Prim Care Respir J 2012; **21**(3): 295-301

Primary Care RESPIRATORY JOURNAL
www.thepcrj.org

RESEARCH PAPER

The Dyspnoea, Obstruction, Smoking, Exacerbation (DOSE) index is predictive of mortality in COPD

***Josefin Sundh[a], Christer Janson[b], Karin Lisspers[c], Björn Ställberg[c], Scott Montgomery[d,e]**

[a] Department of Respiratory Medicine, Örebro University Hospital, School of Health and Medical Science, Örebro University, Örebro, Sweden
[b] Department of Medical Sciences, Respiratory Medicine and Allergology, Uppsala University, Uppsala, Sweden
[c] Department of Public Health and Caring Science, Family Medicine and Clinical Epidemiology, Uppsala University, Uppsala, Sweden
[d] Clinical Epidemiology and Biostatistics Unit, Örebro University Hospital, School of Health and Medical Science, Örebro University, Örebro, Sweden
[e] Clinical Epidemiology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institute, Stockholm, Sweden

Received 16th April 2012; revised 25th April 2012; accepted 22nd May 2012; online 11th July 2012

Abstract

Background: The Dyspnoea, Obstruction, Smoking, Exacerbation (DOSE) index was designed to assess disease severity and for the clinical management of chronic obstructive pulmonary disease (COPD), but has not been evaluated as a prognostic instrument for mortality in a population including primary care patients.

Aims: The aim of this study was to investigate the associations of the DOSE index with mortality in primary and secondary care COPD patients.

Methods: Information was collected from 1,111 COPD patients aged 34–75 years randomly selected from 70 Swedish primary and secondary care centres. Data were obtained using patient questionnaires and record review and the Swedish Board of Health and Welfare provided mortality data. The study population included 562 patients with data on all DOSE index components. The DOSE index was calculated using the MRC dyspnoea scale, forced expiratory volume in 1 second (FEV_1) as percentage of predicted (FEV_1%pred), smoking status, and exacerbation rate. The exacerbation rate over 6 months prior to record review was used to estimate the annual rate. Cox regression analyses estimated survival with adjustment for age, sex, and heart disease.

Results: Over 5 years, 116 patients (20.6%) died. Mortality was higher in patients with DOSE index ≥4 (42.4%) than for lower scores (11.0%) ($p<0.0001$). Compared with a DOSE index score of 0–3, the hazard ratio for mortality was 3.48 (95% CI 2.32 to 5.22) for a score of 4–5, and was 8.00 (95% CI 4.67 to 13.7) for a score of 6–7.

Conclusions: The DOSE index is associated with mortality in COPD patients in primary and secondary care and can be used to assess prognosis in addition to other clinically relevant issues.

J Sundh *et al*. *Prim Care Respir J* 2012; **21**(3): 295-301
http://dx.doi.org/10.4104/pcrj.2012.00054

Keywords COPD, DOSE index, mortality, prognosis

See linked editorial by Chavannes *et al*. on pg 245

Introduction

COPD is a common serious disease with an overall global prevalence of 9–10%,[1] and is predicted to increase from sixth to third place in the international ranking of diseases causing mortality between 1990 and 2020.[2,3] In studies of patients discharged from hospital, 1-year mortality rates of 22%[4] and 23%[5], and 2-year mortality rates of 29.3%[6] and 35.6%[4], have been reported.

The Dyspnoea, Obstruction, Smoking, Exacerbation (DOSE) index combines the modified 5-point version of the Medical Research Council (MRC) dyspnoea scale[7,8] with obstruction (forced expiratory volume in 1 second as percentage of predicted value, FEV_1%pred),[9] smoking status, and exacerbation rate during the previous year.[10] By combining measures relevant to important clinical issues in COPD as well as providing a convenient measure of disease severity for use in routine clinical settings, the DOSE index appears to be a useful complement to other composite measures such as the

* **Corresponding author:** Dr Josefin Sundh, Department of Respiratory Medicine, Örebro University Hospital, School of Health and Medical Science, Örebro University, 701 85 Örebro, Sweden. Tel: +46 196025597, +46 702349517 Fax: +46196021865 E-mail: josefin.sundh@orebroll.se

body mass index, airflow obstruction, dyspnoea, and exercise capacity (BODE) index and the age, dyspnoea and airflow obstruction (ADO) index.[11,12] The DOSE index predicts hospital admission, respiratory failure and exacerbation risk.[10] To our knowledge, only one study has evaluated the DOSE index as a prognostic instrument in a population of male hospital outpatients.[13]

This study examined associations of the DOSE index with mortality in male and female COPD patients receiving primary and secondary care in a multicentre Swedish population.

Table 1. DOSE index scoring system

Components	DOSE index points 0	1	2	3
MRC scale	0–1	2	3	4
FEV_1%pred	≥50	30–49	<30	
Smoking status	Non-smoker	Smoker		
Exacerbations in previous year*	0–1	2–3	>3	

*The annual exacerbation rate was calculated from information on exacerbations in the previous 6 months. Zero exacerbations were classified as a score of 0, 1–2 exacerbations as a score of 1, and >2 exacerbations as a score of 2.

FEV_1%pred=forced expiratory volume in 1 second percentage predicted.

Methods

Procedure

The participants were from a larger cohort of COPD patients in seven Swedish counties.[14,15] A total of 1,548 patients aged 34–75 years with a COPD diagnosis (ICD code J44) recorded in medical records between 2000 and 2003 were randomly selected, 1,084 from primary care and 464 from hospital clinics.

Data collection

Data were collected in 2005 by self-completed questionnaire and record review for 2000–2003. The questionnaire response rate was 75%, and 98% (1,111 patients) consented to medical record review. The Swedish Board of Health and Welfare provided mortality data for 2005 to 2010, including underlying cause of death from death certificates. Two research nurses entered the data.

Measures

Age (<50 years, 51–60 years, 61–70 years and >70 years), sex, level of education, self-reported height and weight, dyspnoea (MRC range 0–4), smoking status (current or non-smoking), exacerbation rate, current treatment, and vaccination status were taken from patient questionnaires. The dichotomous education variable identified those who continued in full-time education for at least 2 years beyond the compulsory period of 9 years and those with shorter education. Obesity was defined as body mass index (BMI) ≥30, overweight as BMI <30 and ≥25, and underweight as BMI <20. An exacerbation was defined as an unscheduled or emergency visit or a course of oral steroids due to worsening of COPD. The questionnaire identified the number of exacerbations during the 6 months prior to questionnaire completion. Current treatment was categorised as: no maintenance therapy besides short-acting beta-agonists (SABA) or ipratropium; maintenance therapy with tiotropium or long-acting beta-agonists (LABA); inhaled corticosteroids (ICS) alone; and ICS combined with LABA or tiotropium therapy. Influenza vaccination in the last year and pneumococcal vaccination in the last 5 years were identified.

Information about co-morbid diagnoses and lung function was taken from patients' records. Heart disease was defined as ischaemic heart disease or heart failure, and types 1 or 2 diabetes mellitus were identified. Depression was defined as a diagnosis combined with antidepressant drug treatment. Lung function data were available for 594 (53%) patients. FEV_1 was expressed as percentage of predicted using the European Community for Steel and Coal reference values.[16] Mortality was categorised as death by respiratory disease, cardiovascular disease, cancer and other causes of death.

The DOSE index

The DOSE index was calculated using the MRC dyspnoea scale, FEV_1%pred, smoking status, and the exacerbation rate in the previous year (Table 1).[10] The DOSE index uses the sum of its components and the total score ranges from 0 to 8; the higher the score, the more severe the disease. Current smoking was defined as daily smoking. The exacerbation rate over the previous 6 months was used to estimate the annual rate (Table 1). Complete information was available for 319 patients from primary health care centres (PHCCs) and 243 from hospital clinics.

Statistical analysis

The analyses were performed using PASW Version 18.0 (SPSS Inc, Chicago, Illinois, USA). Kaplan-Meier curves and Cox regression assessed survival. Assessment using Kaplan-Meier curves indicated that the proportional hazards assumption was justified. The DOSE index was examined as a single score (categorised as scores of 6–8, 4–5 and <4) and other models examined its components separately. The analyses were adjusted for age, sex, and heart disease. Stepwise regression was used to identify the most predictive measure for mortality risk. The analyses were repeated with further adjustment for treatment and vaccination status. Cause-specific mortality associations with the DOSE index were adjusted for age and sex. The study period was from when patients received their questionnaires until death or September 2010. Stratification and interaction analyses investigated potential effect modification by sex, level of care, and age.

The smoking variable was modified to include categories for daily smokers, ex-smokers, never-smokers and occasional smokers, with adjustment for age, sex, and heart disease. Cox regression was used to analyse mortality risk by whether patients had (n=594) or did not have (n=517) spirometry data. A reduced 'DSE index' without lung function was created and its association with mortality analysed among excluded patients (n=549) and patients included in the main analysis (n=562).

Ethics

The study was approved by the Regional Ethical Review Board of Uppsala University (Dnr 2010/090). Written consent to use the information for future analysis was obtained for all participating patients.

Results

Patient characteristics

During the average study period of 5 years, 116 patients (20.6%) died. Information on cause of death was available for 113 patients (97.4%). No patient reached the maximum DOSE index score of 8. The number of deaths was higher in COPD stage 3 and 4,[9] in secondary care, among men, older patients and those with co-morbid heart disease or those who were underweight. Influenza/pneumococcal vaccinations and maintenance therapy with the combination of ICS and LABA or tiotropium were more common among patients who died, and mortality was lower in the group treated with only SABA and ipratropium (Table 2).

In univariate analyses, male sex, older age, lower FEV_1%pred, MRC dyspnoea scale values of 3 and 4, two or more exacerbations in the previous year, underweight, and heart disease were associated with raised mortality. Age, heart disease, smoking status, FEV_1%pred, and MRC dyspnoea scale remained statistically significantly associated with mortality when all variables were included in the model (data not shown).

DOSE index

Mortality was higher in patients with a DOSE index score ≥4 (42.4%) than for lower scores (11.0%, p<0.0001; Table 3). The association between the DOSE index and mortality is shown by Kaplan-Meier curves and Cox regression analyses in Figures 1 and 2. DOSE index scores of 6–7 and 4–5 compared with 0–3 were statistically significantly and independently associated with higher mortality in Cox regression analyses before and after adjustment for age, sex, and heart disease (Table 4).

Components of the DOSE index

When the components were included in the same model, all were statistically significantly associated with mortality, although the association with smoking was not statistically significant in univariate analysis (Table 5, Figure 3). When the DOSE index and its components were combined in a stepwise elimination regression model, the combined index remained, as it explained more variance than the individual components. Chi-square values (with adjustment for age, sex, and heart disease) were 146.4 for combined index, 116.0 for dyspnoea, 91.2 for obstruction, 54.0 for smoking, and 75.5 for exacerbations.

Sex, age and level of care

The relationship between a DOSE index score of 6–7 and mortality was of higher magnitude in men (hazard ratio (HR) 13.9, 95% CI 6.84 to 28.2) than in women (HR 4.00, 95% CI 1.62 to 9.88), with a p for interaction of 0.018. There was no effect modification by age or level of care (data not shown).

Treatment

Additional adjustment for treatment and vaccination did not alter the main results significantly (data not shown).

DOSE index and cause-specific mortality

Cox regression analysis of cause-specific mortality showed that a higher DOSE index score was statistically significantly and independently associated with an increased risk of respiratory disease-specific mortality. A DOSE index score of 4–5 was also independently and statistically significantly associated with an increased risk of cardiovascular mortality. No associations were found for DOSE index with death due to cancer or other diseases (Figure 4).

Table 2. Patient characteristics

	All (n)	Dead (n)	Dead (%)	p value
All	562	116	20.6	
Sex				
Male	241	62	25.7	Ref
Female	321	54	16.8	0.010
Age				
≤50	40	1	2.50	0.003
51–60	122	10	8.20	<0.0001
61–70	288	66	22.9	0.016
>70	112	39	34.8	Ref
Educational level				
Lower	357	81	22.7	Ref
Higher	201	33	16.4	0.078
Level of care				
Primary care	319	39	12.2	Ref
Secondary care	243	77	31.7	<0.0001
Lung function				
FEV_1%pred ≥80	150	14	9.30	Ref
FEV_1%pred ≥50, <80	230	35	15.2	0.097
FEV_1%pred <50, ≥30	140	48	34.3	<0.0001
FEV_1%pred <30	42	19	45.2	<0.0001
Heart disease				
Yes	134	48	35.8	<0.0001
No	428	68	15.9	Ref
Body mass index				
Underweight	65	23	35.4	0.006
Normal weight	194	36	18.6	Ref
Overweight	192	30	15.6	0.445
Obesity	105	25	23.8	0.283
Influenza vaccination				
Yes	300	73	24.3	0.021
No	262	43	16.4	Ref
Pneumococcal vaccination				
Yes	212	53	25.0	0.028
No	350	63	18.0	Ref
Treatment				
None except SABA or ipratropium	102	10	9.80	0.003
LABA or tiotropium*	52	13	25.0	0.849
ICS alone†	55	9	16.4	0.225
ICS with LABA or tiotropium‡	353	84	23.8	Ref

*Maintenance treatment with LABA and/or tiotropium but not ICS.
†Maintenance treatment with ICS but not LABA or tiotropium.
‡Maintenance treatment with ICS and LABA separately or in a fixed combination, or ICS and tiotropium.
FEV_1%pred=forced expiratory volume in 1 second percentage predicted. ICS=inhaled corticosteroids; LABA=long-acting beta-blockers; SABA=short-acting beta-blockers.

Smoking definition and lung function

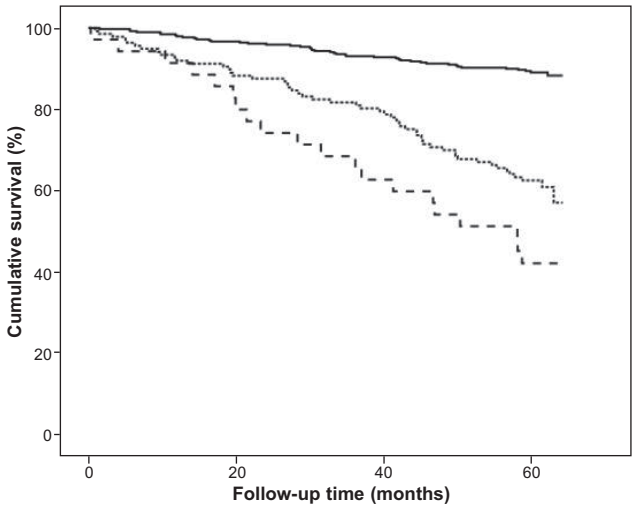
No statistically significant differences in mortality were found between ex-smokers and current smokers (data not shown). Patients with spirometry data (n=594) were compared with those without (n=517). Among patients with missing spirometry data (n=517), 25.0% died and, among patients with available spirometry data (n=594), 21.2% died (p=0.139). In the entire group no

Table 3. DOSE index characteristics

	All (n)	Dead (n)	Dead (%)	p value
DOSE index score				
0–3	390	43	11.0	Ref
4–5	137	53	38.7	<0.0001
6–7	35	20	57.1	<0.0001
Dyspnoea scale				
MRC 0–1	230	18	7.80	Ref
MRC 2	91	12	13.2	0.141
MRC 3	90	21	23.3	<0.0001
MRC 4	151	65	43.0	<0.0001
Obstruction				
FEV_1%pred ≥50	380	49	12.9	Ref
FEV_1%pred 30–49	140	48	34.3	<0.0001
FEV_1%pred <30	42	19	45.2	<0.0001
Smoking				
No	415	93	22.4	Ref
Yes	147	23	15.6	0.083
Exacerbations*				
0	374	56	15.0	Ref
1–2	123	35	28.5	0.001
>2	65	25	38.5	<0.0001

*Number of exacerbations in previous 6 months.
FEV_1%pred=forced expiratory volume in 1 second percentage predicted.
Ref = the reference against which other values are compared

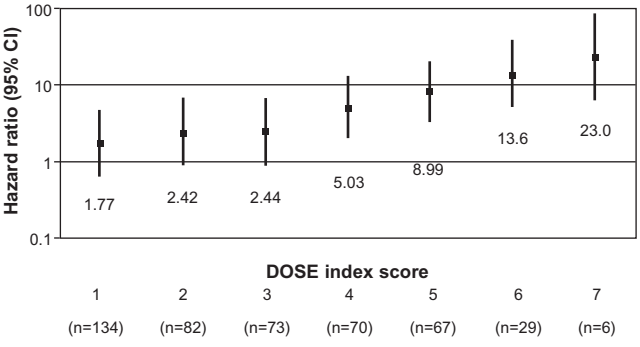
Figure 1. DOSE index and mortality



Kaplan-Meier curves for DOSE index scores.
Solid line = DOSE index score 0-3, dotted line DOSE index score 4-5 and broken line DOSE index score 6-7.

statistical significance was found for mortality associated with missing spirometry data (HR 1.10, 95% CI 0.86 to 1.41). The HR for mortality associated with missing spirometry data was statistically significantly raised when the analysis was restricted to primary care patients (HR 1.68, 95% CI 1.16 to 2.41), but not among secondary care patients (HR 1.20, 95% CI 0.79 to 1.81). In the group included in the main analysis (n=562), 20.6% died and, among patients excluded because of any missing data (n=549), 25.3% died (p=0.064). Excluding FEV_1%pred from the DOSE index among the participants included in the main analysis produced a HR for the 4–5 group compared with the 0–3 group of 3.43 (95% CI 2.37 to 4.95) after adjustment for age, sex, and heart disease (no patients achieved a score of 6). Among the patients excluded from the main analysis due to missing data, the adjusted HR for mortality associated with a DOSE index score was 2.08 (95% CI 1.38 to 3.13) for a score of 4–5, and was 6.19 (95% CI 2.65 to 14.5) for a score of 6.

Figure 2. DOSE index score and mortality



Cox regression analyses, adjusted for age, sex and heart disease.
Reference = DOSE score 0.

Table 4. Results of Cox regression analysis of DOSE index

		HR (95% CI) unadjusted	p value	HR (95% CI) adjusted *	p value
DOSE index score	0–3	Ref			
	4–5	4.12 (2.75 to 6.16)	<0.0001	3.48 (2.32 to 5.22)	<0.0001
	6–7	7.05 (4.14 to 12.0)	<0.0001	8.00 (4.67 to 13.7)	<0.0001
Sex	Male	Ref			
	Female	0.61 (0.42 to 0.88)	0.007	0.79 (0.54 to 1.16)	0.228
Age	≤50	0.06 (0.01 to 0.43)	0.005	0.10 (0.01 to 0.76)	0.029
	51–60	0.20 (0.10 to 0.40)	<0.0001	0.23 (0.12 to 0.47)	<0.0001
	61–70	0.61 (0.41 to 0.91)	0.016	0.63 (0.42 to 0.95)	0.026
	>70	Ref		Ref	
Heart disease		2.62 (1.81 to 3.79)	<0.0001	1.98 (1.35 to 2.92)	0.001

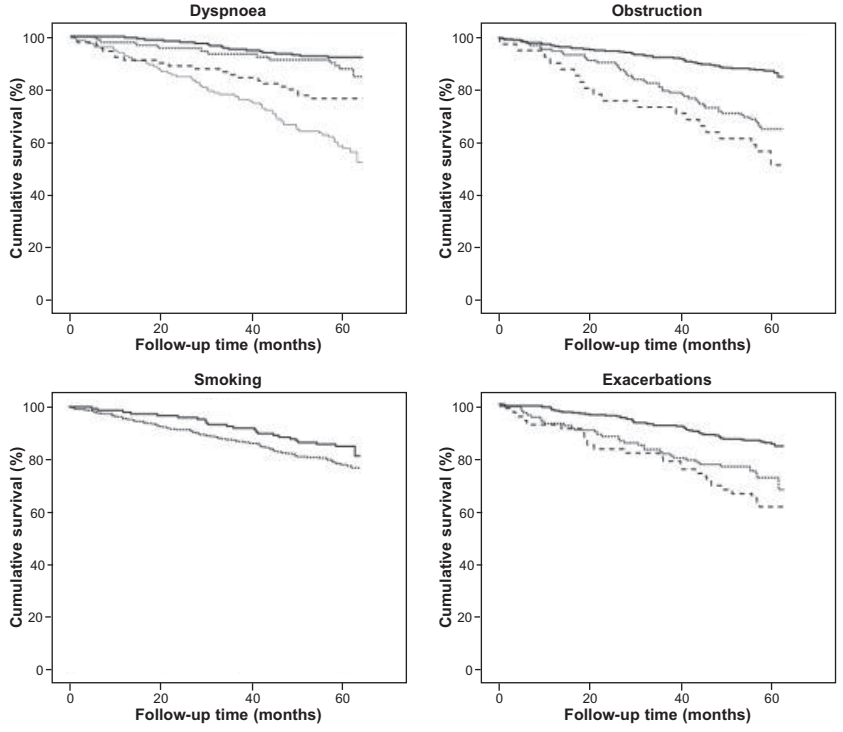
*Adjusted for sex, age and heart disease. HR=hazard ratio. Ref = the reference against which other values are compared.

Table 5. Results of Cox regression analysis of DOSE index components

		HR (95% CI) unadjusted	p value	HR (95% CI) adjusted *	p value
Dyspnoea	MRC 0–1	Ref		Ref	
	MRC 2	1.73 (0.83 to 3.58)	0.143	1.66 (0.80 to 3.45)	0.178
	MRC 3	3.35 (1.78 to 6.29)	<0.0001	2.62 (1.39 to 4.95)	0.003
	MRC 4	6.78 (4.02 to 11.4)	<0.0001	5.57 (3.29 to 9.44)	<0.0001
Obstruction	FEV_1%pred >50	Ref		Ref	
	FEV_1%pred 30–49	3.00 (2.01 to 4.46)	<0.0001	2.41 (1.61 to 3.61)	<0.0001
	FEV_1%pred <30	4.37 (2.57 to 7.42)	<0.0001	3.87 (2.27 to 6.59)	<0.0001
Current smoking	No	Ref		Ref	
	Yes	0.66 (0.42 to 1.05)	0.079	0.85 (0.53 to 1.35)	0.488
Exacerbations†	0	Ref			
	1–2	2.10 (1.37 to 3.20)	0.001	1.87 (1.22 to 2.86)	0.004
	>2	3.03 (1.89 to 4.85)	<0.0001	2.71 (1.68 to 4.36)	<0.0001

*Adjusted for sex, age and heart disease. †Number of exacerbations in previous 6 months. FEV_1%pred=forced expiratory volume in 1 second percentage predicted. Ref = the reference against which other values are compared

Figure 3. DOSE index components and mortality



Kaplan-Meier curves for DOSE score components.

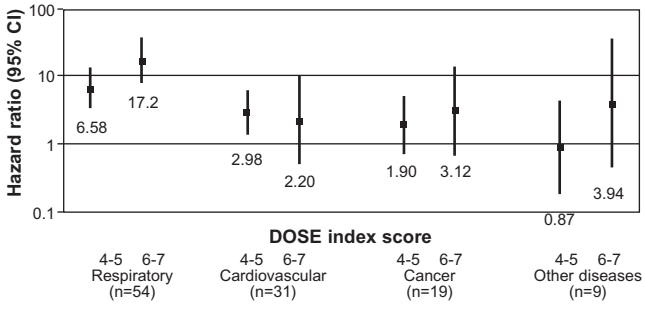
Dyspnoea: Solid line = MRC scale 0-1, dotted line = MRC 2, broken line = MRC 3, thin line = MRC 4.

Obstruction: Solid line = FEV_1%pred ≥50, dotted line FEV_1%pred 30-49, broken line FEV_1%pred <30.

Smoking: Solid line = current smoking, dotted line = no smoking.

Exacerbations: Solid line = 0-1 exacerbations in last year, dotted line = 2-3 exacerbations in last year, broken line = >3 exacerbations in last year.

Figure 4. DOSE index and cause-specific mortality



Cox regression analyses, adjusted for age and sex.
Reference = DOSE index score 0-3.

Discussion

Main findings

The primary finding of this multicentre study of COPD patients from primary and secondary care is that a higher DOSE index score is associated with increased mortality risk independent of sex, age, and level of care.

Interpretation of findings in relation to previously published work

A previous study has shown that the DOSE index can predict hospital admission, respiratory failure, and future exacerbations[10], and another study has found an association with mortality in male hospital outpatients.[13] To our knowledge, this is the first study where an association with mortality is shown for both sexes and in a population

including patients from both primary and secondary care. Thus, this index could be a convenient clinical tool for estimating mortality risk among COPD patients in primary care.

The total DOSE index score was robustly associated with mortality. The majority of the separate components that constitute the index were also associated with mortality. The most established predictor of mortality in COPD is FEV_1%pred,[9,17] although results from one study suggested that dyspnoea measured by the MRC dyspnoea scale is a more reliable predictor.[18] Our study demonstrates that the DOSE index – which includes both of these measures – is an even better predictor of mortality. Our analysis also found that the composite DOSE index was a more effective predictor of mortality than its separate components.

The univariate association between smoking status and mortality was not statistically significant. However, in analyses adjusted for the other DOSE index components, smoking was statistically significantly associated with mortality, thus possibly adding a useful contribution to the combined index. A dichotomous measure of current smoking status is potentially limited in precision since previous smoking is not taken into account. An alternative measure of smoking using pack-years has been shown to predict mortality in stable COPD,[19] but a study of COPD patients with severe obstruction failed to show an independent association with mortality for number of pack-years.[20] Other authors have found current smoking in COPD patients to be associated with increased mortality compared with never or ex-smokers, independent of pack-years.[21-23]

Although the DOSE index was associated with mortality in both men and women, the interaction analysis showed that the associations were not identical. An HR of higher magnitude was found for a specific DOSE index score in men compared with women. In contrast, a study of the BODE index[24] found an HR of higher magnitude in women than in men. In another study,[25] BMI was shown to be a more significant component of the total BODE index score in women than in men. Additional adjustment for BMI and depression[26,27] in our study indicated that these factors did not explain sex differences in the associations with mortality.

The analyses of cause-specific mortality showed that the DOSE index is more predictive of death by respiratory disease than other causes. The association of the DOSE index with cardiovascular disease mortality was only statistically significant for a DOSE index score of 4–5, possibly due to a small number of individuals in the 6–7 score group. Determination of cause of death from death certificates can be problematic as certificates may have been incorrectly completed. Several studies have reported that COPD is predominantly under-reported as the underlying cause of death,[28,29] especially when the primary cause is not pulmonary.[30] This suggests that the association of the DOSE index with cardiovascular mortality might be overestimated due to over-recording of cardiovascular disease instead of COPD. However, the important association between the DOSE index and mortality by respiratory disease should not have been overestimated.

The BODE index combines BMI, obstruction (FEV_1%pred), dyspnoea (MRC scale), and exercise capacity measured by the 6-minute walking distance (6MWD), and has also been demonstrated to predict mortality.[11,12,31,32] Exercise capacity cannot be examined easily, which makes it unsuitable for most clinical settings. Another composite prognostic instrument is the ADO index, including age, dyspnoea (MRC scale) and obstruction (FEV_1%pred).[12] Both the ADO and the DOSE index are convenient to administer in clinical settings. An additional advantage of the DOSE index is that it includes measures of health and behaviour such as exacerbations and smoking that can be modified by intervention. Exacerbations have been associated with lung function decline,[33] lower quality of life,[34] and mortality[5] and can be modified by treatment.[35,36]

Strengths and limitations

The strengths of this study are that it is longitudinal and that the study population is sampled from multiple centres representing both primary and secondary care. The data from medical records were initially recorded prospectively and should be reliable and not subject to recall bias. A possible limitation is that a proportion of the original study population was not included in the main analysis, mainly due to lack of spirometry data.

The fact that many COPD diagnoses are based on clinical findings rather than spirometry has been previously demonstrated.[14] The exclusion of patients without this information may result in selection bias, which could potentially influence the results as there was higher mortality among patients with missing data in both primary and secondary care. Possible explanations might be that the patients with most severe disease have been unable or unwilling to perform a lung function test or that they had a diagnosis confirmed by spirometry before study entry. However, when we analysed the entire population after removal of the lung function component from the index, the association with mortality remained in patients both with and without spirometry data. Thus, an index excluding lung function data could be an alternative measure that can be used to predict mortality when spirometry is not available.

Implications for future research, policy and practice

In our opinion, the DOSE index appears to be very suitable for use in primary care since it combines information relevant to both clinical management and assessment of prognosis. Thus, it could be a useful instrument for clinicians in both primary and secondary care to identify mortality risk in COPD patients, enabling optimised management and treatment.

Conclusions

We conclude that the DOSE index can be used as a prognostic instrument for mortality in COPD. The combined DOSE index was a better predictor of mortality than any of its components alone. Our data also indicate that a composite index with dyspnoea, smoking and exacerbations without spirometry data can be clinically useful for assessing prognosis.

Handling editor Niels Chavannes
Statistical review Gopal Netuveli

Acknowledgements The authors thank Ulrike Spetz-Nyström and Eva Manell for reviewing the patient records and all the participating centres.
Conflicts of interest The authors declare they have no conflicts of interest in relation to this article. BS is an Associate Editor of the *PCRJ*, but was not involved in the editorial review of, nor the decision to publish, this article.
Contributorship All co-authors have made substantial contributions to the conception and design of the study and editing of the manuscript. All co-authors have approved the submitted version of the paper. CJ is the guarantor of the study.

Funding The study was supported by grants from the county councils of the Uppsala-Örebro Health Care region, the Swedish Heart and Lung Association, the Swedish Asthma and Allergy Association, the Bror Hjerpstedts Foundation, and the Örebro Society of Medicine.

References

1. Rabe KF, Beghe B, Luppi F, Fabbri LM. Update in chronic obstructive pulmonary disease 2006. *Am J Respir Crit Care Med* 2007;**175**(12):1222-32. http://dx.doi.org/10.1164/rccm.200704-586UP
2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;**349**(9064):1498-504. http://dx.doi.org/10.1016/S0140-6736(96)07492-2
3. Hurd S. The impact of COPD on lung health worldwide: epidemiology and incidence. *Chest* 2000;**117**(2 Suppl):1S-4S. http://dx.doi.org/10.1378/chest.117.2_suppl.1S
4. Almagro P, Calbo E, Ochoa de Echaguen A, *et al*. Mortality after hospitalization for COPD. *Chest* 2002;**121**(5):1441-8. http://dx.doi.org/10.1378/chest.121.5.1441
5. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003;**124**(2):459-67. http://dx.doi.org/10.1378/chest.124.2.459
6. Gudmundsson G, Gislason T, Lindberg E, *et al*. Mortality in COPD patients discharged from hospital: the role of treatment and co-morbidity. *Respir Res* 2006;**7**:109. http://dx.doi.org/10.1186/1465-9921-7-109
7. Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *BMJ* 1959;**2**(5147):257-66. http://dx.doi.org/10.1136/bmj.2.5147.257
8. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988;**93**(3):580-6. http://dx.doi.org/10.1378/chest.93.3.580
9. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for diagnosis, management, and prevention of COPD 2001 [updated 2009; cited 2012 20th April]; Available from: http://www.goldcopd.com.
10. Jones RC, Donaldson GC, Chavannes NH, *et al*. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE index. *Am J Respir Crit Care Med* 2009;**180**(12):1189-95. http://dx.doi.org/10.1164/rccm.200902-0271OC
11. Celli BR, Cote CG, Marin JM, *et al*. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**(10):1005-12. http://dx.doi.org/10.1056/NEJMoa021322
12. Puhan MA, Garcia-Aymerich J, Frey M, *et al*. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet* 2009;**374**(9691):704-11. http://dx.doi.org/10.1016/S0140-6736(09)61301-5
13. Oga T, Tsukino M, Hajiro T, Ikeda A, Nishimura K. Predictive properties of different multidimensional staging systems in patients with chronic obstructive pulmonary disease. *Int J COPD* 2011;**6**:521-6. http://dx.doi.org/10.2147/COPD.S24420
14. Arne M, Lisspers K, Stallberg B, *et al*. How often is diagnosis of COPD confirmed with spirometry? *Respir Med* 2010;**104**(4):550-6. http://dx.doi.org/10.1016/j.rmed.2009.10.023
15. Sundh J, Stallberg B, Lisspers K, Montgomery SM, Janson C. Co-morbidity, body mass index and quality of life in COPD using the Clinical COPD Questionnaire. *COPD* 2011;**8**(3):173-81.
16. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J* Suppl 1993;**16**:5-40.
17. Siafakas NM, Vermeire P, Pride NB, *et al*. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). The European Respiratory Society Task Force. *Eur Respir J* 1995;**8**(8):1398-420. http://dx.doi.org/10.1183/09031936.95.08081398
18. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002;**121**(5):1434-40. http://dx.doi.org/10.1378/chest.121.5.1434
19. Esteban C, Quintana JM, Aburto M, *et al*. Predictors of mortality in patients with stable COPD. *J Gen Intern Med* 2008;**23**(11):1829-34. http://dx.doi.org/10.1007/s11606-008-0783-x
20. Martinez FJ, Foster G, Curtis JL, *et al*. Predictors of mortality in patients with emphysema and severe airflow obstruction. *Am J Respir Crit Care Med* 2006;**173**(12):1326-34. http://dx.doi.org/10.1164/rccm.200510-1677OC
21. Hansen EF, Phanareth K, Laursen LC, Kok-Jensen A, Dirksen A. Reversible and irreversible airflow obstruction as predictor of overall mortality in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**159**(4 Pt 1):1267-71.
22. Hersh CP, DeMeo DL, Al-Ansari E, et al. Predictors of survival in severe, early onset COPD. *Chest* 2004;**126**(5):1443-51. http://dx.doi.org/10.1378/chest.126.5.1443
23. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005;**142**(4):233-9.
24. de Torres JP, Cote CG, Lopez MV, *et al*. Sex differences in mortality in patients with COPD. *Eur Respir J* 2009;**33**(3):528-35. http://dx.doi.org/10.1183/09031936.00096108
25. de Torres JP, Casanova C, de Garcini AM, Jaime AA, Celli BR. COPD heterogeneity: gender differences in the multidimensional BODE index. *Int J COPD* 2007;**2**(2):151-5.
26. Fan VS, Ramsey SD, Giardino ND, *et al*. Sex, depression, and risk of hospitalization and mortality in chronic obstructive pulmonary disease. *Arch Intern Med* 2007;**167**(21):2345-53. http://dx.doi.org/10.1001/archinte.167.21.2345
27. de Voogd JN, Wempe JB, Koeter GH, *et al*. Depressive symptoms as predictors of mortality in patients with COPD. *Chest* 2009;**135**(3):619-25. http://dx.doi.org/10.1378/chest.08-0078
28. Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur Respir J* 2003;**22**(5):809-14. http://dx.doi.org/10.1183/09031936.03.00031403
29. Jensen HH, Godtfredsen NS, Lange P, Vestbo J. Potential misclassification of causes of death from COPD. *Eur Respir J* 2006;**28**(4):781-5. http://dx.doi.org/10.1183/09031936.06.00152205
30. Drummond MB, Wise RA, John M, Zvarich MT, McGarvey LP. Accuracy of death certificates in COPD: analysis from the TORCH trial. *COPD* 2010;**7**(3):179-85. http://dx.doi.org/10.3109/15412555.2010.481695
31. Cote CG, Pinto-Plata VM, Marin JM, Nekach H, Dordelly LJ, Celli BR. The modified BODE index: validation with mortality in COPD. *Eur Respir J* 2008;**32**(5):1269-74. http://dx.doi.org/10.1183/09031936.00138507
32. Martinez FJ, Han MK, Andrei AC, *et al*. Longitudinal change in the BODE index predicts mortality in severe emphysema. *Am J Respir Crit Care Med* 2008;**178**(5):491-9. http://dx.doi.org/10.1164/rccm.200709-1383OC
33. Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV(1) decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the Lung Health Study. *Am J Respir Crit Care Med* 2001;**164**(3):358-64.
34. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;**157**(5 Pt 1):1418-22.
35. Calverley PM, Anderson JA, Celli B, *et al*. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;**356**(8):775-89. http://dx.doi.org/10.1056/NEJMoa063070
36. Tashkin DP, Celli B, Senn S, *et al*. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;**359**(15):1543-54. http://dx.doi.org/10.1056/NEJMoa0805800