Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

A Unit of Scholars Academic and Scientific Society, India
www.saspublisher.com

Physiotherapy

Reference Values for Spirometry for Healthy Sri Lankan Adults: Age between 20 To 65 Years

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Original Research Article

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Article History
Received: 05.09.2018
Accepted: 16.09.2018
Published: 30.09.2018

DOI:
10.21276/sjams.2018.6.9.38

Abstract: Spirometry is the most important method of investigation in respiratory medicine. When conducting Spirometry, South Indians' references were mostly used as prediction values for Sri Lankans. There can be some misinterpretations of lung function test results when using Indian references for Sri Lankan individuals. Hence, objectives of this study were to develop separate prediction equations, and investigate reference values for Spirometry for healthy Sri Lankan adults' of age between 20 to 65 years and compare these values with reference values which obtained using South Indian references of Sri Lankan individuals. Healthy nonsmoking individuals were selected as the study sample and the sample size was 1021 subjects including 520 (50.9%) males and 501(49.1%) females. Data collection was categorized to 20-25, 26-35, 36-45, 46-55, 56-65 years of age groups to make the data collection more reliable. Prediction equations for Forced Vital Capacity (FVC), Force Expiratory volume within first second (FEV1), FEV1/FVC%, Peak Expiratory Flow Rate (PEFR) were derived using each individuals' age, standing height, weight and BMI for both male and females separately and Lower Limits of Normal (LLN) were calculated to clarify the level of diagnosing of a disease condition. GAMLSS model with Box-Cox-Cole-Green (BCCG) family distribution was selected as the best fitted model to derive prediction equations and prediction values were generated using those equations. When compare these prediction values, FVC, FEV1 and PEFR values were overestimated while FEV1/FVC% was underestimated by reference values which obtained using South Indian references of Sri Lankan individuals for both males and females and there is significant difference between reference values which obtained using South Indian references and Sri Lankan references of Sri Lankan individuals at 5% significant level. Hence, this study is concluded that separate reference values can be used for Sri Lankan individuals when conducting Spirometry instead of using South Indian references.
Keywords: Reference values, Spirometry, Sri Lankans, Healthy adults, GAMLSS model.

INTRODUCTION

Lung function of humans is mainly categorized into three: dynamic flow rates, static lung volumes and gas exchange across alveolar capillary membrane. Dynamic flow rates consist of forced expiratory volume in one second (FEV1), forced vital capacity (FVC), FEV1/FVC% and peak exploratory flow rate (PEFR) which is assessed using Pulmonary function test or spirometry. Spirometry is used to diagnose lung diseases, measure lung volumes, monitor severity of lung diseases, and determine the suitability of an individual for a surgery[1]. Static lung volumes consist of total lung capacity (TLC), vital capacity (VC), residual volume (RV), and functional residual capacity (FRC). A procedure known as diffusion capacity for carbon monoxide (DLCO) is used to measure the gas exchange across alveolar capillary membrane [2, 3]. There are several factors which directly affect the lung function of an individual. Usually individuals achieve their maximum lung function around age 20 years in females and 25 years in males from the birth throughout their growth and the development. These maximum lung volumes are maintained from age 25 to 35 years, and thereafter they start to decline. From age 35 to 45 years, the rate of decline is around 25-30 ml/yr. The decline rate after 70 years is around 60 ml/yr. All these changes occur due to the increase in functional residual capacity and residual volume with age. As a result, vital capacity is reduced but the total lung capacity remains constant [2, 4]. Until puberty all males and females have the same lung volumes, and after puberty males tend to have large lung volumes due to significant growth of the thorax. With increasing height, lungs also get bigger which means taller people have large lung volumes [1]. The lung function increases with the increasing weight until it reaches obesity. Then it declines with increasing obesity [1]. Smoking also heavily affects the lung function and smokers have huge decline in lung function compared to non-smoking. Therefore, smoking individuals are not taken for studies when making prediction equation for the spirometry by considering their abnormalities in lung function [1].

The results of the lung function test are not important unless it is compared with a predicted value. Data collected through the population surveys are used to obtain a prediction value based on a fitted model. Information about the individual such as height, weight, age, sex, ethnicity, smoking habits, environment, working conditions and physical fitness is gathered from the large survey population to build these models [5].In recent studies[6, 7], reference equations were developed using Generalized additive model for location, scale and shape (GAMLSS), and the original LMS method which summarizes the changing distribution by three curves representing the median (M), the coefficient of variation (S) and skewness for which the latter expressed as after a Box–Cox power (L) transformation. Using these methods, the researchers have formulated prediction equations for mean spirometric values (FEV1, FVC, FEV1/FVC% and PEFR) using independent variables (age, height, weight and BMI). Heterogeneity of the explanatory variables is addressed using splines which allow fitted model for dependent variable to run non-linearly on the explanatory variables. Continuous smooth fitted model can be achieved using these splines [8-10].

For the study conducted by Quanjer*et al.* in [7], the data were collected from Latin America, East Asia, African–American, Mexican–American, North Africa and Iran, Indian subcontinent, Oman and Japan to obtain globally applicable multi-ethnic reference values for spirometry for the 3–95 year age range. For the Indian subcontinent, data were collected only from India and Pakistan, but not from Sri Lanka. Therefore, when conducting pulmonary function test, South Indians' references were mostly used as prediction values for Sri Lankans. Using Indian references, there can be some misinterpretations of lung function test results for Sri Lankan individuals. Therefore, developing new reference values of Sri Lankan individuals is important for identifying respiratory diseases.Hence, objectives of this study were to develop separate prediction equations and compare new reference values with reference values which obtained using South Indian references of Sri Lankan individuals.

METHODOLOGY

Study subjects were recruited from Hemas Hospitals, Wattala, Sri Lanka representing geographically diverse and multi ethnic population. According to the previous studies it was noted that the ethnic origin of an individual is also a significant factor of the changes in lung function. Therefore, only the native Sri Lankans were selected and convenient sampling method was used to select participants for this study.Ethical clearance was obtained by the Ethical review committee of Postgraduate Institute of Science, University of Peradeniya, Sri Lanka and data were collected with the consent of the general manager of the hospital.

Further, healthy non-smoking individuals who are engaging in various physical activities were selected as the eligible subjects to preserve the accuracy of the reference value as lung function values change due to smoking status. Those who were diagnosed with acute or chronic pulmonary disease, cardiac disease, systemic diseases (e.g. connective tissue disease or muscular dystrophy) or neurological disability, individuals with morbid obesity, those who had undergone with prior chest surgery, radiotherapy or anomalies of the thorax, individuals with prior use of respiratory medications or cardiovascular medication which potentially affects the respiratory function and subjects had abdominal surgery during last 6 months, pregnancy over 20 weeks of gestation or childbirth less than months prior to the study visit and individuals' who are working in the air pollution environment were considered as exclusion criteria of the study[6]. Lung function and the lung volumes reduce with the age[2]. Hence, the data was categorized to 20-25, 26-35, 36-45, 46-55, 56-65 years of age groups to make the data collection more reliable.

Each individual's standing height, weight, BMI, age, gender, ethnicity, smoking states should be entered to the lung function machine before conducting the test, and these values were considered as the independent variables of the study. Height was measured without shoes using a calibrated stadiometer to the closest full cm, and weight with light clothing in kilograms up to one decimal point. BMI was calculated using individuals' height and weight as given below:

$$BMI = \text{Weight in Kg} / (\text{Height in m})^2$$

Individuals' age was calculated using the difference between the test date and the subject's date of birth nearly full years. Reference values for Spirometry results were calculated separately for males and females since the physical changes usually occur after their puberty. Flow-volume spirometry data were generated electronically in the machine and printed copies of spirometry reports were taken. The largest values of FVC, FEV1 were taken, and their ratio (FEV1/FVC %) was calculated using those values. PEFR was also evaluated as an outcome of this study.

All statistical analyses were performed using R (version 3.3.2) statistical software and Generalized Additive Model for Location Scale and Shape (GAMLSS) model was used to build the model. Reference values for spirometry results were calculated separately for males and females due to the physical changes that occur after their puberty. First, the best fitted model for the location parameter (mean: mu) and for the scale parameter (standard deviation: σ) of GAMLSS was identified by fitting various types of two parametric continuous distributions. The fitted distributions were normal ((NO)), Gamma ((GA)), Gumbel ((GU)) and Weibull ((WEI)). The best fitted distribution for the model was selected using Akaike information criterion (AIC), Bayesian information criterion **(**BIC) and the global deviance. Based on this best fitted model a three parametric best fitted model was selected, and then compared the two models by using AIC, BIC and global deviance. After obtaining the final best fitted model for the test data set, the same model was used to predict values for the validation data set. Using these predictor values 95% of the lower confidence interval (LLN), and upper confidence interval (ULN) were obtained, separately. When individuals' spirometry values are less than LLN, it is diagnosed as having a lung disease. Finally, the reference values which are calculated using the validation data set were compared with reference values which obtained using South Indian references of Sri Lankan individuals to check the suitability of using Indian references for Sri Lankan individuals.

RESULTS AND DISCUSSION

The inclusion and exclusion criteria were applied for defining the study sample and 271 participants were excluded due to exclusion criteria by referring participants' medical reports. The final sample was 1021 subjects including 520 males and 501 females and two third of the data set was taken to build the model, and one third of data set was used for model validation (Figure 1).

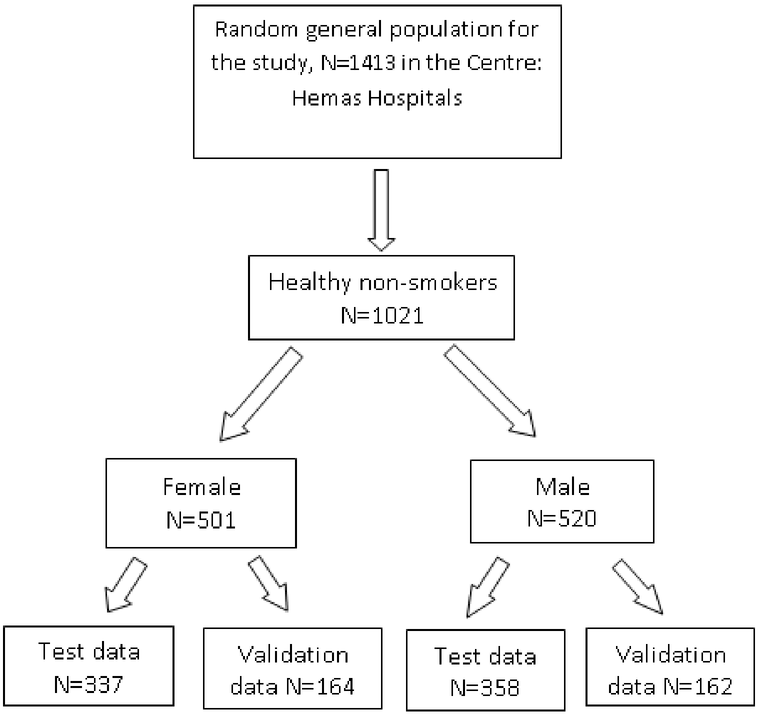

Fig-1: Formation of the study sample

The distribution of the data was determined using summary statistics, before identifying an efficient statistical tool. Results have shown that males are having higher mean values of FVC and FEV1 lung capacities as well as PEFR than females (Table 1).

Table-1: Summary of female and male data for all variables

Variable Name	Mean±SD	
	Male	Female
FVC (l)	3.4±0.59	2.3±0.51
FEV1 (l)	3.0±0.55	2.1±0.45
FEV1/FVC%	88±4.33	90±5.00
PEFR (ls^{-1})	7.9±1.68	5.2±1.31
Age (years)	40±13.02	41±13.09
Height (cm)	167±6.44	155±6.17
Weight (kg)	69±12.43	61±10.48
BMI	25±4.05	25±4.34

SD; Standard Deviation

Further, males' mean values of height and weight are also greater than females' values, and they have higher lung function values than females except FEV1/FVC% ratio. Though males have higher values of height and weight, their BMI is lower than females (Figure 2).

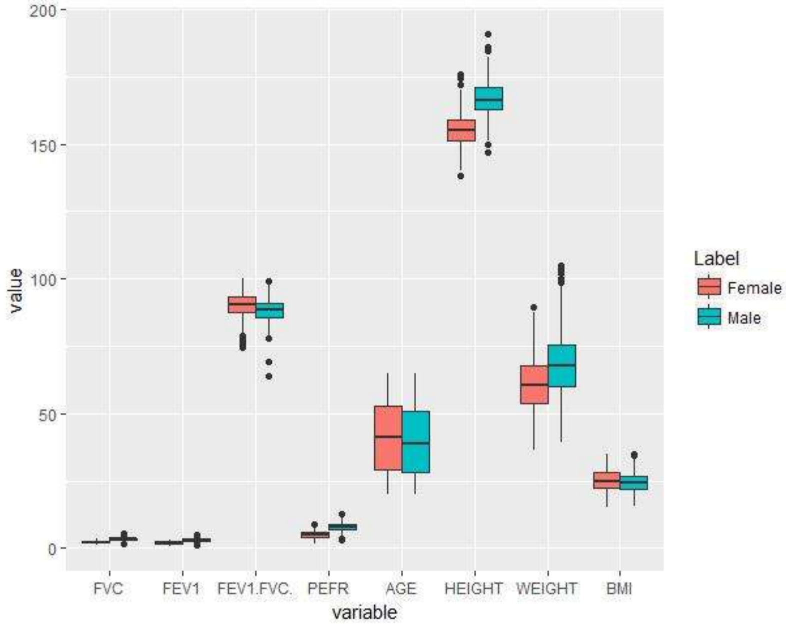

Fig-2: Distribution of male and female data using boxplot

Distributions based on GAMLSS model were fitted to all response variables to select the most suitable distribution (Table 2).According to Table 2, normal distribution have lowest global deviance, AIC and BIC values for all the models for both males and females. Therefore normal distribution is selected as the best distribution for all four response variables for both male and female data.

Table-2: Distributions and relevant selecting criteria of GAMLSS

Name of the Distribution	Responses Variable	Global Deviance Value		AIC Value		BIC Value	
		Male	Female	Male	Female	Male	Female
Normal ((NO))	FVC	381	216	393	228	416	251
	FEV1	295	104	307	116	330	139
	FEV1/FVC%	1994	2034	2006	2046	2029	2069
	PEFR	1337	1069	1349	1081	1372	1104
Gamma ((GA))	FVC	392	227	404	239	427	262
	FEV1	319	122	331	134	355	157
	FEV1/FVC%	2005	2039	2017	2051	2040	2074
	PEFR	1346	1070	1358	1082	1381	1105
Gumbel ((GU))	FVC	461	298	473	309	496	332
	FEV1	360	181	372	193	396	216
	FEV1/FVC%	2024	2040	2036	2052	2059	2075
	PEFR	1405	1139	1417	1151	1441	1173
Weibull ((WEI))	FVC	425	264	437	276	460	299
	FEV1	330	154	342	166	366	189
	FEV1/FVC%	2013	2032	2025	2044	2049	2067
	PEFR	1356	1087	1368	1099	1391	1122

FVC: Forced Vital Capacity, FEV1: Force Expiratory volume within first second, PEFR: Peak Expiratory Flow Rate

Location parameter (mean: mu) was fitted for the variables with normal distribution at the first stage, and smoothing function (MSpline) was fitted secondarily. Then, the scale parameter (standard deviation: σ) was fitted with smoothing function (SSpline) for the model. Finally, the shape parameter (nu) was fitted with Box-Cox-Cole-Green ((BCCG)) distributions, and obtained the best fitted models for all the response variables. Significant coefficients ($p < 0.05$) of the mean (mu) for the best fitted models are shown in Table 3.According to Table 3, all the parameters are contributed equally to fit the model for the mean (mu).Prediction equation for the mean (mu) is given below:

$$M_{pred} = a_0 + a_1(age) + a_2(height) + a_3(weight) + a_4(BMI) + MSpline$$

Table-3: Coefficients of mean (mu) for predictive equations of GAMLSS

Predictor Variable		Parameter coefficient					
		a_0	a_1	a_2	a_3	a_4	MSpline
FVC (l)	Men	-1.413	-0.027	0.033	-	0.014	2.004
	Women	3.234	-0.021	-	0.039	-0.095	4.242
FEV1 (l)	Men	-	-0.027	0.024	0.003	-	2.006
	Women	2.825	-0.021	-	0.038	-0.088	3.458
FEV1/FVC %	Men	133.973	-0.107	-0.247	0.201	-0.573	2.000
	Women	91.113	-0.055	-	-0.103	0.304	2.778
PEFR ($l\ s^{-1}$)	Men	-9.432	-0.032	0.107	-0.061	0.198	3.500
	Women	5.316	-0.033	-	0.072	-0.129	4.039

FVC: Forced Vital Capacity, FEV1: Force Expiratory volume within first second, PEFR: Peak Expiratory Flow Rate, equation for $M_{pred} = a_0 + a_1 age + a_2 hieght + a_3 weight + a_4 BMI + MSpline$ at 5% significant level

Table 4 shows the significant coefficients (*p*< 0.05) of fitted models of standard deviation (σ) for the (BCCG) distribution. According to Table 4, all the variables are equally contribute to fit the model for the standard deviation (σ). Prediction equation for the standard deviation (σ) is

$$S_{pred} = b_0 + b_1(age) + b_2(height) + b_3(weight) + b_4(BMI) + SSpline$$

Table-4: Coefficients of standard deviation (sigma) for predictive equations of GAMLSS

Predictor Variable		Parameter coefficient					
		b_0	b_1	b_2	b_3	b_4	SSpline
FVC (l)	Men	-14.192	0.012	0.069	-0.069	0.194	3.224
	Women	-15.201	0.015	0.085	-0.083	0.176	2.001
FEV1 (l)	Men	-14.209	0.016	0.069	-0.063	0.168	2.002
	Women	-4.760	0.017	0.016	-0.008	-	2.001
FEV1/FVC %	Men	-21.865	-	0.114	-0.128	0.339	-
	Women	-2.661	-	-	-0.007	-	-
PEFR ($l\ s^{-1}$)	Men	-14.864	0.009	0.075	-0.088	0.258	2.002
	Women	-1.754	0.006	-	-	-	-

FVC: Forced Vital Capacity, FEV1: Force Expiratory volume within first second, PEFR: Peak Expiratory Flow Rate, equation for $S_{pred} = b_0 + b_1 age + b_2 hieght + b_3 weight + b_4 BMI + SSpline$ at 5% significant level

Significant coefficients (*p*< 0.05) of the shape parameter (nu) for fitted models of BCCG distribution are shown in Table 5. According to the results, parameters are significant only for the FEV1, and the prediction equation for the shape parameter (nu) can be written as follows;

$$nu = c_0 + c_1(age) + c_2(height) + c_3(weight) + c_4(BMI)$$

Table-5: Coefficients of shape parameter (nu) for predictive equations of GAMLSS

Predictor Variable		Parameter coefficient				
		c_0	c_1	c_2	c_3	c_4
FVC (l)	Men	-	-	-	-	-
	Women	-	-	-	-	-
FEV1 (l)	Men	-83.129	0.065	0.489	-0.526	1.438
	Women	-26.257	-	0.173	-	-
FEV1/FVC %	Men	-	-	-	-	-
	Women	-	-	-	-	-
PEFR ($l\ s^{-1}$)	Men	-	-	-	-	-
	Women	-	-	-	-	-

FVC: Forced Vital Capacity, FEV1: Force Expiratory volume within first second, PEFR: Peak Expiratory Flow Rate, equation for $nu = c_0 + c_1 age + c_2 hieght + c_3 weight + c_4 BMI$ at 5% significant level

Based on the above results, final best fitted models were selected by considering minimum global deviance, AIC and BIC (Table 6). Models which fitted for the test data set are also tested and well fitted with the validation data set. Residuals of the best fitted models were analyzed, and residuals of all models are having constant variance and normal distribution of the residuals and also all the residuals have a better fit with the fitted line of the Q-Q normal plots of FVC, FEV1, FEV1/FVC% and PEFR for both males and females. Warm plots for the fitted values were plotted and they show the minimal deviation of the fitted values of the best fitted models for FVC, FEV1, FEV1/FVC% and PEFR for both males and females. Autocorrelation of the residuals are tested using Durbin-Watson (DW) test and there is no any autocorrelation between residuals at 5% significant level.

Table-6: Selection criteria of the best fitted model for BCCG distribution of GAMLSS

Responses Variable	Global Deviance Value		AIC Value		BIC Value	
	Male	Female	Male	Female	Male	Female
FVC (l)	356	165	386	198	445	260
FEV1 (l)	269	70	297	93	351	136
FEV1/FVC%	1942	2015	1976	2043	2042	2096
PEFR (l s^{-1})	1312	1040	1345	1065	1409	1114

FVC: Forced Vital Capacity, FEV1: Force Expiratory volume within first second, PEFR: Peak Expiratory Flow Rate

Subsequently Predicted values are obtained for predictor variables for both males and females using validation data sets. Actual values and the predictor values for the variables FVC, FEV1, FEV1/FVC % and PEFR of validation data have plotted in Figure 3 to Figure 10 and it shows predictor values are very closer to the actual values and models are well fitted for the data sets. After calculating the variance for validation data, LLN for validation data were calculated.

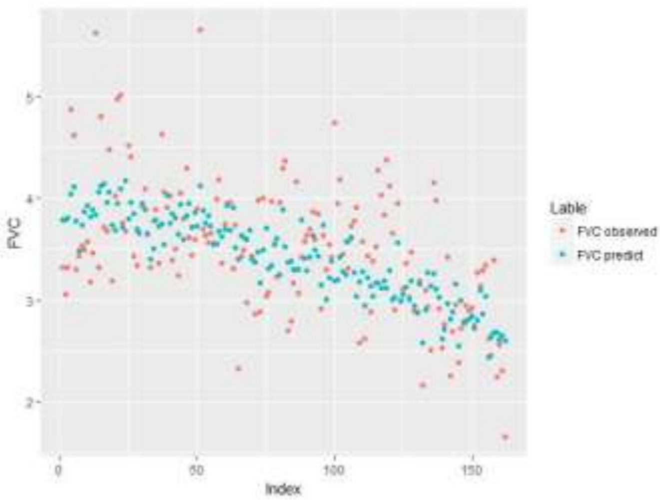

Fig-3: Actual VS. Predicted of FVC for males using GAMLSS model

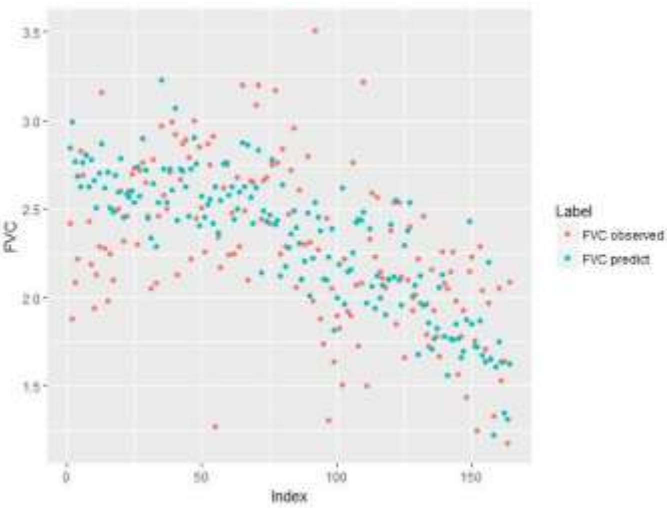

Fig-4: Actual VS. Predicted of FVC for females using GAMLSS model

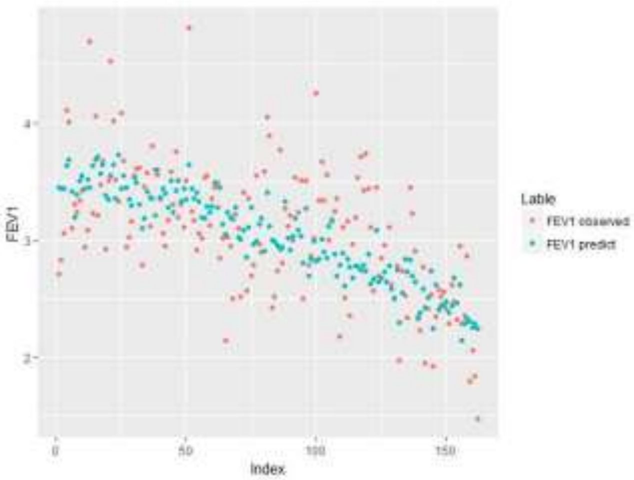

Fig-5: Actual VS. Predicted of FEV1 for males using GAMLSS model

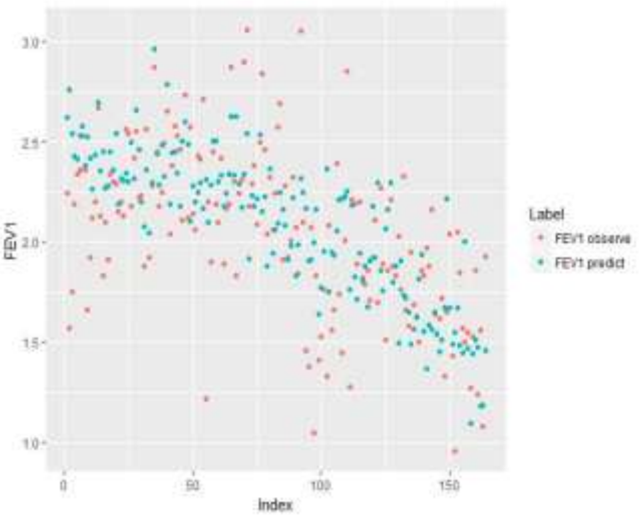

Fig-6: Actual VS. Predicted of FEV1 for females using GAMLSS model

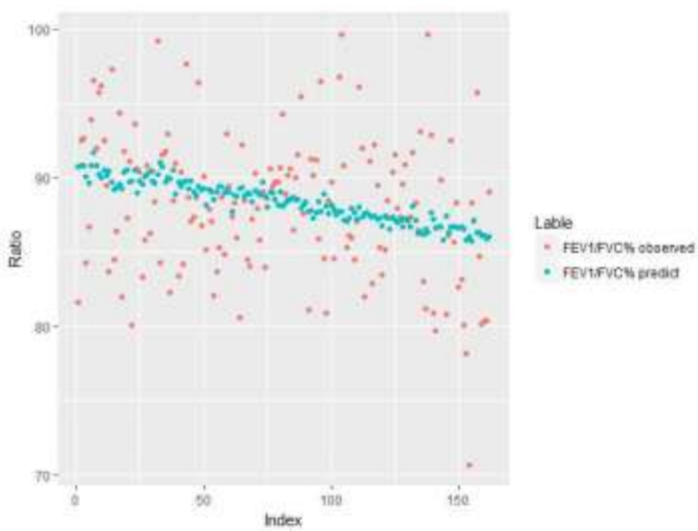

Fig-7: Actual VS. Predicted of FEV1/FVC % for males using GAMLSS model

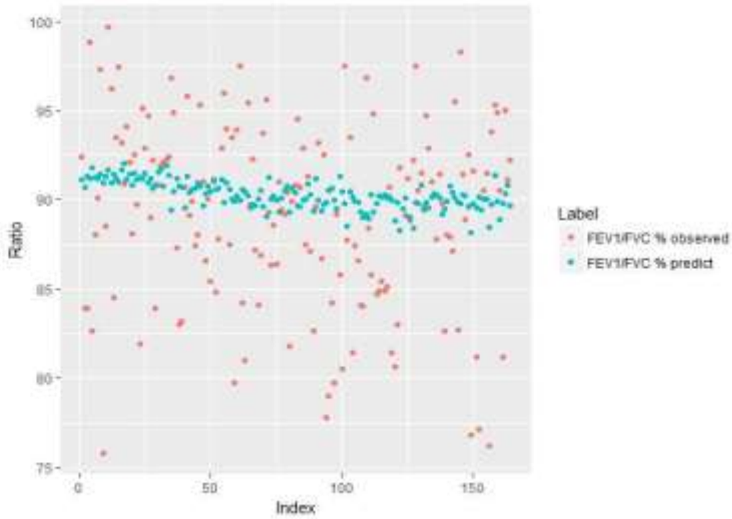

Fig-8: Actual VS. Predicted of FEV1/FVC % for females using GAMLSS model

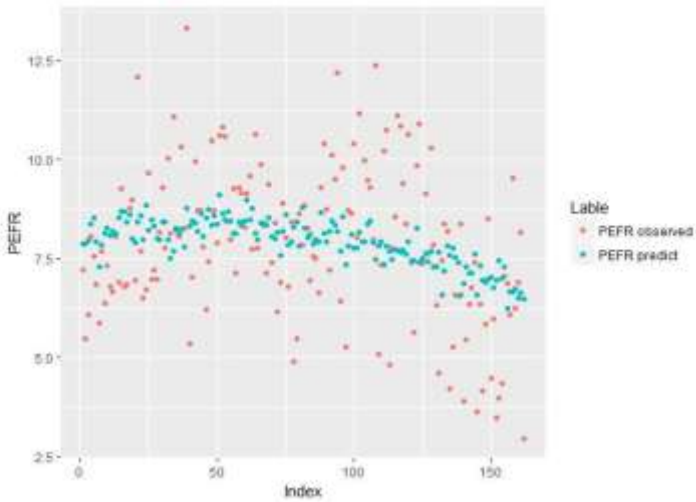

Fig-9: Actual VS. Predicted of PEPR for males using GAMLSS model

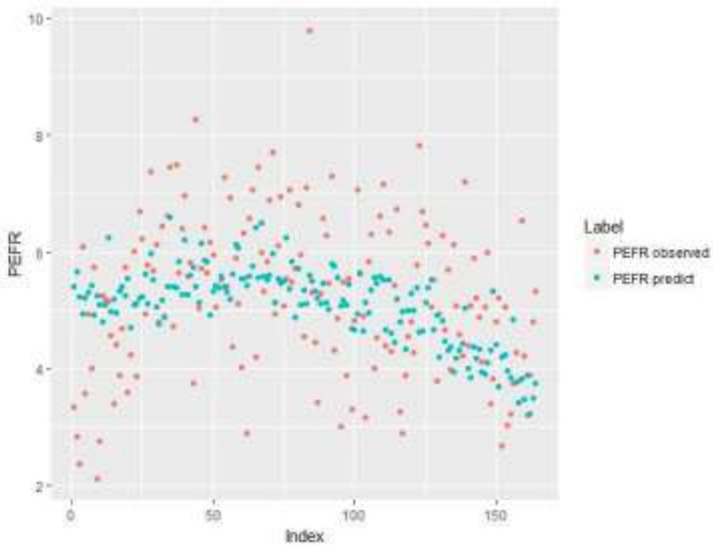

Fig-10: Actual VS. Predicted of PEFR for females using GAMLSS model

Predictor values obtained from GAMLSS model for validation data set was compared with reference values generated using South Indian references of Sri Lankan individuals and results are shown in Figure 11 to Figure 14.

According to Figures, FVC, FEV1 and PEFR values are overestimated by reference values which obtained using South Indian references of Sri Lankan individuals while FEV1/FVC% is underestimated for both males and females. In addition to that, females are having lower predicted values for FVC, FEV1 and PEFR than males while having higher predicted values for FEV1/FVC% than males.

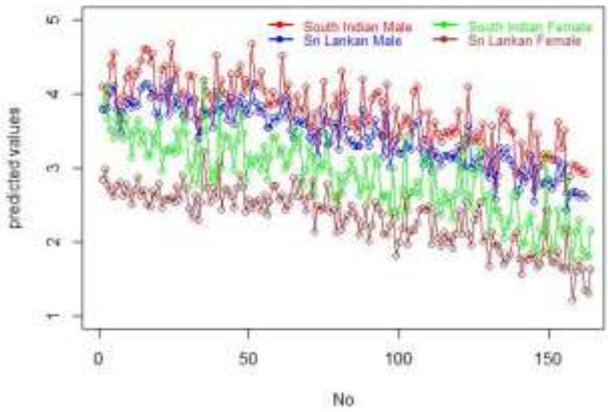

Fig-11: Comparison of Indian Reference Values with predicted values of FVC

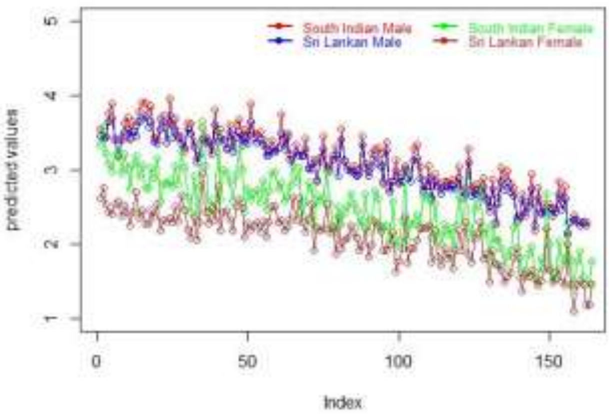

Fig-12: Comparison of Indian Reference Values with predicted values of FEV1

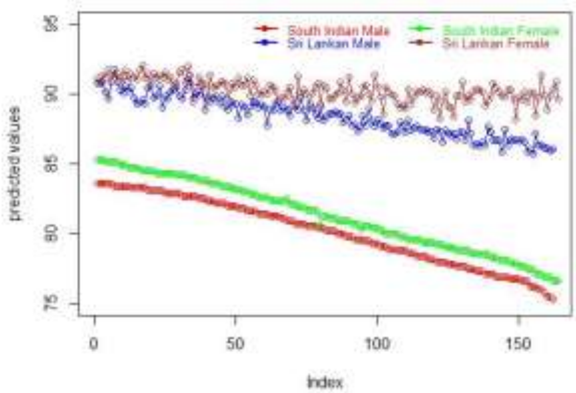

Fig-13: Comparison of Indian Reference Values with predicted values of FEV1/FVC%

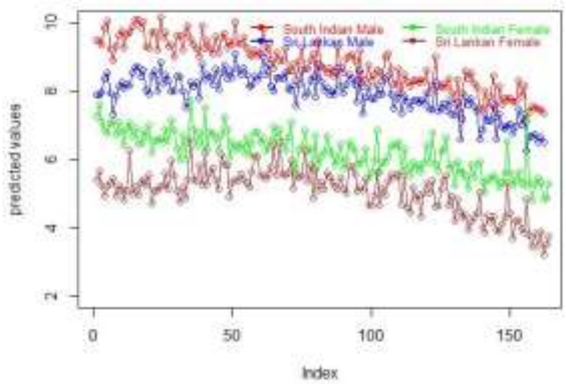

Fig-14: Comparison of Indian Reference Values with predicted values of PEFR

According to the Table 7, there is significant difference between reference values which obtained using South Indian references and Sri Lankan references of Sri Lankan individuals except the FEV1 values of males at 5% significant level. Hence, it is important to have own reference values for Sri Lankan individuals' according to the analysis.

Table-7: Comparison of reference values obtained using South Indian and Sri Lankan references

Prediction variables	Gender	P value of T test
FVC (l)	Male	6.517e-11
	Female	< 2.2e-16
FEV1(l)	Male	0.08468
	Female	3.449e-15
FEV1/FVC%	Male	< 2.2e-16
	Female	< 2.2e-16
PEFR(ls^{-1})	Male	< 2.2e-16
	Female	< 2.2e-16

FVC: Forced Vital Capacity, FEV1: Force Expiratory volume within first second, PEFR: Peak Expiratory Flow Rate, at 5% significant level

Hence, Equations for mean (M_{pred}), standard deviation (S_{pred}), and shape (nu) parameters for all the response variables were generated using GAMLSS model for Sri Lankan males and females separately (Table 3 to Table 5) and common reference equations can be written as;

$$M_{pred} = a_0 + a_1(age) + a_2(height) + a_3(weight) + a_4(BMI) + MSpline$$

$$S_{pred} = b_0 + b_1(age) + b_2(height) + b_3(weight) + b_4(BMI) + SSpline$$

$$nu = c_0 + c_1(age) + c_2(height) + c_3(weight) + c_4(BMI)$$

CONCLUSION

This study led to derivation of prediction equation for Spirometry for healthy Sri Lankan adult's age between 20 to 65 years. Various types of multiple linear regression models, Ordinary generalize ridge regression estimators and GAMLSS models with different distribution families were fitted to select the most suitable fitted model for the data sets. According to the selection criteria, GAMLSS model with three parametric (BCCG) family distributions was selected as the best fitted model for the predictor variables FVC, FEV1, FEV1/FVC% and PEFR of Spirometry. The study conducted by Quanjer, *et al*. [7] also selected the BCCG as the best distribution where the study conducted by Kainu, *et al*. [6] selected the normal distribution as the best for their study sample. When compare these prediction values with reference values which obtained using South Indian references of Sri Lankan individuals, FVC, FEV1 and PEFR values were overestimated while FEV1/FVC% was underestimated by South Indian references for both males and females and there is significant difference between reference values which obtained using South Indian references and Sri Lankan references of Sri Lankan individuals at 5% significant level.

Finally, we can conclude that separate reference values should be obtained and used for Sri Lankan individuals when conducting spirometry instead of using South Indian references. Since there are limited references for this kind of studies among Sri Lankan population, it is important to conduct more researches to develop reference values for spirometry for Sri Lankans.

ACKNOWLEDGEMENTS

We are grateful to In-charge Physiotherapist and General Manager, Hemas hospitals, Wattala, Sri Lanka for their support and the facilitation provided for proper data collection.

REFERENCES

1. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver B, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J. Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. European Respiratory Journal. 2012 Jan 1:erj00803-2012.
2. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. *Clin Interv Aging*. 2006;1(3):253-260.
3. Tu J, Inthavong K, Ahmadi G. *Computational Fluid and Particle Dynamics in the Human Respiratory System*. 2013.
4. Wahba WM. Influence of aging on lung function-clinical significance of changes from age twenty. *Anesth Analg*. 1983;62(8):764-776.
5. Janssens JP. Aging of the respiratory system: Impact on pulmonary function tests and adaptation to exertion. *Clin Chest Med*. 2005.
6. Kainu A, Timonen KL, Toikka J, Qaiser B, Pitkäniemi J, Kotaniemi JT, Lindqvist A, Vanninen E, Länsimies E, Sovijärvi AR. Reference values of spirometry for F innish adults. Clinical physiology and functional imaging. 2016 Sep;36(5):346-58.
7. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver B, Enright PL, Hankinson JL, Ip MS, Zheng J, Stocks J. Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. European Respiratory Journal. 2012 Jan 1:erj00803-2012.
8. Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. Statistics in medicine. 1992;11(10):1305-19.
9. Stasinopoulos M, Rigby B, Voudouris V, Heller G, De Bastiani F. Flexible regression and smoothing: The GAMLSS packages in R. GAMLSS for Statistical Modelling. GAMLSS for Statistical Modeling. 2015.
10. Stasinopoulos D, Rigby R, Akantziliotou C. Instructions on how to use the GAMLSS package in R. ... *Curr GAMLSS Help files,(see* .... 2006. http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Instructions+on+how+to+use+the+gamlss+package+in#0.