Respiratory Medicine 200 (2022) 106899

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Original Research

Emphysema severity index (ESI) associated with respiratory death in a large Swedish general population

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ARTICLE INFO

Keywords:
COPD
Emphysema
Spirometry
Mortality

ABSTRACT

Recently, it has been shown and validated that presence and severity of emphysema on computed tomography could be estimated by a novel spirometry based index, the emphysema severity index (ESI). However, the clinical relevance of the index has not been established.

We conducted cox-regression analyses with adjustment for age, smoking, sex, forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) to study whether ESI was associated with all-cause, respiratory and non-respiratory 10-year mortality. Study population was all participants with acceptable spirometry from the Gott Åldrande i Skåne study, a Swedish general population aged 65–102 years old. ESI is expressed as a continuous numeric parameter on a scale ranging from 0 to 10.

Out of the 4453 participants in the main study, 3974 was included in the final analysis. Higher age, higher ESI, lower FEV_1 and male sex increased hazard of respiratory death. ESI was significantly correlated to respiratory death but not non-respiratory death, while high age, male sex and low FEV_1 was associated with non-respiratory as well as respiratory death. Current smoking habits increased the hazard of respiratory death but did not reach significance (p 0.066) One unit increase in ESI increased hazard of all-cause death by 20% (p 0.0002) and hazard of respiratory death by 57% ($p < 0.0001$). The ESI is a novel clinical marker of emphysema severity that is associated with respiratory death specifically. Since it can be derived from standard spirometry there are potential benefits for clinical practice in terms of more individualised prognosis and treatment alternatives.

1. Introduction

The purpose of the emphysema severity index (ESI) is to provide a standardised and clinically useful marker of emphysema presence and severity using simple spirometry data [1,2]. First presented in 1976, the theory is that the MEFV curve might be altered by the presence of emphysema [3]. It was suggested that the loss of elastic recoil, a positive pleural pressure, structural weakness in the walls of the major airways and high bronchiolar resistance leads to a "kink" in the MEFV curve's descending limb. The ESI is an attempt to quantify this change in shape of the MEFV curve thereby quantifying the level of emphysema with a score ranging from 0 to 10[1]. ESI was shown to correlate with level of estimated emphysema on computed tomography (CT) [1]. The method has now also been validated on 5930 smokers from the COPDgene study [2]. However, no studies on the clinical impact of the ESI have been published. FEV_1 and other spirometric variables such as FEV_1/FVC have been shown to correlate with all-cause mortality in several previous studies and are currently the principal spirometric measures used when establishing severity of airflow obstruction [4–8]. Since ESI is not dependent on reference values or any additional equipment beyond that needed for conducting spirometry, it could be easily implemented in a clinical setting alongside other currently used spirometric parameters such as FEV_1. We wanted to investigate whether ESI increased all-cause mortality and respiratory death specifically.

Abbreviations: ESI, emphysema severity index; SNAC, Swedish National Study on Aging and Care; ATS, American Thoracic Society; TUG, timed get-up-and-go test; MMSE, Mini Mental State Examination; EPD, emphysema-predominant; APD, airway predominant.

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https://doi.org/10.1016/j.rmed.2022.106899
Received 19 January 2022; Received in revised form 2 June 2022; Accepted 3 June 2022
Available online 8 June 2022

The aim of this study was to explore whether raised ESI significantly increases the hazard of 10-year all-cause and respiratory mortality.

2. Methods

This study is part of the longitudinal public health GÅS study, which is part of the Swedish National.

Study on Aging and Care (SNAC). In short, GÅS includes subjects randomly selected from the Swedish municipality register of the rural and urban general population of the southern Swedish province of Skåne. Three separate random selections of participants were made: cohort I, aged 60–95 years at baseline, with baseline examinations in 2001; cohort II, aged 60–81 years at baseline, with baseline examinations in 2006; cohort III with baseline examinations in 2012, aged 60–81. The overall response rate was 71%. The participants were subject to re-examinations at every three to six years depending on their age, consult the study protocol which has been described previously for more details [9]. The study is still ongoing; the most recent examination for those included in this study was in 2017.

Mortality data were collected from the Swedish Cause of Death Register. The Swedish Cause of Death Register comprises data on all deaths of people registered in Sweden and is maintained by the Swedish National Board of Health and Welfare. All deaths before Januari 1st 2017 were available. Each death is registered with date of death, primary causes of death as well as contributing causes of death. Causes of death are registered according to the International Classification of Diseases (ICD-10) system [10]. Only primary causes of death were considered as cause of death for this manuscript.

The inclusion criterion was at least one acceptable spirometry according to American Thoracic Society (ATS) criteria [11].

2.1. Definition of variables

Subjects filled out a self-report questionnaire regarding their history of smoking habits and medical history. Subjects uncertain of their medical history had their medical records reviewed by a physician. A nurse recorded height, weight, timed get-up-and-go test (TUG) and time required to walk 15 m at subjects' maximum speed. TUG was defined as time required to getting up from a straight-backed armchair, walking 3 m and returning to a seated position. Shoes and walking aids were allowed. Smoking habits were categorised as current smokers, ex-smokers or never-smokers. In order to identify cognitive impairment, a Mini Mental State Examination (MMSE) was conducted [12].

2.2. Statistical analysis

In order to assess the impact of ESI on the hazard of total mortality, respiratory and non-respiratory death within 10 years of baseline examination, we conducted Cox regression analyses with adjustment for age, smoking, sex, FEV_1/FVC [7,8] and FEV_1 [7,8,13] in addition to ESI. The covariates included in the statistical analyses were all chosen a priori, i.e. no form of data-driven covariate selection process was applied. A direct acyclic graph (causal diagram), is available as a supplement. The proportional hazards assumption was checked through tests based on cumulative sums of martingale residuals over follow-up times as well as more informal techniques involving time-dependent covariates. There was no indication of violation of model assumptions. In the analysis of respiratory death, the phenomenon of competing risks is present. In this case we model what is known as a cause-specific hazard. The ICD-10 codes for diseases of the respiratory system J00-J99 were used to define a respiratory death [10].

Except for the ESI calculations, all analyses and figures were performed using SAS 9.4 (SAS, Cary, NC, USA).

2.3. Ethics

The study was approved by the regional ethics committee of Lund University (2002; registration number LU 744–00) and all participants or carers provided written consent.

3.

Results are presented in Tables 3-5.

4. Discussion

4.1. Summary of key results

We can confirm three categories of risk factors. First, those that increase the hazard of respiratory death, second those that increase the hazard of non-respiratory death and last those that increase the hazard of respiratory as well as non-respiratory death. ESI was significantly correlated to respiratory death but not non-respiratory death, while male sex and low FEV_1 are associated with non-respiratory as well as respiratory death. Current smoking habits increased the hazard of respiratory death but did not reach significance (p 0.066) One unit increase in ESI increased hazard of all-cause death by 20% (p 0.0002) and hazard of respiratory death by 57% ($p < 0.0001$). FEV_1/FVC was not associated with all-cause mortality or respiratory death.

4.2. ESI score and respiratory death

A recent study demonstrated that ESI correlates well to the extent of emphysema as measured by CT [1]. The ESI methodology has now also been validated in the large multiethnic population of smokers of the COPDGene study with studies on clinical outcome relevant as a further step in estimating the usefulness of ESI [2]. The theoretical background behind the index, and the relation between the presence of emphysema and ESI score have been described previously in detail [1].

Table 1
Baseline characteristics.

	All participants main study[b]	Acceptable spirometry and ESI[c]	In final analysis
Subjects n	4453	4119	3974
Morphology			
Female sex %	55.8	53.5	53.4
Age years	71.3(10.7)	70.9 (9.7)	70.8 (9.7)
Weight kg	75.8(15.4)	76.5 (15.1)	74.5 (14.6)
Height cm	167.5(9.8)	166.3 (9.5)	166.3 (9.5)
BMI kg/m2	26.9(4.5)	27.1(4.5)	27.1 (4.4)
Spirometry			
ESI	NA	1.1(0.8)	1.1 (0.7)
FVC L	NA	3.19 (1.0)	3.20 (1.0)
FEV_1 L	NA	2.47 (0.9)	2.49 (0.8)
Social characteristics			
Current smokers %	13.7	13.8	13.9
Low Socioeconomic status %	3.1	3.1	3.1
Morbidity[a]			
Hypertension %	30.3	35.5	35.1
Type II Diabetes %	7.3	8.0	7.8
Coronary heart disease %	16.4	16.0	15.9
Frailty markers			
Time to walk 15 m s	9.6(3.3)	9.1(3.0)	9.1 (2.9)
Timed Get Up and Go s	8.4(4.6)	8.3(4.6)	8.2 (4.3)
Biomarkers			
CRP >20%	3.1	1.6	1.5

[a] As self-reported in questionnaire.
[b] At time of baseline.
[c] At time of first acceptable spirometry.

Table 2
ESI in analytical sample by background characteristics[a].

	ESI			N
	Mean 95%CI	min	Max	
Male	1.11 (1.08, 1.15)	0.35	8.19	1853
Female	1.09 (1.05, 1.12)	0.38	9.94	2121
Current smoker	1.33 (1.25, 1.41)	0.46	8.87	551
Former smoker	1.11 (1.08, 1.15)	0.38	9.21	1765
Never smoker	1.01 (0.98, 1.04)	0.35	9.94	1658
Age 60 -69	1.04 (1.02, 1.07)	0.35	9.21	2111
Age 70 -80	1.09 (1.03, 1.15)	0.44	8.15	709
Age 80-90	1.18 (1.13, 1.24)	0.39	9.94	1038
Age≥90	1.36 (1.17, 1.54)	0.50	7.28	116

[a] Subjects included in main analysis and with complete covariate data.

Table 3
Effect of ESI on hazard rates for all-cause 10-year mortality.

	Hazard ratio	p
ESI per 1 unit increase	1.20 (1.1, 1.3)	0.0002
FEV_1	0.58 (0.49, 0.69)	<0.0001
FEV_1/FVC	1.8 (0.72, 4.5)	0.20
Female sex	0.46 (0.37, 0.56)	<0.0001
Current smoker	1.1 (0.84, 1.5)	0.40
Former smoker	1.1 (0.89, 1.3)	0.44
Never smoker	1.0 (ref)	.
Age 60-69	1.0 (ref)	.
Age 70-79	2.3 (1.6,3.2)	<0.0001
Age 80-89	9.1 (6.7, 12.2)	<0.0001
Age 90+	8.9 (6.0, 13.2)	<0.0001

Table 4
Effect of ESI on hazard rates for 10-year respiratory death.

	Hazard ratio respiratory death	p	Hazard ratio non-respiratory death
ESI*	1.57 (1.27, 1.94)	p < 0.0001	1.1 (0.99, 1.26)
FEV_1**	0.39 (0.22, 0.69)	0.0013	0.60 (0.50, 0.71)
FEV_1/FVC*	1.40 (0.09, 21.9)	0.8	1.73 (0.64, 4.7)
Female sex	0.35 (0.17, 0.71)	0.0039	0.47 (0.38, 0.59)
Current smoker	2.31 (0.95, 5.6)	0.066	1.07 (0.79, 1.47)
Former smoker	1.57 (0.80, 3.1)	0.19	1.05 (0.86, 1.27)
Never smoker	1.0 (ref)	.	1.0 (ref)

Table 5
Risk factors with significant effects on 10-year mortality overview*.

	Increased hazard of respiratory death	Increased hazard of non-respiratory death
ESI	YES	NO
FEV_1	YES	YES
FEV_1/FVC	NO	NO
Male sex	YES	YES
Current smoker vs Never smoker	NO	NO

*significant effect = $p < 0.05$.

The value of spirometric variables such as FEV_1 in predicting all-cause mortality has been established, with the mechanism not entirely understood [8,13–15]. As these markers have the benefit of being used as more general health markers, perhaps for screening purposes [7] it also means that they have inherent limits in predicting respiratory death specifically. Our findings suggest that if we specifically want to model not all-cause mortality but respiratory death, ESI may be an attractive alternative to both FEV_1 and FEV_1/FVC.

In the present study, we can confirm that ESI significantly correlates to respiratory death at a rate that is of clinical relevance. Moreover, ESI provides added value when modeling future death beyond the predictive value of FEV_1 and smoking habits.

4.3. Consideration of possible mechanisms and comparison with previous studies

While there are no previous studies on the effects of ESI on mortality to compare with, the level of all-cause mortality has been correlated to the level of visually estimated emphysema by CT [8,16]. If the spirometry based ESI can be used to estimate the level of emphysema instead of a CT-based measure it may have advantages for clinical use since it is more time efficient, less expensive and safer as it does not lead to radiation exposure [17,18]. In one study of somewhat younger subjects with a minimum of a 10 year smoking history it was found that COPD characterised as emphysema-predominant(EPD) or airway-predominant (APD) both increased risk for respiratory death by 21–29% respectively [18]. Interestingly, they found that a combination of both APD and EPD had more than twice the mortality rate compared to APD or EPD only. Moreover, EPD only increased risk of respiratory death while APD also increased risk of cardiovascular death. This pattern is consistent with the finding that reduced FEV_1 increased both risk of non-respiratory and respiratory disease while ESI specifically increased the risk of respiratory disease.

4.4. Limitations

The ESI score is measured cross-sectionally for each individual, cross-sectional analysis is always subject to a certain degree of uncertainty as it relies on only one point in time. Further, variations in ESI score are not measured individually but between individuals, that is different ESI scores come from different individuals. A longitudinal analysis on the effects of mortality of individually measured variations in ESI over time could further strengthen the evidence for the effects of ESI on mortality.

Selection bias is an issue that should be considered in all population studies. The underlying population for this study was from a geriatric age-category but otherwise randomly selected from the municipality register. Although the participation rate was relatively high there will always be risk of selection bias with any degree of non-participants, we can suspect selection of the fittest as patients with high degree of morbidity may be less inclined to participate. We aimed to reduce the level of selection of the fittest by making home-calls. Missing data or being unable to complete a spirometry will reduce the final analytical sample further, Table 1demonstrates that 89% of those participating in the main study were included in the final analytical sample, no obvious differences in demographics or health can be observed between the groups (see Table 2).

Current smoking habits did not significantly increase the hazard of respiratory death, but showed a clear trend. This is likely a result of low power due to the relatively small number of 51 subjects with respiratory disease as cause of death. Causes of death are drawn from the official death registers of Sweden, where not all causes of death are verified with autopsy. If clinical diagnoses of cause of death had been confirmed with autopsy in all cases this had likely increased the specificity of respiratory deaths which would likely increase the robustness of the findings. For the analysis of cause-specific death we have used sub-distribution hazards, an alternative would have been to use the method suggested by Fine and Gray which may have yielded different results.

4.5. Sensitivity analysis for BMI and sex

We did not include BMI in the main analysis since a previous large longitudinal study based on a population from which this study-population was drawn did not find that BMI was associated with

relative or longitudinal lung function change [9]. However, a sensitivity analysis was done to see if BMI would have altered the effect of ESI on mortality. With BMI categorised as underweight (BMI <18.5), normal weight (BMI 18.5–25) and overweight (BMI >25), the effect on total mortality of ESI remained unchanged at HR 1.2 (1.1, 1.3). This suggests that it is unlikely that BMI has in any significant way confounded the results of the effect of ESI on total or respiratory mortality.

We conducted sex-stratified analysis in order to explore whether the association between ESI and mortality was different. There seems to be no difference between sexes, the effect of one unit increase of ESI on overall mortality for women was HR 1.19 (1.03, 1.38) and for men HR 1.17 (1.04, 1.33).

5. Conclusion and possible contributions of the study

The ESI is a novel clinical marker of emphysema severity that is significantly associated with respiratory death at group level. Since it can be derived from a standard spirometry we consider it a marker with a potential to be used in the clinical setting as well as in treatment studies with the aim to better individualise treatments as well as prognosis. As a next step, our findings should be replicated and the predictive value of phenotyping based on ESI scores evaluated.

CRediT authorship contribution statement

Johannes Luoto: Conceptualization, Methodology, Formal analysis, Data curation, Writing original draft and review, Funding acquisition. **Mats Pihlsgård:** Methodology, Formal analysis. **Massimo Pistolesi:** Supervision, Resources. **Matteo Paoletti:** Conceptualization, Data curation, Formal analysis. **Mariaelena Occhipinti:** Conceptualization. **Per Wollmer:** Conceptualization, Supervision, Methodology. **Sölve Elmståhl:** Supervision, Resources, Investigation, Funding acquisition.

Declaration of competing interest

Dr. Occhipinti reports grants from Fondazione Menarini, personal fees from Novartis, outside the submitted work; Dr. Wollmer reports grants from Swedish Heart and Lung Foundation, grants from Lund University, grants from Skåne Region, during the conduct of the study; personal fees from Chiesi Pharma, outside the submitted work; In addition, Dr. Wollmer has a patent Device and method for pulmonary function measurement issued.. Dr. Luoto reports grants from Skåne County, during the conduct of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.106899.

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