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MODELING COPD HETEROGENEITY THROUGH BAYESIAN META-ANALYSIS ACROSS LONGITUDINAL STUDIES

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Abstract: *The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has introduced a novel multidimensional approach to assess and manage chronic obstructive pulmonary disease (COPD) patients. This approach combines patient-perceived disease impact, airflow limitation severity, and symptom severity, categorizing COPD patients into four groups (A: few symptoms, better lung function; B: more symptoms, better lung function; C: few symptoms, poor lung function; D: more symptoms, poor lung function). Additionally, potential comorbidities are considered to guide therapy decisions.*

The traditional assessment of COPD severity based solely on forced expiratory volume in 1 s (FEV1) is deemed inadequate, as it poorly reflects other critical aspects of the disease. Recent clinical trials have indicated that FEV1 cutoff values do not align well with pharmacological treatment. The revised GOLD strategy, although primarily empirical and expert opinion-based, has prompted researchers to investigate its applicability in various COPD cohorts.

This multidimensional approach aims to provide more accurate and tailored therapeutic interventions for COPD patients, acknowledging the disease's heterogeneous nature. The proposed classification system and management guidelines represent a significant step toward improving COPD patient care.

Keywords: *COPD, GOLD strategy, multidimensional assessment, patient perception, FEV1, symptom severity, disease management.*

Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has proposed a new multidimensional system for the assessment and management of patients with chronic obstructive pulmonary disease (COPD) that combines the impact of the disease as perceived by the patient with the severity of airflow limitation and severity of symptoms (VestboJ et al, 2013). As a result, COPD patients are now classified into four categories (A: few symptoms, better lung function; B: more symptoms, better lung function; C: few symptoms, poor lung function; D: more symptoms, poor lung function) that, along with the assessment of potential co morbidities, would assist in guiding their therapy. This proposal was based on the recognition that COPD is composed of heterogeneous conditional entities and that severity of airflow limitation (assessed by measuring forced expiratory volume in 1 s (FEV_1)) is poorly related to many other clinically relevant aspects of the disease (AgustiA et al.,2010). In addition, recent trials have shown that the arbitrary cut-off values for FEV_1 did not match the application of pharmacological treatment.

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The revised GOLD strategy is an empirical proposal based largely on expert opinion (Rabe KF et al, 2007). Soon after the release of the new GOLD proposal, a number of investigators rushed to explore, in their existing cohorts (i.e., COPDGene (Han MK et al, 2013), Copenhagen (LangeP, et al., 2012). Collaborative Cohorts to assess Multicomponent Indices of COPD in Spain (SorianoJB, et al., 2013), and Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) (AgustiA, et al., 2011), the distribution, characteristics, temporal stability, and/or relationship with long-term outcomes of these four patient categories. The relative proportion of patients in each quadrant varies with the majority of individuals identified by population screening falling into group A, while in the other studies, where there is a larger input from hospital practice, patients are approximately equally divided between groups A and D with smaller numbers in B and C. Based on the history of exacerbations, this classification predicts future exacerbation risk. Twenty-five percent of the individuals in the study by Hurst et al. (Hurst JR et al., 2010) changed their exacerbation frequency year on year, and relatively few patients were assigned to groups C and D, purely due to a history of frequent exacerbations. The reviewed studies adopted somewhat different approaches to determine symptom intensity with one back calculating an estimated COPD assessment test (CAT) score from their health status data. Contrary to expectations, patients in group B had a prognosis similar to those in group C, which rather challenges the idea of these patients being low risk.

Although Agusti et al. (2013) discuss the top 11 questions about the GOLD 2011 staging system; the following additional questions have not yet been answered: What is the optimal care for each of these groups? Is there a different treatment response and prognosis for subgroups within GOLD C and D? Do the groups tell us anything about disease activity? What is the impact of the recently added variables "history of hospitalization" and clinical COPD questionnaire? What is the optimal instrument to assess current symptoms? To answer these questions, we obtained mathematical expressions for describing changes over time in the distribution of A-B-C-D categories of the ECLIPSE cohort, and proposed that COPD is an entity characterized by the distribution of heterogeneous conditions classified as A-B-C-D categories at the level of individual.

Method and materials

Bayes theorem (de Finetti, B, 1974)is mathematically transformed as follows,

$$P(Y) = \frac{P(Y|X)}{P(X|Y)}P(X) = L(X \to Y)P(X) \quad \cdots (1.1)$$

Where X and Y are events. P(X) and P(Y) are the probabilities of observing X and Y without regard to each other. P(X|Y) and P(Y|X)are conditional probabilities.P(X|Y)is the probability of observing event X given that Y is true, and P(Y|X) is the probability of observing event Y given that X is true. Then, the function $L(X \to Y) = P(Y|X)/P(X|Y)$ is introduced as expressing a process of transition from X to Y. The expression (1.1) is exchangeable in the variables X and Y.

The ECLIPSE is an observational, longitudinal, controlled study that generally recruited patients from outpatient clinics at secondary or tertiary care hospitals and, occasionally, primary care. After a baseline visit, participants were evaluated at 3 months, 6 months, and then every 6 months for 3 years. Each of the COPD patients changed his/her clinical category over time among the A-B-C-D categories. From the ECLIPSE study, the following are four sets of conditional probabilities:

$$\{P(A|A), P(B|A), P(C|A), P(D|A)\}$$
$$\{P(A|B), P(B|B), P(C|B), P(D|B)\}$$
$$\{P(A|C), P(B|C), P(C|C), P(D|C)\}$$

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{P(A |D), P(B |D),|D), P(D
P(C |D)}

These probabilities were calculated as in Table 1, where A , B , C ,and D denotes an A-B-C-D category of cohort in 2011. Four other sets of conditional probabilities were also calculated from the ECLIPSE study in Table 1 as follows,

{P(A|A), P(A|B), P(A|C), P(A|D)}
{P(B|A), P(B|B), P(B|C), P(B|D)}
{P(C|A), P(C|B), P(C|C), P(C|D)}
{P(D|A), P(D|B), P(D|C), P(D|D)}

Then, by using the equation (1.1) changes in A-B-C-D categories are expressed by a matrix of transitional functions Λas follows,

$$\Lambda = \begin{vmatrix} L(A \to A) & L(B \to A) & L(C \to A) & L(D \to A) \\ L(A \to B) & L(B \to B) & L(C \to B) & L(D \to B) \\ L(A \to C) & L(B \to C) & L(C \to C) & L(D \to C) \\ L(A \to D) & L(B \to D) & L(C \to D) & L(D \to D) \end{vmatrix}$$

Therefore, by using Λ a change in the distribution of A-B-C-D categories is described as follows,

$$\begin{pmatrix} P(A) \\ P(B) \\ P(C) \\ P(D) \end{pmatrix} = \Lambda \begin{matrix} P(A) \\ P(B) \\ P(C) \\ P(D) \end{matrix} \quad \cdots (1.2a)$$

Where the sum of probabilities in the distribution of A-B-C-D categories always equals 1.000.
An exchange, however, between the variables X and Y in (1.1) produces a prediction of the prior distribution
as follows,

$$\Delta = \begin{matrix} L(A \to A) & L(B \to A) & L(C \to A) & L(D \to A) \\ L(A \to B) & L(B \to B) & L(C \to B) & L(D \to B) \\ L(A \to C) & L(B \to C) & L(C \to C) & L(D \to C) \\ L(A \to D) & L(B \to D) & L(C \to D) & L(D \to D) \end{matrix}$$

Then, by using,Δ the prediction of prior distribution (A^-, B^-, C^-, D^-) is obtained as follows,

$$\begin{matrix} P(A) \\ P(B) \\ = \Delta \quad \cdots (1.2b) \\ P(C) \\ P(D) \end{matrix} \begin{matrix} P(A) \\ P(B) \\ P(C) \\ P(D) \end{matrix}$$

The similarity between the two distributions of A-B-C-D categories in cohorts was described by aset of Euclidean distances(d_1,d_2) defined as follows,

$$d = \sqrt{(P(A) - P(A))^2 + (P(B) - P(B))^2 + (P(C) - P(C))^2 + (P(D) - P(D))^2} \quad \cdots (1.3a)$$

$$d = \sqrt{(P(A) - P(A))^2 + (P(B) - P(B))^2 + (P(C) - P(C))^2 + (P(D) - P(D))^2} \quad \cdots (1.3b)$$

After the GOLD 2011 proposal, existing cohorts including COPDgene, Copenhagen, and Cocomics were characterized by the distribution of A-B-C-D categories, which we used for this meta-analysis.

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Results

1. By using the conditional probabilities in Table 1, each matrix of transition functions or Δwas obtained as follows (Table 2A),

0.809 1.651 0.925 0.617
0.429 0.875 0.490 0.327
Λ =
0.189 1.672 0.936 0.625
1.619 3.304 1.850 1.235
1.236 0.606 1.081 1.620
2.332 1.143 2.041 3.057
Δ=
1.221 0.598 1.068 1.600
0.618 0.303 0.540 0.810

2. Operation of Λon each A-B-C-D category in the ECLIPSE cohort revealed that every category reached the distribution of(A, B, C, D) = (0.220, 0.117, 0.223, 0.440). Operations of Δ on each category also reached to the distribution of (A, B, C, D) = (0.229, 0.431, 0.226, 0.114). (Table 2B) The latter distribution (the first distribution) has a higher proportion of category B, and the former distribution (the second distribution) has a higher proportion of category D. Each category group therefore in ECLIPSE would be successively shifting over time from the latter distribution of A-B-C-D categories to the former distribution. Operation of Λ on ECLIPSE 2011 from each category group in ECLIPSE 2007 also produced the same single distribution of A-B-C-D categories as the second distribution described above. (Table 2C)

3. To compare similarities in the distribution of A-B-C-D categories among cohorts including ECLIPSE2007/2011, COPDGene, Copenhagen, and Cocomics, the distances defined by (1.3a,b) between each group and the first/second distributions were calculated and plotted in Fig.1: ECLIPSE A/B and Copenhagen cohorts were seen along the equal line, and ECLIPSE C/D, COPDGene, and Cocomics cohorts were seen under the equal line.

Discussion

ECLIPSE is a multi-centered, international, longitudinal study aimed at identifying clinically relevant COPD subtypes (phenotypes) and the genetic factors and biomarkers that correlate with them and predict disease progression.(AgustiA, et al., 2011) ECLIPSE included 2164 clinically stable COPD patients, 337 smokers with normal lung function, and 245 never-smokers, who were extensively characterized and followed up for 3years.The main results were as follows: 1) In addition to the expected differences between groups in the three variables that define them (mMRC, FEV_1, and previous exacerbations), the four groups also differed in many other clinical characteristics studied. Hence, pulmonary emphysema and arterial oxygenation impairment were particularly prevalent in the two high-risk categories (groups C and D), whereas co morbidities and persistent systemic inflammation were worse in the two highly symptomatic categories (groups B and D). By contrast, age, sex, FEV_1 reversibility, and FEV_1 decline were not different between groups, although FEV_1 declinewas numerically higher for patients in the B category. 2) An FEV_1<50% predicted was the most frequent determinant of being classified as a group C or D patient, while a history of frequent exacerbations exclusively was the least prevalent. 3) Group A and D patients were relatively stable over time, whereas those in groups B and C showed marked variability, some patients improving and others deteriorating during follow-up. 4) Finally, the incidence of exacerbations during follow-up increased progressively from groups A to B to C to D.

Bayes probability-model based meta-analysis of this study has defined the complex rule of changes in the AB-C-D categories over time in the ECLIPSE cohort as the matrices Λ and Δ composed of transitional functions. The Λand Δmatrices reveal that the change in A-B-C-D categories belongs to a

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shifting process between two basic distributions of A-B-C-D categories. The first distribution of (A,B,C,D)=(0.229, 0.431, 0.226, 0.114) is composed of a higher proportion of category B, and the second distribution of (A,B,C,D)= (0.220, 0.117, 0.223, 0.440)is composed of a higher proportion of category D. (Table 2B)Each distribution of a group categorized as A, B, C, or D in the 2007 ECLIPSE cohort was also transformed to the same distribution through operation of matrix Λ.(Table 2C) Prior probability in Bayes theorem is often called a subjective probability of the observer.(de Finetti,1974) The first distribution belongs to a kind of prior probability that investigators of the ECLIPSE study would take as their underlying assumption from the consensus of their experiences.

The second distribution is the objective probability obtained through counting patient numbers in 2011. That is, Bayes theory explains the transitional rule from the subjective probability to the objective probability. Although outcomes of epidemiological studies are generally applicable to only the group of COPD patients, matrix Λ according to Bayes theory is applicable to each COPD patient. Each A-B-C-D category thus would become a category of clinical conditions changing over time in a COPD patient. For example, when a COPD patient was classified into category B (more symptoms, better pulmonary function) during a certain period and reclassified into category C (few symptoms, poor pulmonary function) during another period, the clinical condition of the COPD patient can be described by the distribution of A-B-C-D categories along a certain duration (e.g., a year). Our hypothesis is that each COPD patient can be characterized by the distribution of A-B-C-D categories of clinical conditions. The second distribution obtained in this study would be an equilibrium image of clinical conditions of a COPD patient.

In addition to reviewing the ECLIPSE study, the GOLD Science Committee reviewed three large observational studies (COPDGene, Copenhagen, and Cocomics) published since the 2011 GOLD revision became available online. Each of these studies addresses the distribution of COPD patients by the A-B-C-D classification and assigns each patient to oneof the four proposed quadrants. The COPDGene study classification is as follows:33.6% of patients were assigned to group A, 20.5% to group B, 7.9% to group C, and 38.0% to group D. The Copenhagen study was pooled data from two similar but independent general population studies: the fourth examination of the Copenhagen City Heart Study (CCHS) from 2001–2003 and the examination of the Copenhagen General Population Study (CGPS) from 2003–2010. The Copenhagen study showed that1) the vast majority of patients in this study belonged to group A, probably reflecting that this cohort of patients was identified from the general population; 2) the proportion of patients experiencing a COPD exacerbation during the first year of observation increased progressively from groups A to B to C to D (2.2%, 5.8%, 25.1% and 28.6%, respectively); and 3) at the 3-year follow-up, mortality rates were 3.8%, 10.6%, 8.2% and 20.1% in groups A, B, C and D, respectively. The Cocomics study was a pooled analysis of individual patient data (age, sex, mMRC score, post bronchodilator spirometry, and all-cause mortality) from 11 COPD cohorts recruited in seven cities in Spain (Galdakao, Pamplona, Requena, Seville, Tenerife, Terrassa, and Zaragoza) for different purposes. Cocomics showed that 1) of the 3633 patients included in the analysis, 1064 (33.6%) were classified as group A, 515 (16.3%) as group B, 561 (17.7%) as group C, and 1023 (32.3%) as group D. This distribution, however, varied significantly between the 11 cohorts pooled. From the results of three large studies, we calculated Euclidean distances as d_1 and d_2, and plotted them in the (d_2, d_1)-plane (Fig.1).Figure 1 shows degrees of similarity among groups in the distribution of A-B-C-D categories. Based on our hypothesis, we know how far a COPD patient is from the equilibrium distribution through Figure 1.

As a conclusion, we have tried to answer the questions that Franssen asked (Franssen FME, et al., 2013) as follows:

Q1) What is the optimal care for each of these groups?

A) Every COPD patient is characterized by the distribution in the changing conditions of A-B-C-D categories. Each condition should be treated with optimal care including drugs and other options.

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Optimal care is thus a combination of treatments depending on a current condition of the A-B-C-D category.

Q2) Is there a different treatment response and prognosis for subgroups within GOLD C and D?

A) COPD patients cannot sustain themselves in a single A-B-C-D category. Thus, the response to treatment and prognosis should be estimated by the difference in the distribution of A-B-C-D categories.

Q3) Do the groups tell us anything about disease activity?

A) Grouping criteria into the categories are arbitrary. Different variables such as history of hospitalization and new biomarkers would produce different categories. The real entity of disease is the changing clinical condition over time for each COPD patient. It is thus necessary to establish a logical approach to integrating the arbitrary groups into the clinical state of a patient with COPD. This study has suggested the introduction of a mathematical matrix for this purpose.

Q4) What is the optimal instrument to assess current symptoms?

A) It is important to establish the optimal concept of exacerbation for answering this question. Each exacerbation is now recognized dependent only on the severity of symptoms. According to this Bayes model based study, an exacerbation should be classified into the A-B-C-D categories of the GOLD proposal, i.e., an exacerbation that is type A, B, C, or D. The classification of exacerbation according to the GOLD proposal will produce an optimal method to assess current symptoms.

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Table 1: Data of the ECLIPSE Study and Conditional Probabilities

GOLD categories 2007	**N**				**N**	**GOLD categories 2011**	N			**conditional probabilities**		**conditional probabilities**	
A	495	P(A)	0.236	A+	245	**A+**	348	P(A+)	0.220	P(A+|A)	0.570	P(A|A+)	0.705
				B+	56					P(B+|A)	0.130	P(A|B+)	0.303
				C+	82					P(C+|A)	0.190	P(A|C+)	0.232
				D+	47					P(D+|A)	0.110	P(A|D+)	0.068
B	293	P(B)	0.139	A+	46	**B+**	185	P(B+)	0.117	P(A+|B)	0.220	P(B|A+)	0.133
				B+	76					P(B+|B)	0.360	P(B|B+)	0.411
				C+	15					P(C+|B)	0.070	P(B|C+)	0.042

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				D+	74					P(D+|B)	0.350	P(B|D+)	0.106
C	483	P©	0.230	A+	45	**C+**	353	P(C+)	0.223	P(A+|C)	0.120	P(C|A+)	0.130
				B+	19					P(B+|C)	0.050	P(C|B+)	0.102
				C+	177					P(C+|C)	0.470	P(C|C+)	0.502
				D+	136					P(D+|C)	0.360	P(C|D+)	0.195
D	830	P(D)	0.395	A+	11	**D+**	697	P(D+)	0.440	P(A+|D)	0.020	P(D|A+)	0.032
				B+	34					P(B+|D)	0.060	P(D|B+)	0.183
				C+	79					P(C+|D)	0.140	P(D|C+)	0.224
				D+	440					P(D+|D)	0.780	P(D|D+)	0.632

Data were obtained from Agusti et al, 2012. Conditional probabilities were calculated from the data.

Table 2: Transitional functions from the ECLIPSE study

B

A

Λ		**Δ**	
L(A→A+)	0.809	L(A→A-)	1.236
L(A→B+)	0.429	L(A→B-)	2.332
L(A→C+)	0.819	L(A→C-)	1.221
L(A→D+)	1.619	L(A→D-)	0.618
L(B→A+)	1.651	L(B→A-)	0.606
L(B→B+)	0.875	L(B→B-)	1.143
L(B→C+)	1.672	L(B→C-)	0.598
L(B→D+)	3.304		0.303

C

ECLIPSE	**P**	**ΔP**	**Λ(ΔP)**
A	0.236	0.220	0.220
B	0.139	0.117	0.117
C	0.230	0.223	0.223
D	0.395	0.440	0.440
ECLIPSE	**P**	**ΔP**	**Δ(ΔP)**

2011/A	**P**	**ΔP**
A	0.57	0.220
B	0.13	0.117
C	0.19	0.223
D	0.11	0.440
2011/B	**P**	**ΔP**
A	0.22	0.220
B	0.36	0.117
C	0.07	0.223
D	0.35	0.440
2011/C	**P**	**ΔP**

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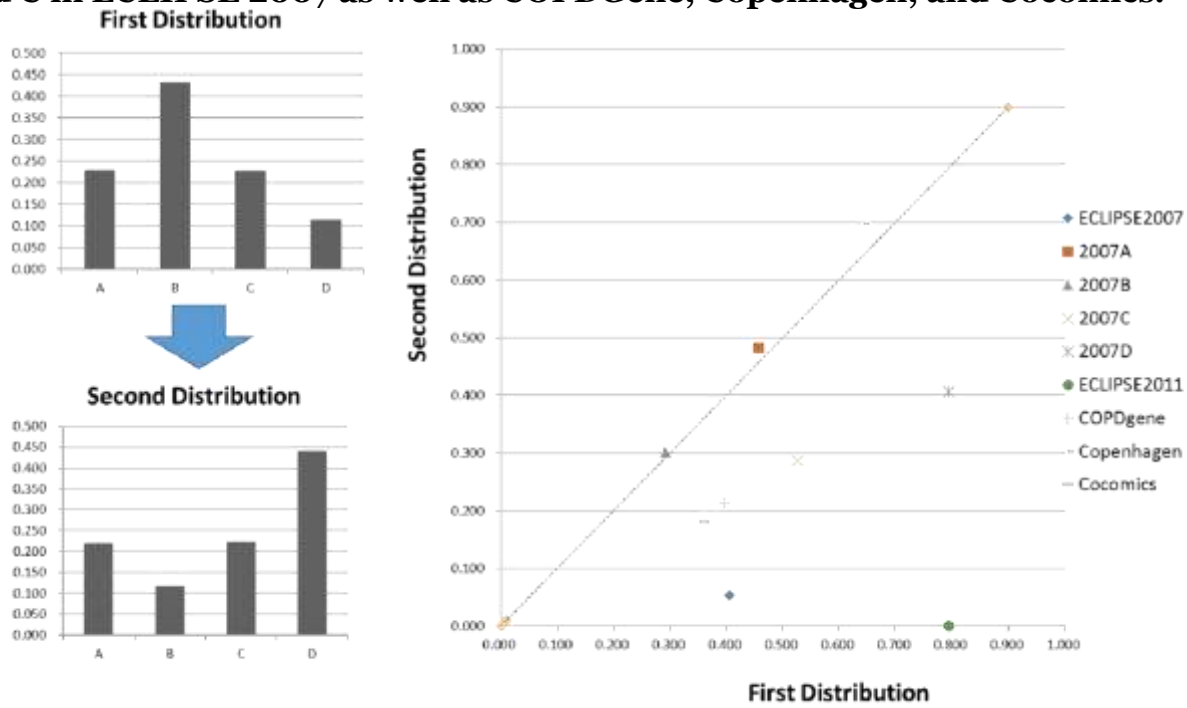
		L(B→D-)						**A**	0.12	0.220
L(C→A+)	0.925	L(C→A-)	1.081							
				A	0.236	0.229	0.229	**B**	0.05	0.117
L(C→B+)	0.490	L(C→B-)	2.041					**C**	0.47	0.223
L(C→C+)	0.936	L(C→C-)	1.068					**D**	0.36	0.440
L(C→D+)	1.850	L(C→D-)	0.540	B	0.139	0.431	0.431	**2011/D**	**P**	**ΔP**
L(D→A+)	0.617	L(D→A-)	1.620	C	0.230	0.226	0.226	**A**	0.02	0.220
L(D→B+)	0.327	L(D→B-)	3.057					**B**	0.06	0.117
L(D→C+)	0.625	L(D→C-)	1.600	D	0.395	0.114	0.114	**C**	0.14	0.223
L(D→D+)	1.235	L(D→D-)	0.810					**D**	0.78	0.440

A: Two matrices Λand Δ were obtained by combinations of conditional probabilities in Table 1.
B and C: Note that two common distributions of A-B-C-D categories were calculated as the equilibrium groupings among the ECLIPSE groups.

Fig.1. Similarities among the A-B-C-D categories in the cohorts including sub-cohorts A, B, and C in ECLIPSE 2007 as well as COPDGene, Copenhagen, and Cocomics.



Note that there is implicitly a shifting trajectory between the first and the second distribution