# Gender in idiopathic pulmonary fibrosis diagnosis: time to address unconscious bias

Mary E Strek

Physicians have long incorporated gender into their diagnostic algorithms of pulmonary disease in an effort to use available clinical clues when a single confirmatory diagnostic test does not exist. Gender is thought to be a relevant patient characteristic in phenotyping lung disease with a female predominance noted in patients with adult-onset asthma and male predominance in idiopathic pulmonary fibrosis (IPF).[1 2] Gender also may be of prognostic value in individual patients; severity of asthma is associated with female sex and increased mortality in interstitial lung disease (ILD) with male gender.[2 3] While gender may increase diagnostic confidence, if the strength of the gender and disease association is not based on rigorously validated data, inaccurate diagnosis or underdiagnosis may result. In an earlier era, the failure to diagnose COPD in women was associated with gender bias when formally studied.[4] More recently, the stereotype of the male smoker with lung cancer has been upended by the surprising data demonstrating higher lung cancer incidence rates in young women as compared with young men, not explained by differences in cigarette smoking.[5]

In this issue, Dr Assayag and colleagues investigate the role of gender in making a confident diagnosis of IPF, and conclude there is evidence for bias when using sex to inform an ILD diagnosis, which may result in men being overdiagnosed and women underdiagnosed with IPF.[6] The authors use clinical cases from one academic centre, evaluated online in a previous study by a large international group of respiratory physicians, who were requested to provide up to five diagnoses along with diagnostic likelihood as a measure of confidence in the ILD diagnosis.[7] Using this data, Assayag and colleagues perform a logistic regression analysis to determine the effect of gender on the odds of an IPF diagnosis and on physician diagnostic confidence. The differing prognosis between patients with IPF and non-IPF, as assessed by Cox proportional-hazards modelling, served as the measure of diagnostic accuracy.

The authors find that respiratory physicians chose IPF as the most likely diagnosis in 37.8% of the male and 10.6% of the female patients. The odds of a male compared with a female patient being given a first-choice diagnosis of IPF were three times greater, after adjustment for age, smoking and exposure history, autoantibodies and serum aspergillus precipitins. The IPF diagnosis was associated with greater confidence when the patients were male. Female patients were more frequently diagnosed with a connective tissue disease–related ILD or hypersensitivity pneumonitis. Interestingly, when the ILD diagnosis was stratified by the presence of usual interstitial pneumonia (UIP) on CT, gender did not affect the odds of an IPF diagnosis. However, when the CT showed a less certain diagnostic CT pattern, clinicians depended more heavily on previously learnt gender patterns of ILD. In cases with IPF as the first-choice diagnosis, the HR for mortality was higher in female patients, suggesting both male and female patients were misclassified as to their ILD diagnosis with an underdiagnosis of IPF in women.

The participating respiratory physicians were 66% male. Male, as compared with female, physicians were less likely to practise in an academic setting. The gender of the respiratory physician did not impact the odds of an IPF diagnosis or the confidence in making that diagnosis, suggesting women physicians may too share this diagnostic gender bias. The difference in mortality from IPF by gender was even greater when the diagnosis of IPF in women was determined by a physician subgroup characterised as ILD experts.

While the conclusions of this novel study have implications for clinical practice and investigations, these findings require confirmation. The single-centre study design, small number of cases, lack of a multidisciplinary team approach for physician participants and the nature of IPF as a diagnosis of exclusion are study limitations. The thoracic radiology assessment of UIP was not blinded to clinical information and of course could not be to blinded to biological sex. Also, in the initial study on which Assayag and colleagues rely, physician gender was not ascertained. As a result, the authors inferred gender from physician names and conducted an internet search to confirm the gender of participants whose names did not clearly delineate their sex.[6 7]

The results of this study suggest a need to revisit our paradigm that IPF is a disease of men and the default diagnosis in male patients without a UIP pattern on CT, as has been recommended in IPF guidelines. It also raises the disconcerting prospect that women were under-represented in IPF trials and may currently be denied antifibrotic therapy due to a failure to accurately diagnose IPF. Male patients might not receive optimal management of their non-IPF ILD and suffer psychological harm from being incorrectly told they have IPF. If IPF were recognised to occur in women with greater frequency, there might be an imperative to investigate a variety of doses of antifibrotic agents and to formally study the effects of gender on medication efficacy and tolerance in clinical trials. The recent observation that women were more likely to discontinue antifibrotic therapy due to an adverse drug reaction, as were those with a lower body mass index, may reflect biological differences in metabolism or smaller body size and is worthy of future investigation.[8]

The study raises interesting questions about the cultural and learnt beliefs or biases we bring to the diagnosis and treatment of illness. Failure to consider group differences confounds our efforts to achieve an accurate diagnosis and prescribe optimal therapy. A study of patient gender disparities in survival rates following acute myocardial infarction, based on the gender of the treating physician, showed a higher mortality among female patients treated by male physicians that was mitigated by increased male physician exposure to female patients and to female physician colleagues.[9] This suggests that greater diversity in clinical and investigative teams improves patient outcomes and could address the potential for gender to confound diagnostic accuracy noted by the authors in this study.

Department of Medicine, Section of Pulmonary and Critical Care, University of Chicago, Chicago, IL, USA

**Correspondence to** Dr Mary E Strek, Section of Pulmonary and Critical Care, Department of Medicine, University of Chicago, Chicago, IL 60637, USA; mstrek@medicine.bsd.uchicago.edu

**Contributors** I contributed solely to this work.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Commissioned; internally peer reviewed.




**To cite** Strek ME. *Thorax* 2020;**75**:365–366.

Accepted 15 February 2020
Published Online First 7 April 2020


► http://dx.doi.org/10.1136/thoraxjnl-2019-213968

*Thorax* 2020;**75**:365–366.

doi:10.1136/thoraxjnl-2020-214569

**ORCID iD**
Mary E Strek http://orcid.org/0000-0002-7671-1023

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