Age and sex variation of spirometry based lung function measures in children and adolescents of Asian Indian origin

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ABSTRACT

Objective: Present study aims to look into age and sex variation of spirometric lung function among Asian Indian children aged 10-18 years and how much Global Lung Initiative (GLI)-South East Asian (SEA) spirometric reference equations are well fitted in the same ethnic children.

Materials and Methods: The study was conducted among 136 rural Asian Indian children, West Bengal, India. All spirometric variables were categorized into sex and age, i.e., G-I (10-12 years), G-II (13-15 years), and G-III (16-18 years)

Result: With few exceptions, the GLI-predicted and baseline value of spirometric variables significantly varied with sex and age. Percentile distribution showed that FVC and FEV_1 were increased with age in both boys and girls but during adolescence, the growth of lung volumes were higher in boys than girls until the age of 18 years and thereafter a certain increment in baseline lung volumes were noted in girls. The mean (SD) Z-score of spirometric variables based on GLI SEA reference equations were exceeded from the acceptable range. The deviation was considerably larger in girls and younger children.

Discussion: Spirometric lung function are highly dependent on height, age, sex and ethnicity. Besides, there are some other confounding factors which may have an influence on variation of lung function. In the present study, GLI-SEA reference equation was not fit with rural Asian Indian children. A large extensive quality control data is necessary for Asian Indian children to develop suitable spirometric reference equations which will facilitate diagnosis of respiratory impairment and monitoring disease progression.

Keywords: Asian Indian children, Lung function, Global Lung Initiative, Reference equation, South East Asian, Spirometry

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INTRODUCTION

Spirometric lung functions are important in diagnosing respiratory impairment and monitoring disease progression in response to treatment. Interpretation of spirometric lung function results relies on comparisons with predicted reference values derived from the healthy population. But spirometric lung functions are strongly dependent on height, age, sex, and ethnicity.[1-3] Over the decades, more than 300 references have been published resulting in difficulties in the selection of appropriate references.[4,5] Furthermore, most of the references have been criticized due to many reasons, such as small sample size, differences in methodological consideration, statistical analysis, equipment, etc.[5] In general, an age-related decline in lung function is noted in adults whereas, in pediatric age, the pattern of lung growth is complex, particularly during puberty marked by an adolescence growth spurt.[6]

In previous studies, reference equations were generated by conventional regression model based on residual distributional assumptions which are suitable for specific age groups but not for wider age range.[3,5] Thus, these reference equations are not adequate to depict age-related complex changes in lung function. However, in 2012, Global Lung Initiative (GLI) published a uniform standardized ethnic-specific reference and transformed specific age group to all age approach (age span 3-95 years) using Generalized Additive Model for Location Scale and Shape (GAMLSS) model among Caucasians, African, North East Asian (NEA), South East Asian (SEA) and Other/Mixed (individuals whose ethnicity did not identify properly).[5]

The present study was aimed to look age and sex variation of spirometric lung function among Asian Indian children and adolescents aged 10-18 years. Furthermore, we also examined how good GLI SEA spirometric reference equations (SRE) were fitted for the Asian Indian children and adolescents.

MATERIALS AND METHODS

Study population

The present study was conducted between July and September, 2021. The data was collected from five villages about 20 km apart from Barasat (Latitude: 22° 07' 48.00" N. and Longitude: 88° 30' 0.00" E.), West Bengal, India. A total of 256 healthy children and adolescents aged 10-18 years were contacted. Out of which 136 were found eligible. Written informed consent was obtained from participants' guardian.

Exclusion criteria

Participants were excluded with one or more of the following conditions:

- poor health status assessed by pulse rate, saturated oxygen, and haemoglobin level using pulse oximeter and hemoglobinometer
- current or chronic lung disease during past 12 months (such as doctor-diagnosed asthma, COPD, etc.) with or without current symptoms i.e., wheeze, shortness of breath, etc.
- any congenital abnormality by which lung function may be influenced
- not meet or unable to perform spirometry as per ATS/ERS recommendation[7,] and technical problems with equipment

Anthropometric measures

Height and lightly clothed weight were measured using a stadiometer (nearest to the 0.1 cm) and an electronic weighing scale (Omron, Tokyo Japan).

Spirometry

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Spirometry was performed using a PC-based spirometer (Medikro Oy, Finland, software version 4.6) with a disposable flow transducer. Before each day of data collection, temperature, humidity, and barometric pressure were set up to the equipment's and then calibrated with a 3 lit. syringe (Medikro Oy, Finland). All assessments were undertaken with participants standing position and a nose clip was used. The test was phased with initially normal breath for 3 times, followed by a deep inhalation, then a maximum exhalation, and a final inhalation as per the investigator's direction. At least 3 manoeuvre was taken for all participants and if not satisfactory, it was continued up to maximum 8 and compare between two best blows within acceptable range (<5% for FVC, FEV_1, and FEV_1/FVC) and then best blow was considered. At least 6 sec. forced expiratory time (FET) was strictly followed with a 5 minutes interval between each exercise.

Statistical analyses

The predicted, baseline and Z-score value for spirometric variables were obtained using GLI SEA SRE installed in the equipment. Descriptive statistics such as mean, standard deviation (SD) and percentile distribution were analysed for spirometric variables and categorized into age and sex. One-way analysis of variance (ANOVA) was performed to observe whether significant differences existed for the spirometric variables according to age and sex.

All statistical analyses were performed using statistical package for social sciences (SPSS, version 25.0). A p value <0.05 was considered as significant.

RESULTS

The present study was conducted on 136 children. Out of which 47.8% (n=65) was boys. The socio-demographic characteristics of studied children are given in Table 1.

Anthropometric characteristics of children are presented in Table 2. The mean age of the participants was 13.6±2.3 years. Mean height, weight, and BMI was 153.0±10.1, 46.0±13.4, and 19.4±4.3 respectively.

Table 1: Socio-demographic characteristics of the study population (n=136)

Variables	n	%
Boys	65	47.8
Girls	71	52.2
Education		
Up to class VIII	84	61.8
Secondary	21	15.4
Higher secondary	31	22.8
Birth order		
One	90	66.2
Two	43	31.6
Number of children		
One	32	23.5
Two	96	70.6
Education – Father		
Up to Primary	27	19.8
Secondary	82	60.4

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Secondary onwards	27	19.8
Education – Mother		
Up to Primary	14	10.3
Secondary	102	75.0
Secondary onwards	20	14.7
Occupation – Father		
Labour	59	43.4
Agriculture	21	15.4
Business	41	30.1
Service	15	11.0
Occupation – Mother		
Home maker	102	75.0
Business	23	16.9
Labour	6	4.4
Service	5	3.7
Family type		
Nuclear	92	67.6
Joint	44	32.4
Annual income (INR)		
<1,20,000	20	14.7
≥1,20,000 - <3,60,000	105	77.2
≥ 3,60,000	11	8.1
Materialistic position		
Gas connection	133	97.8
Refrigerator	63	46.3
Television	128	94.1
Computer	11	8.1
Mobile	136	100
Two-wheeler	48	35.3

Table 2: Anthropometric characteristics of the study population

	Mean±SD	**Range**
Age (years)	13.6±2.3	8.0
Height(cm)	153.0±10.1	55.1
Weight(kg)	46.0±13.4	74.5
BMI	19.4±4.3	24.0

Descriptive statistics for GLI SEA predicted and baseline value of spirometric variables have been shown in Table 3. One-way ANOVA showed significant sex and age effect for most of the spirometric variables. In boys, GLI predicted FVC (P = 0.000), FEV_1 (P = 0.000), FEF_{25-75} (P = <0.05) was significantly higher with lower FEV_1/FVC ratio (P = 0.000) compared to girls. In contrast, significant sex effect was only observed for baseline FEF_{25}, FEF_{25-75} (P = <0.05) but not for lung volumes and their ratio. Except FEV_1/FVC, significant age effect (P = 0.000) was

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also observed for both GLI predicted and baseline lung volumes which were further shown in age and sex-wise percentile distribution (Figure 1).

The z-score of spirometric variables based on GLI SEA reference equation have been presented in Table 4. Overall, mean z-score of most of the spirometric variables were exceeded from the acceptable range (±0.5) which is expected to be 0 with 1 SD, except FEF_{25-75} (-0.34±1.32). The equation largely overestimated (negatively skewed) mean z-score of all spirometric measures, except FVC (largely underestimated, positively skewed). For sex, the deviation from the expected normal for most of the variables were higher in girls compared to boys, except FEV_1 (-1.90±15.04 vs. 0.55±1.70). Similarly for age, the deviation of mean z-score of all variables were comparatively higher in younger children than older indicated an age-related decline trend of skewness, approaching normal. LLN which is defined as 5^{th} percentile, (equivalent to -1.64 z-score) also have been presented in table 4, which is expected to be 5% of the total healthy population. Overall, the proportion of LLN for FVC and FEV_1 was low (<1% and ~2% respectively) which was due to the larger calculated 5^{th} percentile value (z-score = -1.37 and -1.46) than expected but for FEV_1/FVC, a larger proportion of children (18.4%) fall below LLN (as calculated 5^{th} percentile value was small, -2.57 than expected). Due to larger deviation of mean z-score, the proportion of LLN was considerably higher in girls.

DISCUSSION

In 2012, GLI published multi-ethnic SRE based on 74,187 individuals, of which majority was Caucasian (77.4%) and only 11.1% was SEA.[5] However, GLI equations were derived from various studies around the world that published over the past 3 decades. Since the equations have been validated extensively as per ATS/ERS recommendation to reach the level of agreement between these equations and spirometric data on contemporary population.[2,4,5,8,9-12] However, there were some inconsistent findings on validation of GLI equations, where some studies documented that the equations were suitable with their dataset,[1,4,8-10] contrary to other studies.[2,3,11,12]

In the present study, our objective was age and sex variation of spirometric lung function measures among Asian Indian children and adolescents aged 10-18 years. It was observed that a significant sex and age-specific influence for GLI-predicted and baseline value (except for baseline FVC, $FEV_{1,}$ and their ratio). Moreover, our observed baseline value for lung volumes such as FVC and FEV_1 were higher than GLI predicted value which was also noted when stratified into sex and age, but not for FEV_1/FVC ratio and airflow measures (Table 3). The difference between predicted and observed values for lung volumes was further reflected in sex and age-wise percentile distribution (Figure 1). Irrespective of sex, both FVC and FEV_1 had increased with increased age but during adolescence, the growth of lung volumes was higher in boys than girls until the age of 18 years and thereafter, a certain increment in baseline lung volumes was noted in girls. Therefore, during adolescence, age-related changes in lung growth are different in boys and girls. In addition, the difference between predicted and baseline values indicated a number of confounding factors are associated with lung function. Although, the relation between lung function and associated factors are studied mostly based on lung volumes whereas their ratio is independent and unknown for airflows.

Table 3: Descriptive statistics of spirometry based lung function measures by age and sex

Variable	Total (n=136) GLI Mean (SD)	Total (n=136) Baseline Mean (SD)	Boys(n=65) GLI Mean (SD)	Boys(n=65) Baseline Mean (SD)	Girls(n=71) GLI Mean (SD)	Girls(n=71) Baseline Mean (SD)	G-I(n=48) GLI Mean (SD)	G-I(n=48) Baseline Mean (SD)	G-II(n=52) GLI Mean (SD)	G-II(n=52) Baseline Mean (SD)	G-III(n=36) GLI Mean (SD)	G-III(n=36) Baseline Mean (SD)
FVC(L)	2.79 (0.67)	3.02 (0.86)	3.07 (0.78)	3.11 (0.86)	2.54$^{\$\$\$\$}$ (0.40)	2.94$^{n.s.}$ (0.86)	2.22 (0.27)	2.40 (0.51)	2.85 (0.40)	3.17 (0.94)	3.48**** (0.66)	3.63**** (0.56)
FEV_1(L)	2.52 (0.58)	2.60 (0.72)	2.73 (0.69)	2.71 (0.78)	2.33$^{\$\$\$\$}$ (0.37)	2.49$^{n.s.}$ (0.65)	1.99 (0.23)	2.05 (0.43)	2.59 (0.33)	2.71 (0.70)	3.14**** (0.53)	3.17**** (0.53)
FEV_1/FVC	90.80 (1.58)	86.35 (0.72)	89.31 (0.75)	87.27 (5.29)	92.16$^{\$\$\$\$}$ (0.59)	85.51$^{n.s.}$ (7.06)	90.37 (1.47)	85.46 (5.05)	91.08 (1.67)	86.37 (7.66)	90.98$^{n.s.}$ (1.52)	87.52$^{n.s.}$ (5.62)
FEF_{75}(L/s)	1.83 (0.41)	1.60 (0.77)	1.90 (0.51)	1.74 (0.86)	1.77$^{n.s.}$ (0.28)	1.47* (0.65)	1.42 (0.17)	1.16 (0.49)	1.90 (0.20)	1.71 (0.72)	2.29**** (0.32)	2.01**** (0.86)
FEF_{25-75}(L/s)	3.29 (0.63)	3.13 (1.17)	3.41 (0.79)	3.34 (1.31)	3.18$^{\$}$ (0.40)	2.93* (0.99)	2.67 (0.27)	2.43 (0.71)	3.37 (0.30)	3.20 (1.11)	3.99**** (0.49)	3.94**** (1.20)
PEF(L/s)		5.63 (1.74)		6.03 (1.94)		5.28** (1.45)		4.38 (0.88)		5.79 (1.54)		7.10**** (1.66)
FET(s)		5.57 (1.70)		5.42 (1.80)		5.71$^{n.s.}$ (1.61)		6.01 (1.26)		5.20 (1.93)		5.50$^{n.s.}$ (1.77)

FVC – Forced vital capacity, FEV_1 – Forced expiratory volume in 1 sec., FEF_{75} – Forced expiratory flow at 75%, FEF_{25-75} – Forced expiratory flow between 25% and 75%, PEF – Peak expiratory flow, FET – Forced expiratory time, SD – Standard deviation, G-I – 10-12.99y, G-II – 13-15.99 y, G-III – 16-18.99 y, GLI – Global lung initiative, Significant level was compared using analysis of variance (ANOVA), P = 0.05 (*/$^{\$}$), P = 0.01 (**/$^{\$\$}$), P = 0.001 (***/$^{\$\$\$}$), P =

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<0.0001 (****/$$$$), GLI predicted value were based on South East Asian spirometric reference equations

Table 4: GLI predicted z-score and LLN (%) of lung fuction measures (spirometry based) by age and sex

Variable	**Sex**						**Age(y)**					
	Total(n=136)		**Boys(n=65)**		**Girls(n=71)**		**G-I (n=48)**		**G-II (n=52)**			
	Mean (SD)	**%LLN**	**Mean (SD)**	**%LLN**	**Mean (SD)**	**%LLN**	**Mean (SD)**	**%LLN**	**Mean (SD)**	**%LLN**	**Mean**	
z FVC(L)	0.67 (1.66)	0.7	0.12 (1.08)	1.5	1.18 (1.92) $$$$	0.0	0.67 (1.41)	0.0	0.84 (2.11)	0.0	0.43 (1.17) n.s.	2.8
z FEV_1(L)	-0.62 (10.50)	2.2	-1.90 (15.04)	1.5	0.55 (1.70)n.s.	2.8	-2.26 (17.56)	0.0	0.37 (1.76)	3.8	0.13 (0.96)n.s.	2.8
Z FEV_1/FVC	-0.72 (1.05)	18.4	-0.33 (0.91)	7.7	-1.08 (1.03)$$$$	28.2	-0.85 (0.85)	16.7	-0.71 (1.20)	23.1	-0.55 (1.04)n.s	13.9
z FEF_{75}(L/s)	-0.67 (1.36)		-0.55 (1.32)		-0.77 (1.39)n.s.		-0.84 (1.34)		-0.56 (1.46)		-0.60 (1.23)n.s.	
z FEF_{25-75}(L/s)	-0.34 (1.32)		-0.24 (1.23)		-0.44 (1.40)n.s.		-0.49 (1.23)		-0.35 (1.46)		-0.14 (1.24)n.s.	

FVC – Forced vital capacity, FEV_1 – Forced expiratory volume in 1 sec., FEF_{75} – Forced expiratory flow at 75%, FEF_{25-75} – Forced expiratory flow between 25% and 75%, PEF – Peak expiratory flow, FET – Forced expiratory time, SD – Standard deviation, G-I – 10-12.99 years, G-II – 13-15.99 years, G-III – 16-18.99 years, GLI – Global lung initiative, SEA – South East Asian, Significant level was compared using analysis of variance (ANOVA), P = 0.05 (*/$), P = 0.01 (**/$$), P = 0.001 (***/$$$), P = <0.0001 (****/$$$$), LLN (lower limit of normal) – defined as 5th percentile (z-score = -1.64), expected 5% of the total sample, z score were based on GLI SEA spirometric reference equations

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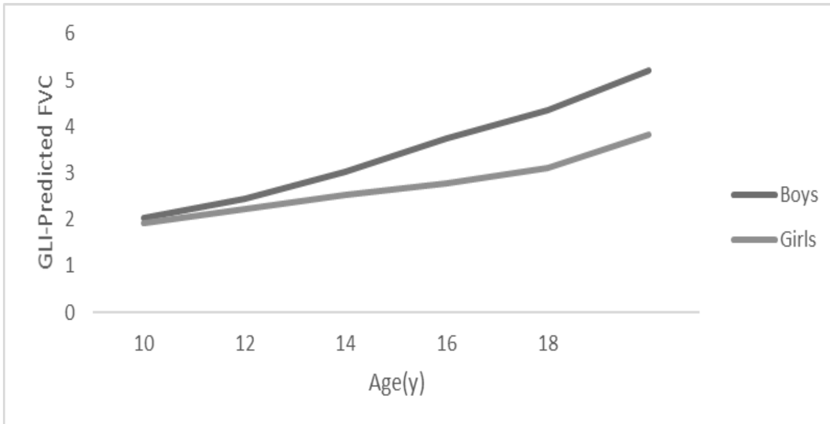
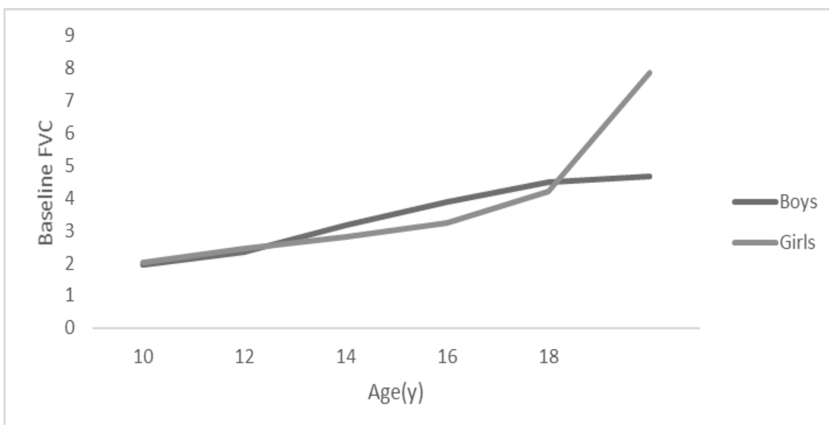
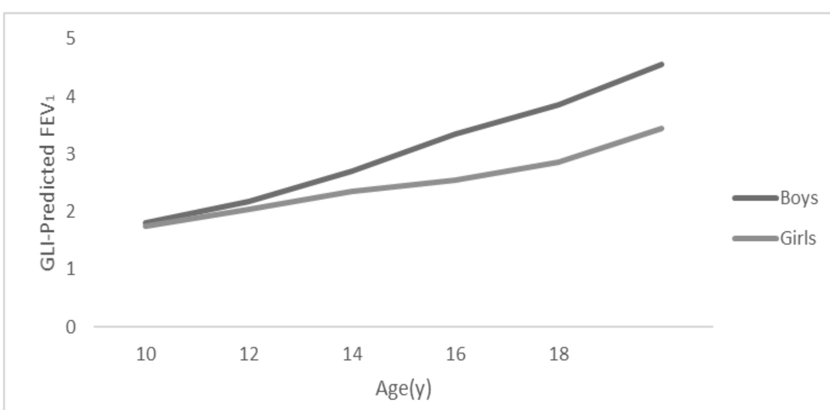
Figure 1: Percentiles distribution of FVC and FEV_1, (a) GLI-predicted FVC, (b) baseline FVC, (c) GLI-predicted FEV_1 and (d) baseline FEV_1 by age and sex



(a)



(b)



(c)

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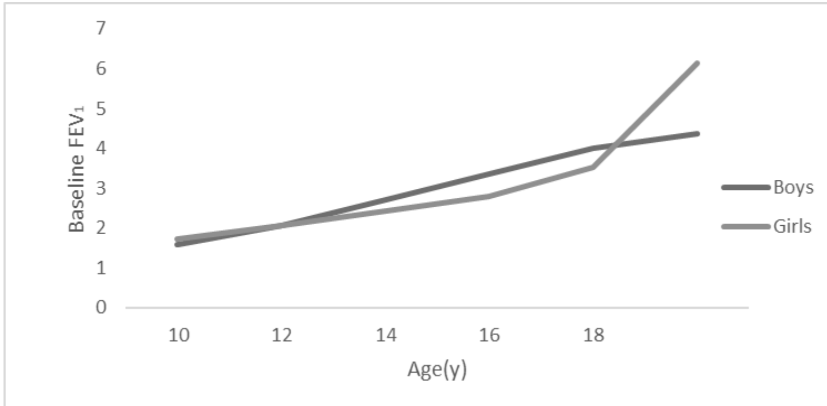

(d)

The predictive value of spirometric lung function is strongly dependent on height, age, sex, and ethnicity. Besides, there are some other confounding factors such as intrauterine environment, parental SES, nutritional status, exposures to air pollution, etc., which may have an influence on the variation of lung function within as well as between population.[9,10] To remove all potential biases, we further consider Z-score value of lung function measures based on GLI SEA equation, instead of % predicted value. In addition, Z-score indicated how many standard deviations a measured value differs from the predicted, taking account height, age, sex, ethnicity. Therefore, Z-score values are free from biases and useful to define lower limit of normal (LLN, 5^{th} percentile or <-1.64 Z-score) which is expected 5% of the healthy population.[5]

In our study, we found that GLI SEA equation largely overestimated (<0) the mean Z-score value of all spirometric measures from the expected normal (0 with 1 SD, acceptable range ± 0.5), except FVC, which was largely underestimated (>0). We also stratified the z-score of spirometric variable into sex and age separately and found no significant difference, except FVC and FEV_1/FVC ratio (sex difference, $P = 0.000$). For sex, the deviation was larger in girls compared to boys for most of the variables, except FEV_1. Similarly for age, the deviation was higher in younger children compared to older suggested an age-related decreasing trend of skewness, approaching normal. Hence, the GLI SEA equation is not perfectly fit for our rural Asian Indian children. Probably, small sample size may be a reason as at least 300 samples are necessary for validation of GLI equation[5] and there is evidence that increasing number of sample decreases the variability of spirometric variables.[4] But, in Size and Lung Function in Children (SLIC) study[8] of migrant Asian Indian, mean z-score for lung volumes and their ratio slightly deviated from 0, but within acceptable range indicated GLI SEA equation was applicable in Asian Indian children living in UK, which was corresponded to another study conducted by Sonappa et al.[9] In this study, spirometric data were compared between children residing in South India and UK (SLIC) and Indian spirometric coefficient was adjusted to the equation. But when Indian children were stratified by habitat, the equation was poorly fit to semi-urban and rural children, similar to our study. Results vindicated that semi-urban and rural children had significantly lower levels of lung volumes (on average ~0.5 and ~0.9 z-score for FVC and FEV_1) compared to its urban counterpart whereas no significant differences were existed between Indian urban children with those living in UK. Probably, better nutritional status, living standard are associated with higher levels of lung function in urban children and those residing in UK.[8,9] On the other hand, in a study, Lum and colleagues[13] collated last 15 y spirometric data on Asian

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Indian children residing in India (4 centers) and UK (5 centers) and applied GLI multi-ethnic reference equation. Results showed that GLI Black equation was more suitable for Asian Indian children living inside and outside India compared to White, SEA, and Others. However, some study[11,12] also reported that GLI ethnic-specific equation including SEA[2,3] (Jiang – 2015, Chang – 2019) was not applicable. In addition, it is noteworthy to mention that GLI multi-ethnic reference equation including SEA were derived from the data collected several decades ago. Furthermore, in SEA equation, the data were mostly based on adult population (South of the Huaihe River and Qinling mountain of China, Thailand, and Taiwan) and Asian Indian data were not included.[5]

Inappropriate selection of SRE misinterpreted test results on the evaluation of lung function.[2,3,11-13] In present study, very lower proportion of children showed abnormal FVC and FEV_1 (<2%) than expected whereas, a larger proportion of children showed obstructive lung function (FEV_1/FVC ratio >18%) which is due to the difference between calculated and expected 5th percentile value (LLN) and opposite direction of the numerator (FEV_1) and the denominator (FVC). However, our study is community-specific and is not representative of Asian Indians as these people are ethnically heterogeneous, culturally varied, and geographically diversified.

CONCLUSION

- The GLI SEA SRE is not suitable for Asian Indian children, demands an urgent need of large extensive quality control data for Asian Indians to develop suitable spirometric reference equations which will facilitate diagnosis of respiratory impairment and monitoring disease progression.
- Identification of appropriate ethnic-specific spirometric coefficients is also necessary to minimize erroneous results of reference equations across population including Asian Indians.

DISCLOSURE

Author Contribution

MD was responsible for data collection, study design, statistical analysis and draft manuscript. AG was responsible for the study design and final version of the manuscript.

Conflict of Interest

There is no conflict of interest so far as the authorship is concerned.

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