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Spirometry Reference Equations: A Comparative Cross-Sectional Study In Egyptian Population Sample

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ORIGINAL STUDY

Spirometry reference equations: A comparative cross-sectional study in Egyptian population sample

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Abstract

Context: **Global Lung Initiative-2012 (GLI-2012) was published and endorsed by many international societies as the standard reference for spirometry interpretation. The European Coal and Steel Community (ECSC) equation, updated in 1993 by the European Respiratory Society (ERS), is still widely used in Egypt as a reference.**

Aims: **Investigating the difference between GLI-2012 and ECSC-ERS93 reference values.**

Settings and design: **Retrospective cross-sectional study in Mataria Teaching Hospital.**

Patients and methods: **Spirometry tests (fulfilling the latest ERS acceptability criteria) for Egyptian participants, from January 2022 to July 2024 were included. GLI-2012 and ECSC-ERS93 values of predicted and lower limit of normal (LLN) for forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and FEV_1/FVC ratio LLN were retrieved and compared.**

Statistical analysis used: **Wilcoxon signed-rank test for comparison, and the agreement was checked using the Bland−Altman plot.**

Results: **Five hundred thirty-five participants were included in the final analysis (56 % were males), median age of 43 years (34−55), median BMI of 29.41 (25.39−34.75), Wilcoxon test revealed statistically significant difference between ECSC-ERS93 and GLI-2102 reference values for predicted and LLN of FVC, FEV_1, and FEV/FVC ratio LLN, more over Bland−Altman analysis; revealed that ECSC-ERS93 underestimated FEV_1/FVC LLN, predicted FVC, FVC LLN, predicted FEV_1, FEV_1 LLN by an average of −0.524 %, −304 mL, −294 mL, −163 mL, −178 mL, respectively.**

Conclusion: **The GLI-2012 equation yields higher values than the ECSC-ERS93 reference equation; shifting to GLI-2012 is strongly warranted in Egypt, with its expected impact on the detection and diagnosis of various respiratory diseases.**

Keywords: European Coal and Steel Community-European Respiratory Society 93, Global Lung Initiative-2012, Reference equations, Spirometry

1. Introduction

Spirometry is a basic pulmonary functions test commonly requested for evaluation of general respiratory health, diagnosis of obstructive airway diseases, preoperative and disability assessment [1].

Many parameters are measured during spirometry, such as forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1), which are then compared to reference values, calculated by many predictive equations, for example, Global Lung Initiative-2012 (GLI-2012), and European Coal and Steel Community-European Respiratory Society 93 (ECSC-ERS93) [2].

GLI reference values were published in 2012 [3] and are now considered the standard in spirometry interpretation; ECSC reference values were first published in 1983, updated in 1993 (ECSC-ERS93), and were derived from individuals of European descent only with an age range of 18−70 years [4].

ESCS-ERS93 equation is the one most commonly used in Egypt, and unfortunately, clinicians usually do not pay attention to the equation employed,

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resulting in inconsistent interpretation between pulmonologists, misdiagnosis, or prescribing unnecessary medications, with a subsequent financial burden to patients, insurance companies, ministry of health and the country as a whole via state-funded medical treatment, in addition to exposing the patients to untoward medications side effects.

2. Patients and methods

This was a retrospective cross-sectional study conducted in Mataria Teaching Hospital, Cairo, Egypt. Spirometry data were retrieved during the period from January 2022 to July 2024 from MIR winspiroPRO software (version 8.5.5). All the tests were performed using Spirobank (MIR, Rome, Italy) and according to the latest published spirometry standards [1]. Spirometry tests for Egyptian participants were only included if meeting the acceptability criteria according to the latest guidelines [1] excluding those with age and anthropometric limits of ECSC-ERS93 reference equation (age <18 or >70 years, height <1.45 m or >1.80 m for females and <1.55 m or >1.95 m for males) (Fig. 1). ECSC-ERS93 and GLI-2012 lower limit of normal (LLN) values for FEV_1/FVC ratio, FEV_1, FVC, Maximal mid-expiratory flow (MMEF), and predicted values for FEV_1, FVC, and MMEF were retrieved and compared.

Ethical approval was obtained from the general organization for teaching hospitals and institutes research council (number HM000176).

2.1. Statistical analysis

The sample size was estimated using a web-based calculator available at *https://sample-size.net/sample-size-means/*. Predicted FEV_1 for males yielded the largest sample size compared with other parameters (FVC, FEV_1/FVC) for males or females. Based on previous literature, the mean predicted FEV_1 for healthy nonsmoker males using GLI-2012 and ECSC-ERS93 predictive equations was 3.45 ± 0.69 and 3.28 ± 0.64 L, respectively [5].

It was estimated that a minimum of 223 tests would achieve a power of 80 % (β error = 0.2) to detect a statistically significant difference between the two equations with a confidence level of 95 % (α error = 0.05).

It was assumed that there is no difference between GLI-2012 and ECSC-ERS93 reference equations for FVC (predicted and LLN), FEV_1 (predicted and LLN), FEV_1/FVC ratio (predicted and LLN), and MMEF (predicted and LLN) under the null hypothesis, while in the alternative hypothesis, there is a significant difference between the two equations for the previous parameters.

Statistical testing was performed using IBM Corp. Released 2015. (IBM SPSS Statistics for Windows, Version 23.0. Armonk, New York, USA) statistics software (version 23). Quantitative data are presented as median (interquartile range) and categorical data as proportions (in tables).

Nonparametric related-samples Wilcoxon signed-rank test was applied to compare medians of the FVC (predicted and LLN), FEV_1 (predicted and LLN), FEV_1/FVC ratio (LLN), and MMEF (predicted and LLN) as the data were not normally distributed.

Agreement testing was performed using a Bland–Altman plot, *x*-axis representing mean ESCS-ERS93 or GLI-2012 predicted, or LLN values, *y*-axis representing the difference between respective ECSC-ERS93 and GLI-2012 values, the solid black line in the plot represents zero line (in case of equal ECSC-ERS93 and GLI-2012 values), the red dotted line represents the mean difference, the upper and lower dotted blue lines represent the 95^{th} and the 5^{th} percentiles, respectively, instead of using upper and lower limits of agreement as the data were not normally distributed [6].

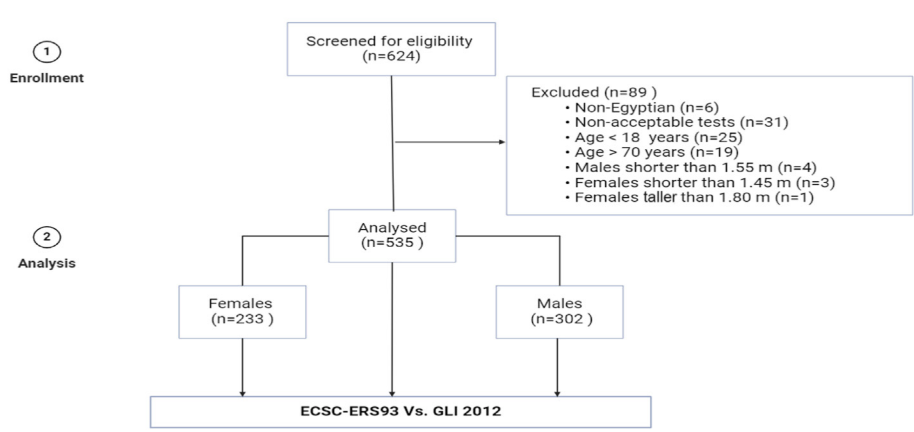

Fig. 1. Study flowchart.

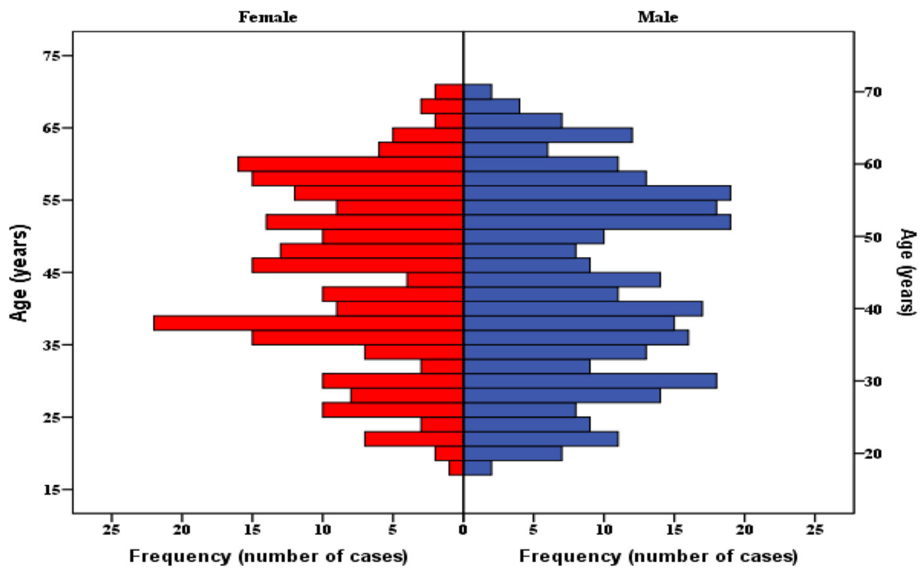

Fig. 2. Population pyramid of age distribution in the study population. The x-axis represents the frequency (number of cases in the respective group). The y-axis represents age in years, and blue and red colors represent males and females, respectively.

3. Results

A total of 535 participants were included in the final analysis; 302 males and 233 females, aged 18–70 years, distributed as shown in Fig. 2. More detailed demographic characteristics are displayed in Table 1.

3.1. Spirometric parameters

After checking the normality of distribution using the Shapiro–Wilk test, the nonparametric Wilcoxon signed-rank test for related samples was conducted and revealed a statistically significant difference between ECSC-ERS93 and GLI-2012 reference values. Specifically, ECSC-ERS93 reference values were consistently lower than GLI-2012 reference values across FEV_1/FVC LLN, predicted FVC, FVC LLN, predicted FEV_1 and FEV_1 LLN (Table 2). By contrast, predicted MMEF and MMEF LLN were lower when derived using the GLI-2012 equation compared to the ECSC-ERS93 equation, as presented in Table 2.

Sex-stratified analysis was also performed to compare the values in males (Table 3) or females (Table 4) separately, showing statistically significant differences for the seven mentioned parameters with similar magnitude and direction of change to the total sample. That is, FEV_1/FVC LLN, predicted FVC, FVC LLN, predicted FEV_1, and FEV_1 LLN were higher, whereas predicted MMEF and MMEF LLN were lower when derived using GLI-2012 equation compared to ECSC-ERS93 equation, irrespective of sex.

3.2. Agreement between ECSC-ERS93 and GLI-2012 reference equations

To gain further insight into the agreement, or lack thereof, between ECSC-ERS93 and GLI-2012 predictive equations, Bland–Altman plots were constructed (Fig. 3). On the one hand, these plots

Table 1. Demographic characteristics of the study population.

Characteristics	Total ($N = 535$)	Males ($N = 302$)	Females ($N = 233$)
Age (years)	43 (34–55)	43 (32–54)	45 (35–55)
Weight (kg)	84 (73–98)	84 (74–96)	83 (72–99)
Height (m)	1.68 (1.60–1.75)	1.74 (1.70–1.79)	1.60 (1.56–1.65)
BMI	29.41 (25.39–34.75)	27.59 (24.53–31.82)	32.05 (28.53–40.21)
Smoking status [*n* (%)]			
Never-smoker	245 (46)	93 (31)	152 (65)
Current smokers	112 (21)	102 (34)	10 (5)
Ex-smoker	35 (6)	32 (10)	3 (1)
Not-reported	143 (27)	75 (25)	68 (29)

Continuous data are presented as median (interquartile range), whereas categorical data are presented as number of cases (percentage of the total count of the respective group).

Table 2. European Coal and Steel Community-European Respiratory Society 93 versus Global Lung Initiative-2012 in the total sample.

Parameters	ECSC-ERS93	GLI-2012	*P* value[a]
FEV_1/FVC ratio LLN (%)	69.40 (67.10–71.60)	70.10 (67.80–71.90)	<0.00001
FVC LLN (l)	2.96 (2.46–3.68)	3.24 (2.76–3.97)	<0.00001
Predicted FVC (l)	3.88 (3.21–4.72)	4.17 (3.51–4.97)	<0.00001
FEV_1 LLN (l)	2.43 (2.04–3.02)	2.61 (2.25–3.19)	<0.00001
Predicted FEV_1 (l)	3.18 (2.72–3.87)	3.35 (2.89–4.04)	<0.00001
MMEF LLN (l/s)	2.18 (1.78–2.67)	1.94 (1.50–2.46)	<0.00001
Predicted MMEF (l/s)	3.73 (3.31–4.33)	3.29 (2.77–4.01)	<0.00001

Data are presented as median (interquartile range).
ECSC-ERS93, European Coal and Steel Community-European Respiratory Society 93; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GLI-2012, Global Lung Initiative-2012; LLN, lower limit of normal; MMEF, maximal mid-expiratory flow.
[a] *P* value calculated using Wilcoxon signed-rank test, significant *P* value less than 0.05, highly significant less than 0.01.

revealed that compared to GLI-2012, ECSC-ERS93 equation underestimated the values of FEV_1/FVC LLN, predicted FVC, FVC LLN, predicted FEV_1, FEV_1 LLN by an average of −0.524 %, −304 mL, −294 mL, −163 mL, −178 mL, respectively. On the other hand, the ECSC-ERS93 equation overestimated the values of predicted MMEF and MMEF LLN by at least 430 and 249 mL/s, respectively, compared to GLI-2012.

Sex-specific Bland−Altman plots were also examined and showed in males that the predicted values of the ECSC-ERS93 equation, compared to GLI-2012 equation, underestimated FEV_1/FVC LLN, predicted FVC, FVC LLN, predicted FEV_1, FEV_1 LLN by an average of −0.622 %, −280 mL, −264 mL, −155 mL, −157 mL, respectively. By contrast, ECSC-ERS93 overestimated the values of predicted MMEF and MMEF LLN by at least 405 and 262 mL/s, respectively, compared to GLI-2012.

A similar pattern was also observed in females, with the Bland−Altman plots showing that ECSC-ERS93 equation underestimated FEV_1/FVC LLN, predicted FVC, FVC LLN, predicted FEV_1 and FEV_1 LLN by an average of −0.397 %, −336 mL, −332 mL, −174 mL, −206 mL, respectively, while overestimating the values of predicted MMEF and MMEF LLN by at least 463 and 234 mL/s, respectively, compared to GLI-2012.

Table 3. European Coal and Steel Community-European Respiratory Society 93 versus Global Lung Initiative-2012 in males.

Parameters	ECSC-ERS93	GLI-2012	*P* value[a]
FEV_1/FVC ratio LLN (%)	68.80 (65.90–71.20)	69.80 (67.20–71.63)	<0.00001
FVC LLN (mL)	3.52 (3.02–4.09)	3.82 (3.36–4.26)	<0.00001
Predicted FVC (mL)	4.54 (4.04–5.09)	4.84 (4.30–5.32)	<0.00001
FEV_1 LLN (mL)	2.89 (2.43–3.38)	3.07 (2.67–3.48)	<0.00001
Predicted FEV_1 (mL)	3.75 (3.27–4.24)	3.89 (3.43–4.37)	<0.00001
MMEF LLN (mL/s)	2.45 (1.91–2.92)	2.22 (1.62–2.69)	<0.00001
Predicted MMEF (mL/s)	4.16 (3.63–4.65)	3.78 (3.13–4.40)	<0.00001

Data are presented as median (interquartile range).
ECSC-ERS93, European Coal and Steel Community-European Respiratory Society 93; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GLI-2012, Global Lung Initiative-2012; LLN, lower limit of normal; MMEF, mid-maximum expiratory flow.
[a] *P* value calculated using Wilcoxon signed-rank test, significant *P* value less than 0.05, highly significant less than 0.01.

Table 4. European Coal and Steel Community-European Respiratory Society 93 versus Global Lung Initiative-2012 in females.

Parameters	ECSC-ERS93	GLI-2012	*P* value[a]
FEV_1/FVC ratio LLN (%)	68.80 (66.20–71.85)	70.20 (66.37–72.40)	<0.00001
FVC LLN (mL)	2.38 (1.58–2.72)	2.73 (2.03–2.97)	<0.00001
Predicted FVC (mL)	3.10 (2.29–3.47)	3.47 (2.69–3.73)	<0.00001
FEV_1 LLN (mL)	2.01 (1.28–2.34)	2.23 (1.59–2.51)	<0.00001
Predicted FEV_1 (mL)	2.65 (1.91–2.97)	2.82 (2.13–3.13)	<0.00001
MMEF LLN (mL/s)	1.96 (1.30–2.29)	1.74 (1.00–2.10)	<0.00001
Predicted MMEF (mL/s)	3.40 (2.70–3.71)	2.94 (1.99–3.36)	<0.00001

Data are presented as median (interquartile range).
ECSC-ERS93, European Coal and Steel Community-European Respiratory Society 93; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GLI-2012, Global Lung Initiative-2012; LLN, lower limit of normal; MMEF, mid-maximum expiratory flow.
[a] *P* value calculated using Wilcoxon signed-rank test, significant *P* value less than 0.05, highly significant less than 0.01.

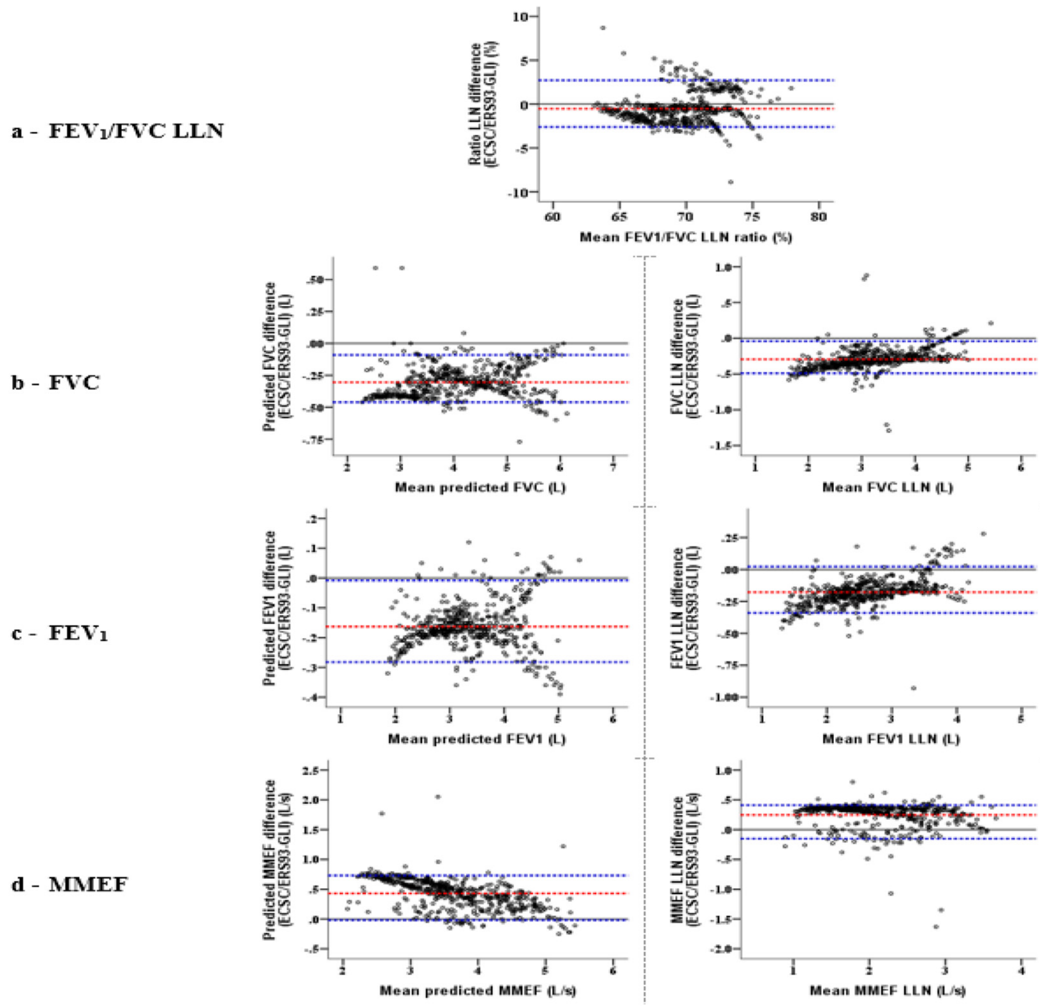

Fig. 3. Bland–Altman plots of the reference values (ECSC-ERS93 and GLI-2012) in the study population, including FEV_1/FVC ratio (a), predicted FVC, FEV_1, MMEF (left panels in b, c, d) LLN FVC, FEV1, MMEF (right panels in b, c, d). Data points are clustered below the red line in all panels except for MMEF (predicted and LLN). ECSC-ERS93, European Coal and Steel Community-European Respiratory Society 93; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GLI-2012, Global Lung Initiative-2012; LLN, lower limit of normal; MMEF, maximal mid-expiratory flow.

4. Discussion

In this retrospective cross-sectional study, we investigated the difference between ECSC-ERS93 and the multi-ethnic GLI-2012 spirometry reference equations regarding the LLN of FEV/FVC ratio, FVC, FEV_1, MMEF, and the predicted FVC, FEV_1, and MMEF values.

We found that ECSC-ERS93 underestimated the values of FEV_1/FVC LLN, predicted FVC, FVC LLN, predicted FEV_1, and FEV_1 LLN by an average of −0.524 %, −304 mL, −294 mL, −163 mL, −178 mL, respectively. On the contrary, predicted MMEF and MMEF LLN were overestimated by at least 430 and 249 mL/s, respectively, compared to the GLI-2012 equation.

Similar trends of overestimation and underestimation were also observed on separate male and female analyses, and were even higher in females compared to males for predicted FVC, FVC LLN, predicted FEV_1, FEV_1 LLN, and predicted MMEF (−336 vs. −280 mL, −332 vs. −264 mL, −174 vs. −155 mL, −206 vs. −157 mL, 463 vs. 405 mL/s, respectively).

Our findings were consistent with Quanjer and colleagues, where predicted FEV_1 and FVC in Caucasian Australian participants aged 18–85 years were higher with the GLI-2012 equation compared to ECSC-ERS93, by an average of 170 and 270 mL in males, 190 and 300 mL in females, respectively [7]. The same findings were also confirmed by Brazzale *et al.* [7], where predicted FEV_1 and FVC were higher with the GLI-2012 equation compared to ECSC-ERS93, by an average of 156 and 276 mL respectively in another Australian study recruiting participants with a wider age range of 5–85 years, respectively.

Similarly, Cioffi and colleagues reported that GLI-2012 reference values compared to ECSC-ERS93 in workers employed in different Italian sectors requiring pulmonary function evaluation for specific occupational risks were higher for FEV_1/FVC LLN, predicted FVC, FVC LLN, predicted FEV_1, FEV_1 LLN by an average of 1.48 %, 330 mL, 270 mL, 190 mL, 170 mL, respectively [8].

Our findings were also in line with Tatsis and colleagues; on investigating healthy Greek adults aged 18–89 years, GLI-2012 values for predicted FVC and FEV_1 compared to ECSC-ERS93, were higher by an average of 20 and 190 mL in the whole study, and 320 and 200 mL in males, and 380 and 180 mL for females [9]. Mangseth *et al.* [10] and Backman *et al.* [11] also reported higher predicted values for FVC and FEV_1 with GLI-2012 compared to ECSC-ERS93 irrespective of sex in adult Norwegian and Swedish participants.

Higher differences for females compared to males between ECSC-ERS93 and GLI-2012 equations were highlighted by Liistro *et al.* [12], who studied adult smokers and ex-smokers between 40 and 95 years in a large retrospective Belgian research; the outcome that also coincides with our findings. Significant differences between the two equations were also emphasized in different disease states with subsequent clinical implications, such as cystic fibrosis, hematopoietic stem-cell transplant, and amyotrophic lateral sclerosis [13–15].

On the contrary, Belo *et al.* [16] concluded that FEV_1/FVC ratio LLN was higher with ECSC-ERS93 (compared to GLI-2012) for both sexes by an average of 0.4 % in males and 14.9 % for females; and this can be explained by the higher age range in their study (65–95 years), compared to 18–70 years in ours.

In conclusion, the multi-ethnic GLI-2012 equation yields higher values compared to the ECSC-ERS93 reference equation published in 1993 (which is widely used in Egypt), and given the fact that the GLI-2012 equation is now considered the standard for spirometry interpretation, shifting from ECSC-ERS93 to GLI-2012 is a logical reasonable step in Egypt, and this expectedly will result in a significant impact on detection and diagnosis of various respiratory diseases. Consequently, changes in respiratory health and economic burden will be evident.

4.1. Recommendations

Validation of multi-ethnic GLI-2012 among Egyptians and its impact on detection of obstructive and restrictive patterns are strongly warranted.

Institutional review board (IRB) approval number

HM000176.

Ethics information

Ethical approval was obtained from the general-organization for teaching hospitals and institutes research council (number HM000176).

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Author contribution

None.

Conflicts of interest

There are no conflicts of interest.

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