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ORIGINAL RESEARCH

Differences in the Spirometry Parameters Between Indigenous and Non-Indigenous Patients with COPD: A Matched Control Study

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Background: Comparison of spirometry parameters between Indigenous and non-Indigenous patients with underlying chronic obstructive pulmonary disease (COPD) has been sparsely reported in the past. In this study, differences in the lung function parameters (LFPs), in particular spirometry values for forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and FEV_1 /FVC ratio between Indigenous and non-Indigenous patients with COPD were assessed.

Methods: In this retrospective study, Indigenous and non-Indigenous patients with a diagnosis of COPD between 2012–2020 according to spirometry criteria (ie; post-bronchodilator (BD) FEV_1/FVC < 0.7) were included. A further analysis was undertaken to compare the differences in the spirometry parameters, including lower limit of normal (LLN) values matching for age, sex, height and smoking status between these two diverse ethnic populations.

Results: A total of 240/742 (32%) Indigenous and 873/4579 (19%) non-Indigenous patients were identified to fit the criteria for COPD. Indigenous patients were significantly younger (mean difference 9.9 years), with a greater proportion of females (50% vs 33%), underweight (20% vs 8%) and current smokers (47% vs 32%). Prior to matching, Indigenous patients' post-BD percent predicted values for FVC, FEV_1, and FEV_1/FVC ratio were 17, 17%, and −2 points lower (Hedges G measure of effect size large (0.91), large (0.87), and small (0.25), respectively). Among the matched cohort (111 Indigenous and non-Indigenous), Indigenous patients LFPs remained significantly lower, with a mean difference of 16%, 16%, and −4, respectively (Hedges G large (0.94), large (0.92) and small (0.41), respectively). The differences persisted despite no significant differences in LLN values for these parameters.

Conclusion: Indigenous Australian patients with COPD display a significantly different demographic and clinical profile than non-Indigenous patients. LFPs were significantly lower, which may or may not equate to greater severity of disease in the absence of normative predictive lung function reference values specific to this population.

Keywords: chronic obstructive pulmonary disease, Global Initiative for Chronic Obstructive Lung Disease, First Nations, Indigenous, lung function test, spirometry

Plain Language Summary

Chronic Obstructive Pulmonary Disease (COPD) is more common among Indigenous Australians compared to non-Indigenous Australians, with a high morbidity and mortality associated. Previous studies have established generally lower lung function parameters in the Indigenous Australian population, however there is lack of published data showing how the lung function parameters would display in the presence of underlying COPD. In this study, we reported the differences in various lung function parameters between Indigenous and non-Indigenous patients who meet criteria for COPD diagnosis in the Top End of the Northern Territory of Australia. Our study showed that Indigenous patients with COPD are generally younger, with a higher proportion of females, and a lower body mass index. They also displayed significantly lower lung function values in comparison to their non-Indigenous counterparts, even after matching against age, sex, height and smoking status with both Forced Vital

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Capacity (FVC) and Forced Expiratory volume in one second (FEV_1) approximately 16% lower. There was no significant difference in the lower limit of normal (LLN) values between the groups. Moreover, most Indigenous patients who demonstrate airflow obstruction, defined by a fixed FEV_1/FVC ratio of <0.7, also demonstrated a FEV_1/FVC ratio below LLN. The current approach to COPD diagnosis, treatment and management is based on recommendations drawn from non-Indigenous populations. There could be a role for correctional factors or use of LLN values when assessing the lung function in our Indigenous patients, so that health practitioners will be able to provide more appropriate care to this unique population.

Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating condition that is characterised by chronic airway inflammation, leading to obstruction of the airway and airflow limitation.[1] In the Australian context, the prevalence of COPD is estimated to be around 7.5% for individuals aged 40 years and above. Amongst those aged 75 and above, the prevalence is increased to 30%.[2] Clinical manifestations of COPD include shortness of breath, chronic cough and mucous production resulting in considerable impact on quality of life.[1,3,4] Furthermore, COPD is noted to be the fifth leading cause of death in Australia.[5] The risk factors for COPD include; genetic predisposition, tobacco smoking, and environmental or occupational exposure to dust, gas or fumes.[1,3]

The Australian Institute of Health and Welfare estimates that COPD is 2.3 times more prevalent among Australians of Aboriginal or Torres Strait Islanders descent (hereafter respectfully referred to as Indigenous Australians/patients), compared to non-Indigenous Australians.[4] In the Northern Territory (NT) of Australia, approximately 30% of the population self-identify as Indigenous Australian, the highest proportion compared to all other Australian states and territories.[6] Several recent studies from the Top End Health Service (TEHS) region of the NT of Australia have reported a significantly higher prevalence of chronic respiratory disorders among the Indigenous population, more specifically a high prevalence of COPD.[7–11]

Measurement of lung function tests including spirometry, static lung volumes using plethysmography and diffusing capacity for carbon monoxide (DLCO) aid in the clinical assessment and diagnosis of COPD.[12] Spirometry, when appropriately performed, is a reproducible and objective measure of airway function and is essential in the diagnosis of COPD, and grading COPD airflow obstruction severity in terms of GOLD 1 to 4 (GOLD for Global Initiative for Chronic Obstructive Lung Disease).[1] Lung function parameters (LFPs) measured on spirometry include: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and FEV_1/FVC ratio.[1,12] FEV_1 and FVC are measured in litres (L), and subsequently calculated as a percentage of predicted values (% predicted) adjusted for age, sex, height, and race/ethnicity.[13] According to the GOLD criteria, a diagnosis of COPD could be considered when post-bronchodilator (BD) spirometry results demonstrate a FEV_1/FVC ratio < 0.7.

Multiple studies have demonstrated significantly lower LFPs, in particular lower FVC and FEV_1 values, amongst Indigenous people.[14–17] These studies have consistently demonstrated that spirometric values could be up to 20 to 30% lower among Indigenous people compared to Caucasian counterparts, even among "apparently healthy" Indigenous adults.[18–21] However, normative spirometric reference values for adult Indigenous Australians are yet to be established.

Currently there is sparse evidence in the literature demonstrating how spirometry parameters display in the presence of underlying COPD amongst the Indigenous Australian population in comparison to their non-Indigenous peers. Moreover, in the absence of normative spirometry reference values for adult Indigenous Australians, and in the presence of a high burden of COPD, this information is sorely needed. Hence, it is imperative to investigate the spirometric parameters among an Indigenous cohort with a diagnosis of COPD against non-Indigenous Australians. Thus, the aim of this study was to ascertain the differences in the spirometric parameters between these two diverse ethnic populations among those who had undergone spirometry testing in the TEHS region of the NT of Australia.

Patients and Methods

Setting and Study Participants

This study was undertaken at the Respiratory and Sleep service based at the Royal Darwin Hospital and Darwin Respiratory and Sleep service/Darwin Private Hospital in the TEHS region of the NT of Australia. The study participants included all patients that performed acceptable and repeatable spirometry between 2012 and 2020. Also

included were datasets from previously published studies of cohorts of participants from the TEHS region NT which included Indigenous and non-Indigenous populations.[15,16,21,22] This study was conducted and reported according to strengthening and reporting of health research involving Indigenous people, including consultation with local institute Indigenous Australian representatives.[23] Individual consent from the study participants was not obtained, as the study was retrospective in nature and no active interventions were investigated in this study. More details regarding the setting and study participants are available from our previous reports, including details regarding lung function testing protocol and clinical data collection.[14–16,21] This study was approved by the Human Research Ethics Committee of the NT, TEHS and Menzies School of Health Research (Reference no: HREC 2019–3445) and was conducted according to the Declaration of Helsinki.

Spirometry Measurements

All spirometry tests were performed according to the American Thoracic Society and the European Respiratory Society guidelines and recommendations, including calibration of equipment and quality assurance.[13] Spirometry was measured using the EasyOne Pro® (ndd Medical Technologies Inc. Zurich, Switzerland). Each individual volume-time and flow-volume graph was inspected for acceptability to assess session quality. Only spirometric tests that were graded as acceptable for session quality were included in this study.

When appropriate, all patients undergoing elective spirometry testing were instructed to refrain from smoking for at least two to four hours prior to spirometry testing. Patients using airway-directed inhaled pharmacotherapy were asked to withhold their medication for 12–24 hours prior to testing. Spirometry was repeated 15–20 minutes after inhalation of 400 µg of salbutamol via a spacer to assess BD responsiveness.[1,2] Throughout this study the National Health And Nutrition Examination Survey (others/Caucasian) reference values were utilised, as is standard in clinical practice in this setting.[24] If the study participants were identified to have undergone multiple LFTs during the study period, the earliest acceptable test for session quality was utilised for analysis. Spirometry parameters included were pre- and post-BD FEV_1, FVC absolute values, % predicted and lower limits of normal (LLN), and FEV_1/FVC (absolute and LLN).

Inclusion Criteria for Presence of COPD

To ascertain the presence of COPD, post-BD FEV_1/FVC ratio < 0.7 was used according to GOLD and the Australian concise tool for COPD (COPD-X) recommendations.[1,3]

Matching of Indigenous and Non-Indigenous Patients with COPD

To assess differences in spirometry parameters, a sub-set analysis was conducted in a cohort of matched Indigenous and non-Indigenous patients. Matching of Indigenous and non-Indigenous patients was conducted based on four categories: sex (male/female); smoking status (never/former/current smoker); age (18–35, 36–50, 51–65, 66–75, 76–85, >85 years); height (cm) (females: < 150, 150–170, > 170, males: < 160, 160–180, > 180). These categorisation criteria were first applied to the Indigenous patient cohort of 240 patients with COPD, and then to the non-Indigenous cohort to identify patients with matched categories. There was an excess of Indigenous patients in multiple categories as compared to the non-Indigenous cohort. There was a greater proportion of Indigenous patients in the younger, shorter and current smoking categories. As such, further refinement was conducted to give an equal number of Indigenous and non-Indigenous patients for each category. In the case of an inadequate number of non-Indigenous patients fitting to an Indigenous patient category or vice versa, the excess patients were dropped from the dataset, resulting in a total of 222 matched patients (111 Indigenous, 111 non-Indigenous).

Statistical Analysis

Continuous parameters were tested for normality via the Shapiro Wilks distribution test, with body mass index (BMI) and smoking pack years displaying a non-parametric distribution, and other continuous variables approximating normal distribution. Non-parametric parameters were presented as medians (interquartile ranges (IQR)), normally distributed parameters as means (95% confidence intervals (CIs)), and categorical parameters as numbers (%). Clinical

characteristics were compared between Indigenous and non-Indigenous patients by 2-tailed Student's *t*-test for normally distributed parameters. Equality of medians test was used for non-parametrically distributed parameters and 2-tailed proportions z-test for categorical parameters. LFPs were compared between Indigenous and non-Indigenous patients by 2-tailed Student's *t*-test. For both matched and unmatched cohorts Hedges G effect size was calculated for FVC % predicted, FEV_1% predicted and FEV_1/FVC ratio and reported as G (95% CI).[25] Hedges G effect size was classified as small (0.2 < 0.5), moderate (0.5 < 0.8) or large (>0.8). All data were analysed in STATA IC 15 (StataCorp, Texas) and alpha set to 0.05 throughout.

Results

A total of 5321 patients were referred for at least one spirometry test between 2012 and 2020. From the total cohort, 240/742 (32%) Indigenous and 873/4579 (19%) non-Indigenous patients were identified as meeting diagnostic criteria for COPD (Figure 1). There was a significantly larger proportion of Indigenous patients with COPD compared to non-Indigenous patients (32% vs 19%, p <0.0001). The demographic/clinical factors for these patients differed significantly by Indigenous status (Table 1).

Indigenous patients had significantly lower values for all spirometry parameters, aside from FEV_1 LLN values (Table 2). The post-BD FVC % predicted, FEV_1% predicted and FEV_1/FVC ratio were a mean 17%, 17%, and 2 points lower respectively among Indigenous patients with COPD in comparison to non-Indigenous patients. In addition to having FEV_1/FVC ratio < 0.7, a significantly greater proportion of the Indigenous cohort also displayed FEV_1/FVC ratio < LLN (92% vs 71%, p<0.001). Hedges G effect size for differences in percent predicted values was large for FVC

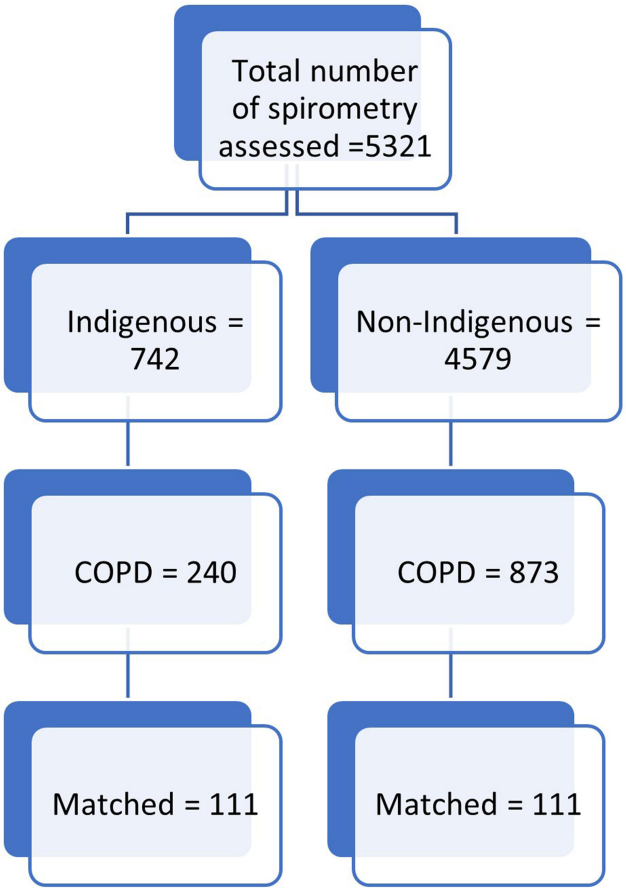

Figure 1 Flow chart of Indigenous and non-Indigenous study participants' inclusion criteria.
Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 1 Clinical Characteristics of Indigenous and Non-Indigenous Patients with COPD

Clinical Variables	Unit/Category	Indigenous (n=240)	Non-Indigenous (n=873)	p-value
Age	(years) (mean, 95% CI)	54.66 (53.14, 56.18)	64.17 (63.35, 65)	<0.001*
Sex	(male) (n, %)	128 (53)	591 (68)	<0.001*
Height	(m) (mean, 95% CI)	1.66 (1.65, 1.67)	1.69 (1.69, 1.7)	<0.001*
BMI	(kg/m^2) (median (IQR))	22.86 (19.33, 27.92)	26.53 (22.31, 31.35)	<0.001*
Corpulence status (n, %)	Underweight: BMI < 18.5 kg/m^2	49 (21)	70 (8)	<0.001*
	Normal weight: BMI: 18.5–24.9 kg/m^2	99 (41)	285 (33)	0.012*
	Overweight: BMI: 25.0–29.9 kg/m^2	50 (21)	246 (28)	0.023*
	Obesity: BMI > 30.0 kg/m^2	41 (17)	270 (31)	<0.001*
Smoking status (n, %)	Reported Smoking status	240 (100)	186 (21)	<0.001*
	Never smoker	20 (8)	43 (23)	<0.001*
	Former smoker	97 (40)	94 (51)	0.037*
	Current smoker	123 (51)	49 (26)	<0.001*
Smoking	(pack years) (median, (IQR))^	21.5 (7, 40)	43.13 (25.4, 68.13)	<0.001*

Notes: ^ Smoking pack years data was available for 160 Indigenous patients and 108 non-Indigenous patients. p-value obtained via 2-tailed Student's *t*-test (continuous, normally distributed parameters), equality of medians test (non-parametric parameters) or 2-tailed proportions z-test (categorical parameters). * p<0.05.
Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

Table 2 Lung Function Parameters (LFPs) of Indigenous and Non-Indigenous Patients with COPD

LFPs	Expression Mode	Indigenous (n=240)	Non-Indigenous (n=873)	p-value
FVC	LLN (L)	2.93 (2.85, 3.02)	3.09 (3.04, 3.14)	0.005*
	Pre-BD (L)	2.06 (1.96, 2.16)	2.77 (2.7, 2.84)	<0.001*
	Pre-BD (%)	55.44 (53.2, 57.67)	71.07 (69.83, 72.31)	<0.001*
	Post-BD (L)	2.2 (2.09, 2.3)	2.95 (2.88, 3.02)	<0.001*
	Post-BD (%)	58.8 (56.55, 61.06)	75.64 (74.4, 76.87)	<0.001*
FEV_1	LLN (L)	2.26 (2.18, 2.33)	2.25 (2.21, 2.29)	0.841
	Pre-BD (L)	1.19 (1.11, 1.26)	1.66 (1.61, 1.71)	<0.001*
	Pre-BD (%)	41.12 (38.79, 43.44)	56.37 (55.04, 57.7)	<0.001*
	Post-BD (L)	1.27 (1.2, 1.35)	1.77 (1.72, 1.82)	<0.001*
	Post-BD (%)	43.55 (41.41, 45.7)	60.18 (58.86, 61.49)	<0.001*
FEV_1/FVC	LLN (absolute)	0.68 (0.67, 0.69)	0.66 (0.66, 0.66)	<0.001*
	< LLN (n (%))	220 (92)	622 (71)	<0.001*
	Pre-BD (absolute)	0.57 (0.55, 0.58)	0.59 (0.58, 0.59)	0.007*
	Post-BD (absolute)	0.57 (0.55, 0.58)	0.59 (0.58, 0.6)	0.001*

Notes: Data were presented as mean (95% CI). * p<0.05 on two tailed Student's *t*-test.
Abbreviations: BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LLN, lower limit of normal.

(0.91, 95% CI 0.77, 1.06), FEV_1 (0.87, 95% CI 0.72, 1.01), and small for FEV_1/FVC (absolute) (0.25, 95% CI 0.11, 0.39).

Matched Data for Indigenous and Non-Indigenous with COPD

A total of 222 patients were matched (111 Indigenous, 111 non-Indigenous) with no statistically significant differences in age, sex, height or smoking status. Despite matching, among the Indigenous cohort a greater proportion of patients were in the underweight BMI category, and among the non-Indigenous patients a greater median pack years of smoking was reported (Table 3). LFPs between the Indigenous and non-Indigenous patients with COPD in each sub-divided aged groups (18–35, 36–50, 51–65, 66–75, 76–85, >85 years) are represented in Table 1S.

Among the matched cohort significant differences were noted in all LFPs aside for LLN values, once again with Indigenous patients displaying lower values than non-Indigenous patients with COPD (Table 4). Post-BD percent predicted values for FVC, FEV_1, and FEV_1/FVC ratio again displayed a mean 16%, 16%, and 4 points lower respectively among Indigenous patients with COPD in comparison to non-Indigenous patients (Figure 2). Hedges G effect size was large for FVC % predicted (0.94, 95% CI 0.66, 1.22), FEV_1% predicted (0.92, 95% CI 0.64, 1.19) and small for FEV_1 /FVC ratio (0.41, 95% CI 0.15, 0.68).

Sub-Set Analysis

Within the cohort of COPD patients 220/240 (92%) Indigenous and 622/873 (71%) non-Indigenous patients were recorded to have FEV_1/FVC < LLN, of which 150 (75 Indigenous and non-Indigenous) were able to be matched (Tables 2S and 5). Pre- and post-BD parameters for FVC and FEV_1 were significantly lower among the Indigenous cohort in both matched and unmatched subgroups (mean difference in post-BD FVC % predicted and FEV_1% predicted; matched: 15% and 12% and unmatched 15% and 13%). In the unmatched subgroup, LLN significantly differed for FVC and FEV_1/FVC, while in the matched subgroup there were no significant differences. FEV_1/FVC values did not significantly differ between Indigenous and non-Indigenous patients in the matched subgroup.

Table 3 Clinical Characteristics of Patients Included in Matched Cohorts (n=222)

Clinical Variables	Unit/Category	Indigenous (n=111)	Non-Indigenous (n=111)	p-value
Age	(years) (mean, 95% CI)	58.76 (56.39, 61.13)	58.92 (56.6, 61.25)	0.923
Sex	(male) (n, %)	70 (63)	70 (63)	0.999
Height	(m) (mean, 95% CI)	1.68 (1.66, 1.69)	1.67 (1.65, 1.69)	0.577
BMI	(kg/m^2) (median (IQR))	23.46 (19.53, 28.98)	26.61 (22.35, 30.47)	0.001*
Corpulence status (n, %)	Underweight: BMI < 18.5 kg/m^2	23 (21)	9 (8)	0.007*
	Normal weight: BMI: 18.5–24.9 kg/m^2	42 (38)	32 (29)	0.141
	Overweight: BMI: 25.0–29.9 kg/m^2	26 (24)	39 (35)	0.061
	Obesity: BMI > 30.0 kg/m^2	19 (17)	31 (28)	0.058
Smoking status (n, %)	Reported smoking status	111 (100)	111 (100)	0.999
	Never smoker	17 (15)	17 (15)	0.999
	Former smoker	56 (50)	56 (50)	0.999
	Current smoker	38 (34)	38 (34)	0.999
Smoking	(pack years) (median, (IQR))^	25.35 (7.75, 48)	42 (26, 60)	0.136

Notes: ^ Smoking pack years data was available for 62 Indigenous patients and 69 non-Indigenous patients. p-value obtained via 2-tailed Student's *t*-test (continuous, normally distributed parameters), equality of medians test (non-parametric parameters) or 2-tailed proportions z-test (categorical parameters). * $p<0.05$.
Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

Table 4 Lung Function Parameters (LFPs) for Matched Indigenous and Non-Indigenous Patients with COPD

LFPs	Expression Mode	Indigenous (n=111)	Non-Indigenous (n=111)	p-value
FVC	LLN (L)	2.97 (2.84, 3.11)	3.13 (2.97, 3.28)	0.142
	Pre-BD (L)	2.13 (1.97, 2.29)	2.77 (2.58, 2.96)	<0.001*
	Pre-BD (%)	56.42 (52.9, 59.95)	71.97 (68.94, 75.01)	<0.001*
	Post-BD (L)	2.27 (2.1, 2.43)	2.94 (2.75, 3.14)	<0.001*
	Post-BD (%)	60.14 (56.7, 63.59)	76.5 (73.43, 79.58)	<0.001*
FEV_1	LLN (L)	2.26 (2.14, 2.37)	2.29 (2.16, 2.41)	0.725
	Pre-BD (L)	1.24 (1.12, 1.35)	1.68 (1.55, 1.81)	<0.001*
	Pre-BD (%)	43.41 (39.61, 47.2)	56.56 (53.31, 59.81)	<0.001*
	Post-BD (L)	1.31 (1.2, 1.43)	1.81 (1.67, 1.95)	<0.001*
	Post-BD (%)	44.93 (41.67, 48.19)	61.01 (57.68, 64.34)	<0.001*
FEV_1/FVC	LLN (absolute)	0.68 (0.67, 0.68)	0.67 (0.67, 0.68)	0.300
	< LLN (n (%))	100 (90)	79 (71)	<0.001*
	Pre-BD (absolute)	0.57 (0.55, 0.59)	0.6 (0.58, 0.62)	0.067
	Post-BD (absolute)	0.56 (0.55, 0.58)	0.6 (0.59, 0.62)	0.002*

Notes: Data presented as mean (95% CI). * p<0.05 on 2-tailed Student's *t*-test.
Abbreviations: BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LLN, lower limit of normal.

Discussion

To the best of the authors' knowledge, this is the first study to match and compare spirometry parameters between Indigenous and non-Indigenous Australian patients diagnosed with COPD, specifically from the NT of Australia. This study has demonstrated several key findings:

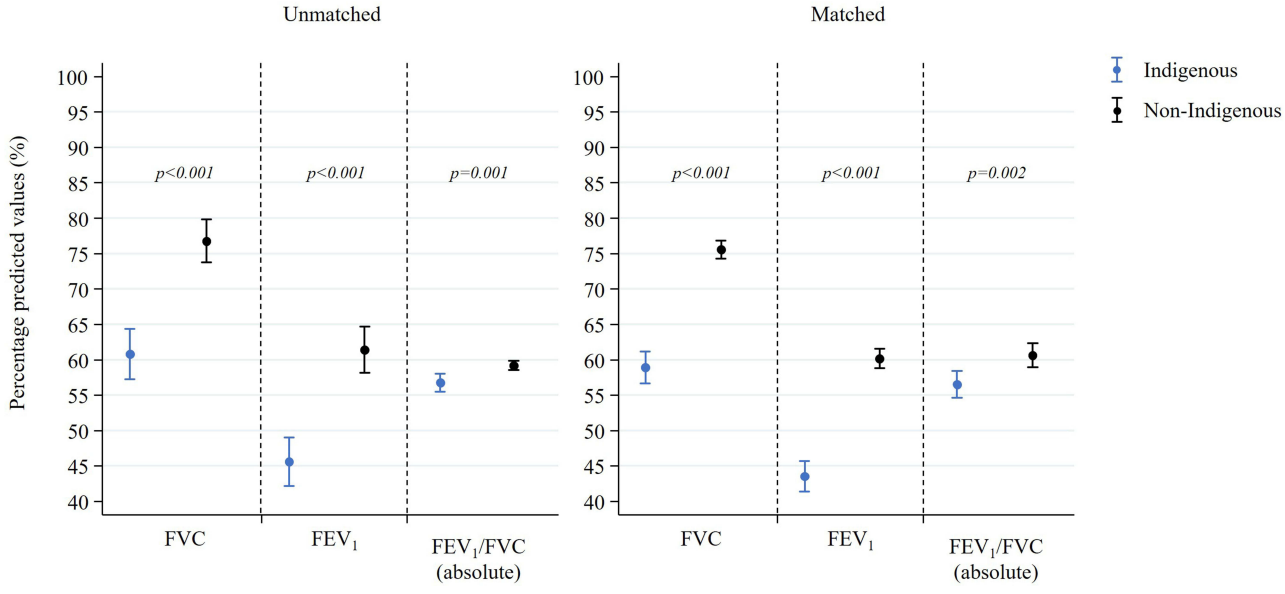

Figure 2 Percentage predicted values of FVC, FEV_1 and FEV_1/FVC ratio (mean (95% CI)) post-BD for unmatched and matched cohorts of Indigenous and non-Indigenous patients with post-BD FEV_1/FVC < 0.7.
Abbreviations: BD, bronchodilator; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity.

Table 5 Lung Function Parameters for Matched Indigenous and Non-Indigenous Patients with $FEV_1/FVC < LLN$

Unmatched	Expression Mode	Indigenous (n=220)	Non-Indigenous (n=622)	p-value
FVC	LLN (L)	2.96 (2.87, 3.05)	3.14 (3.08, 3.2)	0.002*
	Pre-BD (L)	2.04 (1.94, 2.15)	2.73 (2.64, 2.81)	<0.001*
	Pre-BD (%)	54.95 (52.71, 57.2)	68.77 (67.31, 70.23)	<0.001*
	Post-BD (L)	2.19 (2.08, 2.29)	2.91 (2.83, 2.99)	<0.001*
	Post-BD (%)	58.8 (56.58, 61.01)	73.48 (72.03, 74.94)	<0.001*
FEV_1	LLN (L)	2.29 (2.21, 2.36)	2.3 (2.25, 2.35)	0.748
	Pre-BD (L)	1.16 (1.09, 1.24)	1.54 (1.49, 1.6)	<0.001*
	Pre-BD (%)	40.1 (37.74, 42.45)	51.11 (49.64, 52.58)	<0.001*
	Post-BD (L)	1.25 (1.17, 1.33)	1.65 (1.59, 1.71)	<0.001*
	Post-BD (%)	42.42 (40.29, 44.55)	54.67 (53.24, 56.11)	<0.001*
FEV_1/FVC	LLN (L)	0.69 (0.69, 0.69)	0.66 (0.66, 0.67)	<0.001*
	Pre-BD (L)	0.56 (0.54, 0.57)	0.55 (0.55, 0.56)	0.566
	Post-BD (L)	0.56 (0.54, 0.57)	0.56 (0.55, 0.56)	0.977
Matched	**Expression Mode**	**Indigenous (n=75)**	**Non-Indigenous (n=75)**	**p-value**
FVC	LLN (L)	3.02 (2.85, 3.18)	3.14 (2.96, 3.32)	0.309
	Pre-BD (L)	2.14 (1.94, 2.34)	2.7 (2.45, 2.95)	0.001*
	Pre-BD (%)	56.04 (51.93, 60.15)	69.95 (65.93, 73.96)	<0.001*
	Post-BD (L)	2.3 (2.1, 2.5)	2.89 (2.64, 3.15)	<0.001*
	Post-BD (%)	60.25 (56.32, 64.19)	74.79 (70.73, 78.85)	<0.001*
FEV_1	LLN (L)	2.31 (2.17, 2.44)	2.3 (2.16, 2.45)	0.973
	Pre-BD (L)	1.24 (1.1, 1.38)	1.57 (1.4, 1.74)	0.003*
	Pre-BD (%)	41.09 (37.41, 44.78)	52.21 (48.15, 56.28)	<0.001*
	Post-BD (L)	1.32 (1.18, 1.46)	1.7 (1.52, 1.88)	0.001*
	Post-BD (%)	43.93 (40.2, 47.66)	56.73 (52.58, 60.89)	<0.001*
FEV_1/FVC	LLN (L)	0.68 (0.68, 0.69)	0.68 (0.67, 0.69)	0.451
	Pre-BD (L)	0.57 (0.54, 0.6)	0.57 (0.55, 0.6)	0.852
	Post-BD (L)	0.55 (0.53, 0.58)	0.58 (0.55, 0.6)	0.180

Notes: Data presented as mean (95% CI). * p<0.05 on 2-tailed Student's *t*-test.
Abbreviations: BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; LLN, lower limit of normal.

(i) In patients with COPD, Indigenous patients are significantly younger, and have lower BMI compared to non-Indigenous patients.
(ii) Indigenous patients with COPD display significantly lower spirometry results, both as absolute values and as a percent of predicted in comparison to their non-Indigenous counterparts, even after matching against age, sex, height and smoking status.

(iii) The FVC and FEV_1 parameters are significantly lower for Indigenous patients, despite no significant difference in the LLN values between the groups, especially among the matched cohort.
(iv) Most Indigenous patients who demonstrate airflow obstruction, defined by a fixed FEV_1/FVC ratio of < 0.7, also have a FEV_1/FVC ratio below the LLN.

The burden of chronic respiratory diseases is reported to be highly prevalent among various Indigenous populations globally.[7–11,26–29] Existing literature has demonstrated that LFPs generally tend to be lower among Indigenous people.[14–21] There is, however, sparse published quantitative data directly comparing LFPs for patients with COPD among diverse ethnic populations, including the Indigenous Australian population. Hence, the results represented in this study are of significant relevance in bridging our gap in knowledge. Moreover, this study further strengthens the notion that indeed, Indigenous Australians have lower LFPs even in the presence of underlying respiratory conditions such as COPD.

In this study, the absolute FEV_1 and percent predicted values in Indigenous patients with COPD was observed to be significantly lower in comparison to non-Indigenous patients. It may be reasonable to speculate this truly reflects the severity of underlying disease among Indigenous patients with COPD, hence, the lower FEV_1 values noted. However, even after controlling for age, sex, height and smoking status, these differences still persisted. Hence, an alternative explanation is plausible for this observation.

In line with observed lower FEV_1, the FVC value was also similarly lower among Indigenous patients. The lower FVC values have consistently been observed in previous reports among Indigenous Australians.[14,16,19,21,30,31] This may be suggestive of a restrictive ventilatory impairment or a combination of obstructive and restrictive impairments (ie; mixed impairment). The authors do acknowledge that static lung volumes as measured by plethysmography are required to accurately identify restrictive ventilatory impairment. However, it was beyond the scope of this study to assess plethysmography data. Nonetheless, in the real-world scenario, irrespective of the presence of any form or type of underlying respiratory condition, a restrictive ventilatory impairment is one of the most common spirometry patterns observed in this Indigenous population, including among a significant proportion of patients with COPD.[16] The lower FVC (a restrictive ventilatory impairment) may indicate the presence of underlying conditions such as interstitial lung disease (ILD), chest wall deformities or neuromuscular disorders.[32] However, the aforementioned respiratory conditions are very unlikely, as previous reports on chest radiological data have shown that respiratory conditions such as ILD are very rarely observed among this Indigenous Australian population.[8,9] Similar to this study, the lower FVC has been reported in a subset of African ethnic population, indicating certain ethnic populations inherently demonstrate lower FVC values.[33] Hence, it may be reasonable to speculate that a myriad of intrinsic or extrinsic factors[34] may be responsible for the observed lower FVC values in this population, such as: genetics,[35] ethnicity,[36] birth weight,[37] nutrition,[38] childhood infections,[39] and smoking.[40]

Although controversy exists if FEV_1/FVC fixed ratio < 0.7 or the FEV_1/FVC < LLN should be utilised in accurately diagnosing patients with COPD,[41–43] it appears that the FEV_1/FVC< LLN criteria is gaining popularity.[44] However, due to lack of established spirometry reference norms for adult Indigenous Australians, currently there is sparse published data in the literature to demonstrate how the LLN parameters would display among Indigenous patients in comparison to non-Indigenous patients.[45] In this study, we observed that the LLN values did not significantly differ between the Indigenous and non-Indigenous patients. Moreover, among Indigenous patients who demonstrated airflow obstruction by FEV_1/FVC fixed ratio < 0.7 criteria, 92% of them also demonstrated to fit the FEV_1/FVC < LLN criteria, whereas only 71% of the non-Indigenous patients did so. In light of this study's findings and in the absence of spirometry reference norms for adult Indigenous Australians, in the authors' opinion, the LLN parameters may be a better marker in the clinical decision making for the adult Indigenous Australians.

This study has highlighted that health practitioners caring for Indigenous patients should be aware of the implications in utilising spirometry criteria in COPD diagnosis and severity classification when adopting reference values drawn from non-Indigenous populations. A recent study has highlighted, irrespective of which of the recommended classifications used, COPD-X[46] or GOLD,[1] most Indigenous patients with COPD will likely fall into either the "severe" or "very severe" category.[22] Indigenous patients in this study demonstrated 16–17% lower values for FVC and FEV_1, compared to non-Indigenous patients. It is inevitable that an Indigenous patient with COPD will likely be assessed to have a higher

disease burden by adopting spirometry reference values for the non-Indigenous population. In the aforementioned report on spirometry data in Indigenous population, creating a model by arbitrarily inflating FVC and FEV_1 values by 15% (arbitrarily applying a correction factor for Indigenous patients) resulted in a re-categorization of 80% of patients to either "mild" or "moderate" airflow obstruction severity categories - A much closer approximation to the distribution found in non-Indigenous populations.[22]

Understandably, lack of normative lung function reference values may impose unprecedented diagnostic and management challenges among adult Indigenous patients with respiratory conditions, including COPD. Nonetheless, this study has highlighted that there are significant differences along with lower spirometry parameters among the adult Indigenous patients with COPD, in comparison to non-Indigenous patients. Furthermore, despite no significant differences in the LLN FEV_1/FVC ratio values, the FEV_1 values were noted to be substantially lower for Indigenous patients. Once again, as mentioned above, it is unclear at this stage if this truly reflects greater COPD disease burden due to higher smoking prevalence[9,10] amongst Indigenous people or if it is due to inherent lower LFPs values in this Indigenous population.[14,16,19,21,30,31] Indeed, future research should be directed toward elucidating the lived experience of Indigenous Australian patients with respiratory conditions in order to better correlate LFPs with the subjective experience on quality of life and the appropriateness of varied management and treatment plans.

We presume that the results of this study may be of interest for Indigenous health practitioners and primary care physicians. It is not clear at this stage if a correction factor for spirometry could be utilised in day-to-day diagnostic and clinical decision making for Indigenous patients presenting with COPD. There has been significant progress in the recent past in addressing respiratory health issues among the adult Indigenous Australian population, especially, from the Top End NT of Australia.[7–11,14–17,21,22,47–59] Further studies, however, may be useful to better understand if our study findings are comparable to other Indigenous population both in other parts of Australian and globally, that may change the diagnostic and management of COPD paradigm among Indigenous populations.

Limitations

Caution must be exercised in relation to the applicability of the study outcomes in other Indigenous populations, as such, our data is only representative of patients residing in the TEHS region of the NT of Australia. Moreover, the Indigenous population in Australia is a diverse group of people. There exists a proportion of individuals who are descendants of inter-racial relationships, many of whom identify as Indigenous. Furthermore, although we could anticipate and extrapolate a similar trend to other Indigenous population, there may be other variables such as climate (desert vs tropical) or living environments (remote vs metropolitan) that could affect the development of lung and LFPs. The authors also acknowledge that the number of study participants in the matched group may be less than desired and radiological data was not assessed for the severity of underlying COPD between the two groups. It may be reasonable to accept this limitation, as such significant proportion of Indigenous people reside in remote and regional communities, hence imposing substantial challenges in conducting prospective studies. Furthermore, even among the matched cohort, the BMI significantly differed, indicating much reduced weight among the Indigenous cohort, which is reflective of the socioeconomic situation of many Indigenous patients. This study also did not include static lung volumes and DLCO data. Nonetheless, this is the first study to demonstrate differences in the spirometry parameters among Indigenous patients with COPD against non-Indigenous patients and there may be avenues in the future for further prospective research.

Conclusion

Our current approach to all patients with COPD is often based on guidelines that provide recommendations drawn from non-Indigenous general population. In this study we have demonstrated that Indigenous patients with COPD have substantially lower spirometry values for FVC and FEV_1, even after matching for age, sex, height and smoking status. In light of this study's findings, a more tailored approach to the diagnosis and management of this unique Indigenous population with COPD is required, enabling us to improve quality of life and close the health gap.[60]

Abbreviations

BD, bronchodilator; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COPD-X, concise tool for chronic obstructive pulmonary disease; DLCO, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, global initiative for chronic obstructive lung disease; ILD, interstitial lung disease; IQR, interquartile range; LFPs, lung function parameters; LLN, lower limit of normal; NT, Northern territory; TEHS, top end health service.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest for this study.

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