CLUSTER PHENOTYPING AS AN APPROACH TO IDENTIFY COPD PATIENTS AT RISK OF POOR PROGNOSIS

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Introduction

The Czech national COPD guidelines recognize
6 different COPD phenotypes: bronchitic, emphysematous, ACO (asthma/COPD overlap), cachexia, frequent exacerbator and BCO (COPD/bronchiectasis overlap) [1]
The Czech multicenter research database of COPD (CMRD) is a prospective project focused on long-term mortality and on disease evolution in a real-life COPD patient cohort [2]

Aims of the study

Our aim was to assess differences in long-term all-cause mortality in the CMRD cohort with respect to the above mentioned phenotypes and their combinations

Methods

A prospective, observational, non-interventional multicenter study
Inclusion criteria: diagnosis of COPD 12 months prior to enrolment, post-bronchodilator FEV1 <60%, patient's written consent
Data from the CMRD cohort (comprising 784 COPD patients) were analyzed at 4-year follow-up [2]
Patient characteristics (cohort) – descriptive statistics
Mortality analysis – Kaplan-Meier survival estimates for each phenotype and their combinations

Results

Emphysematous (p=0.005), cachectic (p<0.001) and frequent exacerbator (p=0.025) phenotypes were associated with increased all-cause 4-year mortality
The co-presence of cachexia and emphysema or of the cluster of cachexia, frequent exacerbator and emphysema in a single patient were the two most distinctive combinations associated with increased risk of death (p<0.001 both)
No differences in mortality were found if the Spanish phenotypes (i.e., non-exacerbator, exacerbator/bronchitic, exacerbator/non-bronchitic and asthma/COPD overlap) were used

Discussion

The GOLD 2011–16 and GOLD 17– disease classification possess gradual prognostic value for COPD patients, categories A-D (higher long-term mortality in group C compared to group B) [3]
Phenotyping of COPD patients is recommended by several national guidelines for COPD disease management [4,5]
Various COPD phenotyping approaches were reported by a number of research groups [1,4,6,7] and further research is ongoing
The main advantage of COPD phenotyping is the possibility of tailored treatment for specific COPD patient subpopulations [4]
The Czech approach in COPD phenotyping is a unique alternative since it recognizes the possibility of a co-existence of multiple phenotypes in a single COPD patient [1]

Conclusion

Our results show that COPD phenotyping and „cluster" phenotyping – above the possibility of a tailored treatment – may also have a prognostic significance for identifying COPD subpopulations at high risk of poor outcome

Demographic data		
Men		572 (73.0%)
Age at inclusion		N=784; 66,6 (9,2); 66,9 (50,9; 81,1)
Age at COPD diagnosis		N=745; 58,7 (11,0); 59,4 (39,7; 74,5)
BMI		N=784; 27.4 (6.2); 26.9 (18.4; 38.0)
Smoking	Ex-smoker	538 (68.6%)
	Non-smoker	86 (11.0%)
	Smoker	160 (20.4%)

Symptoms		
Dyspnoea – mMRC score	0	38 (4.8%)
	1	145 (18.5%)
	2	310 (39.5%)
	3	165 (21.0%)
	4	126 (16.1%)
CAT score		N=775; 16.0 (7.8); 16.0 (4.0; 29.0)
Fatigue		369 (47.6%)
Cough		563 (71.8%)
Expectoration		455 (58.0%)
Purulent sputum		46 (5.9%)
Haemoptysis		42 (5.4%)
Atopy		94 (12.0%)
Asthma		81 (10.3%)

Exacerbation history – previous 12 months	
Treated at home	N=784; 0.8 (1.3); 0.0 (0.0; 3.0)
> 0	317 (40.4%)
Requiring hospital care	N=784; 0.4 (0.8); 0.0 (0.0; 2.0)
> 0	203 (25.9%)
Total	N=784; 1.2 (1.6); 1.0 (0.0; 4.0)
> 0	412 (52.6%)

Pulmonary function tests	
FEV1 (% PV)	N=784; 45.0 (11.6); 46.1 (25.2; 60.0)
FVC (% PV)	N=784; 68.7 (17.6); 67.9 (40.0; 100.1)
VCmax (% PV)	N=784; 72.2 (17.5); 71.0 (45.0; 100.0)
FEV1/FVC (%)	N=784; 0.5 (0.1); 0.5 (0.3; 0.7)
FEV1/VCmax (%)	N=784; 0.5 (0.1); 0.5 (0.3; 0.7)
RV (% PV)	N=632; 186.7 (60.4); 183.8 (99.0; 291.0)
TLC (% PV)	N=629; 110.8 (26.4); 111.0 (68.0; 155.0)
RV/TLC (%)	N=589; 66.5 (20.5); 64.0 (44.0; 104.0)
IC/TLC (%)	N=457; 42.1 (24.1); 33.0 (17.0; 83.3)
TLCO (% PV)	N=509; 52.4 (21.9); 51.0 (22.0; 96.0)
KCO (%)	N=474; 68.7 (26.4); 67.0 (31.0; 115.0)
FeNO (ppb)	N=285; 18.5 (18.9); 13.0 (3.0; 52.0)
6MWD (m)	N=598; 331.3 (131.7); 351.5 (110.0; 530.0)

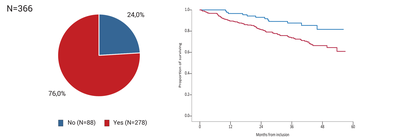
Phenotypes		
Czech	Bronchitic	455 (58.0%)
	Emphysematous	278 (76.0%)
	BCO	112 (31.3%)
	ACO	23 (3.8%)
	Frequent exacerbactor	245 (31.3%)
	Cachexia	111 (14.2%)
Spanish	ACO	92 (11.7%)
	NON-AE	485 (61.9%)
	AE CB	143 (18.2%)
	AE NON-CB	64 (8.2%)

GOLD		
GOLD (1–4)	1	0 (0.0%)
	2	267 (37.0%)
	3	362 (50.1%)
	4	93 (12.9%)
GOLD 2016 (A–D)	A	35 (4.7%)
	B	150 (20.1%)
	C	39 (5.2%)
	D	523 (70.0%)
GOLD 2017 (A–D)	A	64 (8.2%)
	B	412 (52.7%)
	C	13 (1.7%)
	D	293 (37.5%)

Predictive indices	
BODE	N=598; 4.2 (2.1); 4.0 (1.0; 8.0)
ADO	N=774; 4.7 (1.6); 5.0 (2.0; 7.0)
CPS	N=565; 6.7 (2.4); 7.0 (3.0; 11.0)

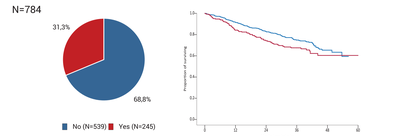
Categorical variables are presented as absolute or relative frequencies.
Continuous parameters are presented as valid N, mean value (SO) and median (5^{th}; 95^{th} percentile).

Long-term survival of patients with emphysematous phenotype



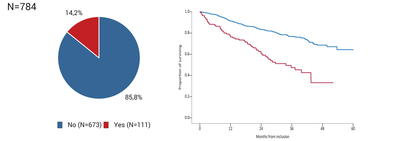
	N	N deaths	12 months	24 months	36 months	48 months	P-value
No	N=88	12 (13.6%)	0.966 (0.928–1.000)	0.930 (0.876–0.984)	0.876 (0.804–0.949)	0.816 (0.710–0.923)	**0.005**
Yes	N=278	78 (28.1%)	0.895 (0.859–0.931)	0.813 (0.766–0.860)	0.737 (0.681–0.792)	0.664 (0.597–0.730)	

Long-term survival of patients with frequent exacerbator phenotype



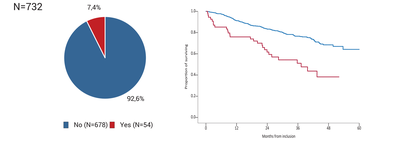
	N	N deaths	12 months	24 months	36 months	48 months	P-value
No	N=539	130 (24.1%)	0.914 (0.890–0.938)	0.828 (0.795–0.862)	0.748 (0.706–0.790)	0.653 (0.595–0.712)	**0.025**
Yes	N=245	74 (30.2%)	0.842 (0.796–0.888)	0.741 (0.683–0.799)	0.675 (0.609–0.741)	0.603 (0.522–0.685)	

Long-term survival of patients with cachectic phenotype



	N	N deaths	12 months	24 months	36 months	48 months	P-value
No	N=673	150 (22.3%)	0.913 (0.891–0.934)	0.833 (0.803–0.862)	0.768 (0.731–0.804)	0.686 (0.637–0.735)	**<0.001**
Yes	N=111	54 (48.6%)	0.763 (0.683–0.843)	0.615 (0.520–0.710)	0.475 (0.368–0.582)	0.332 (0.185–0.479)	

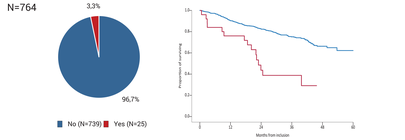
Long-term survival of patients with concurrent emphysematous and cachectic phenotypes*



	N	N deaths	12 months	24 months	36 months	48 months	P-value
No	N=678	152 (22.4%)	0.912 (0.890–0.933)	0.833 (0.803–0.862)	0.766 (0.730–0.802)	0.684 (0.635–0.734)	**<0.001**
Yes	N=54	27 (50.0%)	0.759 (0.645–0.873)	0.617 (0.483–0.750)	0.511 (0.365–0.657)	0.382 (0.212–0.553)	

* Irrespective of other concurrent phenotypes

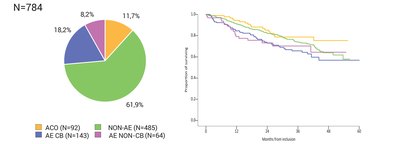
Long-term survival of patients with concurrent emphysematous, cachectic and frequent exacerbator phenotype*



	N	N deaths	12 months	24 months	36 months	48 months	P-value
No	N=739	176 (23.8%)	0.902 (0.881–0.924)	0.825 (0.796–0.854)	0.751 (0.716–0.787)	0.663 (0.614–0.711)	**<0.001**
Yes	N=25	15 (60.0%)	0.760 (0.593–0.927)	0.437 (0.230–0.644)	0.388 (0.183–0.593)	0.291 (0.066–0.516)	

* Irrespective of other concurrent phenotypes

Long-term survival of patients according to Spanish phenotypes



	N	N deaths	12 months	24 months	36 months	48 months	P-value
ACO	N=92	17 (18.5%)	0.944 (0.896–0.992)	0.852 (0.774–0.930)	0.787 (0.692–0.882)	0.754 (0.644–0.865)	
NON-AE	N=485	121 (24.9%)	0.908 (0.883–0.934)	0.823 (0.787–0.859)	0.739 (0.694–0.784)	0.639 (0.576–0.702)	
AE CB	N=143	48 (33.6%)	0.845 (0.786–0.905)	0.730 (0.653–0.806)	0.657 (0.571–0.742)	0.568 (0.462–0.675)	**0.054**
AE NON-CB	N=64	18 (28.1%)	0.792 (0.691–0.893)	0.732 (0.617–0.846)	0.702 (0.579–0.826)	0.644 (0.486–0.802)	

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