, in particular in the use of spirometry for diagnosis and severity stratification along with a sub-optimal use of several management options. Hospitalisation per se was confirmed as a major determinant of further exacerbations and hospitalisations since COPD patients with a second hospitalisation within 12 months for an exacerbation had about 3 times the risk of a new exacerbation and new hospitalisation in the following 6 months.

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References

1. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *JAMA* 1995; 274: 1852-1857.
2. Connors AF, Dawson NV, Thomas C, *et al.* Outcomes following acute exacerbation of severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996; 154: 959-967.
3. Garcia-Aymerich J, Barreiro E, Farrero E, Marrades RM, Morera J, Antò JM, and the EFRAM investigators. Patients hospitalized for COPD have a high prevalence of modifiable risk factors for exacerbation (EFRAM study). *Eur Respir J* 2000; 16: 1037-1042.
4. Garcia-Aymerich J, Monsò E, Marrades RM, Escarribill J, Fèlez MA, Sunyer J, Antò JM, and the EFRAM Investigators. Risk Factors for Hospitalisation for a Chronic Obstructive Pulmonary Disease Exacerbation. EFRAM STUDY. *Am J Respir Crit Care Med* 2001; 164: 1002-1007.
5. Almagro P, Calbo E, Ochoa de Echaguen A, *et al.* Mortality after hospitalisation for COPD. *Chest* 2002; 121: 1441-1448.
6. Groenewegen KH, Schols AMWJ, Wouters EFM. Mortality and mortality-related factors after hospitalisation for acute exacerbation of COPD. *Chest* 2003; 124: 459-467.
7. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60: 925-931.
8. Gunen H, Hacievliyagil SS, Kosar F, *et al.* Factors affecting survival of hospitalised patients with COPD. *Eur Respir J* 2005; 26: 234-241.
9. Miravittles M, Murio C, Guerriero T, Gisbert R, for the DAFNE Study Group. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. *Chest* 2002; 121: 1449-1455.
10. Mannino DM. COPD: epidemiology, prevalence, morbidity, and mortality, and disease heterogeneity. *Chest* 2002; 121: 121S-126S.
11. Lucioni C, Donner CF, De Benedetto F, *et al.* I costi della broncopneumopatia cronica ostruttiva in Italia: la fase prospettica dello studio ICE. *Pharmacoeconomics Italian Research Articles* 2005; 7: 119-134.
12. Celli BR, Cote CG, Marin JM, Casanova C, *et al.* The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 1005-1012.
13. Ong K-H, Earnest A, Lu S-J. A multidimensional grading system (BODE Index) as predictor of hospitalisation for COPD. *Chest* 2005; 128: 3810-3816.
14. Roberts CM, Barnes S, Lowe D, Pearson MG, on behalf of the Clinical Effectiveness Evaluation Unit, Royal College of Physicians and the Audit Subcommittee of the British Thoracic Society. Evidence of a link between mortality in acute COPD and hospital type and resources. *Thorax* 2003; 58: 947-949.
15. Price LC, Lowe D, Hosker H, Anstey K, Pearson M, Roberts CM. The UK National COPD Audit 2003: impact of hospital resources and organisation of care on patient outcome following admissions for acute COPD exacerbation. *Thorax* 2006; 61: 837-842.
16. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2006. Available from: <http://www.goldcopd.org>.
17. Barr RG, Bourbeau J, Camargo CA, Ram FSF. Tiotropium for stable chronic obstructive pulmonary disease: a meta-analysis. *Thorax* 2006; 61: 854-862.
18. Casas A, Troosters T, Garcia-Aymerich J, Roca J, Hernandez C, Alonso A, del Pozo F, de Toledo P, Antò JM, Rodriguez-Roisin R, Decramer M and members of the CHRONIC project. Integrated care prevents Hospitalizations for exacerbations in COPD patients. *Eur Respir J* 2006; 28: 123-130.
19. Charlson ME, Pompei P, Ales KL, McKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373-383.
20. Roberts CM, Ryland I, Lowe D, Kelly Y, Bucknall CE, Pearson MG, on behalf of the audit sub-committee of the standards of care committee of the British Thoracic Society and the Clinical Effectiveness and Evaluation unit at the Royal College of Physicians. Audit of acute admissions of COPD: standards of care and management in the hospital setting. *Eur Respir J* 2001; 17: 343-349.
21. Roberts CM, Lowe D, Bucknall CE, Ryland I, Kelly Y, Pearson MG, on behalf of the British Thoracic Society Audit sub-committee of the standards of care committee and the Royal College of Physicians of London. Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. *Thorax* 2002; 57: 137-141.
22. Price LC, Lowe D, Hosker HSR, Anstey K, Pearson MG, Roberts CM, on behalf of the British Thoracic Society and the Royal College of Physicians Clinical Effectiveness Evaluation Unit (CEEu). UK National COPD Audit 2003: impact of hospital resources and organisation of care on patient outcome following admission for acute COPD exacerbation. *Thorax* 2006; 61: 837-842.
23. Connolly MJ, Lowe D, Anstey K, Hosker HSR, Pearson MG, Roberts CM and on behalf of the British Thoracic Society and the Royal College of Physicians Clinical Effectiveness Evaluation Unit (CEEu). Admissions to hospital with exacerbations of chronic obstructive pulmonary disease: effect of age related factors and service organisation. *Thorax* 2006; 61: 843-848.
24. Kommann O, Beeh KM, Beier J, Geis UP, Ksoll M, Buhl R. Newly diagnosed chronic obstructive pulmonary disease. Clinical features and distribution of the novel stages of the Global Initiative for Obstructive Lung Disease. *Respiration* 2003; 70: 67-75.
25. Viegi G, Scognamiglio A, Baldacci S, Pistelli F, Carrozzi L. Epidemiology of chronic obstructive pulmonary disease (COPD). *Respiration* 2001; 68: 4-19.
26. Antò JM, Vermeire P, Vestbo J, Sunyer J. Epidemiology of chronic obstructive pulmonary disease. *Eur Respir J* 2001; 17: 982-994.
27. Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Mørkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J* 2002; 20: 1117-22.
28. Sethi S, File TM. Managing patients with recurrent acute exacerbations of chronic bronchitis: a common clinical problem. *Curr Med Res Opin* 2004; 20: 1511-1521.
29. Lode H, Allewelt M, Balk S, *et al.* A Prediction Model for Bacterial Etiology in Acute Exacerbations of COPD. *Infection* 2007; 35: 143-149.
30. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26: 1138-1180.
31. Patil SP, Krishnan JA, Lechtzin N, Diette GB. In-hospital mortality following acute exacerbations of COPD. *Arch Intern Med* 2003; 163: 1180-1186.
32. Garcia-Aymerich J, Farrero E, Felez MA, Izquierdo J, Marrades RM, Antò JM, Estudi del Factors de Risc d'Agudització de la MPOC investigators. Risk factors for readmission to hospital for a COPD exacerbation: a prospective study. *Thorax* 2003; 58: 100-105.