



Airflow limitation by the Global Lungs Initiative equations in a cohort of very old adults

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ABSTRACT The cut-off for forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) defining airflow limitation for chronic obstructive pulmonary disease (COPD) is still contested. We assessed airflow limitation prevalence by the lower limit of normal (LLN) of Global Lungs Initiative (GLI) 2012 reference values and its predictive ability for all-cause mortality and hospitalisation in very old adults (aged ≥ 80 years) compared with the fixed cut-off.

In a Belgian population-based prospective cohort of 411 very old adults, airflow limitation prevalence by the 5th percentile of GLI 2012 z-scores (GLI-LLN) and fixed cut-off (0.70) were compared with COPD reported by general practitioners (GPs). Survival and Cox regression multivariable analysis assessed the association of airflow limitation by both cut-offs with 5-year all-cause mortality and first hospitalisation at 3 years.

9.2% had airflow limitation by GLI-LLN and 27% by fixed cut-off, without good agreement (κ coefficient ≤ 0.40) with GP-reported COPD (9%). Only airflow limitation by GLI-LLN was independently associated with mortality (adjusted hazard ratio 2.10, 95% CI 1.30–3.38). FEV₁/FVC < 0.70 but \geq GLI-LLN (17.8%) had no significantly higher risk for mortality or hospitalisation.

In a cohort of very old adults, airflow limitation by GLI-LLN has lower prevalence than by fixed cut-off, independently predicts all-cause mortality and does not miss individuals with significantly higher all-cause mortality and hospitalisation.



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Introduction

Chronic obstructive pulmonary disease (COPD) is projected to become an important cause of morbidity and mortality, especially due to worldwide population ageing [1]. Its diagnostic hallmark is irreversible airflow limitation based on the ratio of forced expiratory volume in 1 s (FEV₁) to forced vital capacity (FVC), yet its cut-off and the definition of COPD diagnosis are still contested [2, 3].

Both the Global Initiative for Chronic Obstructive Lung Disease and the American Thoracic Society (ATS)/European Respiratory Society (ERS), in their guidelines for COPD diagnosis and treatment, recommend the use of the fixed cut-off of 0.70 to define airflow limitation [2, 4]. Yet, in their guidelines for the interpretation of lung function tests, ATS/ERS support the use of the lower limit of normal (LLN) at the 5th percentile of the frequency distribution of values of a reference “healthy” never-smoker population of equivalent age and sex. The fixed cut-off approach leads to overdiagnosis of COPD in older adults, as it does not take into account the age-related decline in respiratory parameters, while the LLN cut-off approach is dependent on age-specific reference values [5, 6]. These have been lacking for adults aged >80 years or have been extrapolated from younger populations, until recently when the Global Lung Initiative (GLI) all-age reference equations for different ethnic groups and populations aged 3–95 years were made available [5, 7]. The Lambda Mu Sigma (LMS) approach of calculating the LLN that uses the 5th percentile of the distribution of z-scores (similar to growth charts and bone mineral density) is considered more appropriate, as it takes into account the age-related decline in FEV₁/FVC, variability of spirometry values and skewness of reference data [5, 8, 9]. It has also been found to be clinically valid based on its association with all-cause mortality, respiratory symptoms, incident mobility disability, COPD-related hospitalisations and FEV₁ decline [10–12]. However, previous studies on the LMS approach of calculating the LLN did not use the GLI 2012 reference equations or focus on people aged ≥80 years, the fastest growing age group among older adults [10, 13].

This study will compare the prevalence of airflow limitation based on the 5th percentile of GLI 2012 z-scores distribution (GLI-LLN) and the fixed cut-offs and their agreement with the COPD diagnosis reported by the general practitioner (GP) in a population-based cohort of very old adults (aged ≥80 years). It will also evaluate and compare the predictive ability of airflow limitation defined by either/both cut-offs for all-cause mortality and first unplanned hospitalisation.

Methods

Study design and population

The BELFRAIL study (BF_{C80+}) is a prospective, observational, population-based cohort study of people aged ≥80 years living in Belgium. Its aim is to improve the understanding of the epidemiology and pathophysiology of chronic diseases in this age group. The study protocol and sampling methods have already been described in detail [14]. Briefly, between November 2008 and September 2009, in 29 GP centres, 567 community-dwelling individuals aged ≥80 years were recruited, excluding only those with known severe dementia, in palliative care and medical emergencies (acute illnesses needing urgent hospitalisation). At baseline, the participants' GPs recorded sociodemographic data and medical history. An extensive standardised assessment by a clinical research assistant included spirometry and blood sample collection. Hospitalisation data were collected from the GPs until 2.93±0.21 years and mortality data until 5.19±0.22 years from baseline. The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain (UCL) in Brussels, Belgium, and all participants gave informed consent.

Baseline spirometry

All spirometry tests were administered by two trained clinical research assistants using a Spirobank spirometer (MIR, Rome, Italy) that has been found to be reliable for research purposes [15]. After demonstration of the correct spirometry manoeuvre, participants performed up to eight FVC manoeuvres or until exhaustion. Reversibility testing was not done. Repeatability of the spirometry was automatically calculated in accordance with ATS/ERS criteria [16]. Two independent researchers evaluated all spirometry tests by the ATS/ERS criteria and classified them in the following levels: 1) all acceptability and repeatability criteria were fulfilled; 2) all criteria were fulfilled except duration of expiration >6 s; 3) spirometry tests had good starts and no cough during the 1 s of manoeuvre; 4) none of the criteria were fulfilled. Participants with spirometry tests of level 1–2 were included in this study. Standardised measurements of height were performed during the clinical research assistant visit. The GLI 2012 all-age reference equations were used for sex-, age- and height-specific mean predicted values of FEV₁ and FVC and calculation of z-scores to determine GLI-LLN using the GLI 2012 Microsoft Excel Sheet Calculator (Global Lung Function Initiative, www.lungfunction.org).

Outcomes and variables

All-cause mortality and time to first unplanned hospitalisation after baseline were used as outcome measurements. In addition to age and sex, other potential confounding variables were included in the statistical analysis as follows: smoking status (never, previous or current smoker), number of nonrespiratory comorbidities (unweighted disease count including anaemia, Parkinson's disease, arthritis, arthrosis, osteoporosis, cancer, depression, hypertension, diabetes, angina pectoris, myocardial infarction, cardiomyopathy, transient ischaemic attacks, cerebrovascular accidents, peripheral arterial disease, decompensated heart failure, valvular disease, thyroid dysfunction, renal failure, hyperlipidaemia and atrial fibrillation), high-sensitivity C-reactive protein (hsCRP), N-terminal pro-brain natriuretic peptide (NT-proBNP) and estimated glomerular filtration rate (eGFR). The GPs reported the recorded status of smoking and morbidities at baseline. Blood samples were collected in the morning and serum samples were stored frozen at -80°C until analysis. Serum NT-proBNP levels were measured with Dade-Dimension Xpand (Siemens, Deerfield, IL, USA). Serum creatinine and hsCRP were measured with UniCel Dx C 800 Synchron (Beckman Coulter, Brea, CA, USA). The eGFR was estimated according to the equation from the Modification of Diet in Renal Disease Study Group [17].

Statistical analysis

Based on the two FEV₁/FVC cut-offs, the study population was divided into three airflow limitation categories: 1) participants with FEV₁/FVC ≥ 0.70 and \geq GLI-LLN (no airflow limitation by both cut-offs); 2) participants with FEV₁/FVC < 0.70 and \geq GLI-LLN (airflow limitation by fixed cut-off only); 3) participants with FEV₁/FVC < 0.70 and $<$ GLI-LLN (airflow limitation by both cut-offs). There were no participants with FEV₁/FVC ≥ 0.70 and $<$ GLI-LLN. The baseline variables and outcomes across the three categories were compared using ANOVA for parametric data, Kruskal–Wallis test for nonparametric data and Pearson's Chi-squared test for categorical data. Descriptive statistics are presented as the mean \pm SD or median with interquartile range for continuous variables and as numbers with frequencies for categorical variables. Cohen's kappa coefficient was used to measure agreement between airflow limitation defined by the two cut-offs and GP-reported COPD diagnosis. Kaplan–Meier curves for all-cause mortality and hospitalisation during follow-up were plotted for airflow limitation by each cut-off, as well as the three airflow limitation categories, with log-rank tests for comparison. Cox proportional hazards regression models were used to estimate the all-cause mortality and hospitalisation hazard ratio (HR) for airflow limitation by each cut-off, with adjustment in two consecutive models using those with no airflow limitation as the reference category. Variables were first checked for multicollinearity. The category-based net reclassification improvement (NRI) was calculated for airflow limitation defined by GLI-LLN *versus* fixed cut-off for all-cause mortality and hospitalisation during the follow-up [18, 19]. A two-tailed probability value $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the study population

In total, 567 patients (aged 85 ± 3.9 years, 36.9% males) were included in the BELFRAIL cohort. Spirometry was performed by 522 participants at baseline. After exclusion of those with asthma diagnosis in the medical chart, those aged > 95 years (for whom no GLI 2012 reference values were available) and those with level 3 and 4 spirograms, 411 participants were included in this study's analysis (fig. 1). This subset was comparable to the BELFRAIL cohort, being aged 84.6 ± 3.4 years and comprising 37% males. The baseline characteristics and outcomes of the total study population and the three categories based on the two cut-offs are presented in table 1.

The airflow limitation prevalence was 9.2% by the GLI-LLN and 27% by the fixed cut-off. 17.8% of the participants had airflow limitation by fixed cut-off only (FEV₁/FVC < 0.70 and \geq GLI-LLN). There was no statistically significant difference between the airflow limitation categories with regard to age, number of comorbidities or levels of hsCRP, NT-proBNP or eGFR. Participants with airflow limitation by both cut-offs were more often male, taller, smokers/ex-smokers and with lower body mass index compared with those with no airflow limitation by both cut-offs. The GPs reported 37 (9%) participants with COPD at baseline and only 17 (46%) of these had airflow limitation by both cut-offs. Agreement between airflow limitation and GP-reported COPD diagnosis was higher for the GLI-LLN cut-off, but Cohen's kappa coefficients were < 0.70 for both cut-offs (table 2).

Prediction of all-cause mortality and hospitalisation

Data on all-cause mortality were available for all participants and on hospitalisation for 406 participants. During 2.93 ± 0.21 years, 203 (50%) had at least one unplanned hospitalisation and, at 5.12 ± 0.22 years' follow-up, 164 (39.9%) participants had died. The absolute numbers of deaths and times to first

hospitalisation for each of the three categories based on the two cut-offs are presented in table 1. For either cut-off, those with airflow limitation had higher mortality than those with no airflow limitation (figs 2 and 3), but after adjustment only airflow limitation by GLI-LLN had a statistically significant higher risk, with HR 2.10 (95% CI 1.30–3.38; $p=0.002$) (table 3).

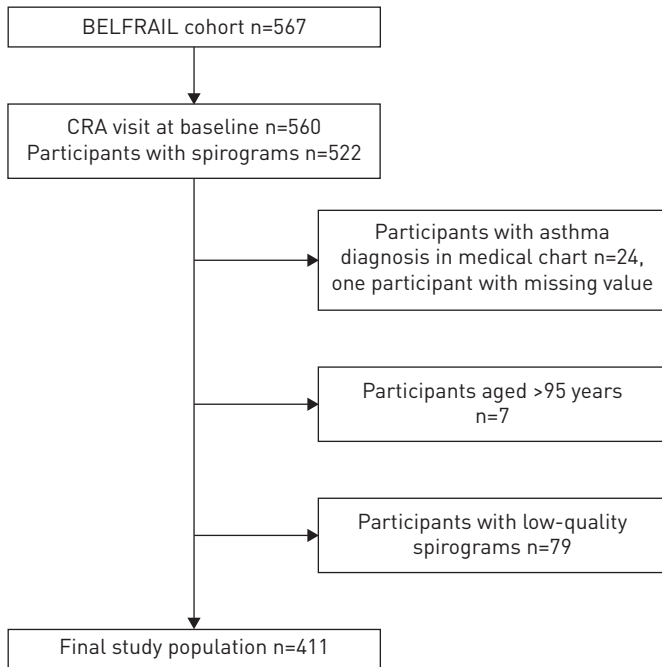


FIGURE 1 Flowchart of the selection of the study population. CRA: clinical research assistant.

TABLE 1 Baseline characteristics and outcomes of the total population and across categories based on fixed and Global Lungs Initiative lower limit of normal (GLI-LLN)[#] cut-offs for forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC)

	Total population	FEV ₁ /FVC ≥0.70 and ≥GLI-LLN	FEV ₁ /FVC <0.70		p-value
			≥GLI-LLN	<GLI-LLN	
Subjects	411	300	73	38	
Age years	84.6±3.4	84.5±3.4	84.8±3.3	85.0±3.1	0.73 ^f
Males	152 (37)	88 (29.3)	35 (47.9)	29 (76.3)	<0.001 ^{##}
Height cm	159.6±9.0	158.5±8.6	161.6±8.6	164.4±10.7	<0.001 ^f
BMI kg·m⁻²	27.3±4.8	28.0±4.9	26.0±4.2	24.43±4.16	<0.001 ^f
Smoker/ex-smoker	125 (30.4)	67 (22.3)	29 (39.7)	29 (76.3)	<0.001 ^{##}
Comorbidities[¶]	5 (3–7)	5 (3–6)	4 (2.5–7.5)	4.5 (3–6)	0.97 ^{¶¶}
hsCRP mg·dL⁻¹	0.17 (0.07–0.40)	0.18 (0.08–0.38)	0.12 (0.05–0.38)	0.20 (0.07–0.45)	0.19 ^{¶¶}
eGFR[*] mL·min⁻¹ per 1.73 m²	62.6 (48.8–77.2)	62.8 (49.7–77.5)	62.7 (44.0–73.1)	60.2 (47.1–82.8)	0.50 ^f
NT-proBNP pg·mL⁻¹	195.1 (97.8–531.4)	192.5 (91.5–466.8)	193.1 (107.6–589.3)	257.6 (107.3–689.1)	0.92 ^{¶¶}
FEV₁ L	1.7±0.6	1.8±0.6	1.8±0.6	1.3±0.5	<0.001 ^f
FVC L	2.4±0.8	2.3±0.7	2.7±0.9	2.6±0.9	<0.001 ^f
FEV₁/FVC	0.73±0.11	0.78±0.05	0.65±0.10	0.51±0.08	<0.001 ^f
COPD diagnosis in medical chart	37 (9)	8 (2.7)	12 (16.4)	17 (44.7)	<0.001 ^{##}
Mortality at 5 years	164 (39.9)	110 (36.7)	29 (39.7)	25 (65.8)	<0.05 ^{##}
Time to first unplanned hospitalisation[§] years	2.0±1.0	2.1±1.0	1.9±1.0	1.7±1.1	0.08 ^f

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. BMI: body mass index; hsCRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate; NT-proBNP: N-terminal pro-brain natriuretic peptide; COPD: chronic obstructive pulmonary disease. [#]: 5th percentile of Global Lungs Initiative 2012 z-scores distribution; [¶]: number of nonrespiratory comorbidities reported by the general practitioner; ^{*}: estimated according to the equation from the Modification of Diet in Renal Disease Study Group [17]; [§]: at 3-year follow-up; ^f: based on one-way ANOVA; ^{##}: based on Pearson's Chi-squared test; ^{¶¶}: based on Kruskal–Wallis test. There were no missing values for the baseline variables except for hsCRP (n=8), eGFR (n=10) and NT-proBNP (n=7).

TABLE 2 Frequency of airflow limitation by the two cut-offs for forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) and degree of agreement with general practitioner-reported chronic obstructive pulmonary disease (COPD) diagnosis

	Subjects	FEV ₁ /FVC <0.70		FEV ₁ /FVC <GLI-LLN	
		Positive	Negative	Positive	Negative
With COPD diagnosis	37	29	8	17	20
No COPD diagnosis	374	82	292	21	353
Total	411	111	300	38	373
Kappa coefficient (95% CI)		0.30 (0.19–0.39)		0.40 (0.24–0.54)	
p-value		<0.001		<0.001	

Data are presented as n, unless otherwise stated. GLI-LLN: Global Lungs Initiative lower limit of normal, 5th percentile of Global Lungs Initiative 2012 z-scores distribution.

The proportion of participants with a first hospitalisation was higher in those with airflow limitation by both cut-offs, but the difference was not statistically significant (figs 2 and 3).

The participants with airflow limitation by fixed cut-off only (FEV₁/FVC <0.70 and ≥GLI-LLN) did not have a higher number of deaths or proportion with hospitalisation compared with those with no airflow limitation by both cut-offs, while those with airflow limitation by GLI-LLN only (FEV₁/FVC ≥0.70 and <GLI-LLN) had a significantly higher number of both deaths and proportion with hospitalisation (fig. 4).

Based on the total NRI and its components, the use of the GLI-LLN cut-off worsened the classification for 17.7% of the dead participants and 19.2% of those with at least one hospitalisation, but improved it for 17.8% of those alive and 16.8% of those with no hospitalisation during the follow-up (table 4). In total, there was no significant net loss for all-cause mortality and hospitalisation when using the GLI-LLN cut-off compared with the fixed one (table 4).

We also tested how the results with GLI 2012 equations compared against extrapolating from the US National Health and Nutrition Examination Survey (NHANES) III equations for our population. We found a very good level of agreement between the NHANES III and GLI 2012 LLN of FEV₁/FVC (kappa coefficient 0.892, p<0.001), while airflow limitation based on the NHANES III LLN had a smaller adjusted HR for 5-year mortality (1.88, 95% CI 1.19–2.97) compared with airflow limitation based on GLI 2012 LLN (2.10, 95% CI 1.30–3.38).

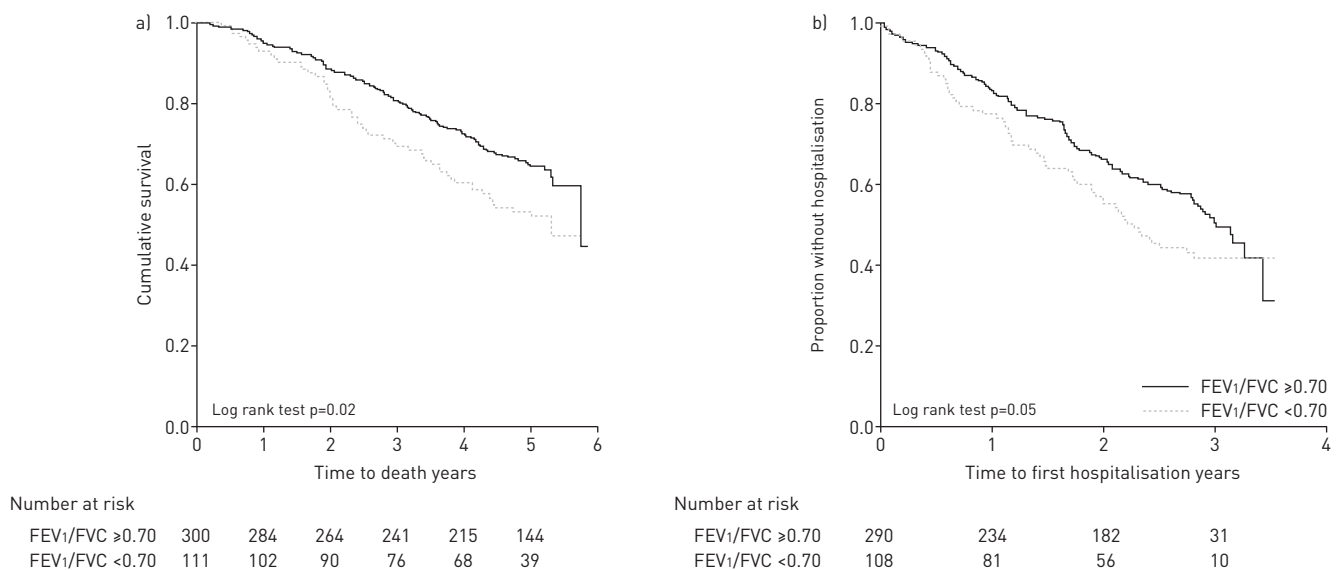


FIGURE 2 Kaplan–Meier survival curves for a) all-cause mortality and b) hospitalisation, for airflow limitation by the fixed cut-off of forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC).

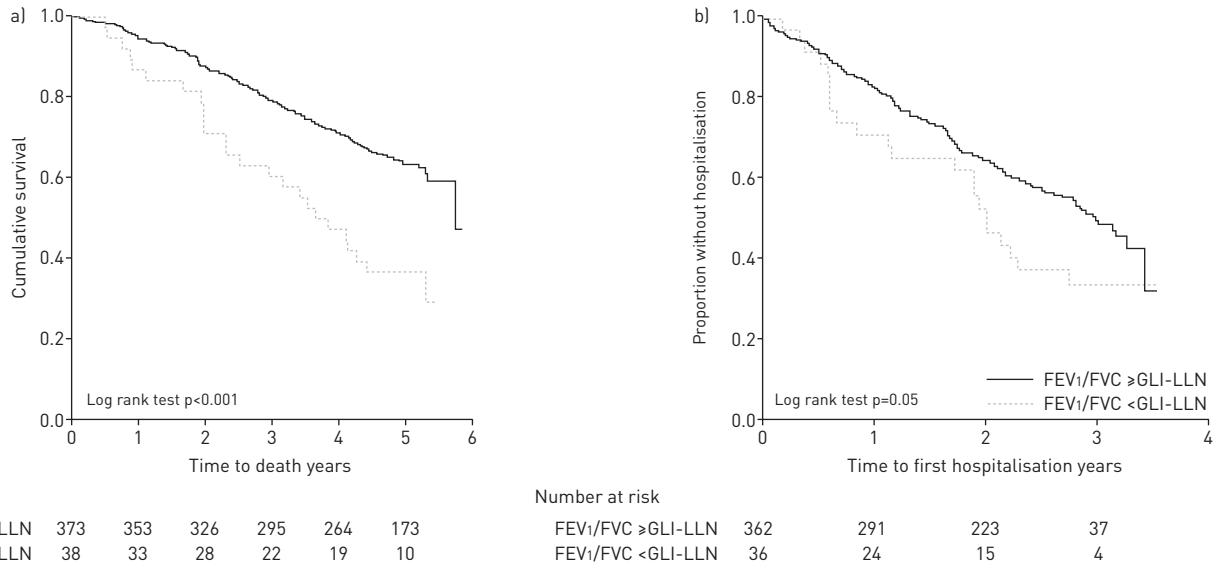


FIGURE 3 Kaplan-Meier survival curves for a) all-cause mortality and b) hospitalisation, for airflow limitation by the Global Lungs Initiative lower limit of normal (GLI-LLN) cut-off of forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC).

TABLE 3 Multivariable Cox proportional hazard analysis for all-cause mortality and airflow limitation defined by the two cut-offs

	FEV ₁ /FVC < 0.70 [#]			FEV ₁ /FVC < GLI-LLN [¶]		
	Unadjusted	Model 1 [*]	Model 2 [§]	Unadjusted	Model 1 [*]	Model 2 [§]
FEV₁/FVC	1.50 [1.08–2.08]*	1.38 [0.98–1.95]	1.38 [0.98–1.97]	2.27 [1.48–3.47]***	2.16 [1.35–3.44]**	2.10 [1.30–3.38]**
Age		1.12 [1.08–1.17]***	1.10 [1.05–1.15]***		1.12 [1.08–1.17]***	1.10 [1.05–1.15]***
Sex male		1.00 [0.68–1.49]	1.02 [0.69–1.50]		1.03 [0.69–1.53]	1.06 [0.72–1.58]
Smoker/ex-smoker		1.09 [0.72–1.66]	1.07 [0.72–1.60]		0.97 [0.63–1.50]	0.94 [0.61–1.45]
Comorbidities			1.08 [1.02–1.14]**			1.09 [1.03–1.15]**
hsCRP > 0.3 mg·dL⁻¹			1.30 [0.93–1.81]			1.27 [0.92–1.77]
NT-proBNP highest tertile			1.77 [1.25–2.49]**			1.72 [1.22–2.42]**
eGFR < 45 mL·min⁻¹			1.30 [0.89–1.89]			1.34 [0.92–1.95]

FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; GLI-LLN: Global Lungs Initiative lower limit of normal, 5th percentile of Global Lungs Initiative 2012 z-scores distribution; hsCRP: high-sensitivity C-reactive protein; NT-proBNP: N-terminal pro-brain natriuretic peptide; eGFR: estimated glomerular filtration rate according to the equation from the Modification of Diet in Renal Disease Study Group [17]. #: reference category FEV₁/FVC ≥ 0.70; ¶: reference category FEV₁/FVC ≥ GLI-LLN; *: adjusted for age, sex and smoking status; §: model 1 adjusted for number of nonrespiratory comorbidities reported by the general practitioner, hsCRP > 0.3 mg·dL⁻¹, highest sex-specific tertile of NT-proBNP and eGFR < 45 mL·min⁻¹; *: p < 0.05; **: p < 0.01; ***: p < 0.001.

Discussion

Main findings in relation to previous studies

In a cohort of very old adults, using the 5th percentile of the z-scores derived from the recent all-age GLI 2012 reference values as a cut-off for the FEV₁/FVC produced much lower airflow limitation prevalence compared with the fixed cut-off, with both cut-offs having no good agreement with the GP-reported COPD. Participants with airflow limitation by either cut-off had a statistically significant higher risk for all-cause mortality but not for hospitalisation. After adjustment, only airflow limitation by GLI-LLN had a statistically significant risk for all-cause mortality. Those with airflow limitation by fixed cut-off only (discordant group) did not show a statistically significant higher risk for all-cause mortality and hospitalisation compared with those with no airflow limitation by both cut-offs. Based on total NRI, the use of GLI-LLN as a cut-off for airflow limitation causes no significant loss in predicting all-cause mortality or hospitalisation.

Previous studies have reported overdiagnosis of airflow limitation in older adults when using the fixed cut-off of FEV₁/FVC versus the age- and sex-specific LLN, yet these studies did not use the GLI 2012

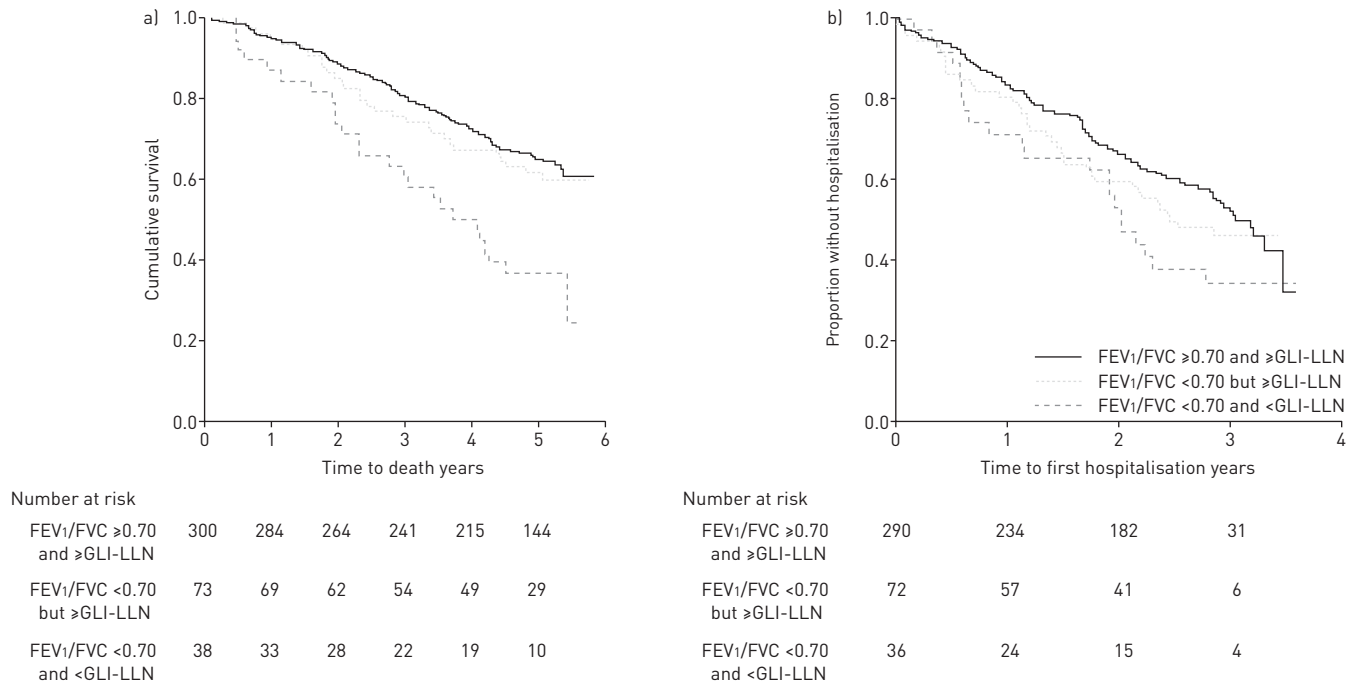


FIGURE 4 Kaplan–Meier survival curves for a) all-cause mortality and b) hospitalisation, for the three groups of airflow limitation based on both the Global Lungs Initiative lower limit of normal (GLI-LLN) cut-off and the fixed cut-off of forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC). Pair-wise log rank test for mortality: FEV₁/FVC <0.70 but ≥GLI-LLN *versus* FEV₁/FVC ≥0.70 and ≥GLI-LLN p=0.51; FEV₁/FVC <0.70 and <GLI-LLN *versus* FEV₁/FVC ≥0.70 and ≥GLI-LLN p<0.001; FEV₁/FVC <0.70 and <GLI-LLN *versus* FEV₁/FVC <0.70 but ≥GLI-LLN p=0.01. Pair-wise log rank test for hospitalisation: FEV₁/FVC <0.70 but ≥GLI-LLN *versus* FEV₁/FVC ≥0.70 and ≥GLI-LLN p=0.24; FEV₁/FVC <0.70 and <GLI-LLN *versus* FEV₁/FVC ≥0.70 and ≥GLI-LLN p=0.04; FEV₁/FVC <0.70 and <GLI-LLN *versus* FEV₁/FVC <0.70 but ≥GLI-LLN p=0.30.

TABLE 4 Reclassification table and net reclassification improvement (NRI) for Global Lungs Initiative lower limit of normal (GLI-LLN)[#] *versus* fixed cut-off for all-cause mortality and hospitalisation

	All	Reclassified up [¶]	Reclassified down ⁺	NRI (95% CI) %	p-value
Mortality					
Dead	164	0	29	-17.7 [-24.2–-12.1]	<0.01
Alive	247	0	44	17.8 [13.3–23.1]	<0.01
Total	411			0.001 [-0.08–0.08] [§]	0.99
Hospitalisation					
With	203	0	39	-19.2 [-25.2–-14]	<0.001
Without	203	0	34	16.8 [11.9–22.5]	<0.001
Total	406			-0.02 [-0.10–0.05] [§]	0.63

Data are presented as n, unless otherwise stated. [#]: 5th percentile of Global Lungs Initiative 2012 z-scores distribution; [¶]: if no airflow limitation by fixed cut-off, but airflow limitation by GLI-LLN; ⁺: if airflow limitation by fixed cut-off, but no airflow limitation by GLI-LLN; [§]: total NRI expressed as a proportion [19].

reference equations and few have used the LMS approach [20, 21]. To our knowledge, there are no data available yet on the prevalence of airflow limitation using the GLI-LLN for people aged ≥80 years, as the GLI 2012 reference equations have been made available only recently [7, 10]. Their application in clinical populations so far shows a 16–23% decrease of airflow limitation prevalence in adults aged >55 years compared with the fixed cut-off [22]. In two samples of community-dwelling people aged 65–80 years, airflow limitation prevalence was 13.2–13.8% for LLN (using the LMS approach but based on other reference equations) *versus* 36.7–37.7% for fixed cut-off [9, 20]. Our findings in very old adults and using the GLI 2012 equations are similar (9% for GLI-LLN *versus* 27% for fixed cut-off).

In our cohort, only 46% of GP-reported COPD diagnoses were confirmed by both cut-offs and 32% by the fixed cut-off only, while 22% had no airflow limitation by either cut-off. Although GP-reported COPD diagnosis is not the gold standard, it is the real-life situation. In another study, even when using diagnosis by a panel of lung disease experts, 17% of cases were missed by the fixed and 28% by the LLN cut-off, while airflow limitation by the fixed cut-off had higher agreement with the expert panel's diagnosis [23]. In our study, neither of the cut-offs had good agreement with the GP-reported COPD diagnosis, but we had a non-clinical study population with a small number of participants with COPD diagnosis ($n=37$), no information on the diagnostic process, as well as a different age group (aged ≥ 80 years). Spirometry is required for COPD diagnosis [2, 4], yet most COPD cases in primary or secondary care are not confirmed by spirometry especially with increasing age [24]. Besides spirometry, COPD diagnosis requires assessment of respiratory symptoms, risk factors and comorbidities [2, 4], as even similar degrees of airflow limitation have different effects on symptoms, comorbidities and outcomes [25, 26]. In very old adults, COPD diagnosis becomes even more complex, as respiratory symptoms such as dyspnoea may be assigned to ageing and common comorbidities such as heart failure [27]. Thus, a comprehensive diagnostic approach, which recognises the heterogeneity and clinical phenotypes of COPD and includes spirometry, needs to be applied [2, 3, 25, 26].

As concluded in two recent systematic reviews, due to a lack of gold standard for COPD diagnosis it is not possible to state which FEV₁/FVC cut-off for airflow limitation is best, and longitudinal studies are needed to evaluate association with adverse health outcomes [12, 21]. In line with previous findings in large population-based studies of people aged 65–80 years (using the LMS approach but based on other reference equations) [9, 20], in our cohort of very old adults airflow limitation defined by GLI-LLN was associated with increased HR for mortality even after adjustment for number of comorbidities (out of 21), systemic inflammatory marker levels (hsCRP) and a heart failure marker (NT-proBNP adjusted for eGFR levels), which have not been included in previous studies. Heart failure is a common comorbidity in very old adults that can influence the spirometry parameters, causing either restrictive or obstructive changes, and is also associated with mortality [28]. NT-proBNP has been found to be valuable in ruling out heart failure in older adults (including those with COPD) and to be a predictor of mortality in very old adults [29, 30]. We corrected NT-proBNP for renal dysfunction (eGFR <45 mL·min⁻¹) [31].

Some studies have reported that individuals with FEV₁/FVC <0.70 and \geq LLN have higher adjusted risk for all-cause mortality compared with those with no airflow limitation by both cut-offs, cautioning that the use of the LLN cut-off would miss individuals at risk [32, 33]. However, these findings have been contested [34, 35], and other studies have reported no significant difference in mortality as well as COPD-related outcomes (COPD hospitalisation, exacerbations, FEV₁ decline) [10–12]. Studies on COPD phenotypes also show that the discordant cases in older adults mostly have milder airflow limitation and better survival [25, 36]. In line with these findings, in our cohort of very old adults, those with FEV₁/FVC <0.70 and \geq GLI-LLN had no statistically significant higher all-cause mortality and hospitalisation compared with those with no airflow limitation by both cut-offs. In addition, we found that, although GLI-LLN was less sensitive (events NRI, *i.e.* dead/with hospitalisation) and more specific (non-events NRI, *i.e.* alive/without hospitalisation) compared with the fixed cut-off, in total its use caused no significant loss in predicting either all-cause mortality or hospitalisation.

Strengths and limitations of this study

This study has several strengths. It is based on a large heterogeneous population, representative of very old adults in Belgium, with follow-up for around 5 years [14]. The majority (92%) of the original cohort performed spirometry and almost 79% achieved quality spirograms according to ATS/ERS criteria. Rigorous quality control of spirometry performance and interpretation based on the ATS/ERS quality criteria were followed and various confounders were included in the analysis, covering demographics, smoking status and number of comorbidities, as well as markers of systemic inflammation and heart failure. The use of pre-bronchodilator values introduces the risk for overestimation of irreversible airflow limitation by 25–29% [37]. This limitation is partly reduced by the exclusion of participants with GP-reported asthma diagnosis. Pre- and post-bronchodilator values have also been found to have similar accuracy for mortality prediction [38]. All-cause mortality and hospitalisation were used as outcomes instead of COPD-related outcomes. In our population of very old adults with several comorbidities, it is difficult to assign these adverse events to COPD, which itself is associated with comorbidities, and many COPD deaths/hospitalisations are assigned to cardiovascular diseases and lung cancer [9]. The exclusion of participants with low-quality spirometry and those aged >95 years (the age limit of the GLI 2012 reference values) is also a limitation, but this caused no statistically significant differences in baseline and outcome variables. We did not exclude individuals with restrictive pulmonary dysfunction as we had no measurements of total lung volumes [6]. As a restrictive pattern in spirometry (reduced FVC with normal FEV₁/FVC) has been found to be associated with mortality, this might have influenced our results [20, 32]. However, we found no statistically

significant differences in frequencies of FVC <80% predicted and FVC <GLI-LLN between the three airflow limitation categories. We also had similar results after excluding those with FVC <80% predicted and FVC <GLI-LLN from those with FEV₁/FVC ≥0.70 and FEV₁/FVC ≥GLI-LLN, respectively.

Implications for future research and practice

The LMS-derived LLN cut-off of FEV₁/FVC is preferred over the fixed cut-off of 0.70, as it takes into account the age-related decline in FEV₁/FVC, variability of spirometry values and skewness of reference data, and has also been shown to be clinically relevant [8, 10, 12]. The recent GLI 2012 all-age reference values allow its use for people aged 80–95 years and are easy to access and apply [7]. In our representative cohort of very old adults in Belgium, using the GLI-LLN reduced airflow limitation prevalence compared with the fixed cut-off of FEV₁/FVC and did not miss individuals with significantly higher all-cause mortality or hospitalisation. After adjustment for a number of confounders including a heart failure biomarker, only airflow limitation by GLI-LLN was an independent predictor for 5-year all-cause mortality. More longitudinal studies are needed on the clinical validation of the GLI-LLN using COPD-related adverse outcomes and focusing on people aged ≥80 years, which is a growing age group worldwide [10]. Correct identification of airflow limitation in very old adults is important as it may reduce inappropriate COPD diagnosis and use of COPD medications, along with their side-effects [10].

It has recently been suggested that, for very old adults, extrapolating from the NHANES III equations may be better than using GLI 2012 for predicting survival from FEV₁ [39]. However, we found that GLI 2012 gave better survival predictions than NHANES III when used to identify airflow limitation from FEV₁/FVC in our cohort of very old adults. Although there is still room for improvement of the GLI 2012 reference values for those aged ≥80 years [7, 39], the use of these global all-age and multi-ethnic reference equations in future studies would help the comparison across research findings, as well as their translation into practice to optimise diagnosis and treatment of respiratory diseases, especially in very old adults.

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