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Restrictive pulmonary dysfunction at spirometry and mortality in the elderly

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Summary
Objectives: To evaluate the association between pulmonary restriction and mortality in the elderly, taking into account potential confounders not considered in the past (disability, cognitive dysfunction, diabetes, and visceral obesity).
Design: Longitudinal study.
Setting: Community-based.
Participants: Twelve hundred sixty-five patients (51.9% men) aged 65—97 years old from the Salute Respiratoria nell'Anziano (SaRA) Italian multicentric study.
Measurements: Participants were divided in 4 groups: normal spirometry (NS): FEV1/FVC ≥ 70%, FVC ≥ 80% of predicted; restrictive ventilatory pattern (RVP): FEV1/FVC ≥ 70%, FVC < 80%; obstructive ventilatory pattern (OVP): FEV1/FVC < 70%, FVC ≥ 80%, and mixed ventilatory pattern (MVP): FEV1/FVC < 70%, FVC < 80%. We calculated the association between restriction and mortality corrected for potential confounders using a multivariable Cox regression model.
Results: We found a prevalence of RVP, OVP and MVP of 10.9%, 25.4%, and 17.3%, respectively. Compared to people with normal spirometric pattern, disability (19.6% vs. 10.1%), poor physical performance (35.4% vs. 22.3%), cognitive impairment (21.0% vs. 11.5%), increased waist circumference (62.1% and 26.8%), and kyphoscoliosis (56.8 and 13.5%) were more prevalent in the RVP group. After correction for potential confounders, RVP was associated with increased mortality (HR: 1.89; 95% CI: 1.15—3.11), as well as OVP (HR: 2.33; 95% CI: 1.58—3.11) and MVP (HR: 2.60; 95% CI: 1.74—3.93). Other factors associated with mortality were disability (HR: 1.92; 95% CI: 1.35—2.72), poor physical performance (HR: 1.37; 95% CI: 1.01—1.85),

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cognitive impairment (HR: 1.55; 95% CI: 1.06–2.27), depression (HR: 1.57; 95% CI: 1.16–2.13) and diagnosis of stroke (HR: 1.90; 95% CI: 1.18–3.05).

Conclusions: RVP is associated with higher mortality in the elderly and, thus, deserves the same attention paid to an obstructive pattern. However, mechanisms mediating this association need to be clarified.

Introduction

Lung restriction is a multi-factorial clinical condition featured by a reduction of lung volumes. Its estimated prevalence is 6% in the overall adult and up to 15% in the elderly population.[1,2] The diagnosis of pulmonary restriction requires the measurement of lung volumes, but a reduction of the forced ventilatory capacity without bronchial obstruction at simple spirometry is commonly used as a proxy for this condition. This restrictive ventilatory pattern (RVP) has been associated with mortality in the NHANES I population, with adjusted hazard ratios ranging from 1.4[3] to 1.7,[4] depending on different analytic approaches. Similar results were found in the Atherosclerosis Risk in Communities (ARIC) study[5] and Cardiovascular Health Study (CHS).[6] Elderly people have been excluded from the studies performed using NHANES (maximum age: 75 years, with only 3% if the sample aged over 70 years) and ARIC (maximum age: 66 years) data; therefore, the only information on elderly people comes from the CHS study, which did not include people aged less than 65 years. The focus of the published study,[6] however, was on the association between decline of pulmonary function and mortality, and data relative to people with RVP were provided separately for rapid and non-rapid decliners. Furthermore, this study selected the subsample of participants who had spirometry performed at both baseline and follow-up (approximately 4 years later); as a consequence, 32% of the baseline population was excluded, and the risk of being excluded increased with age.

Given the lack of information about the prognosis associated with RVP in the elderly population, we used the data coming from the Respiratory Health in the Elderly (Salute Respiratoria nell'Anziano – SARA) study to estimate the risk of mortality associated with this pattern compared with normal and pathologic spirometry in a population aged 65 years and older.

Methods

Data source

Between January 1996 and July 1999 a total of 1970 outpatients were recruited from 24 departments of geriatrics or respiratory medicine participating in the Respiratory Health in the Elderly (Salute Respiratoria nell'Anziano – SARA) study. This is a multi-centre Italian project, investigating various aspects of chronic airway diseases in the elderly population (age ≥ 65 years) affected by pulmonary and non-pulmonary diseases. Details on the recruitment criteria, studied population and diagnostic procedures are available elsewhere.[7] The study design was approved by

the Ethical Committees of the participating institutions. Patients gave their written consent to participate in the study.

Clinical assessment

Physical functioning was explored using the six-minute walk test (6′ WT) and the Barthel index, cognitive function using the Mini-Mental Status Examination (MMSE), and mood status using the 15-item Geriatric Depression Scale (GDS). Patients underwent a complete physical examination. Co-morbid diseases, identified on the basis of history and physical examination, were recorded according to the ICD9. Asthma was diagnosed according to previously reported criteria.[8]

Respiratory function assessment

All the centres were provided with an identical fully computerized water-sealed Stead–Wells spirometer (Baires System; Biomedin; Padua, Italy) matching the standards of the American Thoracic Society recommendations for diagnostic spirometry. Baseline and post-bronchodilator spirometry were performed according to the guidelines of the American Thoracic Society.[8] All the centres achieved a high quality performance in spirometry. Spirometric flow–volume curves were considered acceptable if they had Extrapolated Volume (VEXT) <5% of the FVC or 0.150 L. According to recommendations by ATS, we did not exclude curves which did not satisfy the repeatability criteria to avoid the exclusion of data in which an abnormal lung function causes a greater coefficient of variation than in normal subjects. FVC was measured only on curves with an end expiratory phase ≥1 s with a volume change lower than the minimal detectable volume of 0.026 L.[9]

Current guidelines define RVP as a vital capacity below the lower limit of normal in absence of obstruction.[9] The studies performed so far on this topic, however, have used a different definition (forced vital capacity [FVC] < 80% of predicted) based on older guidelines.[10] To provide results comparable to the available evidence, we decided to maintain the previous definition and, therefore, defined RVP on the basis of an FVC < 80% of predicted in absence of pulmonary obstruction (FEV1/FVC ratio < 0.7). We also included in our analysis an obstructive ventilatory pattern (OVP), defined as a FEV1/FVC ratio < 0.7 with normal FVC, and a mixed defect (MVP) as the co-existence of FVC < 80% of predicted and FEV1/FVC ratio < 0.7.

Sample selection and follow-up

From the initial sample we excluded those with incomplete spirometric data, with spirometries that did not meet the

ATS standards ($N = 474$). All the subjects were followed-up throughout January 30, 2002 with regard to their vital status and cause of death by contacting the registry office of the last municipality of residence. Information on vital status was obtained for 1265 of the 1496 patients selected (84.6%). Follow-up time was calculated from the date of recruitment (first visit) until the date of death or January 30, 2002, censoring participants if they were still alive at the end of follow-up or after 60 months. Causes of death were coded using the 9th revision of the WHO-ICD.

Analytic approach

We compared the demographical and clinical characteristics of people with normal spirometry (NS), RVP, OVP and MVP, respectively, and evaluated the between-groups difference using the chi-square test. MMSE and GDS scores were categorized using a cut-off of 24 and 5, respectively.[11,12] We considered physically impaired people who were not independent in at least 1 activity of daily living (corresponding to a Barthel's score < 90), and used the 25th percentile to categorize the distance walked in 6 min (cut-off value: 57% of predicted, corresponding to an average of 229.6 meters). Smoking status was defined as former, current or non-smoker. The following factors expected to be related to both pulmonary restriction and mortality were included in the analyses: undernutrition (BMI < 20) and overweight (BMI > 30); visceral obesity (waist circumference >100 cm in men and >90 cm in women)[13]; spine deformities, as reflected by an occiput-

wall distance (OWD) greater than the 75th percentile (8 cm); selected active diseases (asthma, respiratory diseases, diabetes mellitus, heart disease, ischemic stroke history).

We compared the mortality rates of people with RVP relative to controls and other spirometric ventilatory patterns. To evaluate the association between ventilatory pattern and mortality taking into account potential confounders, we used a multivariable Cox proportional hazard model. The proportional hazard assumption was checked using a plot of the log-log of the survival function vs. the log of follow-up time. We selected the variables to be included in the model on the basis of clinical judgement as well as the results of the univariable analysis. People with asthma are likely to show a RVP,[14] but they are functionally to be considered obstructed, not restricted. Since we felt that analytic adjustment for the diagnosis of asthma might not be sufficient to eliminate this possible confounding, we repeated the analysis in people without asthma.

All analyses were performed using the SAS for Windows V9.0 (SAS Institute, Cary, NC).

Results

We studied 1265 patients aged 65–97 years (mean age 73.4; SD 6.21), men were 51.8%. Of these, 138 (10.9%) showed a RVP, 322 (25.4%) had an OVP and 219 (17.3%) had MVP. Socio-demographic and clinical characteristics are shown in Table 1. The prevalence of people aged 80 years or older was 26.8% in the group with RVP (OR 1.65; 95% CI:

Table 1 Demographic, clinical and anthropometric characteristics

|	Respiratory pattern				
	Normal (586) %	Restrictive (138) % (OR; 95% CI)	Obstructive (322) % (OR; 95% CI)	Mixed (219) % (OR; 95% CI)	P
Age over 80	18.1 (1.00)	26.8 (1.66; 1.08–2.55)	18.6 (1.03; 0.73–1.47)	17.8 (0.98; 0.65–1.47)	0.11
Gender (male)	35.8 (1.00)	49.3 (1.74; 1.20–2.53)	65.2 (3.36; 2.52–4.46)	76.3 (5.75; 4.03–8.19)	<0.001
Smoking status					
Never	55.1 (1.00)	58.4 (1.14; 0.78–1.67)	27.4 (0.30; 0.23–0.42)	23.7 (0.25; 0.17–0.36)	<0.001
Former	32.4 (1.00)	34.1 (1.09; 0.73–1.61)	52.2 (2.29; 1.72–3.04)	63.0 (3.55; 2.53–4.98)	<0.001
Current	12.5 (1.00)	7.3 (0.55; 0.27–1.10)	20.2 (1.78; 1.23–2.58)	13.2 (1.07; 0.68–1.70)	<0.001
Disability in at least 1 ADL	10.1 (1.00)	19.6 (2.17; 1.32–3.58)	12.1 (1.23; 0.80–1.89)	24.7 (2.92; 1.94–4.40)	<0.001
Poor physical performance[a]	21.4 (1.00)	32.3 (1.75; 1.15–2.67)	24.3 (1.18; 0.85–1.65)	36.0 (2.06; 1.45–2.93)	<0.001
Cognitive impairment[b]	11.5 (1.00)	21.0 (2.05; 1.27–3.32)	10.6 (0.91; 0.59–1.41)	15.2 (1.38; 0.88–2.17)	0.009
Depression[c]	35.1 (1.00)	36.9 (1.08; 0.73–1.60)	30.2 (0.80; 0.59–1.08)	41.4 (1.31; 0.94–1.80)	0.068
Body mass index < 20	3.8 (1.00)	5.1 (1.37; 0.57–3.27)	5.0 (1.34; 0.69–2.59)	5.9 (1.62; 0.80–3.27)	0.570
Body mass index > 30	18.6 (1.00)	23.9 (1.37; 0.88–2.14)	15.5 (0.80; 0.56–1.16)	16.9 (0.89; 0.59–1.34)	0.180
Increased waist circumference[d]	56.8 (1.00)	62.1 (1.24; 0.84–1.83)	44.1 (0.60; 0.45–0.79)	51.2 (0.80; 0.58–1.09)	<0.001
Spine kyphosis[e]	21.1 (1.00)	39.0 (2.40; 1.58–3.64)	32.3 (1.79; 1.30–2.47)	40.7 (2.57; 1.81–3.66)	<0.001
Ischemic stroke	5.3 (1.00)	8.8 (1.71; 0.85–3.41)	2.2 (0.40; 0.17–0.92)	4.6 (0.85; 0.41–1.77)	0.020
Heart disease	10.8 (1.00)	15.3 (1.49; 0.87–2.54)	12.3 (1.16; 0.76–1.77)	16.5 (1.63; 1.05–2.54)	0.130
Diabetes mellitus	11.9 (1.00)	18.2 (1.66; 1.00–2.74)	10.4 (0.87; 0.56–1.34)	14.7 (1.28; 0.81–2.01)	0.090
Asthma	5.5 (1.00)	21.0 (4.61; 2.68–7.93)	19.9 (4.29; 2.74–6.73)	26.5 (6.24; 3.91–9.94)	<0.001

[a] Six-minute walk distance < 25th percentile (57% of predicted).
[b] Mini-Mental State Examination score < 24.
[c] Geriatric depression scale ≥ 5.
[d] Waist circumference ≥ 90 (women) or ≥ 100 (men).
[e] Occiput-wall distance > 75th percentile (8 cm).
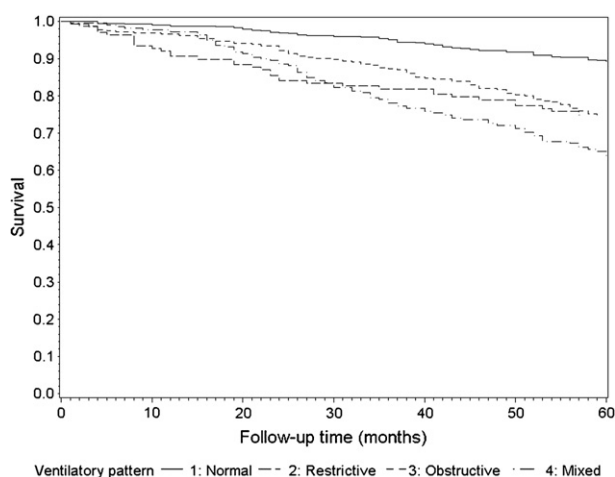
Figure 1 Survival of people with normal, restrictive, obstructive and mixed spirometric pattern.

1.10—2.47) compared with values between 17.8 and 18.6% among people with NS, airways obstruction and mixed defect ($P = 0.11$); men were more prevalent in pathologic ventilatory patterns compared to NS. Smoking was associated with OVP, but not with RVP. In RVP and MVP, but not in the OVP groups, we found a higher prevalence of disability and poor physical performance. Cognitive impairment was more frequent in RVP, as well as a history of stroke and diabetes. No significant differences were found among groups with regard to BMI indexes or visceral obesity. The prevalence of asthma was similar in the RVP, OVP and MVP groups (21.0%, 19.9%, 26.5%, respectively, $P = 0.179$); as expected, the prevalence in the NS group was markedly lower (5.5%).

We observed 253 deaths during a mean of 53.2 months follow-up (range: 1—60, cumulative: 5,613 years), yielding an estimated mortality rate (MR) of 4.51 deaths/100 persons/year, with higher rates in the group with RVP (34 deaths; MR: 5.95 deaths/100 persons/year), OVP (80 deaths; MR: 5.69 deaths/100 persons/year) and MVP (78 deaths; MR: 8.65 deaths/100 persons/year) vs. 2.23 deaths/100 persons/year in the NS group. The Kaplan—Meier estimators of the survival function in the different groups are shown in Fig. 1. Compared to controls the unadjusted hazard ratios (HR) for death relative to RVP, OVP, and MVP were 2.70 (95% CI: 1.78—4.11), 2.57 (95% CI: 1.84—3.59), and 3.96 (95% CI: 2.83—5.53) respectively. The age- and sex-adjusted HR was 2.19 (95% CI: 1.44—3.35) in the RVP group, 2.12 (95%

CI: 1.52—2.99) in the OVP, 3.42 (95% CI: 2.41—4.85) in the MVP group.

Table 2 shows the cause-specific mortality rates. Compared to the NS group, those with RVP had an increased mortality by cerebrovascular causes (mortality rate ratio [MRR]: 4.79; 95% CI: 1.28—17.91). As expected, mortality by cardiac and pulmonary diseases was higher in all groups compared to normal controls. In the RVP group, however, the mortality rate for pulmonary causes was heavily influenced by the higher prevalence of people with asthma in this group: when we repeated the analysis excluding people with asthma, total mortality in this group remained unchanged (5.7/100 persons/year), while pulmonary mortality fell to 0.44/100 persons/year. In the OVP and MVP groups, exclusion of people with asthma changed the estimated pulmonary mortality rate to a much lesser degree (0.53/100 persons/year and 1.68/100 persons/year, respectively). Finally, mortality for neoplasm was increased in OVP (MMR: 2.79; 95% CI: 1.41—5.66) and MVP (MMR: 3.22; 95% CI: 1.53—6.81) but not in RVP (MMR: 0.90; 95% CI: 0.17—3.13).

After correction for potential confounders (Table 3), a RVP was still associated with an increased mortality (HR: 1.89; 95% CI: 1.15—3.11), as well as OVP (HR: 2.33; 95% CI: 1.59—3.42) and MVP (HR: 2.61; 95% CI: 1.74—3.93). Other factors associated with mortality were age over 80 years (HR: 2.52; 95% CI: 1.85—3.43), male sex (HR: 2.12; 95% CI: 1.42—3.16), current smoking (HR: 2.01; 95% CI: 1.29—3.14), disability (HR: 1.92; 95% CI: 1.35—2.72), physical limitation (HR: 1.37; 95% CI: 1.01—1.85), cognitive impairment (HR: 1.55; 95% CI: 1.06—2.27), depression (HR: 1.57; 95% CI: 1.16—2.13) and a diagnosis of stroke (HR: 1.90; 95% CI: 1.18—3.05). When the analysis was repeated after exclusion of people with asthma ($N = 183$), the point estimate of association between restriction and mortality was unchanged (HR: 1.89; 95% CI: 1.09—3.26), and also confirmed the association of mortality with OVP (HR: 2.33; 95% CI: 1.59—3.42) and MVP (HR: 2.62; 95% CI: 1.74—3.93).

Discussion

We found that a RVP at spirometry is associated with a higher mortality in elderly people. To our knowledge, this is the first report on the prognostic value of spirometric restriction in this age group that takes into account important confounders, such as cognitive function, objectively measured physical performance, and visceral obesity. Our point

Table 2 Cause-specific mortality rates among groups

	Respiratory pattern			
	Normal (/100 PY)	Restrictive (/100 PY) (MRR[a]; 95% CI)	Obstructive (/100 PY) (MRR[a]; 95% CI)	Mixed (/100 PY) (MRR[a]; 95% CI)
Cardiac	0.69 (1.00)	1.05 (1.51; 0.60—3.78)	1.71 (2.45; 1.35—4.48)	2.77 (3.98; 2.19—7.23)
Pulmonary	0.07 (1.00)	1.05 (14.36; 2.89—71.16)	0.71 (9.72; 2.13—44.36)	1.66 (21.72; 5.19—49.37)
Cerebrovascular	0.22 (1.00)	1.05 (4.79; 1.54—14.84)	0.28 (1.30; 0.36—4.59)	0.22 (1.01; 0.20—5.00)
Neoplasms	0.58 (1.00)	0.52 (0.90; 0.26—3.08)	1.63 (2.79; 1.47—5.29)	1.88 (3.22; 1.62—6.37)

[a] Mortality rate ratio.

Table 3 Multivariable Cox regression analysis for 5-years mortality rates

	Hazard ratio	95% Hazard ratio confidence limits
Restrictive respiratory pattern	1.89	1.15—3.11
Obstructive respiratory pattern	2.33	1.58—3.42
Mixed respiratory pattern	2.60	1.74—3.93
Age over 80	2.52	1.85—3.43
Male gender	2.17	1.42—3.16
Current smoker	2.01	1.29—3.13
Former smoker	1.12	0.76—1.66
Disability in at least 1 ADL	1.92	1.35—2.72
Poor physical performance[a]	1.37	1.01—1.85
Cognitive impairment[b]	1.55	1.06—2.27
Depression[c]	1.57	1.16—2.13
Increased waist circumference[d]	0.85	0.64—1.13
Spine kyphosis[e]	0.93	0.67—1.29
Diagnosis of ischemic stroke	1.90	1.18—3.05
Diagnosis of diabetes	1.32	0.92—1.90
Diagnosis of asthma	0.86	0.57—1.28

[a] Six-minute walk distance < 25th percentile (59% of predicted).
[b] Mini-Mental State Examination score < 24.
[c] Geriatric depression scale ≥ 5.
[d] Waist circumference ≥ 90 (women) or ≥ 100 (men).
[e] Occiput-wall distance > 75th percentile (7 cm).

estimate of the hazard ratio of dying (HR: 1.89) is strikingly similar to the one reported by Mannino et al. in the NHANES population aged less than 75 years (HR: 1.70),[4] indicating that age does not influence the prognostic value of restriction.

We are not able to directly compare our results with those coming from the Cardiovascular Health Study, which included people with an age distribution (mean age: 77 years) similar to the one of the present study, because the hazard rate estimates of people with restriction are reported separately for those with and without rapid pulmonary function decline. Nonetheless, the mortality rate in our restricted patients is similar to the one reported by the CHS investigators for the group with restriction and without rapid decline of the pulmonary function (5.4/100 person/year).[6] We also found similar mortality rates for obstructive and mixed ventilatory patterns. Compared to people without both restriction and rapid pulmonary decline (1.9/100 person/year), the unadjusted mortality rate ratio was 2.84, once again very close to the hazard ratio that we calculated in our sample (2.87). Our data provide information beyond those coming from the CHS for several reasons. First, survival estimation in the CHS was conditional to remaining in the study cohort between baseline and follow-up spirometry, and this condition was met for only 60% of people with restriction; second, we provide an adjusted estimate of the hazard ratio for mortality in people with restriction regardless of the rapidity of decline of their lung function. Furthermore, we could take into account potential confounders that have not been considered before: waist circumference, cognitive status, and an objectively measured index of physical performance such as the six-minute walk test.

The increased mortality for pulmonary causes in the MVP group was not confirmed after correction for the higher prevalence of asthma in this group. People with asthma are at increased risk of having a RVP pattern because of air trapping with reduced vital capacity. Nevertheless, asthma had a comparable prevalence in the RVP, OVP, and MVP groups, but only in the RVP the strength of the association with mortality declined noticeably (from 1.05 to 0.44/100 persons/year) in the analysis excluding asthmatics. The association between asthma and restriction has been also shown in the NHANES population.[15] In a study on post-puberal asthmatic patients, it was found that the prevalence of RVP was 24%, but only 8% had a true reduction in lung volumes measured using plethysmography.[14] Interestingly, both in the CHS and ARIC studies, restriction was associated with an increased risk for hospitalization caused by COPD[5,6]: this might depend upon the inclusion of people with asthma in the group with restriction.

The interpretation of the association between RVP and total mortality, but not mortality by pulmonary causes, is not straightforward. We could not find in the literature other studies reporting cause-specific mortality associated with restriction, and we can only speculate on the causal link between this respiratory pattern and mortality. We derived the causes of death from ICD9 codes reported on death certificates, and this can introduce some misclassification.[14] Another possible explanation is that RVP may be a risk factor for other diseases, in the same way as COPD is a risk factor for cardiovascular diseases,[16] or that restriction is an early indicator of a disease that was not diagnosed yet at the time of spirometry.

We found only a weak association between RVP and history of cerebrovascular diseases, and no association between RVP and cardiovascular diseases and diabetes. This seems to be counterintuitive, because these disorders have been linked to pulmonary lung volume reduction.[17—19] Our point estimates for these association, however, are similar to the ones found by Mannino et al. in the NHANES population.[3] Therefore, lack of statistical power seems to be the most likely explanation for this negative finding.

RVP was associated with visceral obesity, but not with increased BMI. Therefore, in an elderly population, the measurement of waist circumference should be preferred or used in addition to the simple BMI estimation to identify people at risk for ventilatory dysfunction. The recently proved relationship between insulin resistance, which is strictly associated with visceral obesity, and RVP supports this conclusion.[20]

This study presents some limitations. First, the diagnosis of restriction was based on FVC and not on total lung capacity. Thus, we might have overestimated the number of patients with reduced lung volumes,[21] especially those with air trapping, although the exclusion of people with bronchial obstruction (FEV1/FVC < 0.7) reduces this possibility. Second, we were unable to identify all causes of restriction, some of which are diseases like, thyroid gland dysfunction or metabolic syndrome, that remain frequently unrecognized in the elderly.[21—23] Third, the causes of death were derived from the death certificates and not from clinical chart review; this guarantees for an uniform collection of data, but carries some risk of misclassification.[24]

Conclusion

This study has shown that the association between RVP and mortality described in people aged less than 75 years is also present in a population of people aged up to 95 years. Research is needed to verify whether a RVP also predicts an accelerated decline of physical capabilities. Collecting this information might expand our knowledge of the indicators of frailty in the elderly, contributing to define the profile of risk for disability as well as to clarify the clinical meaning of and, then, the indications to spirometry in the elderly.

Conflict of interest statement

The authors have no conflict of interest.

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