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Racial disparities in lung function by pulmonary function testing among lung transplant candidates and race-specific reference equations

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Non-White patients with interstitial lung disease (ILD) experience racial disparities in lung transplant waitlist mortality. Race-specific equations for spirometry may contribute by underestimating restriction severity in non-White candidates. We analyzed US lung transplant candidates to assess for disparities in forced vital capacity (FVC) at listing, comparing absolute and adjusted values using race-specific and race-neutral equations. We identified 17,457 adults with ILD listed May 4, 2005 to September 31, 2023. At listing, mean absolute FVC was higher for White patients (2.03 ± 0.80 liters) than Black patients (1.61 ± 0.67 liters) and Asian patients (1.49 ± 0.86 liters). Differences were attenuated after applying race-specific equations (White patients 50.0 ± 17.5%, Black patients 47.7 ± 17.9%, Asian patients 46.2 ± 24.2%). Compared with race-neutral equations, race-specific equations had higher odds of classifying FVC as severe (≤40%) requiring listing in White patients (OR 1.37, 95% CI 1.28–1.40) but lower odds in Black patients (OR 0.82, 95% CI 0.74–0.90). Using race-neutral equations might help improve racial disparities for lung transplant candidates with ILD.
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Racially minoritized patients with interstitial lung disease (ILD) experience accelerated disease progression and reduced access to advanced treatments and transplantation.[1–3] Race-specific reference equations for spirometry measures like forced vital capacity (FVC) could contribute to these disparities. Reference equations compare a patient's lung function with

Abbreviations: BMI, Body mass index; CI, Confidence interval; cm, Centimeter; FVC, Forced vital capacity; GLI, Global lung initiative; IPF, Idiopathic pulmonary fibrosis; ILD, Interstitial lung disease; kg/m^2, Kilogram per meter squared; L, Liter; OR, Odds ratio; Sep, September; STAR, Standard Transplant Analysis Research; UNOS, United Network of Organ Sharing

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populations of healthy controls matched by age, sex, and height to help translate the raw value into a relative or normalized value that can aid its interpretation.[4] However, when these equations include race-based adjustments, they can obscure clinically meaningful differences in lung function and perpetuate historical disparities in lung health across diverse clinical scenarios with impacts on diagnosis, severity classification, disability compensation qualification.[5] For non-White patients with ILD, race-specific reference equations have the potential to over-estimate percent-predicted FVC and inappropriately classify ILD as less severe, which may delay lung transplant referral for patients with ILD. As such, pulmonary research societies have called for discontinuing the use of race-specific equations.[6] Our single center retrospective analysis found that, compared with race-neutral alternatives, race-specific equations classified FVC as meeting guideline criteria[7] for transplant evaluation significantly more often for White patients with ILD compared with Black patients with ILD.[8] The purpose of this study was to assess for racial disparities in FVC values at the time of lung transplant listing in a national cohort of transplant candidates and assess the role race-specific reference equations may play.

Material and methods

We performed a retrospective analysis of the Standard Transplant Analysis Research (STAR) file provided by the United Network of Organ Sharing (UNOS), a cohort of all US participating transplant centers. We included patients who had a reported race with a race-specific reference equation for FVC (White, Black, and Asian), were at least 18 years old at listing, were listed for a first-time lung transplant, had a group D category of native lung disease (restrictive lung disease or ILD), and were listed May 4, 2005 to September 31, 2023. We excluded patients simultaneously listed for multiple organs, patients with a history of prior transplant, patients removed from the waitlist for being too well, and patients who received a living donor transplant. We collected patient demographics including race and ethnicity data as well as absolute FVC values recorded in the STAR file reported by the transplant listing center.

Categorical characteristics were summarized as frequency and percent of non-missing values. Continuous characteristics were summarized as mean ± standard deviation (SD). We applied the Global Lung Initiative (GLI) 2012 reference equations to convert absolute FVC values into percent-predicted values using both race-specific reference equations and a race-neutral equation (GLI "other"). Both adjusted values were then categorized using a proposed published FVC threshold for ILD as severe requiring transplant (FVC ≤ 40%).[9] By patient race, we compared how race-specific and race-neutral equations classified FVC (≤40% and severe or not) using unadjusted conditional logistic regression models; we report odds ratios (ORs) with 95% confidence intervals (CIs) and *p*-values for each patient race. Statistical significance was assessed at $\alpha = 0.05$.

Statistical analyses were conducted using R version 4.1.3. This study was approved by Duke University Medical Center's Institutional Review Board (Pro00112871) as exempt from informed consent and complies with the International Society for Heart and Lung Transplantation Ethics statement.

Results

We identified 17,457 first-time lung-only transplant candidates with ILD during our study period, including 14,731 (84.4%) White patients, 2,095 (12.0%) Black patients, and 631 (3.6%) Asian patients (Table 1). At the time of listing, White patients had a higher mean age (61.1 ± 8.9 years) compared with Black patients (52.5 ± 10.3 years) and Asian patients (59.0 ± 10.7 years). Male sex was more common for White patients (68.9%) and Asian patients (63.4%) as compared with Black patients (42.8%). Height and BMI were similar between all groups. In comparing FVC value at listing, White patients had the highest mean FVC (2.03 ± 0.80 liters) compared with Black patients (1.61 ± 0.67 liters) and Asian patients (1.49 ± 0.86 liters). These differences were reduced when comparing percent-predicted values using race-specific reference equations; FVC percent-predicted values were more similar

Table 1 Patient Characteristics for Included First-Time Lung-Only Transplant Candidates with ILD

Characteristic at listing	White N = 14,731	Black N = 2,095	Asian N = 631
Age	61.14 (8.91)	52.54 (10.33)	58.98 (10.73)
Sex			
Female	4,576 (31.1%)	1,199 (57.2%)	231 (36.6%)
Male	10,155 (68.9%)	896 (42.8%)	400 (63.4%)
Height, cm	171.97 (9.72)	169.14 (9.93)	164.09 (8.51)
BMI, kg/m^2	27.37 (4.03)	27.36 (4.32)	24.71 (4.04)
FVC			
Absolute value (L)	2.03 (0.80)	1.61 (0.67)	1.49 (0.86)
Percent-predicted, race-specific	50.0 (17.5)	47.7 (17.9)	46.2 (24.2)
Percent-predicted, race-neutral	54.3 (19.1)	44.1 (16.5)	44.1 (23.4)

BMI, body mass index; cm, centimeter; FVC, forced vital capacity; ILD, interstitial lung disease; kg/m^2, kilogram per meter squared; L, liters. Continuous variables are presented as means (standard deviation), categorical variables as frequency (percent).

Table 2 Comparison of Race-Specific and Race-Neutral Reference Equations in Classifying FVC as Meeting Transplant Listing Threshold for Waitlist Candidates with ILD

FVC classification as meeting transplant listing criteria (≤40%)	Asian N = 631	Black N = 2,095	White N = 14,731
Percent Classified as Warranting Listing			
Race-Specific Equation	41.7% (263/631)	36.4% (763/2,095)	30.6% (4,503/14,731)
Race-Neutral Equation	47.4% (299/631)	44.4% (931/2,095)	22.8% (3,364/14,731)
Absolute Difference	−5.7% (−36/631)	−8.0% (−168/2,095)	+7.8% (+1,139/14,731)
Odds of Classification as Warranting Listing (OR with 95% CI)			
Race-Specific Equation	0.88 (0.74–1.04)	0.82 (0.74–0.90)[a]	1.34 (1.28–1.40)[a]
Race-Neutral Equation	Reference	Reference	Reference

CI, confidence interval; FVC, Forced vital capacity; ILD, interstitial lung disease; OR, odds ratio.
[a]Denotes p-value < 0.001.

between White patients (50.0 ± 17.5%), Black patients (47.7 ± 17.9%), and Asian patients (46.2 ± 24.2%). However, when race-neutral equations were applied, differences were more apparent between White patients (54.3 ± 19.1%) and Black patients (44.1 ± 16.5%) and Asian patients (44.1 ± 23.4%).

Table 2 outlines comparisons of FVC classification at the time of waitlisting between race-specific and race-neutral reference equations. Race-specific reference equations led to lower rates of classifying FVC as meeting guidelines criteria for Asian patients (41.7% vs 47.4, difference −5.7%) and for Black patients (36.4% vs 44.4%, difference −8.0%) but higher rates for White patients (30.6% vs 22.8%, difference +7.8%). In conditional logistic regression analysis, the odds of classifying FVC as warranting transplant listing using a race-specific reference equation versus a race-neutral equation were significantly elevated for White patients (OR 1.34, 95% CI 1.28–1.40) but were significantly lower for Black patients (OR 0.82, 95% CI 0.74–0.90). The odds of classifying FVC and warranting transplant listing were not significantly different using a race-specific equation for Asian patients (OR 0.88, 95% CI 0.74–1.04).

Discussion/Conclusions

Among US first-time lung transplant candidates with ILD, there were substantial disparities in lung function at the time of listing as determined by absolute FVC value. These differences in FVC at listing remained apparent when adjusted using race-neutral equations but were attenuated by race-specific reference equations. Compared with race-neutral equations, race-specific equations classified FVC as meeting guideline criteria for lung transplant listing at greater odds for White patients and lower odds for Black patients. This finding suggests race-specific reference equations could contribute to delayed listing at a more advanced stage of ILD and could impact their pre-listing and pre-transplant disease management. The proposed published FVC threshold[9] used in our study proposes a single threshold of 40% for all patients, regardless of race. However, the use of race-specific reference equations effectively creates different absolute thresholds by race with a lower absolute FVC value required for a Black and an Asian patient to meet the threshold compared with a White patient. Race-specific reference equations therefore likely contribute a distinct barrier to lung transplant access and could partially explain known disparities in waitlist mortality for Black and Asian patients with ILD,[10] potentially through delaying referral until a more advanced state of disease and/or through affecting the pre-listing and pre-transplant management of non-White patients with ILD. Lung transplant listing is complex. The decision incorporates many factors of FVC, including the absolute and relative value as well as FVC trajectory; other important factors include other spirometry values impacted by race-specific equations such as forced expiratory volume in 1 second (FEV1) and other clinical and socioeconomic factors. Thus, changes in classification of FVC at the time of listing play only a part in the decision to list a patient. It is also important to note that spirometry values like FVC continue to play a role in decision-making after transplant listing. FVC percent predicted values were formerly incorporated into the lung allocation score (LAS) but are no longer employed in the current composite allocation score (CAS) for allocating donor organs. Nonetheless, our results show a racial disparity in FVC at listing and implicate race-specific reference equations in that disparity. Given the presence of race-neutral alternatives, we need to critically evaluate and reconsider the use of race-specific reference equations for transplant decision-making in patients with ILD. The lung transplant community should join other international societies[6] in calling for the use of race-neutral equations.

CRediT authorship contribution statement

DG was responsible for project design, data collection, data analysis, and manuscript writing. MW was responsible for data analysis and manuscript writing. EP was responsible for data analysis and manuscript writing. SP was responsible for project design and manuscript writing. LE was responsible for project design and manuscript writing.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Daniel Guidot reports financial support was provided by National Heart Lung and Blood Institute. Lisa McElroy reports financial support was provided by National

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