Reference Values of Impulse Oscillometry (IOS) for Healthy Indian Adults

Running title: Indian prediction equation of IOS

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To the Editor,

Impulse oscillometry (IOS) is gaining position within clinical lung function laboratories globally for its effort-independency allowing paediatric, elderly and differently abled patients to breathe at tidal volumes, without necessitating forced effort-dependent respiratory manoeuvres.¹ IOS indices of resistance (R), reactance (X) and impedance (Z) provide a comprehensive assessment of the functional status of the airways, particularly the small airways, which is not achieved by conventional lung function testing.¹

India comprises 18% of the global population and with 93.2 million patients suffering from asthma and chronic obstructive pulmonary disease (COPD), India contributes to 32% of the global disability-adjusted life years (DALYs) in chronic respiratory diseases.² The aetiology and disease manifestations in patients with asthma and COPD are different than those observed in Caucasian populations due to several non-classical exposures such as biomass fuel, frequent childhood respiratory illnesses, under-nutrition, and industrial/occupational exposures.² IOS could provide much-needed diagnostic support to Indian clinicians to overcome cases of misdiagnosis.

Current reference models for IOS for adults are limited, and with large heterogeneity in terms of model construction. Moreover, due to ethnic and physiological variations between Indians and other population, those equations do not fit well for Indians. Therefore, we undertook to develop reference equations of the clinically important IOS indices for Indian adults.

Based on an *a priori* evidence of the standard deviation of airway resistance values at 5Hz (R_{5Hz}) of 0.07 kPaL⁻¹Sec⁻¹ in healthy Indians,³ with a precision of 5%, an alpha risk of 0.05, and an anticipated non-cooperation rate of 15%, we estimated a total sample size of 202 (101 for each gender). We recruited non-smoking healthy volunteers aged between 18 and 88 years with no clinical history of asthma, COPD, emphysema, allergic rhinitis, respiratory tuberculosis, respiratory infections within four weeks of testing, chest deformity (as observed by chest x-ray); cardiovascular disease; obesity (body mass index >30kg/m²), hospitalization in the last 6 months, pregnancy, or concomitant drug therapy affecting muscarinic and adrenergic receptors. We also excluded those non-smokers who reported exposure to biomass fuel or vapour, dust, gas and fume (VGDF) at work. The study was ethically approved by the Clinical Research Ethics Committee of the Allergy & Asthma Research Centre, Kolkata (CREC-AARC) and all the participants provided signed informed consent.

Spirometry and IOS were performed in all participants using a Jaeger MasterScreen™ PFT system (Jaeger Co, Wurzburg, Germany) equipped for both tests. Spirometry was performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.⁴ Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and FEV₁/FVC ratio were measured using established Indian reference equations,⁵ coherent with ATS/ERS criteria for acceptability and repeatability.⁶

IOS was undertaken according to the ATS/ERS statement.⁶ Airway impedance (Z) between 5Hz and 20 Hz frequencies was measured and at least three successive efforts were recorded and quality inspected by at least two clinicians with substantial subject expertise. We reported respiratory impedance at 5Hz (Z_{rs}), resistance (R_{rs}) at 5Hz and 20Hz (R₅, R₂₀), reactance (X_{rs}) at 5Hz, resonant frequency (F_{res}), integrated area of low-frequency reactance (AX), and the absolute difference of R₅ and R₂₀ (R₅₋₂₀).

We tested the linear relationships between each of the IOS indices and age, height and weight using generalized additive models (GAM), respectively, taking natural or natural-logarithmic transformations of both the IOS and principal factors, age, height and weight. Based on GAM results, we created different sets of linear regression models for each of the IOS indices taking their natural-logarithmic transformation. We also created additional models using quantile regression with quadratic terms of age, height and weight; but due to the best fit, only the linear models were retained. Heteroskedasticity and goodness of fit of the models were tested using *k*-fold cross-validation (*k*=5), root mean square error (RMSE) of the residuals, and Akaike's information criteria (AIC). Collinearity between the explanatory variables was measured using variance inflation factor (VIF). All analyses were performed in STATA v15.1 (StataCorp, College St. TX, USA).

After excluding 9 males and 2 females for non-reproducible spirometry, suspected air-leaks during oscillometry, and non-tidal breathing patterns at rest, we incorporated data on 92 males (mean age 45±18 years) and 99 females (mean age 41±17 years). All participants were non-obese (mean body mass index 23.5±4.5 kg/m²) and had normal spirometry (mean FEV₁ %predicted= 93.4±19.1 and mean FEV₁/FVC= 80.3±9.5). In case of IOS, compared to males, females had consistently higher overall impedance (Z₅) [median (IQR) 0.46 (0.35, 0.57) vs. 0.63 (0.55, 0.80) kPa/L/sec]. Resistance

(R_5 , R_{20} , and R_{5-20}) and reactance (X_5) values were consistently higher among females than their male counterparts. (data not shown).

Gender-specific reference models of the commonly used IOS indices are presented in Table 1. We found weight had the most significant influence on the models while height had the lowest, in both genders. All IOS indices achieved high goodness of fit values as measured by adjusted R^2 and RMSE, except AX for males. No collinearity between the explanatory variables was observed ($VIF < 2$) in any of the models.

In this study, we observed all oscillometry resistance values were higher among females, which is consistent with other studies,^{7,8} however, unlike other studies, we found higher overall reactance (more negative X_5) among females.^{7,8} One plausible explanation of this alternative finding could be because of the fact that unlike the Europeans, Indian females have higher BMI than their male counterparts,⁹ and as higher BMI reduces airway elastance,¹⁰ Indian females are likely to have higher (more negative) reactance values than the males.

Despite the increasing use of IOS in clinical practice, population-wise reference equations for the adults are still lacking except for only a handful number of reference models for the Caucasian,^{7,8} Australian,¹¹ and Japanese populations.¹² Our prediction equations differ significantly from both Caucasian, Australian and Japanese models (data not shown), however, are more accurate for Indian population. The utility of IOS is fast gaining acceptability for accurate clinical diagnosis, and because of the availability of low-cost and portable IOS instruments, its use has increased significantly among Indian clinicians over the last few years. Therefore, developing reference equations for the Indian population has now become important and for the first time, we present predictive models for the clinically relevant IOS indices in an adult Indian population aged between 18 and 88 years which would boost up the clinicians to use IOS more frequently and help estimate the degree of airway obstruction more precisely.

One of the major strengths of our equations is that our model building approach consisted of a series of methods that were tested for 1) nature of relationship (linear vs. nonlinear) between the IOS indices and the explanatory variables, 2) heteroskedasticity, 3) goodness of fit, and 4) cross-validation. Moreover, we tested the collinearity between the explanatory variables (using VIF), that may often lead of inaccurate estimation of the effects.¹³ However, one of the limitations of this study is that we did not

have a cohort for external validation. Therefore, large epidemiological studies are a next-step to confirm the robustness of our models.

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194 **Table 1:** Gender-specific prediction models for IOS indices

Parameters	Models	Adjusted R ²	RMSE	Mean VIF
Males				
lnR ₅	$-0.30 + 0.003(Age) + 0.01(Weight) - 0.83(Height)$	0.04	0.40	1.48
lnR ₂₀	$-0.14 - 0.001(Age) + 0.01(Weight) - 0.99(Height)$	0.10	0.26	1.48
lnR ₅₋₂₀	$-4.05 + 0.02(Age) + 0.004(Weight) + 0.68(Height)$	0.02	1.13	1.47
lnZ ₅	$0.79 + 0.008(Age) + 0.008(Weight) - 1.42(Height)$	0.09	0.43	1.25
X ₅	$-0.23 - 0.002(Age) - 0.002(Weight) + 0.15(Height)$	0.01	0.23	1.48
lnAX	$-0.20 + 1.24(\ln Age) + 0.01(Weight) - 2.98(Height)$	0.20	1.02	1.25
lnFres	$2.44 + 0.39(\ln Age) + 0.001(Weight) - 0.55(Height)$	0.15	0.34	1.25
Females				
lnR ₅	$0.003 + 0.004(Age) + 0.007(Weight) - 0.66(Height)$	0.08	0.33	1.07
lnR ₂₀	$0.164 + 0.0003(Age) + 0.007(Weight) - 0.92(Height)$	0.12	0.22	1.07
lnR ₅₋₂₀	$-3.35 + 0.007(Age) + 0.01(Weight) + 0.68(Height)$	0.02	0.86	1.06
lnZ ₅	$-0.68 + 0.27(\ln Age) + 0.003(Weight) - 0.53(Height)$	0.08	0.32	1.06
X ₅	$-0.60 - 0.004(Age) - 0.001(Weight) + 0.37(Height)$	0.16	0.16	1.07
lnAX	$-2.33 + 0.76(\ln Age) + 0.004(Weight) - 0.004(Height)$	0.08	0.80	1.06
lnFres	$1.19 + 0.27(\ln Age) + 0.0002(Weight) + 0.68(Height)$	0.07	0.31	1.06

195 Models built using linear regression analysis taking age (in years), weight (in kg) and height (in meters) as
 196 main explanatory variables. ln: natural logarithm. VIF: variance inflation factor. For other abbreviations, see
 197 the text.