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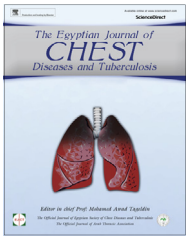

ORIGINAL ARTICLE

Spirometric "Lung Age" estimation for North African population

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KEYWORDS

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Abstract *Background:* Published reference equations predicting Estimated-Lung-Age (ELA) did not reliably predict Chronological-Lung-Age (CLA) data in North African population.

Aims: To develop and to validate novel reference equations for ELA from varied anthropometric data and FEV_1.

Methods: Applying multiple regression analysis, equations predicting ELA were invented using data from 540 never-smokers with normal spirometry (*group I*). Validation was made based on data from 41 never-smokers with normal spirometry (*group II*). Equations were further applied for 91 subjects with confirmed COPD.

Abbreviations: BMI, Body-Mass-Index; BSA, Body-Surface-Area; CLA, Chronological-Lung-Age; COPD, Chronic Obstructive Pulmonary Disease; deltaLA, CLA minus ELA; ELA, Estimated-Lung-Age; FEF_x, Forced Expiratory Flow when x% of FVC has been exhaled; FEV_1, first second Forced Expiratory Volume; FVC, Forced Vital Capacity; LA, Lung-Age; LOA, Limits-Of-Agreement; LLN, Lower-Limit-of-Normal; MMEF, Maximal Mid-Expiratory Flow; *n*, number; OSA, Obstructive Sleep Apnea; PEF, Peak Expiratory Flow; RSD, Residual Standard Deviation; SD, Standard-Deviation; ULN, Upper-Limit-Of-Normal; *r*, coefficient of correlation; r^2, coefficient of determination; 95% CI, 95% confidence interval.

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Results: Novel regression equations allowing prediction of reference value of ELA and normal limits of difference between ELA and CLA were elaborated in both sexes. In males, ELA (yrs) = 42.85 − 20.74 × FEV_1 (L) + 47.41 × Body Surface Area (m^2) − 0.62 × Body-Mass-Index (BMI, kg/m^2). In females, ELA (yrs) = 64.64 − 8.00 × FEV_1 (L) − 0.17 × BMI (kg/m^2) + 8.82 × Height (m). Normal limits of difference between ELA and CLA were ±16.9 yrs in males and ±14.8 yrs in females. Established equations predicted ELA of *group II* with no significant difference between CLA and ELA in either sex (respectively, 42.9 ± 16.6 vs. 40.3 ± 13.7 yrs in males, 42.0 ± 13.5 vs. 45.6 ± 7.7 yrs in females) ELA was significantly older than CLA age only in COPD with grades III and IV ((ELA minus CLA) (yrs) averaged, respectively, +21.7, +26.4).

Conclusion: North African reference equations enrich the World Bank of reference equations from which the physician should choose according to the patient's ethnic background.

Introduction

The single most useful intervention to improve lung function in smokers, with or without, Chronic Obstructive Pulmonary Disease (COPD) is smoking cessation [1,2]. One way to increase the quit rate in smokers could be to communicate lung function results in a manner that is easily understood and stimulates the desire to quit [1].

To conquer the difficulty existing in the raw results of spirometric measurements, the concept of Estimated-Lung-Age (ELA) has been proposed [3]. ELA is an estimate that uses the observed spirometric variable (often FEV_1 for first second Forced Expiratory Volume) of a smoker to calculate the approximate age of a healthy non-smoker with the same spirometric variable based on reference values [3]. Its basis of interpretation relies upon comparison of the Chronological-Lung-Age (CLA) values with ELA predicted from available reference equations [3–6]. Morris and Temple [3] proposed the concept of ELA about 28 years ago, for USA population using earlier American spirometry reference equations [7]. Four models of ELA reference equations were developed and the most relevant model to determine ELA values was the one using FEV_1 [3].

To extend the clinical application of Lung-Age (LA), three other reference equations predicting ELA have been recently published [4–6]. In 2010, two reference equations were developed by Newbury et al. and by Hansen et al. for, respectively, South Australian and USA populations [4,5]. In 2012, Yamaguchi et al. [6] have developed novel regression equations for Japanese population. Hansen et al. [5] proposed a simplified equation allowing LA estimation from the ratio between FEV_1 and Forced Vital Capacity (FVC). Newbury et al. [4] applied the same methods described by Morris and Temple [3] with the equations being solved for age. Yamaguchi et al. [6] have presented equations including various spirometric parameters such as FVC, FEV_1, FEV_1/FVC ratio, Peak Expiratory Flow (PEF), Forced Expiratory Flow when x% of FVC has been exhaled (FEF_x, FEF_{50} and FEF_{25}) and Maximal Mid-Expiratory Flow (MMEF). Only two authors [3,6] have proposed algorithms for judging the abnormality from spirometry ELA with presentation of a recommended sequence to interpret ELA [3] or a recommendation to use the Upper-Limit-of-Normal and Lower-Limit-of-Normal (ULN, LLN, respectively) [6], as recommended for spirometry [8]. These four published studies [3–6] presented several limitations, previously described [9]: low sample size [4], sample may not be representative of a normal population [3,4], skewed age distribution [3], use of old spirometric data or equipment [3,5], application of old spirometric methods [4], mathematical and statistical flaws [3–5], wide variation in ELA [4]. These methodological shortcomings explain some discrepancies in the findings [9]. In North African population, it was strongly suggested that existing LA equations [3–6] are in need of review [9]: these reference equations did not reliably predict CLA data in a large group of Tunisian healthy adults. In addition, among the four published equations [3–6], it was recommended to use, those developed for healthy Japanese subjects aged 25–87 years [6]. The recommendation was justified by several reasons [9].

How to evaluate "spirometric" ELA and what method is approvable? This question was asked in 2011 [10], in order to promote the development of ethnic-specific ELA regression equations in various races. The need for normal values specific to North African populations has been demonstrated for several physiological parameters [9,11–18]. So, the applicability and the reliability of published ELA reference equations [3–6] should be assessed with regard to North African adult's population, in order to avoid erroneous clinical interpretation of ELA data in this population.

Based on these backgrounds, the aims of the present study are

(i) To establish novel regression equations allowing prediction of the reference value of ELA and its normal limits using the data harvested from a large number of healthy Tunisian never-smokers with normal spirometric measurements; and to propose an algorithm for judging the abnormality of the ELA.
(ii) To validate the developed equations using the data obtained from a second group of healthy never-smokers with normal spirometry and two groups of subjects with deteriorating pulmonary function; and
(iii) To compare the novel North African ELA reference equations with those of Yamaguchi et al. [6].

Population and methods

Study design

A large part of the design and methods was previously described [9].

The present cross-sectional study was performed over 16 month's period in two Functional Exploration Laboratories at the Occupational Medicine Group and at the Farhat HACHED Hospital of Sousse, Tunisia.

The study was conducted in accordance with the Declaration of Helsinki. Approval for the study was obtained from the Hospital Ethics Committee, and written informed consent was obtained from all study participants.

Subjects

Four groups were recruited: *group I* (equation group), *group II* (validation group), *groups III* and *IV* (patients' validation groups).

Group I (equation group): healthy never-smokers with normal spirometric measurements

Information about target population, previously detailed [9], is presented in Appendix A. Subjects who declared, in the questionnaire, that they never smoked (cigarettes and/or narghile) or having no more than incidental smoking experience before the visit examination were selected and defined as "*never-smokers*". Criteria to define a healthy and "normal" person, previously detailed [9], are presented in Appendix A. "*Healthy never-smokers*" in whom spirometric measurements were within normal ranges were defined as "*healthy never-smokers with normal spirometric measurements*". The spirometric normality was judged by consulting the following criteria: FEV_1, FVC and $FEV_1/FVC > LLN$ of each parameter [8]. Thus, the total of 540 participants (176 males) with age distribution ranging between 19 and 90 years-old, who visited the two laboratories from February 2011 to January 2012, met the criteria of "*healthy never-smokers with normal spirometric measurements*". These participants were categorized as *group I*. Their diverse parameters were used for constructing the novel prediction equations of ELA in both sexes.

Group II (healthy subject's validation group): healthy never-smokers with normal spirometric measurements

Similarly, 41 participants (20 males) with age distribution ranging between 22 and 89 years-old, who visited the two laboratories from February 2012 to April 2012, satisfied the criteria of "*healthy never-smokers with normal spirometric measurements*" and were assigned to *group II*. Members of *group II*, who did not overlap those of *group I*, were devoted to validation of the novel prediction equations of ELA in both sexes.

Group III (patients' validation group): COPD patients

Ninety one smoker subjects (65 males) with age ranging from 19 to 80 years-old, visiting the Functional Exploration Laboratory at the Farhat HACHED Hospital from February 2012 to April 2012, showing an after bronchodilator FEV_1/FVC less than 0.70, satisfied the criteria of COPD [19].

Group IV (patient's validation group): obstructive sleep apnea patients

Sixty severe OSA patients (42 males; apnea hypopnea index > 30/h) with age ranging from 26 to 70 years-old, were addressed to the Functional Exploration Laboratory at the Farhat HACHED Hospital from February 2012 to April 2012, for spirometry and 6-min walk test [20].

Data of participants allocated to *groups III and IV* were used for certifying whether the newly developed equations would reliably detect the abnormal ELA in subjects with COPD or severe OSA.

Collected data

Dependent variable: CLA.

Independent variables: sex (male, female), anthropometric data (age, weight, height, Body Mass Index (BMI), Body Surface Area (BSA)), parity, spirometric data (FVC, FEV_1, PEF, MMEF, FEF_x, FEV_1/FVC ratio).

Data collection procedure

Medical questionnaire and tobacco use evaluation

Data were collected using a medical questionnaire [21]. It was used to assess subject characteristics (cigarettes and narghile use [22–24], medical, surgical, and gynecologic–obstetric histories and medication use).

Measurement technique and applied definition

Anthropometric measurements and parity: the decimal age (accuracy to 0.1 years) was calculated from the date of measurement and the date of birth [25]. Standing height and weight were measured using a stadiometer and expressed to the nearest centimeter and kilogram, respectively. Depending on calculated BMI (kg/m^2), six obesity statuses, described in Appendix A, were defined [26]: underweight, normal weight, overweight and moderate or severe or massive obesity. BSA was calculated [27]. Parity referred to the number of offspring.

Spirometry measurements: spirometry, performed according to the international recommendations [28], was previously described [9]. A standard uni-directional digital volume transducer equipment (Micro Medical Limited. PO Box 6, Rochester. Kent ME1 2AZ England) was used. The spirometric data [FVC (L); FEV_1 (L); FEFx (L/s), PEF (L/s), FEV_1/FVC ratio (absolute value)] were measured/calculated. Additional information about spirometry measurements is included in Appendix A. The reversibility test, done according international recommendations [8,29,30], was applied only to *group III* (COPD patients). The international classification of severity of airflow obstruction in COPD, based on post-bronchodilator FEV_1, was applied [19]: *grade I (mild)*: $FEV_1 > 80\%$; *grade II (moderate)*: $50\% \leqslant FEV_1 < 80\%$; *grade III (severe)*: $30\% \leqslant FEV_1 < 50\%$; *grade IV (very severe)*: $FEV_1 < 30\%$.

Statistical analysis

Expression modes of results

The Kolmogorov–Smirnov test was used to analyze distribution of variables [31]. When the distribution was normal and the variances were equal, the results were expressed by their mean ± Standard-Deviation (SD) and 95% confidence-interval (95% CI). If the distribution was not normal, the results were expressed by their median (1st–3rd quartiles). The chi-2 test was used to compare percentages. Preliminary descriptive analysis included frequencies for categorical variables and mean ± SD or median (1st–3rd quartiles) for continuous ones.

Univariate and multiple regression analysis (influencing factors of ELA)

The dependent variable (CLA) was normally distributed. T-tests were used to evaluate the associations between CLA and categorical variables (sex) and the Pearson product-moment correlation coefficients (r) and determination coefficient (r^2) evaluated the associations between CLA and continuous measures [height, weight, BMI, BSA, spirometric data expressed in absolute values]. The linearity of the association between the CLA and the continuous measures was checked graphically (scatterplots) by plotting each regressor against CLA. Only significantly and linearly associated variables were entered into the model. A linear regression model was used to evaluate the independent variables explaining the variance in CLA. Candidate variables were stepped into the model with a stepwise selection method. To determine entry and removal from the model, significance levels of 0.15 and 0.05 were used, respectively. No colinearity between predictors was detected with variance inflation factors.

The method was well exposed by Yamaguchi et al. [6]. The implicit assumption in the original method of Morris and Temple [3] is that LA is expressed by a linear function of FEV_1 and height, the latter of which works as the factor supplementing the influence of anthropometric difference on FEV_1. However, other data (such as sex, weight, BSA, BMI, parity) and spirometric parameters may provide useful information on ELA, as well. We, therefore, hypothesized that CLA (dependent variable) would be predicted from a function including anthropometric data (sex (0. Male; 1. Female), height (m), weight (kg), BMI (kg/m^2), BSA (m^2), parity (numerical)) for females and various spirometric parameters as independent variables and defined it as ELA (Box 1).

Box 1Eq. (1)

$$\text{ELA (yrs)} = a_0 + a_1 \times \text{Sex} + a_2 \times \text{Height} + a_3 \times \text{Weight} + a_4 \times \text{BMI} + a_5 \times \text{BSA} + a_6 \times \text{FVC} + a_7 \times \text{FEV}_1 + a_8 \times \text{FEV}_1/\text{FVC ratio} + a_9 \times \text{PEF} + a_{10} \times \text{MMEF} + a_{11} \times \text{FEF}_{25} + a_{12} \times \text{FEF}_{50} + a_{13} \times \text{FEF}_{75} + a_{14} \times \text{Parity (if women)}.$$

In Eq. (1), a_i (i = 1–14) is the partial regression coefficient for a particular explanatory variable, while a_0 is the invariable constant.

ELA simplified reference equations

Due to the inadequacy of the published ELA equations [9] and for practical reasons and daily interpretation especially in patient screening, a reference equation should include only data which can be easily measured/calculated and are significantly associated with ELA. Therefore, we established another stepwise linear regression model using FEV_1 and previously significant anthropometric data shown to be predictors of ELA (Box 2).

Box 2Eq. (2)

$$\text{ELA (yrs)} = a_0 + a_1 \times \text{Sex} + a_2 \times \text{Height} + a_3 \times \text{Weight} + a_4 \times \text{BMI} + a_5 \times \text{BSA} + a_6 \times \text{FEV}_1$$

In Eq. (2), a_i (i = 1–6) is the partial regression coefficient for a particular explanatory variable, while a_0 is the invariable constant.

The normal limits, i.e., ULN and LLN for the disparity between ELA and CLA, defined as deltaLA (CLA minus ELA), were evaluated with the standardized residual called Z-score [31]. The ULN and LLN were assumed to be equal to 95th and 5th percentiles of Z distribution, corresponding to Z-scores of ± 1.64, respectively [95% CI = $1.64 \times$ Residual SD (RSD)).

Validation of prediction equations

Since the concept of ELA is lacking in the physiological basis, Eq. (2) should be taken as the empirical one and needs validation concerning its applicability to ELA prediction. Therefore, ELAs of *groups I and II* subjects (normal spirometric measurements) and that of *groups III and IV* subjects (patients groups') were calculated by applying the regression equations constructed on the ground of Eq. (2). CLAs were compared with ELAs calculated from the local retained reference equation (Eq. (2)) in many ways:

(i) A non parametric test (Wilcoxon matched pairs test) was used to compare ELA vs. CLA for males, females and the total sample of *groups I-IV*
(ii) As proposed by Bland and Altman [32], comparisons between CLA and ELA, of *groups I and II*, were performed by means of the Limits-Of-Agreement (LOA), where deltaLA were plotted against the corresponding mean value. From these data, LOA were then calculated (mean deltaLA ± 1.96 SD).
(iii) CLA values of *group II* were compared with ELA using scatterplots and paired T-tests,
(iv) The numbers (relative frequencies) of subjects of *groups II–IV*, in whom the ELA exceeded its ULN were determined.
(v) The difference between the four COPD grades was judged in terms of the one-way ANOVA followed by the multiple comparison of the Tukey test.

Comparison with the ELA from the Japanese reference equations

Yamaguchi et al. [6] have developed two reference equation models presented in Appendix A (Box A.1) for the Japanese population aged 25–87 years. CLAs of the *group II* were compared with ELAs calculated from the Japanese reference equations [6] in two ways:

(i) CLA values, for males and females, were compared with ELA using scatterplots and paired T-tests,
(ii) Determination of the number of subjects in whom the ELA exceeded its ULN.

Analyses were carried out using Statistica software (Statistica Kernel version 6; StatSoft, Paris, France). Significance was set at the 0.05 level.

Results

Descriptive data

Group I *(equation group)*

An initial sample of 669 volunteer adults was examined. Non-inclusion criteria, previously detailed [9], were found in 129

subjects. The dependent variable (CLA) was normally distributed (Kolmogorov–Smirnov = 0.07, $p < 0.05$). The age and sex distribution of the 540 healthy subjects (176 males) was previously described [9]. Table 1 exposes the anthropometric and spirometric data of the included 540 healthy never-smokers with normal spirometric measurements. The main conclusions are: (i) female subgroup is significantly older and shorter than the male subgroup and contains a significantly lower percentage of subjects with a normal weight; (ii) spirometry data of the females' subgroup are significantly higher than those of the males' subgroup (except for FEV_1/FVC).

Group II (healthy subject's validation group)

Table 1 exposes the anthropometric and spirometric data of the included 41 healthy never-smokers with normal spirometric measurements. The main remark is that spirometry data (expressed as% reference) of the females' subgroup are significantly higher than those of the males' subgroup (except for FEV_1/FVC and FEF_{25}).

Groups III and IV (patients' validation groups)

Table 2 exposes the anthropometric and spirometric data of the 91 COPD (*group III*) and the 60 severe OSA patients (*group IV*). Compared to the total sample *group I*, the total sample *group III* is significantly older and thin and has a significantly lower spirometric data. Compared to the total sample *group I*, the total sample *group IV* is significantly heavier and has a significantly lower spirometric data.

Analytical data

Univariate analysis

CLA was different between males and females (Table 1). Coefficient correlation (r) between the CLA and the quantitative subject's data is shown in Table A.1 (Appendix A). In brief, in males of *group I*, CLA was significantly correlated with all the studied parameters except of height, PEF and FEF_{75}. In females and total sample of *group I*, CLA was significantly correlated with all the studied parameters except FEV_1/FVC ratio.

Multiple regression analysis (ELA influencing factors)

Data about multiple regression analysis are shown in Table 3. In the females, three anthropometric data (parity, height and BMI) and five spirometric parameters (FEV_1, PEF, MMEF, FVC, and FEF_{25}) were picked up as significant influencing factors of ELA. In the males, two anthropometric data (BSA and BMI) and five spirometric parameters (FEF_{25}, FVC, FEV_1, FEF_{50}, and MMEF) were statistically selected as influencing factors of ELA. In the total sample, five anthropometric data (height, sex, BSA, weight and BMI) and five spirometric

Table 1 Anthropometric and spirometric data of groups I and II: healthy never-smokers with normal spirometric measurements.

	Group I: equation group			*Group II*: validation group		
	Male (n = 176)	Female (n = 364)	Total sample (n = 540)	Male (n = 20)	Female (n = 21)	Total sample (n = 41)
Chronological-Lung-Age (Yr)	45.4 ± 15.5	50.5 ± 11.4[a]	48.8 ± 13.1	42.9 ± 16.6	42.0 ± 13.5[c]	42.5 ± 14.9[c]
Estimated-Lung-Age (Yr)	45.4 ± 11.6	50.5 ± 7.1[a]	48.8 ± 9.1	40.3 ± 13.7	45.6 ± 7.7[c]	43.0 ± 11.2[c]
Height (m)	1.66 ± 0.08	1.63 ± 0.11[a]	1.64 ± 0.10	1.65 ± 0.10	1.65 ± 0.12	1.65 ± 0.11
Weight (kg)	74 ± 12	73 ± 12	73 ± 12	70 ± 9	70 ± 12	70 ± 10
Body-Mass-Index (kg/m^2)	26.8 ± 3.8	27.5 ± 3.5[a]	27.3 ± 3.6	25.8 ± 3.3	25.7 ± 3.7[c]	25.8 ± 3.5[c]
Body-Surface-Area (m^2)	1.81 ± 0.17	1.79 ± 0.19	1.79 ± 018	1.78 ± 0.16	1.76 ± 0.20	1.77 ± 0.18
Parity (numerical)		5 ± 3			3 ± 2	
FEV_1 (L)	3.22 ± 0.62	2.97 ± 1.00[a]	3.05 ± 0.90	3.42 ± 0.72	3.64 ± 1.08[c]	3.53 ± 0.92[c]
FEV_1 (%)	97 ± 11	114 ± 21[a]	109 ± 20	102 ± 16	127 ± 21[a,c]	115 ± 22
FVC (L)	3.81 ± 0.72	3.51 ± 1.19[a]	3.61 ± 1.07	4.01 ± 0.84	4.25 ± 1.32[c]	4.13 ± 1.10[c]
FVC (%)	95 ± 11	114 ± 22[a]	108 ± 21	99 ± 13	127 ± 25[a,c]	113 ± 25
FEV_1/FVC (absolute value)	0.85 ± 0.06	0.85 ± 0.06	0.85 ± 0.06	0.85 ± 0.06	0.86 ± 0.07	0.86 ± 0.06
PEF (L/s)	7.32 ± 1.58	6.45 ± 2.23[a]	6.73 ± 2.08	7.10 ± 2.08	7.35 ± 2.33	7.23 ± 2.19
PEF (%)	88 ± 19	100 ± 27[a]	96 ± 25	84 ± 22	108 ± 27[a]	96 ± 27
FEF_{25} (L/s)	1.99 ± 0.74	1.93 ± 1.16	1.95 ± 1.04	2.04 ± 0.62	2.20 ± 0.79	2.12 ± 0.70
FEF_{25} (%)	111 ± 36	123 ± 71[a]	119 ± 62	124 ± 79	122 ± 34	123 ± 59
FEF_{50} (L/s)	4.69 ± 1.37	4.28 ± 1.54[a]	4.41 ± 1.50	4.64 ± 1.03	5.15 ± 1.77[c]	4.90 ± 1.46[c]
FEF_{50} (%)	103 ± 27	108 ± 30	107 ± 29	103 ± 26	122 ± 34[a,c]	113 ± 32
FEF_{75} (L/s)	6.68 ± 1.55	5.80 ± 2.42[a]	6.09 ± 2.21	6.43 ± 2.01	6.95 ± 2.31[c]	6.70 ± 2.16
FEF_{75} (%)	92 ± 20	102 ± 37[a]	99 ± 33	88 ± 25	116 ± 32[a]	103 ± 32
MMEF (L/s)	4.04 ± 1.13	3.75 ± 1.60[a]	3.84 ± 1.47	3.98 ± 0.76	4.70 ± 1.78[c]	4.35 ± 1.41[c]
MMEF (%)	102 ± 24	113 ± 40[a]	110 ± 36	101 ± 28	129 ± 38[a]	115 ± 36
Obesity status						
Normal weight	58 (33)	88 (24)[b]	146 (27)	6 (30)	8 (38)	14 (34)
Overweight	81 (46)	178 (49)	259 (48)	11 (55)	9 (43)	20 (49)
Moderate obesity	37 (21)	98 (27)	135 (25)	3 (15)	4 (19)	7 (17)

For abbreviations, see abbreviation list. Data are mean ± SD except for obesity status (data are number (percentage)).

[a] $p < 0.05$ (Student-test for the same group): male vs. female.

[b] $p < 0.05$ (Chi-2 for the same group): male vs. female.

[c] $p < 0.05$ (Student-test for *group I* vs. *group II*): (male vs. male), (female vs. female) and (total sample vs. total sample).

[d] $p < 0.05$ (Chi-2): male *group I* vs. male *group II*, female *group I* vs. female *group II*.

[e] $p < 0.05$ (non parametric-test for each group): ELA vs. CLA for male, female and the total sample.

parameters (FEV_1, PEF, MMEF, FVC and FEF_{25}) were statistically selected as influencing factors of ELA. Thus, the independent variables included in the linear stepwise multiple regression models are presented in Table 3. The linear stepwise multiple regression equation for the total sample is shown by Eq. (3) (Box 3).

Box 3Eq. (3)

$$ELA\ (yrs) = 210.67 - 5.48 \times FEV_1\ (L) + 2.17 \times PEF\ (L/s) - 265.41 \times Height\ (m) + 3.84 \times Sex\ (0.\ Male;\ 1.\ Female) - 2.97 \times MMEF\ (L/s) - 3.99 \times FVC\ (L) - 0.857 \times FEF_{25}\ (L/s) + 289.51 \times BSA\ (m^2) - 1.94 \times BMI\ (kg/m^2)$$

The cumulative r^2 were 0.45, 0.62 and 0.47, respectively for females, males and the total sample. The 95% CI (in years) were 14.04, 15.91 and 15.70, respectively for females, males and the total sample.

ELA simplified reference equations

The simplified reference equations are exposed in Table 4. The regression lines predicting the reference value of ELA (yrs) for the females and that for the males are given by Eq. (4) and 5 (Box 4).

Box 4ELA simplified reference equations

Eq. (4) for females: $ELA\ (yr) = 64.64 - 8.00 \times FEV_1\ (L) - 0.17 \times BMI\ (kg/m^2) + 8.82 \times Height\ (m)$

Eq. (5) for males: $ELA\ (yr) = 42.85 - 20.74 \times FEV_1\ (L) + 47.41 \times BSA\ (m^2) - 0.62 \times BMI\ (kg/m^2)$

The cumulative r^2 was 0.38 for the female equation and 0.56 for the male equation.

The ELA in either sex followed the normal distribution with no dependence on the ELA and its ULN and LLN were ± 14.77 years in females and ± 16.90 years in males (Table 4).

Fig. 1 shows the Bland and Altman [32] representation for the *group I*, of CLA with ELA determined from local retained reference equations presented in Box 4. The means ± SD of the deltaLA of males and females are closest to zero, respectively, −0.00 ± 10.22 years and −0.00 ± 8.97 years.

Validation of the retained reference equations

ELA in group II (*healthy subject's validation group*): the overall relationship between ELA (*X*-axis) predicted from respective regression line and CLA (*Y*-axis) was $Y = 10.88 + 0.79 \times X$ for the males (Fig. 2A) and $Y = -20.26 + 1.37 \times X$ for the females (Fig. 2B). There was no significant difference between CLA and ELA in either sex (Table 1, Fig. 3). The male and female means ± SD deltaLA were not significant (respectively, 2.70 ± 12.80 years and −3.50 ± 9.00 years). The number (relative frequency) of participants in whom ELA exceeded the ULN or LLN was two (9.5%) in females and three (15.0%) in males (Fig. 3), indicating an acceptable agreement between ELA and CLA in either sex.

ELA in group III (COPD validation group): the ELAs (evaluated from the regression Eqs. (4 and 5)) of COPD males, females and total sample patients were significantly higher than their CLA (Table 2) (respectively, 81.10 ± 12.00 vs. 62.40 ± 9.50 yrs; 65.80 ± 3.00 vs. 57.00 ± 15.20 yrs and 76.70 ± 12.40 vs. 60.80 ± 111.60 yrs). The relative frequency of COPD patients in whom ELA exceeded the ULN was 26.9% in the female and 56.9% in the male. The 93 COPD were divided into four categories for the sake of convenience,

Table 2 Anthropometric and spirometric data of validation groups: groups III and IV.

	Group III: COPD patients			*Group IV*: OSA patients		
	Male (n = 65)	Female (n = 26)	Total sample (n = 91)	Male (n = 42)	Female (n = 18)	Total sample (n = 60)
Chronological-Lung-Age (Yr)	62.4 ± 9.5[a]	57.0 ± 15.2[a]	60.8 ± 11.6[a]	46.2 ± 10.4	54.5 ± 8.08	48.7 ± 10.4
Estimated-Lung-Age (Yr)	81.1 ± 12.0[a,c]	65.8 ± 3.0[a,c]	76.7 ± 12.4[a,c]	57.8 ± 17.1[a,c]	55.5 ± 2.8[a]	57.1 ± 14.4[a,c]
Height (m)	1.70 ± 0.06[a]	1.53 ± 0.06[a]	1.65 ± 0.09	1.72 ± 0.06[a]	1.55 ± 0.07[a]	1.66 ± 0.10
Weight (kg)	71 ± 13	63 ± 18[a]	69 ± 15[a]	102 ± 15[a]	96 ± 13[a]	101 ± 14[a]
Body-Mass-Index (kg/m^2)	24.8 ± 4.2[a]	26.9 ± 7.0	25.4 ± 5.2[a]	34.9 ± 4.8[a]	40.4 ± 5.4[a]	36.5 ± 5.6[a]
Body-Surface-Area (m^2)	1.81 ± 0.17	1.60 ± 0.21[a]	1.75 ± 0.20[a]	2.14 ± 0.15[a]	1.93 ± 0.151[a]	2.08 ± 0.18[a]
Parity (numerical)		Not determined			4 ± 2	
FEV_1 (L)	1.57 ± 0.63[a]	0.96 ± 0.33[a]	1.40 ± 0.62[a]	3.13 ± 0.83	1.97 ± 0.40[a]	2.78 ± 0.90[a]
FEV_1 (%)	52 ± 19[a]	41 ± 17[a]	49 ± 19[a]	88 ± 19[a]	93 ± 13[a]	89 ± 17[a]
FVC (L)	2.75 ± 0.84[a]	1.65 ± 0.49[a]	2.44 ± 0.90[a]	3.86 ± 0.94	2.38 ± 0.52[a]	3.42 ± 1.08
FVC (%)	72 ± 18[a]	56 ± 19[a]	68 ± 20[a]	89 ± 18[a]	94 ± 11[a]	(90 ± 16[a]
FEV_1/FVC (absolute value)	0.56 ± 0.11[a]	0.58 ± 0.08[a]	0.57 ± 0.10[a]	0.81 ± 0.08[a]	0.83 ± 0.07	0.81 ± 0.07[a]
MMEF (L/s)	0.80 ± 0.41[a]	0.54 ± 0.23[a]	0.73 ± 0.39[a]	3.40 ± 1.36[a]	2.37 ± 0.64[a]	3.09 ± 1.27[a]
MMEF (%)	24 ± 12[a]	19 ± 8[a]	23 ± 11[a]	83 ± 30[a]	79 ± 20[a]	82 ± 27[a]
Obesity status						
Normal weight	34 (52)[b]	11 (42)[b]	45 (50)[b]	1 (2[b]	0 (0)[b]	1 (2)[b]
Overweight	26 (40)	7 (27)[b]	33 (36)[b]	2 (5)[b]	0 (0)[b]	2 (3)[b]
Obesity	5 (8)[b]	8 (31)	13 (14)[b]	39 (93)[b]	18 (100)[b]	57 (95)[b]

For abbreviations, see abbreviation list. Data are mean ± SD except for obesity status (data are number (%)).

[a] $p < 0.05$ (Student-test for groups III or IV vs. *group I*): male vs. male, female vs. female or total sample vs. total sample).

[b] $p < 0.05$ (Chi-2 for groups III or IV vs. *group I*): male vs. male, female vs. female or total sample vs. total sample).

[c] $p < 0.05$ (Non parametric-test): ELA vs. CLA for male, female and the total sample.

Table 3 Influencing factors of the Estimated-Lung-Age (ELA): linear stepwise multiple regression models.

Independent variables		Partial regression coefficient	95% CI	*p*-Level	Cumulative r^2	SE	1.64 × Residual Standard Deviation
Female (n = 364)							
Constant		52.83	34.37 to 71.30	0.01		11.26	14.04
FEV_1	(L)	−3.64	−7.81 to 0.54	0.15	0.3798		
Parity	(numerical)	1.16	0.81 to 1.58	0.01	0.4310		
PEF	(L/s)	1.08	0.33 to 1.83	0.02	0.4363		
MMEF	(L/s)	−1.54	−2.80 to −0.28	0.04	0.4419		
FVC	(L)	−3.30	−6.28 to −0.32	0.07	0.4452		
Height	(m)	11.27	−1.01 to 23.56	0.13	0.4488		
Body-Mass-Index (kg/m^2)	−0.15	−0.37 to 0.08	0.28	0.4508			
FEF_{25}	(L/s)	−0.47	−1.22 to 0.29	0.31			
Male (n = 176)							
Constant		53.37	39.67 to 67.08	0.01		8.36	15.91
FEF_{25}	(L/s)	−4.12	−7.21 to −1.04	0.03	0.4262		
FVC	(L)	−6.26	−11.25 to −1.27	0.04	0.4972		
Body-Surface-Area (m^2)	36.54	25.20 to 47.89	0.01	0.5677			
FEV_1	(L)	−8.19	−15.33 to −1.05	0.06	0.5809		
Body-Mass-Index (kg/m^2)	−0.45	−0.90 to 0.01	0.11	0.5909			
FEF_{50}	(L/s)	3.66	1.95 to 5.36	0.01	0.5999		
MMEF	(L/s)	−5.17	−7.79 to −2.56	0.01			
Total sample (n = 540)							
Constant		210.67	104.20 to 317.14	0.01		64.92	15.70
FEV_1	(L)	−5.48	−9.33 to −1.63	0.02	0.3504		
PEF	(L/s)	2.17	1.55 to 2.78	0.01	0.3883		
Height	(m)	−265.40	−407.95to −122.86	0.01	0.4125		
Sex	(0. Male; 1. Female)	3.84	2.34 to 5.34	0.01	0.4308		
MMEF	(L/s)	−2.97	−4.08 to −1.86	0.01	0.4529		
FVC	(L)	−3.98	−6.72 to −1.25	0.02	0.4582		
FEF_{25}	(L/s)	−0.84	−1.66 to −0.03	0.09	0.4621		
Body-Surface-Area (m^2)	289.51	137.28 to 441.74	0.01	0.4640			
Weight	(kg)	−2.27	−3.85 to −0.69	0.02	0.4713		
Body-Mass-Index (kg/m^2)	−1.94	−3.59 to −0.28	0.06				

For abbreviations, see abbreviations list. 95% CI: 95% confidence interval around each partial regression coefficient. p: probability. SE: standard error.
Proposed model for females: ELA (yr) = $52.83 - 3.64 \times FEV_1 + 1.16 \times$ Parity $+ 1.08 \times$ PEF $- 1.54 \times$ MMEF $- 3.30 \times$ FVC $+ 11.27 \times$ Height $- 0.15 \times$ Body Mass Index $- 0.47 \times FEF_{25}$.
Proposed model for males: ELA (yr) = $53.37 - 4.13 \times FEF_{25} - 6.26 \times$ FVC $+ 36.54 \times$ Body Surface Area $- 8.19 \times FEV_1 - 0.45 \times$ Body Mass Index $+ 3.66 \times FEF_{50} - 5.17 \times$ MMEF.
Proposed model for the total sample: ELA (yr) = $210.67 - 5.48 \times FEV_1 + 2.17 \times$ PEF $- 265.41 \times$ Height $+ 3.84 \times$ Sex $- 2.97 \times$ MMEF $-3.99 \times$ FVC $- 0.85 \times FEF_{25} + 289.51 \times$ Body Surface Area $- 1.94 \times$ Body Mass Index.

Table 4 Simplified reference equation for the Estimated-Lung-Age (ELA).

Independent variables		Partial regression coefficient	95% CI	*p*-Level	Cumulative r^2	SE	Lower-limit-of-normal (LLN) Upper-limit-of-normal (ULN)
Female (n = 364)							
Constant		64.64	45.75 to 83.53	0.01		11.52	14.77
FEV_1	(L)	−8.00	−9.39 to −6.61	0.01	0.3798		
Body-Mass-Index	(kg/m^2)	−0.17	−0.41 to 0.06	0.22	0.3825		
Height	(m)	8.82	−3.79 to 21.43	0.25			
Male (n = 176)							
Constant		42.85	29.12 to 56.58	0.01		8.37	16.90
FEV_1	(L)	−20.74	−23.17 to −18.31	0.01	0.3957		
Body-Surface-Area	(m^2)	47.41	36.55 to 58.28	0.01	0.5527		
Body-Mass-Index	(kg/m^2)	−0.62	−1.09 to −0.14	0.03			
Total sample (n = 540)							
Constant		259.28	148.89 to 369.68	0.01		67.31	16.43
FEV_1	(L)	−11.54	−12.80 to −10.28	0.01	0.3504		
Height	(m)	−335.75	−483.01 to −188.50	0.01	0.3874		
Sex	(0. Male; 1. Female)	2.68	1.14 to 4.22	0.01	0.3997		
Body-Surface-Area	(m^2)	359.87	202.45 to 517.29	0.01	0.4031		
Weight	(kg)	−2.75	−4.39 to −1.10	0.01	0.4144		
Body-Mass-Index	(kg/m^2)	−2.60	−4.32 to −0.88	0.01			

For abbreviations, see abbreviations list. 95% CI: 95% confidence interval around each partial regression coefficient. p: Probability. SE: standard error. Proposed models: Female: ELA (yrs) = 64.64106 − 8.00049 × FEV_1 − 0.17411 × Body Mass Index + 8.82107 × Height. To calculate LLN or ULN subtract or add 14.77 yrs to the ELA. Male: ELA (yrs) = 42.8499 − 20.7404 × FEV_1 + 47.4141 × Body Surface Area − 0.6164 × Body Mass Index. To calculate LLN or ULN subtract or add 16.90 yrs to the ELA.

i.e., *grade I* (9 males/1 female), *grade II* (31 males/9 females); *grade III* (21 males/12 females) and *grade IV* (4 males/4 females). The deltaLA averaged −1.84 years in the COPD patients with *grade I*, +13.34 years in those with *grade II*, +21.68 years in those with grade *III*, or +26.42 years in those with *grade IV* (Fig. 4). The deltaLA in COPD patients with grades III and IV, but not in those with grades I and II, certainly exceeded the ULN, indicating that allowance was made for judging that only the ELA in subjects with COPD *grades-III* or *IV* was significantly older than the CLA.

ELA in group IV (severe OSA validation group): the ELAs (evaluated from the regression Eqs. (4 and 5)) of severe OSA males and total sample patients were significantly higher than their CLA (Table 2). The relative frequency of severe OSA patients in whom ELA exceeded the ULN was 5.5% in females and 30.9% in males.

Effect of parity: in the entire female population ($n = 364$), a positive univariate linear correlation was found between CLA and parity (Table A.1, Appendix A) ($r = 0.51$, $p < 0.05$). Parity also appeared to be a positive independent variable included in the forward linear stepwise multiple regression model for ELA (Table 3). No correlation between parity and BMI ($p = 0.90$) was found. But there exist significant ($p < 0.05$) correlations between parity and weight, height and FEV_1 ($r = -0.43$, $r = -0.28$, $r = 0.16$, respectively).

ELA from the Japanese reference equations: the ELA in participants of *group II* was calculated according to Yamaguchi et al. [6] reference equations. The overall relation between ELA [6] (*X*-axis) and CLA (*Y*-axis) was expressed as $Y = 7.54 + 0.68 \times X$ in males and $Y = 1.42 + 0.56 \times X$ in females (Fig. 5). The determination coefficients (=0.20 (Fig. 5A) and 0.32 (Fig. 5B), respectively for males and females) were lower than those determined from retained local reference equations (=0.43 (Fig. 2A) and 0.60 (Fig. 2B), respectively for males and females). The fitted lines revealed a discrepancy between CLA and ELA (Fig. 5). This suggests that the Japanese reference equations [6] inevitably overestimated the CLA in males (Fig. 5A) (mean ± SD difference = −9.40 ± 15.20 yrs, $p < 0.05$) and underestimated the CLA in females (Fig. 5B) (mean ± SD difference = 1.50 ± 12.70 yrs, $p = 0.72$). The relative frequency of participants in whom ELA determined from Japanese reference equations [6] exceeded the ULN or LLN was 29.2%.

Algorithm for judging the abnormality from ELA: when judging the abnormality in ELA three-step procedures are recommended (Fig. 6). The first thing to do is to examine whether the deltaLA exists within normal limits formed by ULN and LLN, i.e., ±16.90 years in the male and ±14.77 years in the female. If deltaLA:

(i) Exists within ULN and LLN, the ELA of a person should be interpreted to be consistent with his/her CLA, even when the ELA is above or below the CLA.
(ii) Exceeds ULN, the ELA is judged to be older than the CLA.
(iii) Is below LLN, the ELA is judged to be younger than the CLA.

Discussion

Novel regression equations allowing prediction of reference value of ELA and normal limits of difference between ELA and CLA were elaborated in both sexes for North African

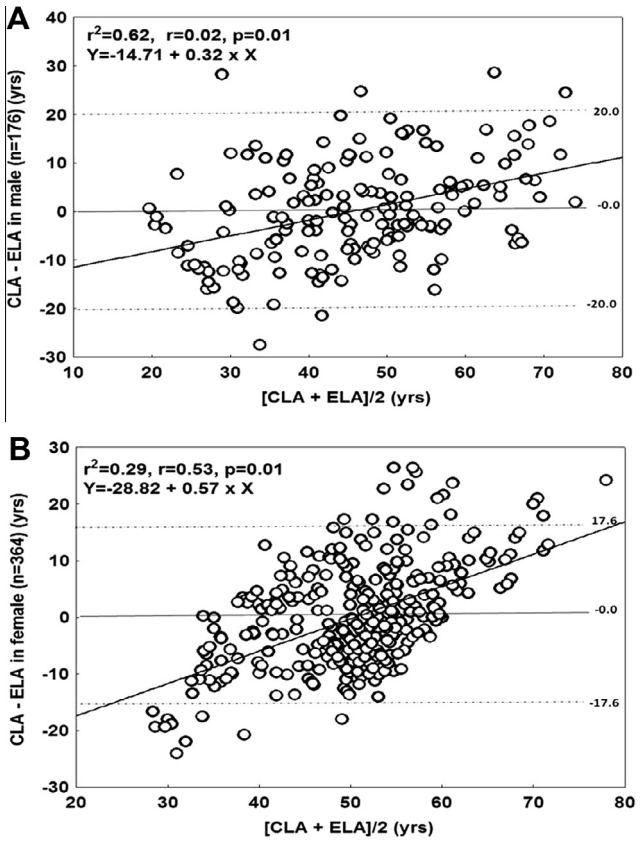

Figure 1 *Group I* (equation group: healthy never-smokers with normal spirometric measurements): Bland and Altman representation of Chronological-Lung-Age (CLA) with Estimated-Lung-Age (ELA) determined from retained local reference equations. (A) Male. (B) Female. r^2: determination coefficient; r: correlation coefficient; p: probability; n = number of subjects. ——: Mean; ·····: mean ± 1.96 ± SD; ／: regression line.

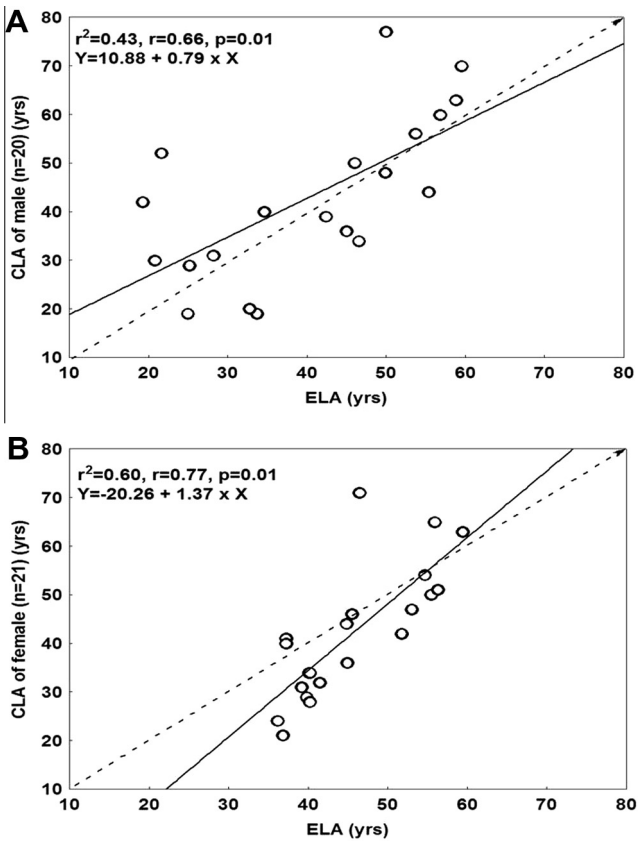

Figure 2 *Group II* (validation group: healthy never-smokers with normal spirometric measurements): comparison of Estimated-Lung-Age (ELA) determined from the retained local reference equations with Chronological-Lung-Age (CLA). (A) Male. (B) Female. r^2: determination coefficient; r: correlation coefficient; p: probability; n = number of subjects. ／: regression line. ·····: identity line.

adult population. In additional groups of healthy or adult-patients prospectively assessed, the present reference equations yielded satisfactory predictions.

Methodology discussion

The study design, the population source, the sample size and characteristics of *group I* subjects, the applied inclusion and non-inclusion criteria, the spirometry measurements were previously discussed [9]. In addition, the ELA published reference equation was extensively described in a previous paper [9].

The statistical analysis was similar to that previously very well described by Yamaguchi et al. [10]. The regression equation predicting the normal value of a given pulmonary functional parameter for non-smoking healthy adults is generally constructed by taking spirometric parameter as dependent variable, while sex, age and height as independent variables, in terms of least-square minimization. In the original method of Morris and Temple [3], calculation of ELA (X) was made by counting back the regression equation predicting the normal value of a given spirometric parameter expressed by $Y = a + b \times X$ in a fixed condition of sex and height, i.e., $X = -a/b + Y/b$. According to Yamaguchi et al. [10], this may not be approvable in a statistical sense and, for estimating LA with statistical validity, it is necessary to establish the new regression equation by taking age as dependent variable but spirometric parameter as independent variable using the same data set. In addition, normal value of a spirometric parameter at a given age exists within a certain range between ULN and LLN, corresponding to maximum and minimum ends of 95% CI, which are defined as mean ± 2·RSD [10].

Study limitations

As for the Japanese study [6], one of the crucial issues acknowledged is that we have no reliable grounds for supporting the idea that the relationship between lung aging and various spirometric parameters can be approximated by the linear function. However, it was demonstrated that, in the male, peak of FEV_1 or FVC would be attained at an age between 20 and 25 years-old and then declined with age, but, in the female, full lung growth would be achieved earlier than the male [33]. These findings suggest that the relation between CLA and most of the spirometric parameters is approximated by a linear function as far as the subjects studied are over 20 years-old and their spirometry is normal [10]. However, it may be difficult to

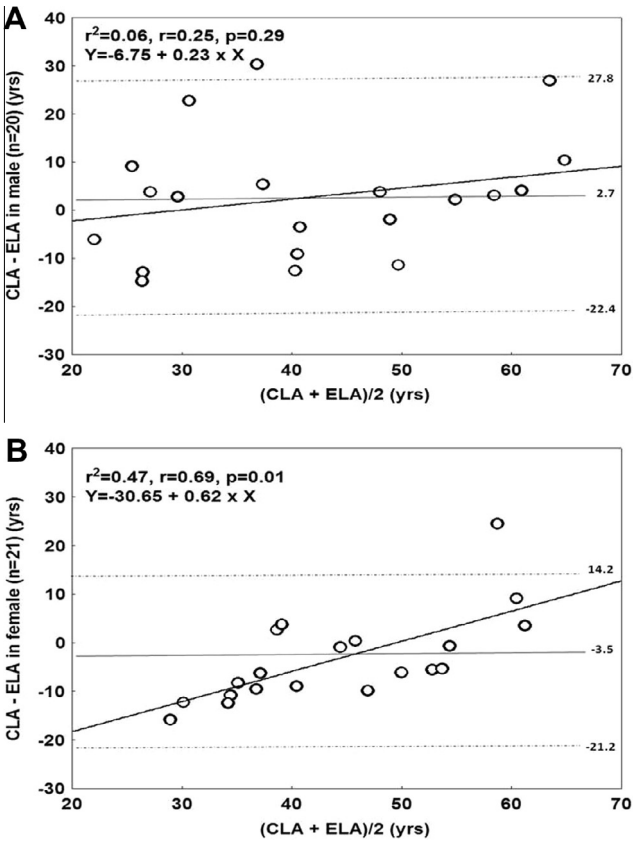

Figure 3 *Group II* (validation group: healthy never-smokers with normal spirometric measurements): Bland and Altman representation of Chronological-Lung-Age (CLA) with Estimated-Lung-Age (ELA) determined from retained local reference equations. (A) Male. (B) Female. r^2: Determination coefficient; r: correlation coefficient; p: probability; n = number of subjects. ——: Mean; ·····: mean ± 1.96 ± SD; ⁄: regression line.

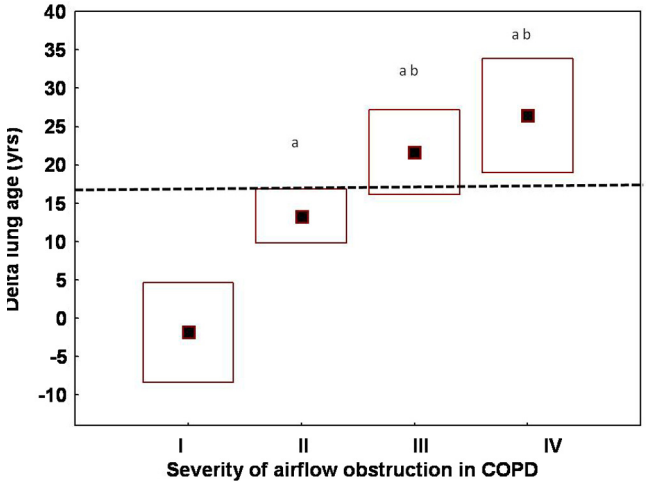

Figure 4 *Group III* (patients' validation group: Chronic Obstructive Pulmonary Disease (COPD)): difference between Estimated-Lung-Age (ELA) and Chronological-Lung-Age (CLA) (delta LA). Values are means and their 95% confidence intervals. Severity of airflow obstruction in COPD: grade I (n = 10): −1.84 yrs (−8.35 to 4.66), grade II (n = 40): + 13.34 yrs (9.81 to 16.88), grade III (n = 33): + 21.68 yrs (16.17 to 27.19) and grade IV (n = 8): + 26.42 yrs (18.96 to 33.88). ▰: mean. ▱: 95% CI. Dotted line: average of male ULN and female ULN for delta LA (+ 15.84 yrs). The difference between the 4 COPD grades was judged in terms of the one-way ANOVA followed by the multiple comparison of the Turkey test. [a]: Larger than grade I ($p < 0.05$). [b]: Larger than grade II ($p < 0.05$). [c]: Larger than grade III ($p < 0.05$).

say that these findings sufficiently provide the physiologically relevant grounds for the linear assumption between ELA and various spirometric parameters [10]. Therefore, as in another study [6], their applicability was validated by calculating the ELAs of subjects with normal spirometry and those with deteriorating pulmonary function.

Results and discussion

How to evaluate "spirometric" ELA for North African population? What method is approvable?

The spirometric ELA is offered as a tool to impress upon the smoker the degree of ventilatory defect caused by tobacco smoke inhalation. As part of an educational program used by a physician or health professional, it can provide additional incentive to prevent further loss of pulmonary function and the potential for improved function and LA reduction [3].

Morris and Temple [3] deserve credit for introducing the concept of ELA to assess airflow obstruction. Parkes et al. [34] found their ELAs useful, but they are not routinely calculated. Using the new formulas (Eqs. (4) and (5)) presented in the present study, anyone can easily manually calculate and inform patients of their ELAs from any spirometric report. This should elicit a response and open discussion regarding the dangers of continuing smoking. Referral to support groups, educational and counseling sessions, and the use of newer pharmaceuticals all offer avenues for success [34,35]. The recommended sequence (Fig. 6) is to identify a smoker, perform spirometry, and, if the FEV_1, is less than the LLN, estimate the LA.

The variability of spirometry results of normal healthy subjects is itself quite wide, being approximately 80–120% predicted, and consequently wide variation in ELA exists. There continues to be a considerable debate about the use of LLN or percent predicted, with the definitions of stages of disease easily described by percent predicted [6]. Instead of a single ELA value it may be possible to communicate ELA as being "LLN and ULN", based on 95% CI [6,10]. LA's relationship to smoking may also be controversial as there is also a decline in lung function with increasing age as well as with diseases such as COPD. However, there is continued support in the literature for the more rapid decline in FEV_1 in smokers than in non-smokers [36,37].

It should be noted that the Eqs. (4) and (5) are only applicable to the North African population. However, we anticipate that the findings obtained in the present study will promote the development of ethnic-specific regression equations allowing prediction of ELA in various races.

Effect of parity

Parity was positively correlated with CLA of the *group I* female and appeared as a positive independent variable included in the multiple regression model for ELA. This result may be

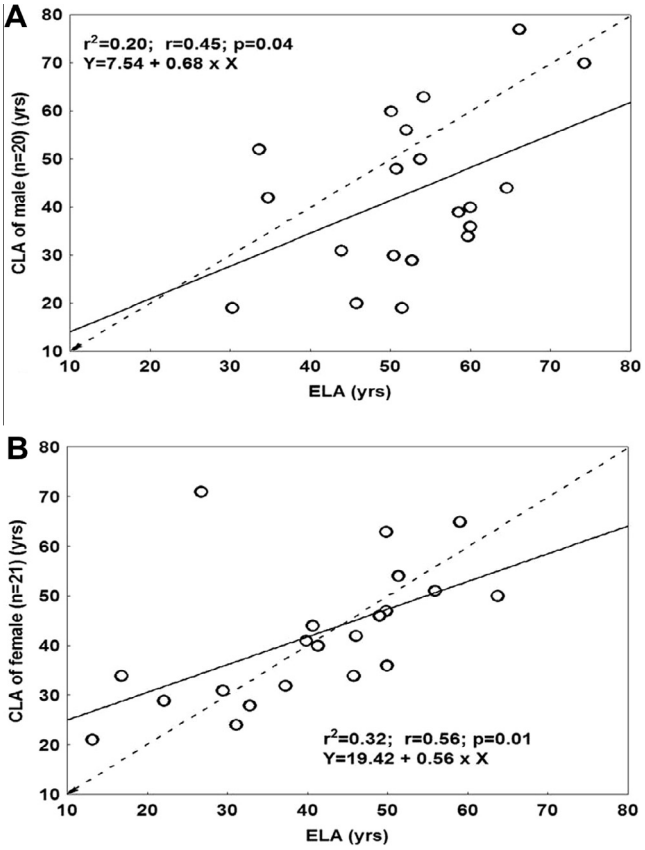

Figure 5 *Group II* (validation group: healthy never-smokers with normal spirometric measurements): comparison of Estimated-Lung-Age (ELA) determined from Japanese reference equations with Chronological-Lung-Age (CLA). r^2: determination coefficient; r: correlation coefficient; p: probability; n = number of subjects. ——: regression line. ·····: identity line.

clinically relevant when interpreting ELA in females from North Africa. A simple way to solve this problem would be to subtract, from their ELA reference value some years equal to the number of parity multiplied by 1.16. This phenomenon may reflect the general findings about aging and parity effects on health [38] and several hypotheses, discussed in some previous paper [11–13,39], have been advanced (detailed discussion appears in the Appendix A). Medical studies provide very little information on the influence of parity on LA, however, this may be a promising new direction for physiological and pathophysiological research, particularly for developing countries.

Validity of the North African ELA reference equations

The newly developed equations could predict not only the equality between ELA and CLA in *group II* (Table 1) within an allowable margin of error but also the incremental disparity between ELA and CLA in *groups III and IV* with COPD or severe OAS (Table 2). Thus, we concluded that the Eqs. (4) and (5) would be practically useful in a clinical setting in North African population. Similar to the findings of the Japanese study [6], in the COPD group, the North African ELA equations produced an ELA greater than CLA suggesting that smoking causes lungs to deteriorate more quickly than the expected age-related decline, as predicted by Fletcher and Peto [40].

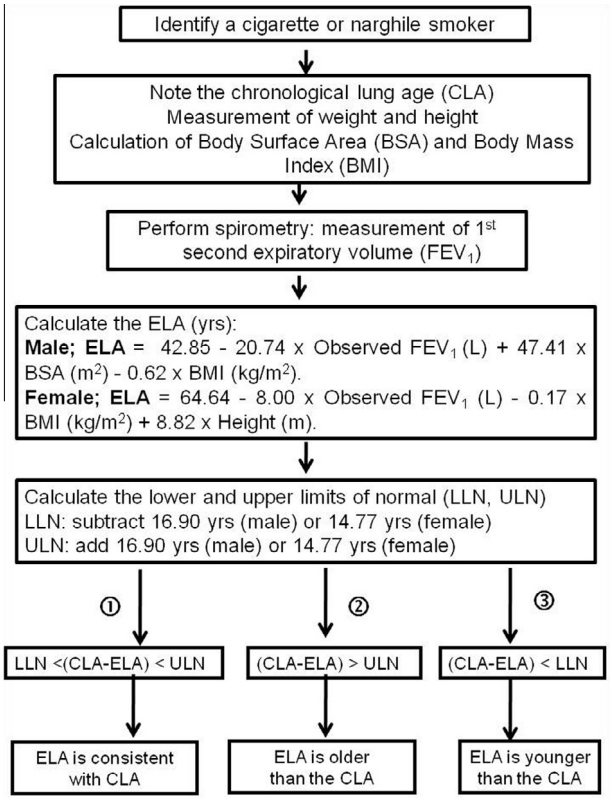

Figure 6 Three-step procedure for judging the abnormality of Estimated-Lung-Age (ELA) in North African population. For abbreviations, see abbreviations list.

In conclusion, reliable reference equations to interpret the ELA in healthy North African adults were established. The ELA can be easily predicted from sex and easily measured/calculated anthropometric data (height, BMI, BSA) in addition to a reproducible spirometric parameter (FEV_1). In additional groups of healthy or adult-patients prospectively assessed, the present novel reference equations yielded satisfactory predictions. These reference equations enrich the World Bank of reference equations (see the Excel "Software "Lung Age" in Appendix B), from which the physician should choose according to the patient's locale and ethnic background.

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None.

Author's contributions

HBS conceived the study, participated in its design, performed the statistical analysis and coordination and helped to draft the manuscript.

HS conceived the study and participated in its design, performed the statistical analysis.

KHM conceived the study and participated in its design, performed the statistical analysis.

IG conceived the study and participated in its design.

AN conceived the study and participated in its design.

HSL conceived the study and participated in its design.

CM performed the spirometry tests.

HB conceived the study and participated in its design.

SC conceived the study and participated in its design, performed the statistical analysis.

SR conceived the study, participated in its design, performed the statistical analysis and coordination, and helped to draft the manuscript.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejcdt.2014.01.003.

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